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Screening for Prediabetes and Type 2 Diabetes Mellitus: An Evidence Review for the U.S. Preventive Services Task Force

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The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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Structured Abstract

Purpose: To systematically review the evidence on benefits and harms of (1) screening for abnormal blood glucose and type 2 diabetes and (2) interventions for prediabetes or type 2 diabetes that was screen detected or recently diagnosed for populations and settings relevant to primary care in the United States.

Data Sources: PubMed/MEDLINE, the Cochrane Library, and trial registries through September 10, 2019; reference lists of retrieved articles; outside experts; and reviewers, with surveillance of the literature through May 21, 2021.

Study Selection: English-language controlled studies evaluating screening for abnormal blood glucose or evaluating interventions for prediabetes or type 2 diabetes that was screen detected or recently diagnosed.

Data Extraction: One investigator extracted data and a second checked accuracy. Two reviewers independently rated quality for all included studies using predefined criteria.

Data Synthesis: This review included 89 publications. Two randomized, controlled trials (RCTs) (ADDITION-Cambridge and Ely; described in 5 articles; 25,120 participants) evaluated invitations to screening for diabetes with (1) a stepwise approach (starting with random glucose) or (2) oral glucose tolerance test every 5 years. The trials found no significant difference between screening and control groups for all-cause or cause-specific mortality at 10 years or self-reported cardiovascular disease (CVD) events or quality of life at 7 through 13 years, but the trials were missing data from most participants for outcomes other than mortality. For harms, the trials reported no significant differences between screening and control groups for anxiety, depression, worry, or self-reported health, but one reported a short-term increase in anxiety (at 6 weeks) among persons screened and diagnosed with diabetes mellitus (DM) versus those not diagnosed with DM (State-Trait Anxiety Inventory scores: 46.7 vs. 37.0; p=0.031).

For screen-detected diabetes, one trial (ADDITION-Europe, described in 8 articles, 3,057 participants) evaluated a multifactorial intervention aimed at controlling glucose, blood pressure, and cholesterol and found no difference over 5 years in the risk of all-cause mortality, cardiovascular-related mortality, cardiovascular events, or other health outcomes between intervention and routine care groups. A post hoc analysis at about 10-years followup similarly found that differences remained nonsignificant for the primary composite outcome and for all-cause mortality. For recently diagnosed (not screen-detected) diabetes, five RCTs (8 publications, 5,138 participants) were included. In the United Kingdom Prospective Diabetes Study, long-term health outcomes were improved with intensive glucose control with sulfonylureas or insulin: decreased risk for all-cause mortality (relative risk [RR], 0.87 [95% confidence interval {CI}, 0.79 to 0.96]), diabetes-related mortality (RR, 0.83 [95% CI, 0.73 to 0.96]), and myocardial infarction (RR, 0.85 [95% CI, 0.74 to 0.97]) over 20 years (10-year post-trial assessment) but not at shorter followups. For overweight people, intensive glucose control with metformin decreased the risk for all-cause mortality (RR, 0.64 [95% CI, 0.45 to 0.91]), diabetes-related mortality [RR, 0.58 [95% CI, 0.37 to 0.91]), and myocardial infarction (RR, 0.61 [95% CI, 0.41 to 0.89]) at the 10-year followup, and benefits were maintained longer term.

For prediabetes interventions, most trials reporting on health outcomes had insufficient duration of followup for long-term health outcomes, reported few events, and found no difference between groups. One trial of a 6-year lifestyle intervention conducted in China (Da Qing, n=576) reported lower all-cause mortality (28.1% vs. 38.4% [hazard ratio {HR}, 0.71 {95% CI, 0.51 to 0.99}]) and CVD-related mortality (11.9% vs. 19.6% [HR, 0.59 {95% CI, 0.36 to 0.96}]) for intervention groups than for controls at 23 years but not at earlier followups; 30-year followup also reported lower all-cause mortality (HR, 0.74 [95% CI, 0.61 to 0.89]) and CVD-related mortality (HR, 0.67 [95% CI, 0.48 to 0.94]) for intervention groups than for controls. Lifestyle interventions (most involving >360 minutes contact) for obese or overweight people with prediabetes were associated with reductions in the incidence of diabetes (23 RCTs, pooled RR, 0.78 [95% CI, 0.69 to 0.88]). Lifestyle interventions were also associated with reduced systolic blood pressure and diastolic blood pressure (pooled weighted mean difference [WMD] -1.7 mm hg [95% CI, -2.6 to -0.8] and -1.2 mm hg [95% CI, -2.0 to -0.4], respectively), weight (pooled WMD, -1.2 kg [95% CI, -1.6 to -0.74]), and body mass index (BMI) (pooled WMD, -0.54 kg/m^2 [95% CI, -0.76 to -0.33]). For medications, metformin, thiazolidinediones (TZDs), and alpha glucosidase inhibitors (AGIs) were associated with a reduction in diabetes incidence (pooled RRs, 0.73 [0.64, 0.83], 0.50 [0.28, 0.92], and 0.64 [0.43, 0.96], respectively), but evidence for TZDs and AGIs was limited by imprecision, inconsistency, and risk of bias. Most trials of medications found no statistically significant association between hypoglycemic agents and changes in blood pressure or lipids, but they did find a reduction in weight and BMI for metformin, acarbose, or liraglutide, but TZDs were associated with weight gain (pooled WMD, 1.9 kg [95% CI, 0.8 to 3.1]).

Limitations: No trials assessed initial screening with A1c or fasting glucose and none assessed screening for prediabetes. For outcomes other than mortality, screening trials were missing data from most participants. Duration of followup was too short to assess health outcomes in most studies. A single trial evaluated interventions for screen-detected diabetes. The Da Qing trial conducted in China (n=576 participants enrolled in 1986) has not been replicated and was limited by at least medium risk of bias because of unclear randomization and allocation concealment methods and baseline differences likely to bias results in favor of the intervention. Harms were rarely assessed; none of the trials reported on labeling, harms from false-positive results, burden, inconvenience, or unnecessary testing and treatment.

Conclusions: Trials of screening for diabetes found no mortality benefit at 10 years but had insufficient data to assess other health outcomes. Evidence on harms of screening was scant. For people with screen-detected diabetes, one trial found no improvement in health outcomes over 5 to 10 years. For people with recently diagnosed (not screen-detected) diabetes, interventions improved health outcomes over 10 to 20 years. For obese or overweight people with prediabetes, interventions were associated with reduced incidence of diabetes and improvement in other intermediate outcomes, and limited evidence suggests that very high contact lifestyle interventions improve health outcomes after more than 20 years.

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Chapter 1. Introduction

Scope and Purpose

The U.S. Preventive Services Task Force (USPSTF) will use this report to inform an update of its recommendation on screening asymptomatic adults for abnormal blood glucose and type 2 diabetes mellitus (DM). In 2015, the USPSTF recommended screening for abnormal blood glucose as part of cardiovascular risk assessment in adults ages 40 to 70 years who are overweight or obese. In addition, it recommended that clinicians offer or refer patients with abnormal blood glucose to intensive behavioral counseling interventions to promote a healthful diet and physical activity (B recommendation). Screening for gestational DM and screening of children are not addressed in this review.

Condition Definition

DM refers to a range of metabolic disorders characterized by hyperglycemia. **Table 1** shows general categories and definitions of DM used by the American Diabetes Association (ADA).[1] The 2019 ADA guidelines emphasize that type 1 and type 2 DM are heterogeneous diseases in which clinical presentation and disease progression may vary considerably and that both may occur in adults or children.[2] Type 2 DM is characterized by insulin resistance and relative insulin deficiency.

The ADA criteria identify three tests that can be used to identify type 2 diabetes or prediabetes: A1c, fasting plasma glucose, or oral glucose tolerance test (OGTT) (**Table 2**). The ADA guidelines note that a second test is required for confirmation unless there is a clear clinical diagnosis (e.g., patient in hyperglycemic crisis). Prediabetes is the term used for individuals potentially at increased risk for diabetes whose glucose levels are considered higher than normal but do not meet criteria for diabetes.[1] Prediabetes includes individuals who meet criteria for impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and those with a glycated hemoglobin (A1c) from 5.7 to 6.4 percent.

Etiology and Natural History

DM is caused by a combination of insulin resistance and relative insulin deficiency.[3] The development of DM has been attributed to a complex interaction between genetic susceptibility and environmental factors (including diet and obesity).[3] Resulting hyperglycemia may be symptomatic or asymptomatic. Classic symptoms of hyperglycemia include polyuria, polydipsia, polyphagia, blurred vision, and unintentional weight loss. Left untreated, hyperglycemia can lead to acute and chronic morbidity and mortality. The natural history of asymptomatic screen-detected type 2 diabetes is unclear. In the United Kingdom Prospective Diabetes Study (UKPDS, N=3,867), adults with clinically detected diabetes based on mean fasting plasma glucose (FPG) levels of 6.1 to 15.0 mmol/L (110 to 270 mg/dL) without symptoms of hyperglycemia were randomized to intensive treatment (with a sulphonylurea or insulin) compared with conventional care (diet alone, drugs were only added if there were hyperglycemic symptoms or FPG > 15 mmol/L [270 mg/dL]).[4] In the conventional care group, incident outcomes of multiple diabetes-related microvascular and macrovascular outcomes were measured over 10 years of followup

(**Appendix A Table 1**). The estimates reflect the natural history of diabetes detected early (prior to developing symptoms of hyperglycemia); estimates for the 10-year risk of outcomes among populations identified with prediabetes or screen-detected diabetes would be lower. In addition, the UKPDS was started in 1977; usual care for comorbid conditions (e.g., use of statins, hypertension treatment) has changed over time, likely reducing the risk of adverse health outcomes (compared with those reported in the study).

Evidence from observational studies suggests that glucose levels in the prediabetes range are associated with increased risk of cardiovascular disease (CVD). A meta-analysis of prospective cohort studies (k=53) found that having IFG, IGT, or A1c levels between 5.7 and 6.4 percent was associated with a significantly higher risk of CVD (relative risk [RR], 1.13 to 1.30) and coronary heart disease (RR, 1.10 to 1.20) than normoglycemia.[5] IFG and IGT (but not A1c levels in the prediabetes range) were also associated with increased risk of stroke (RR, 1.06 to 1.20) and overall mortality (RR, 1.13 to 1.32) compared with normoglycemia.[5] The Supplemental Questions in Appendix B have additional information about the natural history of prediabetes.

Risk Factors

Many risk factors are associated with development of DM in adults, including older age, family history, overweight and obesity, dietary and lifestyle factors, environmental exposures, and others.[6] Contextual Question 1 in **Appendix A** provides additional information about risk assessment tools for predicting the risk of prediabetes or type 2 DM.

Individuals with prediabetes are thought to be at highest risk of developing incident DM. As noted above, observational studies have shown an association between prediabetes and CVD. Despite this evidence, adding A1c to CVD risk assessment for individuals without known CVD or diabetes has not shown incremental benefit for prediction of CVD risk.[7] In an analysis of individual-participant data from 73 prospective studies (294,998 individuals) without known DM or CVD, adding information on levels of A1c to conventional CVD risk factors was associated with only slight improvement in risk discrimination and was not associated with significant improvement in reclassification of participants across clinical risk categories recommended to inform decisions about preventive treatment.[7]

Prevalence and Burden

According to the Centers for Disease Control and Prevention's 2017 National Diabetes Statistics Report, an estimated 12.2 percent of all U.S. adults (≥18 years) had diabetes in 2015.[8] Of those with diabetes, 23.8 percent were not aware of or did not report having diabetes. The estimated percentages of people with diabetes and prediabetes were derived from the National Health and Nutrition Examination Survey, National Health Interview Survey (NHIS), and other sources. Diagnosed diabetes was determined by self-report among survey respondents and by diagnostic codes; both fasting glucose and A1c levels were used to derive estimates for undiagnosed diabetes and prediabetes (most estimates do not differentiate between type 1 and type 2 diabetes).[8] Prevalence increases with age; it was lowest in younger adults (4.0% in adults ages 18 to 44 years) and highest in those age 65 years or older (25.2%). Prevalence was similar in women and men (11.7% and 12.7%, respectively). Age-adjusted estimates from the same data source for 2013-2015 showed a higher prevalence of diabetes among American Indians/Alaska

Natives (15.1%), non-Hispanic blacks (12.7%), and people of Hispanic ethnicity (12.1%) than non-Hispanic whites (7.4%) and Asians (8.0%). Prevalence of diagnosed diabetes also varied by education level; higher rates were reported by those with less than a high school education (12.6%) than those with a high school education (9.5%) or more than a high school education (7.2%).[8] Counties in the southern and Appalachian regions of the United States tended to have the highest prevalence of diagnosed diabetes.

A more recent report from CDC scientists found that the number of people newly diagnosed with diabetes decreased from 2009 to 2017 (from about 1.7 million cases per year to about 1.3 million cases per year in 2017), after having increased from 1990 to 2009.[9] The data (self-reported data from NHIS) do not distinguish between type 1 and type 2 diabetes, but over 90% of people with diabetes in the United States have type 2 diabetes.

According to CDC's 2017 report, an estimated 33.9 percent of U.S. adults met criteria for prediabetes in 2015 based on their fasting glucose or A1c level.[8] Similar to diabetes prevalence, estimates of prediabetes were higher in older adults. Nearly half (48.3%) of adults age 65 years or older met criteria for prediabetes in 2015. Across all age categories, 11.6 percent of adults who met criteria for prediabetes had been told by a health professional that they had prediabetes.[8]

In terms of burden of disease, diabetes was estimated to be the seventh leading cause of death in the United States in 2015 based on the Underlying Cause of Death database.[10] Approximately 3 percent of deaths (79,535 of 2,712,630 total deaths) were attributed to diabetes based on death certifications for U.S. residents. Cause of death was based on ICD-10 codes, and estimates do not differentiate between type of diabetes. Morbidity from type 2 diabetes is due to macrovascular disease (atherosclerosis), microvascular disease (retinopathy, nephropathy, and neuropathy), and acute complications (of hyperglycemia or hypoglycemia). Diabetes is the leading cause of kidney failure, lower-limb amputations other than those caused by injury, and new cases of blindness among adults in the United States.[11] Estimates based on results of the Global Burden of Disease Study indicate that diabetes was the third leading cause of years lived with disability in 2016, which is an approximate 30 percent increase from 1990 (when it ranked 8th).[12] In terms of causes of disability-adjusted life-years in the United States, diabetes ranked 4th in 2016, an increase from the 6th leading cause in 1990 (an approximate 11% increase).[12]

Rationale for Screening and Screening Strategies

Screening asymptomatic adults for type 2 diabetes may allow earlier detection, diagnosis, and treatment, with the ultimate goal of improving health outcomes. Earlier detection of prediabetes may allow for interventions to prevent progression to diabetes and a shorter exposure to the hyperglycemic states associated with adverse outcomes. When screening results in a diagnosis of diabetes, treatment to prevent or reduce the risk of diabetic complications can be initiated.[1, 13, 14]

Screening tests and thresholds for a positive test are summarized in **Table 2**. Strategies for screening for prediabetes and type 2 diabetes are the same and include screening individuals of prespecified age groups or targeted screening based on the presence of risk factors assessed either without or with formal risk assessment instruments.[1, 13, 14] If not using a formal instrument, assessing for diabetes risk factors (e.g., age, overweight, history of gestational diabetes, identifying as a member of a race or ethnicity with a higher risk of diabetes, hyperlipidemia) is

followed by fasting glucose, hemoglobin A1c, or oral glucose tolerance testing for those at increased risk. Examples of formal risk assessment tools include the ADA risk test,[15] Canadian Diabetes Risk Assessment Questionnaire (CANRISK),[16] Finnish Diabetes Risk Score (FINDRISC),[17] and Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK).[18]

Treatment Approaches

For Reducing Progression From Prediabetes to Diabetes

Intensive lifestyle interventions to achieve weight loss and increase physical activity are the first-line therapies for preventing progression of prediabetes to diabetes. The U.S. Food and Drug Administration (FDA) has not approved any medications specifically to prevent progression of prediabetes to diabetes, nor has the Canadian Medicare System.[19, 20] The National Institute for Clinical Excellence (NICE), in contrast, has approved the use of metformin among prediabetic individuals with worsening glucose control despite lifestyle changes or inability to participate in lifestyle change.[21] For people with prediabetes, the ADA recommends that metformin should be considered for prevention of diabetes, especially for those with BMI 35 or greater, those under 60 years of age, and women with prior gestational DM.[22]

Hypoglycemic Agents

Lifestyle interventions are the first-line therapies for patients diagnosed with diabetes. Recommendations and formal programs to improve diet and increase exercise are often accompanied or followed by pharmacotherapy. Pharmacotherapy includes the biguanide metformin, sulfonylureas (e.g., glipizide, glyburide, glimepiride), GLP-1 receptor agonists (liraglutide, exenatide, lixisenatide, dulaglutide, semaglutide), sodium glucose cotransporter 2 (SGLT-2) inhibitors (empagliflozin, canaglifozin, dapaglifozin, ertugliflozin), dipeptidyl peptidase 4 inhibitors (saxagliptin, sitagliptin, alogliptin, linagliptin), thiazolidinediones (pioglitazone, rosiglitazone), alpha glucosidase inhibitors (acarbose, miglitol, voglibose), and insulin.[23, 24] The ADA recommends monotherapy with metformin along with lifestyle modification as initial therapy.[22] The intensity of recommended pharmacotherapy regimens depends on A1c level. The ADA also recommends considering insulin for those with evidence of ongoing weight loss and symptoms of hyperglycemia when A1c or blood glucose levels are very high (>10% or ≥300 mg/dL, respectively) and initiating dual therapy for those who have A1c 1.5% or more above their glycemic target (which could range from <6.5% to <8%, depending on their individualized goal).[22] The American College of Physicians (ACP) also suggests metformin as the first-line pharmacotherapy for diabetes with the addition of other agents (e.g., sulfonylureas, thiazolidinedione, SGLT-2 inhibitors or dipeptidyl peptidase-4 [DPP-4] inhibitor) as needed.[25] **Appendix A** provides additional information on treatments for people with diabetes aiming to reduce CVD risk and microvascular complications (e.g., hypertension treatment).

Clinical Practice in the United States

The majority of outpatient care for people with diabetes in the United States is provided by primary care.[26] Analysis of data from the 2009 through 2015 National Ambulatory Medical Care Survey (NAMCS) found that the mean number of total yearly visits for people with diabetes was

much higher for primary care offices than for specialist offices, hospital outpatient departments, and hospital emergency departments (61.4 million vs. 32.0, 11.1, and 12.1 million, respectively).[26] Similarly, the mean number of total yearly visits for which diabetes was a reason for the visit was much higher for primary care offices than for specialist offices, hospital outpatient departments, and hospital emergency departments (14.4 million vs. 4.9, 2.4, and 0.3, respectively).[26]

Recent studies have described the uptake of screening for diabetes in the United States. One study using NAMCS data reported a low rate of annual screening for people meeting ADA criteria (age 45 years or older and those <45 years of age with BMI ≥25 and an additional risk factor) of less than 15 percent in each year from 2012 to 2015 (covering a total of 105,721 office visits), although screening increased from 2012 to 2015 from 10 percent to 13.4 percent.[27] The study also reported the prevalence of and treatment patterns for prediabetes (identified by fasting blood glucose, A1c, or ICD-9 codes). Of those screened, 16.7 percent had prediabetes. Of all visits for people with prediabetes (5,406 visits), lifestyle management was provided at 21.3 percent, and antihyperglycemic medications were prescribed at 2.9 percent. Metformin was by far the most commonly prescribed medication in visits for prediabetes (accounting for 76.1% of antihyperglycemic medications).

An evaluation of 12,772 people without diabetes who were at least 45 years of age reported high rates of screening, with 78 percent being screened at least once over 3 years from 2010 through 2013.[28] Subjects were members of a health maintenance organization assigned to primary care providers in a large academic health system. Screening was defined as the first OGTT, A1c, or any glucose test performed. Glucose was (by far) the most common test, accounting for 86 percent of the initial screening tests versus 14 percent for A1c (OGTT accounted for <1%). It is uncertain whether many of the glucose tests should truly be considered screening tests because they were not required to be fasting tests for the main analysis. When limiting the screening definition for the analysis to glucose tests specifically marked as fasting tests (and still including OGTT and A1c), they reported a much lower rate of screening, at 20 percent of participants. Of the participants screened with A1c, 63 percent met criteria for prediabetes or diabetes.

Recommendations of Other Organizations

All current clinical practice guidelines (CPGs) recommend screening high-risk groups for diabetes (**Appendix A Table 2**) but with some variation in how high risk is defined, including the number of risk factors necessary before screening. When screening tests are normal, repeat screening is generally recommended every 3 years. Annual screening is typically recommended for those with prediabetes. Most guidelines recommend using either validated diabetes risk assessment tools/calculators or a set of criteria for increased risk (e.g., BMI, family history, hypertension) to determine whether to screen. In the United Kingdom for example, the assessment of diabetes risk has two stages; the first step recommends using a validated risk tool (or in the absence of an available validated tool a diabetes risk filter) to identify people at risk before performing the second step, a blood test to confirm whether an individual has or is at risk of type 2 diabetes. The Canadian Task Force on Preventive Health Care recommends the use of a validated diabetes risk assessment tool (FINDRISC) to determine who should be screened using HbA1c testing. In Australia, diabetes risk assessment is recommended every 3 years from age 40

with blood test screening for those identified as high risk (using the risk calculator) or with other known risk factors.

Clinical practice guidelines vary with respect to recommending universal blood test screening for type 2 diabetes (**Appendix A Table 2**). Most organizations recommend against universal blood test screening without the presence of risk factors. The ADA along with the American Association of Clinical Endocrinologists and American College of Endocrinology recommend screening all adults, using a plasma glucose test or HbA1c, beginning at age 45 regardless of risk factors (the ADA also recommends screening overweight or obese adults of any age with at least one risk factor). The Canadian Diabetes Association and the Singapore Ministry of Health recommend blood sugar screening for all adults beginning at age 40.

Chapter 2. Methods

Key Questions and Analytic Framework

The scope and key questions (KQs) were developed by the Evidence-based Practice Center (EPC) investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers. The analytic framework and KQs that guided the review are shown in **Figure 1**. Nine KQs were developed for this review:

1. a. Is there direct evidence that screening for type 2 diabetes and prediabetes in asymptomatic adults improves health outcomes?
   b. Does the effectiveness of screening differ for subgroups defined by age, sex, race/ethnicity, socioeconomic status, or BMI?
2. a. What are the harms of screening for type 2 diabetes and prediabetes in asymptomatic adults?
   b. Do the harms of screening differ for subgroups defined by age, sex, race/ethnicity, socioeconomic status, or BMI?
3. a. Do interventions for screen-detected type 2 diabetes and prediabetes provide an incremental benefit in health outcomes when delivered at the time of detection compared with initiating interventions later, after clinical diagnosis?
   b. Does the effectiveness of these interventions differ for subgroups defined by age, sex, race/ethnicity, socioeconomic status, or BMI?
4. a. Do interventions for screen-detected type 2 diabetes and prediabetes improve health outcomes compared with no intervention, usual care, or interventions with different treatment targets?
   b. Does the effectiveness of these interventions differ for subgroups defined by age, sex, race/ethnicity, socioeconomic status, or BMI?
5. a. Do interventions for recently diagnosed type 2 diabetes improve health outcomes compared with no intervention, usual care, or interventions with different treatment targets?
   b. Does the effectiveness of these interventions differ for subgroups defined by age, sex, race/ethnicity, socioeconomic status, or BMI?
6. What are the harms of interventions for prediabetes, screen-detected type 2 diabetes, or recently diagnosed type 2 diabetes?
7. a. Do interventions for prediabetes delay or prevent progression to type 2 diabetes?
   b. Does the effectiveness of these interventions differ for subgroups defined by age, sex, race/ethnicity, socioeconomic status, or BMI?
8. After interventions for prediabetes are provided, what is the magnitude of change in health outcomes that results from the reduction in type 2 diabetes incidence?
9. Do interventions for prediabetes improve other intermediate outcomes (blood pressure, lipid levels, BMI, weight, and calculated 10-year cardiovascular disease risk)?

In addition to addressing the KQs, this review also looked for evidence related to five contextual questions (CQs) that focused on risk assessment tools, agreement among screening tests, screening tests' prediction of future adverse health outcomes, yield of rescreening at different intervals in adults with an initial normal screening test, and recently published modeling studies

that assess screening (vs. no screening) and examine health outcomes. These CQs were not a part of this systematic review. They are intended to provide additional background information. Literature addressing the contextual questions is summarized in **Appendix A**. This review also included nine supplemental questions that were added during the USPSTF deliberation process. The supplemental questions focused on the use of metformin for prediabetes, the natural history of prediabetes, overdiagnosis and overtreatment, disutilities, patient-reported health status measures, uptake, and adherence. Literature addressing the supplemental questions is summarized in **Appendix B**.

Data Sources and Searches

PubMed/MEDLINE and the Cochrane Library were searched for English-language articles published from January 1, 2014, through September 10, 2019. Medical Subject Headings were used as search terms when available and keywords when appropriate, focusing on terms to describe relevant populations, tests, interventions, outcomes, and study designs. The search relied primarily on the previous systematic review for the USPSTF to identify potentially relevant studies published before 2014 (we reassessed all articles included in that systematic review using the eligibility criteria). Complete search terms and limits are listed in **Appendix B**. Targeted searches for unpublished literature were conducted by searching ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform. To supplement electronic searches, the reference lists of pertinent review articles and studies that met the inclusion criteria were reviewed. Studies suggested by peer reviewers or public comment respondents were reviewed and, if appropriate, incorporated into the final review. Since September 10, 2019, ongoing surveillance was conducted through article alerts and targeted searches of journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on May 21, 2021, and did not identify any additional studies that would affect the conclusions. All literature search results were managed using EndNote™ version 9.2 (Thomson Reuters, New York, NY).

Study Selection

Inclusion and exclusion criteria for populations, interventions, comparators, outcomes, timing, settings, and study designs were developed with input from the USPSTF (**Appendix B**). English-language studies of asymptomatic, nonpregnant adults age 18 years or older conducted in countries categorized as medium or higher on the 2016 Human Development Index were included. For all KQs, controlled clinical trials were eligible. Controlled prospective cohort studies were also eligible for KQs on harms of screening and treatment (KQs 2 and 6) and the change in health outcomes after reduction in type 2 DM incidence (KQ 8); case-control studies were eligible for KQs on harms (KQs 2 and 6).

For KQs 1 and 2 (direct evidence of benefits and harms of screening), studies that compared screening with A1c, fasting glucose, or OGTT with no screening or alternative screening strategies were eligible. KQs 3 through 6 (benefits and harms of interventions for health outcomes among people with prediabetes and DM) evaluated primary care–relevant behavioral counseling interventions or pharmacologic interventions for prediabetes and type 2 DM but

differed in eligible populations, comparisons, or outcomes. KQs 3 and 4 required participants to have screen-detected DM or prediabetes but differed in their comparison (with KQ 3 comparing sooner vs. later intervention and KQ 4 comparing interventions vs. no intervention, placebo, usual care, etc.), whereas KQ 5 assessed studies of people with recently diagnosed DM (but not required to be screen detected). For KQ 6 (harms of interventions), all populations and comparisons eligible for KQs 3 through 5 (on benefits of interventions) that reported on harms were eligible. For KQs 7 and 9, studies of interventions for people with prediabetes that reported on incidence of diabetes (KQ 7) or other intermediate outcomes (blood pressure, lipids, BMI, weight, or calculated 10-year ASCVD risk) were eligible. For KQ8, we included studies of interventions for prediabetes that reported both the change in incidence of diabetes and health outcomes (from KQs 4 and 7). Studies with too few events to adequately address KQ 8 (<20 people with the relevant events) were not included, nor were studies that only reported composite outcomes that included intermediate outcomes if they did not report the health outcome components of the composite separately. For KQ 8, studies of interventions that do not address glycemic status were not included (e.g., blood pressure medications). We used the adjusted hazard ratios reported by study authors, when available, and calculated relative risks and 95% confidence intervals when only numbers of events were reported.

Titles and abstracts were independently reviewed by two investigators; those marked for potential inclusion by either reviewer were retrieved for evaluation of the full text. The full texts were then independently reviewed by two investigators to determine final inclusion or exclusion. Disagreements were resolved by discussion and consensus.

Quality Assessment and Data Abstraction

We assessed the quality of studies as good, fair, or poor, using predefined criteria developed by the USPSTF and adapted for this topic (**Appendix B**). Two independent investigators assigned quality ratings for each study. Disagreements were resolved by discussion. Only studies rated as having good or fair quality were included.

For each included study, one investigator extracted pertinent information about the methods, populations, interventions, comparators, outcomes, timing, settings, and study designs. All data extractions were checked by a second investigator for completeness and accuracy.

Data Synthesis and Analysis

Findings for each KQ were summarized in tabular and narrative format. The overall strength of the evidence for each KQ was assessed as high, moderate, low, or insufficient based on the overall quality of the studies, consistency of results between studies, precision of findings, risk of reporting bias, and limitations of the body of evidence, using methods developed for the USPSTF (and the EPC program).[29] Additionally, the applicability of the findings to U.S. primary care populations and settings was assessed. Discrepancies were resolved through consensus discussion.

To determine whether meta-analyses were appropriate, the clinical and methodological heterogeneity of the studies was assessed according to established guidance.[30] The populations, tests, treatments, comparators, outcomes, and study designs were assessed qualitatively, looking

for similarities and differences. For KQs 7 and 9, when at least three similar studies were available, quantitative synthesis was conducted with random-effects models using the inverse-variance weighted method (DerSimonian and Laird) to estimate pooled effects.[31] For binary outcomes (e.g., progression to type 2 diabetes) relative risks and 95 percent CIs were calculated. Statistical significance was assumed when 95 percent CIs of pooled results did not cross the null. All testing was two sided. For continuous outcomes (e.g., blood pressure), we calculated the weighted mean difference (WMD) between intervention and control. Whenever possible, we used the number of all randomized patients as the denominator to reflect a true intention-to-treat analysis. For all quantitative syntheses, the I^2 statistic was calculated to assess statistical heterogeneity in effects between studies.[32, 33] An I^2 from 0 to 40 percent might not be important, 30 to 60 percent may represent moderate heterogeneity, 50 to 90 percent may represent substantial heterogeneity, and 75 percent or greater represents considerable heterogeneity.[34] We conducted additional analyses to explore heterogeneity or robustness of findings, stratifying by duration of followup (i.e., timing of outcome assessment), lifestyle intervention contact time (i.e., dose), and baseline BMI of study participants. We estimated the total hours of interventionist contact time (i.e., dose) based on the planned number and length of contacts. If a study did not report the length of sessions, we estimated session length as follows: a session described as brief was assumed to last 15 minutes if it was a face-to-face individual contact and 5 minutes if it was a phone session; for sessions that were not described as brief, individual face-to-face or interactive web-based sessions were assumed to last 30 minutes and group sessions were assumed to last for 60 minutes. We categorized an intervention as low dose if the number of minutes was estimated to be 30 or less, medium if the number of minutes was 31 to 360, and high if the number of minutes was greater than 360. Interventions that consisted of only print materials were categorized as low dose. Mailings and print materials were not included in the estimated of number of sessions or session length. For KQ 7, we calculated the number needed to treat to prevent one person from developing diabetes for interventions with moderate or high strength of evidence (for benefit), using our pooled RRs and the control group event rate from the Diabetes Prevention Program (DPP) (over 3 years) and the DPP Outcomes Study (DPPOS) (over 15 years). When studies reported raw numbers of events but did not report hazard ratios, RRs, or ORs, we calculated RRs. Quantitative analyses were conducted using Comprehensive Meta-Analysis version 3.3 (Biostat, Inc., Englewood, NJ) and Stata version 14 (Stata Corp).

Expert Review and Public Comment

A draft Research Plan for this topic was posted on the USPSTF Web site for public comment from July 5, 2018 to August 1, 2018. In response to comments, we made the following changes: 1) added a KQ about other intermediate outcomes after interventions for prediabetes (KQ 9), 2) clarified the types of eligible interventions, 3) added socioeconomic status to the subgroups listed in the KQs, 4) revised the terminology used to describe counseling interventions (including revisions for consistency with other topics in the USPSTF portfolio), 5) expanded the list of eligible outcomes, and 6) clarified that eligible study settings include those in which screening and interventions could feasibly be implemented in or referred from primary care. The final version of the research plan was posted on the USPSTF Web site on November 15, 2018. A draft report was reviewed by content experts, representatives of Federal partners, USPSTF members, and AHRQ Medical Officers. Reviewer comments were presented to the USPSTF during its deliberations and addressed in revisions of this report when appropriate. Revisions included

clarifications to the introduction, addition of longer-term followup publications from included studies (those studies were also identified in the literature surveillance), and edits to clarify wording and interpretation of the results of included studies. The draft report was posted for public comment from March 16, 2021, to April 12, 2021, and no substantive changes were made based on public comments.

USPSTF Involvement

This review was funded by AHRQ. AHRQ staff and members of the USPSTF participated in developing the scope of work and reviewed draft reports, but the authors are solely responsible for the content.

Chapter 3. Results

Literature Search

We identified 9,349 unique records and assessed 2,997 full-text articles for eligibility (**Figure 2**). We excluded 2,908 studies for various reasons, detailed in **Appendix C**, and included 89 publications. Details of quality assessments of included studies and studies excluded because of poor quality are in **Appendix D Tables 1** through **5.**

Results by Key Question

KQ 1a. Is There Direct Evidence That Screening for Type 2 Diabetes and Prediabetes in Asymptomatic Adults Improves Health Outcomes?

KQ 1b. Does the Effectiveness of Screening Differ for Subgroups Defined by Age, Sex, Race/Ethnicity, Socioeconomic Status, or BMI?

Characteristics of Included Trials

Two RCTs (described in 5 articles) conducted in the United Kingdom evaluated screening for type 2 diabetes: Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care (ADDITION)-Cambridge (n=20,184 participants)[35, 36] and Ely (n=4,936 participants) (**Table 3**).[37-39] This review found no trials that assessed screening for prediabetes or described identifying prediabetes, IGT, or IFG during screening. ADDITION-Cambridge was a cluster RCT of 33 general practices that evaluated a stepwise screening approach starting with the result of a random capillary blood glucose (if < 5.5 mmol/L [100 mg/dL] participants were determined to have no diabetes; if ≥5.5 mm/L, then additional tests were used to determine diabetes status), whereas the Ely study was a parallel group RCT at a single practice that evaluated screening every 5 years with an OGTT along with screening for CVD risk factors (cholesterol and blood pressure). Both trials relied on invitations to screening. ADDITION-Cambridge was a screening and intervention study that randomized practices 1:3:3 to no screening, screening invitations followed by intensive treatment of screen-detected diabetes (A1c target <7.0%, blood pressure target ≤135/85, and cholesterol targets, and low-dose aspirin use unless contraindicated), or screening followed by routine care of screen-detected diabetes; analyses combined the screening groups (comparing 5 control practices with 27 screening practices). The Ely study had no protocol for standard interventions for those with screen-detected diabetes (test results were provided to primary care providers to use as they deemed appropriate). The risk of bias for the Ely trial was rated as medium because of unclear methods of randomization, unclear allocation concealment, and baseline differences between groups.

Participants in ADDITION-Cambridge were age 40 to 69 years without known diabetes and at high risk of diabetes (based on a risk score of ≥1.7 on a diabetes risk score that included age, gender, BMI, steroid and antihypertensive medication, family and smoking history),[40] whereas those in the Ely study were age 40 to 65 years and required to be free from known diabetes (not selected based on risk). Mean age of participants ranged from 51 (Ely) to 58 (ADDITION-Cambridge), 36 percent (ADDITION-Cambridge) to 51 percent (Ely) were female, and neither

study reported the percentage of nonwhite participants. Mean BMI was 30.5 in ADDITION-Cambridge and was not reported for the Ely study. The trials began screening in 1990 (Ely) and 2002 (ADDITION-Cambridge). Duration of followup ranged from 7 to 13 years for the outcomes reported.

In ADDITION-Cambridge, 78 percent of those invited were screened (11,737/15,089) and 466 of those (4% of those screened, 3% of those invited) were diagnosed with diabetes based on 1999 World Health Organization (WHO) criteria (number diagnosed with diabetes was not reported for the control group). In the initial 10-year phase of the Ely study, 68 percent of those invited were screened (1,157/1,705) and 116 of those (10% of those screened, 7% of those invited) were diagnosed with diabetes. Among a subset of participants who were diagnosed with diabetes and attended a health assessment after 12 years (n=152 persons), the Ely study reported that diabetes cases were identified 3.3 years earlier on average for those in the screening group (n=92) than in the control group (n=60).[38]

Both trials reported data on all-cause mortality, CVD mortality, other mortality, CVD events, and quality of life. For a subgroup of participants with diabetes, the Ely study reported some information related to nephropathy and peripheral neuropathy.[38] Neither trial reported on amputations, skin ulcers, visual impairment, or periodontitis.

Mortality

Neither trial found a reduction in all-cause or type-specific mortality for screening compared with no screening over about 10 years of followup (all-cause mortality in ADDITION-Cambridge HR 1.06 [95% CI, 0.90 to 1.25]; in the Ely study unadjusted HR 0.96 [0.77 to 1.20] and adjusted HR 0.79 [0.63 to 1.00]) (**Table 4**).

Cardiovascular Events, Quality of Life, Nephropathy, and Neuropathy

Neither trial found statistically significant differences between screening and control groups for these outcomes, but data collection was limited to a minority of participants from the trials who completed followup surveys at 7 years (ADDITION-Cambridge) or attended a health assessment at 12 to 13 years (Ely), and results were imprecise (**Table 4**). A postal questionnaire sent to a random sample of participants in ADDITION-Cambridge (15% from the screening group and 40% from the control group) 7 years after randomization found no statistically significant differences between screening and control groups in the proportion reporting heart attack or stroke (OR 0.90 [95% CI, 0.71 to 1.15]), self-rated functional status, or quality of life (**Table 4**).[36] Of 3,286 questionnaires mailed, 1,995 were returned (61% response rate; data provided for 10% of all ADDITION-Cambridge participants).[36] For the Ely trial, two separate publications reported outcomes for those diagnosed with diabetes[38] and those not diagnosed with diabetes[39] who attended a health assessment. Together, the two publications provide results for less than a third of participants from the Ely trial. Neither publication reported any statistically significant differences between screening and control groups in self-reported heart attack or stroke, symptoms of ischemic heart disease, or quality of life (**Table 4**). Regarding nephropathy and neuropathy, for the subgroup of participants with diabetes who attended a health assessment at 12 years (n=152) one publication from the Ely trial reported no statistically significant difference

between those in the screening and control groups for nephropathy (4/92 vs. 1/60, p=0.37) or peripheral neuropathy (39/92 vs. 32/60, p=0.47).[38]

KQ 2a. What Are the Harms of Screening for Type 2 Diabetes and Prediabetes in Asymptomatic Adults?

KQ 2b. Do the Harms of Screening Differ for Subgroups Defined by Age, Sex, Race/Ethnicity, Socioeconomic Status, or BMI?

Characteristics of Included Trials

Five articles that evaluated participants in the ADDITION-Cambridge pilot phase, ADDITION-Cambridge trial, or Ely trial were included (**Table 3**).[38, 39, 41-43] The ADDITION-Cambridge and Ely trials were described in KQ 1. The ADDITION-Cambridge pilot (n=354 participants) was an RCT of two practices (that were not included in the subsequent ADDITION-Cambridge trial) in the United Kingdom to assess the feasibility of a diabetes screening program and the effects of invitation to diabetes screening on anxiety.[41] Participants were randomized 2:1 to noninvited and invited groups. Those who attended screening underwent a stepwise screening process starting with a random capillary blood glucose. Participants were age 40 to 69 years without known diabetes and at high risk of diabetes (based on a risk score). Mean age was 59 years, 36 percent were female, and mean BMI was about 31 (all similar to the larger ADDITION-Cambridge trial). Duration of followup was 6 weeks. Of those invited, 82 percent were screened (95/116) and six of those were diagnosed with diabetes.

Results of Included Trials

All three trials reported some information on anxiety from screening, two reported on depression, two reported on self-reported health, and one reported on worry about diabetes (**Table 5**). No two studies used the same outcome measures at similar timepoints. None of the trials reported on labeling, harms from false-positive results, burden, inconvenience, or unnecessary testing and treatment. Overall, results of the three trials did not find clinically significant differences between the screening and control groups in measures of anxiety, depression, worry, or self-reported health, but the results suggest possible short-term increases in anxiety (at 6 weeks) among persons screened and diagnosed with diabetes compared with those screened and not diagnosed with diabetes.

A substudy of the ADDITION-Cambridge trial surveyed participants from 10 of the screening practices and all five control practices (n=7,380) and found no differences between the screening and control groups in measures of anxiety, depression, worry about diabetes, or self-reported health immediately after screening, at 3 to 6 months, or at 12 to 15 months (**Table 5**). The study was limited by response rates on questionnaires, with missing data for many participants, especially among those invited to screening who did not attend screening. Specifically, response rates varied across timepoints and measures, from 37 percent to 54 percent for control group participants (n=964), from 34 percent to 81 percent for screening group participants who attended screening (n=4,370), and from 11 percent to 18 percent for those invited to screening who did not attend screening (n=2,046). The Ely trial found no differences between the screening and control groups in the proportion of participants taking antidepressant medications or taking

anxiolytic medications, for both the subgroup of participants with diabetes (n=152) and the subgroup without diabetes (n=1442) at the 12- to 13-year followup (**Table 5**). Results from the Ely study, like those from ADDITION-Cambridge, were limited by missing data for many participants (e.g., of those without diabetes invited to attend a health assessment, 1442/3390 [43%] attended for outcome assessment). The ADDITION-Cambridge pilot (n=354) reported higher levels of anxiety at 6 weeks for those in the screening group than in the control group (mean State-Trait Anxiety Inventory [STAI] anxiety score 37.6 vs. 34.1; p=0.015). Although the difference between groups was statistically significant, the between-group difference of less than 4 (on STAI anxiety score) is of uncertain clinical significance (scale range 20 to 80, higher scores indicating more anxiety), and the total scores for both groups were below the suggested cut point for clinically significant symptoms (a cut point of 39 to 40 has been suggested for most persons, with some authors suggesting a higher cut point of 54 to 55 for older adults).[44-46]

Among persons screened in the ADDITION-Cambridge pilot, the six individuals diagnosed with diabetes after screening had higher levels of anxiety than those screened and not diagnosed with diabetes (STAI score: 46.7 vs. 37.0; p=0.031).

KQ 3a. Do Interventions for Screen-Detected Type 2 Diabetes and Prediabetes Provide an Incremental Benefit in Health Outcomes When Delivered at the Time of Detection Compared With Initiating Interventions Later, After Clinical Diagnosis?

KQ 3b. Does the Effectiveness of These Interventions Differ for Subgroups Defined by Age, Sex, Race/Ethnicity, Socioeconomic Status, or BMI?

We found no eligible studies that addressed this question.

KQ 4a. Do Interventions for Screen-Detected Type 2 Diabetes and Prediabetes Improve Health Outcomes Compared With No Intervention, Usual Care, or Interventions With Different Treatment Targets?

KQ 4b. Does the Effectiveness of These Interventions Differ for Subgroups Defined by Age, Sex, Race/Ethnicity, Socioeconomic Status, or BMI?

In summary, one cluster RCT (ADDITION-Europe, described in 8 articles) that evaluated interventions for individuals with screen-detected type 2 diabetes and 38 RCTs (described in 56 articles) that evaluated interventions for individuals with prediabetes were included. No new studies on interventions for screen-detected type 2 diabetes were identified that were published since the previous review for the USPSTF. Low strength of evidence from one cluster RCT (described in 8 articles) found no difference over about 5-years of followup between an intensive multifactorial intervention aimed at controlling glucose, blood pressure, and cholesterol and routine care in the risk of all-cause mortality, cardiovascular-related mortality, and the

occurrence of a first cardiovascular event (myocardial infarction, stroke, revascularization or amputation) Differences remained non-significant at 10-years followup. There was also no difference between groups in the risk of outcomes related to chronic kidney disease, visual impairment, and neuropathy. All but one site (U.K.-Leicester) found no difference between groups across a range of quality of life outcomes.

For trials of interventions for people with prediabetes, the duration of followup in most trials was insufficient to assess for effects on mortality, CVD events, and other health outcomes. Most trials reporting mortality or CVD events over a followup duration of 6 years or less had few events with no difference between groups. In the two trials reporting outcomes beyond six years, one (the Finnish DPP) found no statistically significant difference for all-cause mortality (2.2 vs. 3.8 deaths per 1000 person years; HR, 0.57, 95% CI, 0.21 to 1.58) or composite CVD events (22.9 vs. 22.0 events per 1000 person years; HR, 1.04, 95% CI, 0.72 to 1.51) over 10 years of followup.[47] The second trial (Da Qing) found lower all-cause mortality (28.1% vs. 38.4%; HR, 0.71 [95% CI, 0.51 to 0.99]) and CVD-related mortality (11.9% vs. 19.6%; HR, 0.59 [95% CI, 0.36 to 0.96]) for a 6-year combined lifestyle intervention group compared with controls at 23 years but not at earlier followups; 30-year followup was subsequently published and also reported lower mortality for those who received lifestyle intervention compared with controls. Five trials reporting quality of life found either no difference between groups,[48, 49] mixed results (improvements on some domains but not others),[50] or small improvements in scores that are not likely clinically significant.[51, 52] The DPPOS study found no difference in an aggregate microvascular outcome (nephropathy, retinopathy, and neuropathy) at 15 years (placebo 12.4%, metformin 13.0%, intensive lifestyle 11.3%).[53]

Interventions for Screen-Detected Type 2 Diabetes

For screen-detected diabetes, the included publications all used data from the multicenter ADDITION-Europe that evaluated intensive multifactorial therapy for screen-detected type 2 diabetes compared with routine care (**Table 6**).[54-61] Five publications (N=3,057) reported outcomes from across all three ADDITION-Europe countries (United Kingdom, Netherlands, and Denmark),[56, 58-61] two publications (N=498) reported outcomes for participants in the Netherlands (ADDITION-Netherlands),[54, 55] and one (N=1,161) reported outcomes for participants in Denmark (ADDITION-Denmark).[57]

The intensive multifactorial intervention was guideline driven and included the use of medications and the promotion of healthy lifestyle to achieve the following targets: HbA1c ≤7.0 percent, blood pressure ≤135/85 mm Hg, cholesterol <5.0 mmol/L (<193 mg/dL) in patients with no history of CVD, and <4.5 mmol/L (<174 mg/dL) in patients with a history of CVD. Physicians and nurses received training in a stepwise treatment algorithm that included initiating insulin if HbA1c remained above 7.0 percent with oral medications, antihypertensives for blood pressure, 75 mg aspirin daily (unless contraindicated), and statins for cholesterol. Treatment targets were similar across centers and practices, but decisions related to choice of medications were made by the physicians and patients. Lifestyle education generally included small group or practice-based (one-on-one) educational meetings to discuss treatment targets, algorithms, and lifestyle advice. Participating practices were asked to provide the equivalent of up to three 10-minute consultations with a family physician and three 15-minute consultations with a nurse, per patient, per year for 3 years. Routine care was based on the national guidelines in each center.

Population-based stepwise screening took place between April 2001 and December 2006 among individuals age 40 to 69 years (50 to 70 years in the Netherlands) without known diabetes. Screening programs varied by center and included a risk score assessment (the Cambridge diabetes risk score assessment, the Danish Diabetes Risk Score Questionnaire, and the Hoorn study Symptom Risk Questionnaire) followed by glucose testing or an invitation to attend an oral glucose tolerance test without prior risk assessment (Leicester U.K. center). Diabetes diagnosis was based on WHO's 1999 criteria (FPG ≥7.0 mmol/L [≥126 mg/dL] 2-hour plasma glucose ≥11.1 mmol/L [≥200 mg/dL]) including the requirement for confirmatory followup testing. In ADDITION-Europe, the mean duration of followup was 5.3 years (range 4.5 to 6), mean age of participants was about 60 years, about 42 percent were female, participants were predominantly white (95%), mean baseline HbA1C was 7 percent (median 6.5), mean BMI was 31.5 kg/m^2, and mean blood pressure was 148/86 mm Hg. One post hoc study reported results at the 10-year followup (5 years post-intervention).[61]

The primary outcome of ADDITION-Europe was a composite of first cardiovascular events, defined as cardiovascular death, myocardial infarction, stroke, revascularization, or amputation.[56] ADDITION-Europe also reported on all-cause mortality, cardiovascular mortality, amputations, chronic kidney disease, retinopathy, neuropathy, and quality of life at 5 years;[56, 58, 60] and a post hoc study reported on the primary outcomes at 10 years (mean followup duration of 9.61 years).[61]

For the subset of participants in ADDITION-Netherlands, quality of life outcomes at 1[54] and 3 years were also reported.[55] For the subset of participants in ADDITION-Denmark, neuropathy was also reported at 6 years.[57, 60] No study assessed skin ulcers or periodontitis.

Mortality and Cardiovascular Events

At a mean of 5.3 years of followup, ADDITION-Europe found no statistically significant difference in the risk of all-cause mortality (6.2% vs. 6.7%, HR, 0.91 [95% CI, 0.69 to 1.21]), cardiovascular mortality (1.5% vs. 1.6%, HR, 0.88 [95% CI, 0.51 to 1.51]), or first cardiovascular event (7.2% vs. 8.5%, respectively, HR, 0.83 [95% CI, 0.65 to 1.05]) between intensive multifactorial treatment (n=1,678) and routine care (n=1,377) (**Table 7**).[56] A post hoc analysis at about the 10-year followup similarly found that differences remained nonsignificant for the primary composite outcome (HR, 0.87 [95% CI, 0.73 to 1.04]) and its components and for all-cause mortality (HR, 0.90 [95% CI, 0.76 to 1.07]).[61] Results for all-cause mortality at a mean of 5.3 years varied across countries. In the United Kingdom, the risk of all-cause mortality was lower in the intensive treatment group than in the routine care group (HR, 0.59 [95% CI, 0.35 to 0.98], whereas there was no significant difference between groups in the Netherlands (HR, 0.85 [95% CI, 0.35 to 2.06] or in Denmark (HR, 1.15 [95% CI, 0.80 to 1.66]).

Quality of Life, Nephropathy, Visual Impairment, and Neuropathy

Detailed description of the results for quality of life, nephropathy, retinopathy, and neuropathy are provided in **Appendix E**. In brief, ADDITION-Europe found no difference between groups in diabetes-specific or general quality of life measures, nephropathy (defined as microalbuminuria or macroalbuminuria), retinopathy (assessed using digital images), or peripheral neuropathy (**Appendix E Tables 1, 2,** and **3**). For quality of life, one of the two U.K.

sites (the U.K.-Leicester site) found improvement favoring the intensive treatment group (for the SF-36 physical component score, the EQ-VAS, and the ADDQoL) (**Appendix Table 2**).[59] None of the included publications reported on symptomatic chronic kidney disease, end-stage renal disease, requirement for dialysis, need for transplantation, vision changes, symptoms of retinopathy, or blindness.

Subgroups

In a predefined subgroup analysis, ADDITION-Europe reported a decreased risk of first composite cardiovascular event in people age 60 years or older (HR, 0.70 [95% CI, 0.52 to 0.95]) but not in people younger than 60 years (HR, 1.12 [95% CI, 0.70 to 1.79]), but the test for interaction between intervention and age was not statistically significant (p>0.1). A post hoc analysis found that the decreased risk of first composite cardiovascular event in people age 60 years or older was maintained at about the 10-year followup, and the test for interaction was statistically significant (p=0.046).[61] It should be noted that following the initial 5-year intervention there were no attempts to maintain assigned study group treatments; therefore, observed differences at 10 years may reflect factors other than the study-group intervention. No effect of age or sex was found in outcomes related to the presence of albuminuria or retinopathy. The included studies did not provide subgroup results for race/ethnicity, socioeconomic status, or BMI.

Interventions for Prediabetes

Thirty-eight trials (described in 56 articles) assessing interventions for prediabetes reported on health outcomes (**Appendix E Table 4**).[47-53, 62-110] The majority (k=24) compared lifestyle interventions with controls (of these, three also included a separate pharmacologic intervention arm[68, 77, 83]) and 14 (described in 20 articles) compared a pharmacologic intervention with placebo.[52, 90-95, 97-109] Thirty-seven studies were RCTs (4 of those were cluster RCTs[51, 79, 86, 89]) and one was a non-randomized trial.[49] Eight trials were set in the United States, and others (k=30) were set in various other countries, including Canada (k=1),[108] the United Kingdom (k=5),[51, 63, 78, 82, 89] other European countries (k=7, including Sweden,[74, 76, 99] Denmark,[71] Finland,[47] the Netherlands,[104] and Germany[48]), India (k=3),[83, 105, 106] Japan (k=6),[73, 84-86, 97, 98] China (k=4),[75, 79, 100, 109] and multinational settings (k=4).[52, 90, 94, 101] Most studies enrolled populations with a mean or median age between 50 and 60 years; 6 studies enrolled younger populations (mean or median age ranging from 43 to 49 years),[52, 77, 83, 86, 88, 105] and 8 studies enrolled populations with a mean or median age ranging from 60 to 69 years.[49, 51, 74, 75, 89, 97, 100, 101] Two trials enrolled females only[77, 88] and four enrolled only males[73] or less than 20 percent females.[49, 86, 105] All other trials enrolled both males and females, and most enrolled an equal proportion of both. All studies enrolled adults with prediabetes; however, studies varied in terms of how prediabetes was defined and measured; five focusing on criteria for IFG only,[49, 72, 84, 86, 99] 18 on IGT only,[73, 74, 76, 78, 79, 82, 83, 85, 87, 89, 90, 93, 97, 98, 104, 105, 108, 109] 10 on IFG and/or IGT,[48, 51, 63, 66, 75, 88, 94, 100, 101, 106] three on IFG and/or A1c,[65, 71, 77] and two on IFG or IGT or A1c.[52, 62]

Among studies assessing lifestyle interventions, most (19 of 24) included intervention components that focused on both diet/nutrition and physical activity,[48, 51, 62, 63, 65, 66, 72, 73, 75-78, 82-88] while three focused on physical activity alone[49, 74, 89] and one compared three arms (diet, exercise, or diet plus exercise) with a control group.[79] One RCT did not specify whether the

focus of the intervention was diet, exercise, or both.[71] In the 14 trials evaluating pharmacologic interventions, the following medications were compared with placebo or another control group, with or without a minimal intervention (e.g., written diabetes materials, general healthy lifestyle advice): metformin,[66, 77, 83, 106] pioglitazone,[93, 105] rosiglitazone,[95] acarbose,[90, 104] voglibose,[98] liraglutide,[52] nateglinide,[101] glimepiride,[100] sitagliptin,[97] a combination of metformin and rosiglitazone,[108] and acarbose or metformin (depending on whether patients had IGT vs. IFG or IFG and IGT, respectively).[100] Two studies also evaluated antihypertensives, including valsartan[102] and ramipril.[94]

The primary outcome of most studies was to prevent the development of type 2 diabetes in participants with prediabetes. Eleven studies followed participants for 1 year or less;[48, 49, 62, 65, 71, 74, 75, 77, 78, 89, 97] others usually had a followup duration ranging from 2 to 5 years for primary outcomes. Three included post-trial followup assessments that reported outcomes ranging from 10 to 30 years postrandomization. The DPP RCT enrolled participants in 1996 and compared an intensive lifestyle intervention or masked metformin with placebo over a mean followup duration of 3.2 years.[66] All participants were invited to be followed in the DPPOS, and 88 percent (n=2,776) consented to enroll in DPPOS. Placebo was discontinued, and the metformin group received unmasked metformin; all groups were offered maintenance group lifestyle sessions to reinforce the basic lifestyle content. Participants who had originally been randomly assigned to the lifestyle intervention in DPP were offered supplementary group programs and individual lifestyle check-ins twice yearly.[53] The DPPOS reported on incidence of microvascular outcomes and other risk factors for CVD but not all-cause mortality or CVD events. The Da Qing Diabetes Prevention Study randomized Chinese clinics in 1986 (33 primary care clinics, 577 participants) to a control or one of three lifestyle interventions (diet, exercise, or diet plus exercise).[79] The active intervention occurred over 6 years; study participants were followed up to 23 years postrandomization to assess CVD events and mortality.[80, 81] In the 20-, 23-, and 30-year followup analyses, the three intervention groups were combined (n= 439) and compared with the control group (n=138). The Finnish Diabetes Prevention Study (DPS) (n=522) randomized participants enrolled from 1993 through 1998 into an intensive lifestyle intervention or control; the median intervention period was 4 years, and included followup 10 years postrandomization to assess mortality and CVD events.[47, 87]

Mortality and Cardiovascular Events

Sixteen studies (described in 18 publications) reported on all-cause mortality (**Appendix E Table 5**);[47, 49, 52, 67, 71, 74, 80, 81, 83, 84, 94, 98, 99, 101, 104-106, 110] six of these also reported on CVD-related mortality[52, 67, 80, 94, 99, 101] and one reported on renal mortality.[101] CVD events were reported in 16 studies (described in 18 publications) using heterogenous CVD outcome definitions (**Appendix E Table 6**).[47, 49, 52, 62, 67, 78, 80-83, 86, 91, 93, 94, 101, 105, 108, 110] Few studies (k=6) reported on both mortality and CVD events,[47, 49, 67, 80, 83, 105] and only two (the Finnish DPS and Da Qing study) reported mortality and CVD events beyond 6 years of followup.[47, 80]

Among studies reporting mortality and/or CVD events over a followup duration of 6 years or less, 14 reported on all cause-mortality; of these, 7 compared a lifestyle intervention to usual care and found no difference between groups (2 reported no deaths,[71, 106] 4 reported 2 or fewer deaths per arm,[49, 74, 83, 84] and 1 reported 0.10 to 0.20 deaths per 100 person-years across groups[67]), and 7 assessing pharmacologic interventions found low rates of all-cause mortality with no difference

between groups.[52, 94, 98, 99, 101, 104, 105] Five studies reported on disease-specific mortality over 3 to 3.7 years of followup, and all reported few CVD-related deaths with no differences between groups[52, 67, 94, 99, 101] and one found no difference in renal mortality.[101] Thirteen studies reporting on CVD events followed participants for 6 years or less, 12 found no difference between groups, and one trial (STOP-NIDDM) found benefit associated with acarbose.[90] Most studies (k=11) reported few CVD events (0 to 5 events per group, or rates ranging from 0 to 2% per group) with no between-group differences.[49, 52, 62, 78, 82, 83, 86, 93, 96, 105, 108] One trial (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research [NAVIGATOR]) enrolled participants with prediabetes and established CVD and/or risk factors for CVD; over 6 years of followup, CVD event rates for some measures were relatively high in both groups (**Appendix E Table 6)**, but there was no difference between groups for composite or individual CVD event rates.[101, 102] One study, STOP-NIDDM trial (n=1,429), found benefit in favor of acarbose among participants at relatively high risk of CVD.[90] Eligibility criteria required participants to have prediabetes, high BMI (25 to 40), and no CVD events within 6 months of enrollment; however, 5 percent of enrolled participants had a history of CVD and 21 percent were taking a CVD-related medication (13% were current smokers, 51 percent had hypertension, and 58 percent has dyslipidemia).[90] Over 3.3 years of followup, fewer participants in the acarbose group had any CVD event (composite outcome, including coronary heart disease, CVD death, congestive heart failure, cerebrovascular event, and peripheral vascular disease) than the placebo group (15 vs. 32 events, respectively; HR, 0.51[95% CI, 0.28 to 0.95]).[91]

Two studies reported on mortality and CVD events over a longer duration of followup (10 to 30 years). The Finnish DPS (n=505) found no statistically significant difference between groups for all-cause mortality (2.2 vs. 3.8 deaths per 1,000 person years; HR, 0.57 [95% CI, 0.21 to 1.58]) or composite CVD events (incident fatal and nonfatal acute coronary events, coronary heart disease, stroke, and hypertensive disease) (22.9 vs. 22.0 events per 1000 person years; HR, 1.04 [95% CI, 0.72 to 1.51]) over 10 years of followup.[47] The Da Qing study found no significant difference between the combined intervention group and the control group for all-cause mortality (25.0% vs. 29.3%; HR, 0.96 [95% CI, 0.65 to 1.41]) or for CVD-related mortality (12% vs. 17%; HR, 0.83 [95% CI, 0.48 to 1.40]) at 20 years postrandomization.[80] However, at 23 years, the combined intervention group was associated with a significantly lower all-cause mortality rate than the control group (28.1% vs. 38.4%; HR, 0.71 [95% CI, 0.51 to 0.99]) as well as lower CVD-related mortality (11.9% vs. 19.6%; HR, 0.59 [95% CI, 0.36 to 0.96]).[81] Results at 30 years postrandomization were consistent with the 23-year results but were more precise, with a significantly lower all-cause mortality rate among the combined intervention group than the control group (45.7% vs. 56.3% [HR, 0.74 {95% CI, 0.61 to 0.89}]) as well as lower CVD-related mortality (29.6% vs. 22.0% [HR, 0.67 {95% CI, 0.48 to 0.94}]).[110]

Quality of Life

Five studies assessing interventions for prediabetes reported quality of life (**Appendix E Table 7**).[48-52] Two found statistically significantly higher quality of life scores associated with the intervention group (but differences were below the minimal clinically important difference),[51, 52] one found mixed results (improvement on some quality of life domains but not others),[50] and two found no difference between groups.[48, 49] In the three trials that found benefit, or mixed results, the difference in score changes between groups was small and below that considered to be a minimally important difference. The Let's Prevent Diabetes trial (n=880) found a statistically

significant greater change from baseline in the lifestyle intervention group (receiving a 6-hour structured group education session with 3-hour refresher sessions after 12 and 24 months) than the usual care group on the 15-dimensional quality of life scale at 3 years (+0.01; 95% CI, 0.001 to 0.02); the intervention group experienced a small improvement in scores, while the control group had a slight decline.[51] The difference between groups (and change from baseline in the intervention group) is below the minimal clinically important change to determine improvement (+0.015) recommended by some.[111] One trial assessing liraglutide (2,254 participants) found a significantly higher change from baseline score on the SF-36 physical component summary among the liraglutide group than placebo (+ 0.9; p=0.0156) and a similar difference between groups on the SF-36 mental component summary score that was not statistically significant (+0.8; p=0.08).[52] The differences between groups was below the threshold considered to be a minimal clinically important difference by the DPP study authors (3% difference) and others.[112] In the DPP study[50] (n=3,234), summary scores worsened in all groups for the SF-6D and SF-36 PCS and MCS; the decline for SF-6D and PCS was lower in the intensive lifestyle intervention group than placebo or metformin groups but did not meet the minimally important difference of 3 percent (defined by authors based on the literature).[50] For individual SF-36 domain scores, differences between the intensive lifestyle group and placebo reached the minimally important difference for general health (+3.2; p<0.01) and physical function (+3.6; p<0.01); there was no difference between metformin and placebo on any SF-36 component score.[50] In the two trials that found no benefit, one found no difference between physical activity counseling and usual care groups in the change from baseline SF-36 general health domain score (p=0.92) or physical function score (p=0.09) at 1 year,[49] and the other found no difference between lifestyle intervention (12 sessions on lifestyle modification) and control groups in the change from baseline score on the WHO-5 Well-being Index (1.4 vs. 0; p=0.101).[48]

Other Health Outcomes

Few studies reported other health outcomes associated with abnormal blood glucose (**Appendix E Table 7**). One study (the NAVIGATOR trial, n=9,306) randomized participants to valsartan (160 mg daily) or placebo and nateglinide (60 mg three times daily) and placebo.[103] At 5 years, 0.1 percent (5 participants) in the valsartan and placebo groups developed end-stage renal disease (HR, 0.96 [95% CI, 0.28 to 3.31]), and few participants in any group (0.1% or less) experienced amputations with no differences between groups. No studies reported on visual impairment. In the open-label extension of the DPP trial (DPPOS 15-year followup), the prevalence of the aggregate microvascular outcome (nephropathy, retinopathy and neuropathy) was not significantly different between groups (placebo 12.4%, metformin 13.0%, intensive lifestyle 11.3%).[53] Individual microvascular outcome rates were not reported separately by group. A post hoc analysis among participants whose most recent HbA1c was 6.5 percent or greater (n=607, approximately 26% of the DPPOS cohort) found lower rates of retinopathy (RR, 0.61 [95% CI, 0.37 to 1.01]) and neuropathy (RR, 0.38 [95% CI, 0.19 to 0.75]) for the intensive lifestyle group than placebo; there were no significant differences between the metformin and placebo groups.[53]

Subgroups

Two studies reporting health outcomes described results for eligible subgroups.[53, 81] In the Da Qing study, mortality rates were reported by sex at the 23- and 30-followup.[81, 110] Among women 23-years postrandomization, all-cause mortality (15% vs. 38.8% [HR 0.46 {95% CI, 0.24 to

0.87}]) and CVD mortality (6.0% vs. 17.0%; [HR 0.28 {95% CI, 0.11 vs. 0.71}]) were lower in the combined intervention group than in the control group. Among men, there was no significant difference between the combined intervention and control groups for all-cause mortality (39.6% vs. 45.6%[HR 0.97 {95% CI, 0.65 to 1.46}]) and for CVD mortality (17.0% vs. 21.5% [HR 0.91 {95% CI, 0.50 to 1.65}]). However, the test for interaction between sex and intervention was not statistically significant. At baseline, a higher proportion of men than women were smokers (61% vs. 16%). This pattern persisted at 30 years (for women, all-cause mortality in the intervention group compared with the control group: HR, 0.59 [95% CI, 0.38 to 0.91]; for men, HR, 0.85 [95% CI, 0.66 to 1.09]).[110]

In the DPPOS, rates of the aggregate microvascular outcome were reported for subgroups defined by age, sex, race, and ethnicity at 15 years postrandomization. There were no significant differences in treatment effects among subgroups defined by age at DPP enrollment. Sex-specific analyses found a significant interaction between sex and intervention, with benefit only in women. Among women (n=1,887), the lifestyle intervention was associated with a lower prevalence than the placebo group (8.7% vs. 11.0%; $p<0.05$) or the metformin group (8.7% vs. 11.2%; $p<0.05$); rates were similar among women in the metformin and placebo groups (11.2% vs. 11.0%).[53] Among men, rates were similar for those in the placebo group (15.1%), metformin group (16.8%), and lifestyle intervention group (16.6%). No significant differences in treatment effects were found among groups defined by race or ethnicity. Among Hispanic Americans (n=426), the lifestyle intervention was associated with a lower prevalence than placebo (4.5% vs. 10.5%; $p<0.05$), and rates were similar among the metformin and placebo groups (10.7% vs. 10.5%), but the test for interaction between race or ethnicity and treatment was not significant.

KQ 5a. Do Interventions for Recently Diagnosed Type 2 Diabetes Improve Health Outcomes Compared With No Intervention, Usual Care, or Interventions With Different Treatment Targets?

KQ 5b. Does the Effectiveness of These Interventions Differ for Subgroups Defined by Age, Sex, Race/Ethnicity, Socioeconomic Status, or BMI?

In summary, moderate strength of evidence from five RCTs in people with recently diagnosed type 2 diabetes found no statistically significant difference in all-cause mortality, diabetes-related mortality, and cardiovascular outcomes between intensive glucose control with sulfonylureas or insulin and conventional care at 10 years or shorter followup. However, over longer-term followup (20 years after randomization) intensive glucose control with sulfonylureas or insulin decreased the risk for all-cause mortality, diabetes-related mortality, and myocardial infarction. Tighter control of blood pressure compared with less tight control (<150/85 vs. <180/105) resulted in a reduced risk of diabetes-related mortality and stroke after 9 years of followup, but there was no difference between groups at longer-term followup (10 years post-trial). Intensive glucose control with metformin compared with conventional care in overweight people reduced the risk of all-cause mortality, diabetes-related mortality, and myocardial infarction at both 10 and 20 years after randomization.

Characteristics of Included Trials

We included five RCTs (described in 8 articles) evaluating interventions for recently diagnosed type 2 diabetes (**Table 8**).[4, 113-118] Three were related to the UKPDS, which was a randomized multicenter trial that ran for 20 years (from 1977 to 1997) in 23 sites across the United Kingdom. The primary UKPDS (n=3,867) compared intensive blood-glucose control with sulphonylureas or insulin with conventional treatment in people with newly diagnosed type 2 diabetes.[4, 114] The hypertension in diabetes study embedded in the UKPDS (n=1,148) compared tight control of blood pressure with less tight control.[115, 116] The third included trial from the UKPDS (n=753) compared metformin in overweight individuals with conventional care.[119] Another study, based in China (n=150), compared an intensive multifactorial intervention including the use of medications (metformin or glipizide followed by acarbose and insulin for glucose control, and the use of antihypertensives and statins) and healthy lifestyle advice (on diet, exercise, and smoking cessation) with conventional treatment.[118] The fifth RCT (described in 2 articles) was conducted in the United Kingdom and examined the effectiveness of the Diabetes Education and Self Management for Ongoing and Newly Diagnosed (DESMOND) program for people with newly diagnosed type 2 diabetes (n=824).[113, 117]

The duration of interventions ranged from 6 hours to 10 years. The DESMOND program focused on lifestyle, food, physical activity, and cardiovascular risk factors with standard clinical management and was delivered over 6 hours (either in a 1-day single session or in 2 half-day sessions).[113, 117] Treatment duration in studies involving the use of medications ranged from 7 to 10 years. The intensive multifactorial treatment study based in China included 7 years of treatment.[118] The UKPDS ran for 20 years with a median of 10 years of intensive treatment in the primary study,[4] a median of 8.4 years in the hypertension for diabetes study (embedded in the UKPDS),[116] and a median of 10.7 years in the UKPDS metformin substudy.[119] Upon completion in 1997, all surviving individuals from the UKPDS (including patients from the hypertension and metformin studies) were entered into a 10-year post-trial monitoring study.[114, 115] For the intensive multifactorial treatment study conducted in China, lifestyle advice included guidance for proper diet (e.g., 60 to 70% of daily caloric intake from carbohydrates, grains, fruits, and vegetables together with monounsaturated fat), physical activity (e.g., ≥ three 30-minute sessions of light to moderate exercise per week), and reducing or quitting smoking.[118] The glucose target for studies of intensive treatment was HbA1c <7%,[118] fasting plasma glucose <7 mmol/l (126 mg/dL),[118] or fasting plasma glucose <6 mmol/l (108 mg/dL).[4, 119] Blood pressure targets were 130/85 mmHg in the intensive multifactorial treatment study,[118] <150/85 mmHg for more tightly controlled blood pressure, and <180/105 for less tightly controlled blood pressure in the hypertension for diabetes study,[116] and the total cholesterol target in the intensive multifactorial study was <4.66 mmol/L (180 mg/dL).[118] Conventional treatment was not regulated in the trial but involved no treatment targets and involved either ill-defined outpatient management,[118] some form of access to diabetes education,[113, 117] or dietary advice every 3 months with the aim of maintaining near-normal bodyweight.[4, 119] Medications used varied across studies and often included a stepped approach to care with individuals progressing to additional treatments when targets were not met.

The mean age of participants ranged from 50 years to 60 years. From 39 to 53 percent of participants were female and participants were predominantly white (range 81% to 88%). Mean baseline HbA1c ranged from 6.6 percent to 8.7 percent, and fasting plasma glucose ranged from

a median of 7.4 mmol/L (133 mg/dL) to a mean of 10 mmol/L (180 mg/dL). Mean baseline systolic/diastolic blood pressure ranged from 129/78 mm Hg to 160/94 mm Hg.

Mortality and Cardiovascular Events

Four studies (described in 7 articles) reported on all-cause mortality (**Figure 3**);[4, 113-117, 119] three (described in 5 articles) reported on diabetes-related mortality (**Figure 4**),[4, 114-116, 119] four (described in 6 articles) on myocardial infarction (**Figure 5**),[4, 114-116, 118, 119] and three (described in 5 articles) on stroke (**Figure 5**).[4, 114-116, 119] Most studies found no statistically significant differences between intervention and control groups in all-cause mortality, diabetes-related mortality, myocardial infarction, and stroke over 1-, 3-, and 10-year followups (**Figures 3, 4** and **5** and **Appendix E Table 8**). An exception to this were the 10-year followup results from the metformin for overweight individuals substudy of the UKPDS, which found a decreased risk of all-cause death (14.6% vs. 21.7%; RR, 0.64 [95% CI, 0.45 to 0.91]), diabetes-related death (8.2% vs. 13.4%; RR, 0.58 [95% CI, 0.37 to 0.91]), and myocardial infarction (11.4% vs. 17.8%; RR, 0.61 [95% CI, 0.41 to 0.89]) among overweight (>120% of ideal body weight) participants (n=342) receiving intensive blood glucose control with metformin compared with those receiving conventional treatment (n=411).[119] Over the longer term (20 years followup), results from the 10-year post-trial monitoring of all surviving participants of the UKPDS trial (n=3,277 out of 4,209) found a decreased risk of all-cause mortality (43% vs. 47%; RR, 0.87 [95% CI, 0.79 to 0.96]), diabetes-related mortality (23% vs. 26%; RR, 0.83 [95% CI, 0.73 to 0.96]), and myocardial infarction (25% versus 28%; RR, 0.85 [95% CI, 0.74 to 0.97]) among those receiving intensive blood glucose control with sulphonylureas or insulin compared with those receiving conventional treatment (**Figures 3, 4,** and **5**). For overweight (>120% of ideal body weight) participants (n=342) receiving intensive blood glucose control with metformin compared with those receiving conventional treatment (n=411), the decreased all-cause mortality risk observed at 10 years was maintained after a further 10-year post-trial monitoring period (44% vs. 53%; RR, 0.73 [95% CI, 0.59 to 0.89])[114] (**Figure 3**). The longer-term benefits favoring intervention over control observed for mortality and myocardial infarction were not found for stroke (**Figure 5**).

For blood pressure control, the hypertension for diabetes trial (embedded in the UKPDS study) found no statistically significant difference in the risk of all-cause mortality or myocardial infarction between participants receiving tighter blood pressure control (using mainly angiotensin-converting enzyme [ACE] inhibitors and beta blockers) (n=758) compared with those receiving less tight blood pressure control after 9 years of followup or at the post-trial followup (20 years after randomization) (**Figures 3** and **5**). However, the trial found a decreased risk of diabetes-related mortality (10.8% versus 15.9%; RR, 0.68 [95% CI, 0.49 to 0.94]) and stroke (5.0% vs. 8.7%; RR, 0.56 [95% CI, 0.35 to 0.89]) after 9 years of followup; differences between groups were not statistically significant at the 10-year post-trial followup for the 884 surviving participants (**Figures 4** and **5**).

One study reported on transient ischemic attack (**Appendix E Table 8**).[118] At the 7-year followup, the small study conducted in China (n=150) found no difference in the risk of myocardial infarction (1.3% vs. 1.3%; RR, 1.0 [95% CI, 0.06 to 15.7]) or transient ischemic attack (RR, 2.0 [95% CI, 0.01 to 4.71]) among people with newly diagnosed type 2 diabetes receiving a multifactorial intensive intervention and those receiving conventional care.[118]

Quality of Life Outcomes

Only the DESMOND study (described in 2 articles) reported on quality of life outcomes.[113, 117] Measuring quality of life with the short version of the WHO's quality of life instrument (WHOQOL-BREF) at 4, 8, and 12 months and at the 3-year followup, it found no differences between the intervention and control groups at any time point across six dimensions of quality of life (overall satisfaction, overall satisfaction with health, physical, psychological, social, and environmental) (**Appendix E Table 9**).

Chronic Kidney Disease

Two studies, both from the UKPDS, reported on outcomes related to chronic kidney disease, and neither found a statistically significant difference between intervention and control groups, although results were generally imprecise (**Appendix E Table 10)**.[4, 116] At the 10-year followup, the UKPDS found no difference in the risk of renal failure (defined by dialysis or creatinine >250 μmol/L not related to any acute intercurrent illness) among people with newly diagnosed type 2 diabetes receiving intensive blood glucose control with sulfonylureas (chlorpropamide, glibenclamide, and glipizide) or with insulin (n=2,729) and those receiving conventional treatment (n=1,138) (0.6% vs. 0.8%; RR, 0.73 [95% CI, 0.25 to 2.14]).[4] There was also no difference in the risk for renal failure for the comparison of each of the three medication groups (chlorpropamide, glibenclamide/glipizide, and insulin) with conventional care (**Appendix E Table 10**).[4] After 9 years of followup, the hypertension for diabetes trial (embedded in the UKPDS) found no difference in the risk of renal failure among people with newly diagnosed type 2 diabetes receiving tight blood pressure control, using mainly ACE inhibitors and beta blockers (n=758) and those receiving less tight blood pressure control (n=390) (1.1% vs. 1.8%; RR, 0.53 [95% CI, 0.15 to 2.21]).[116] The trial also found no statistically significant difference between groups in the risk of microalbuminuria (≥50 mg/l) (28.8% vs. 33.1%; RR, 0.77 [95% CI, 0.55 to 1.09]) or macroalbuminuria (≥300 mg/l) (3.2% vs. 5.7%; RR, 1.06 [95% CI, 0.42 to 2.67]).[116]

Visual Impairment

Three studies, all from the UKPDS, reported on a variety of clinical endpoints for visual impairment with mixed findings (**Appendix E Table 10**)[4, 116, 119] At the 10-year followup, the UKPDS found a decreased risk of retinal photocoagulation among people with newly diagnosed type 2 diabetes receiving intensive blood glucose control with sulfonylureas (chlorpropamide, glibenclamide, and glipizide) or with insulin (n=2,729) and those receiving conventional treatment (n=1,138) (7.6% vs. 10.3%; RR, 0.71 [95% CI, 0.53 to 0.96]).[4] There was no statistically significant difference in the risk for vitreous hemorrhage (0.7% vs. 0.88%; RR, 0.77 [95% CI, 0.28 to 2.11]), blindness in one eye (2.9% vs. 3.3%; RR, 0.84 [95% CI, 0.51 to 1.40]), or cataract extraction (5.5% vs. 7.0%, RR, 0.76 [95% CI, 0.53 to 1.08]) (**Appendix E Table 10**).[4] At the 10-year followup, the metformin for overweight individuals substudy of the UKPDS found no difference in the risk of blindness in one eye among overweight (>120% of ideal body weight) participants (n=342) receiving intensive blood glucose control with metformin compared with those receiving conventional treatment (n=411) (3.5% vs. 3.2%; RR, 1.07 [95% CI, 0.38 to 2.99]). At a median of 7.5 years followup, the hypertension for diabetes trial (embedded in the UKPDS) found a decreased risk for progression to retinopathy (by ≥2 steps) among newly

diagnosed type 2 diabetes patients receiving tight blood pressure control, using mainly ACE inhibitors and beta blockers (n=300) and those receiving less tight blood pressure control (n=152) (34.0% vs. 51.3%, respectively; RR, 0.66 [95% CI, 0.50 to 0.89]).[116] The trial also found a decreased risk for deterioration in vision (defined as best vision in either eye deteriorating by three or more lines on an Early Detection of Diabetic Retinopathy Study chart) (10.2% vs. 19.4%; RR, 0.53 [95% CI, 0.30 to 0.93]).[116]

Amputations

Three studies, all from the UKPDS, reported on amputations (**Appendix E Table 10**) and found no statistically significant differences between the intervention and control groups, although results were generally imprecise.[4, 116, 119] At the 10-year followup, the UKPDS found no difference in the risk of amputations among newly diagnosed type 2 diabetes patients receiving intensive blood glucose control with sulfonylureas (chlorpropamide, glibenclamide, and glipizide) or with insulin (n=2,729) and those receiving conventional treatment (n=1,138) (1.0% vs. 1.6%, respectively; RR, 0.61 [95% CI, 0.28 to 1.33]).[4] At the 10-year followup, the metformin for overweight individuals substudy of the UKPDS found no difference in the risk of amputation among overweight (>120% of ideal body weight) participants (n=342) receiving intensive blood glucose control with metformin compared with those receiving conventional treatment (n=411) (1.8 % vs. 2.2%; RR, 0.74 [95% CI, 0.19 to 2.89]) Similarly, after 9 years of followup, the hypertension for diabetes trial (embedded in the UKPDS) found no difference in the risk of amputations among newly diagnosed type 2 diabetes patients receiving tight blood pressure control, using mainly ACE inhibitors and B-blockers (n=758) and those receiving less tight blood pressure control (n=390) (1.1% vs. 2.1%, respectively; RR, 0.51 [95% CI, 0.14 to 1.86]).[116]

Subgroups

The included studies did not provide results for subgroups defined by age, sex, race/ethnicity, or socioeconomic status. Results from the metformin for overweight people with newly diagnosed type 2 diabetes substudy of the UKPDS is described above. Overweight patients (n=753) were randomized to intensive glucose control with metformin or conventional care (i.e., care primarily with diet alone).[119] Treatment began with 850 mg of metformin per day and was increased to a maximum dose of 2,550 mg per day with the aim of maintaining FPG below 6.0 mmol/L (108 mg/dL). Mean BMI was 31.5 kg/m^2. Results were not stratified by BMI.

KQ 6. What Are the Harms of Interventions for Prediabetes, Screen-Detected Type 2 Diabetes, or Recently Diagnosed Type 2 Diabetes?

Harms of Interventions for Screen-Detected or Recently Diagnosed Type 2 Diabetes

Overall, harms were sparsely reported, rare, and (when reported) not significantly different between intervention and control groups across trials. Four RCTs (described in 6 articles) reported on harms of interventions for screen-detected or recently diagnosed type 2 diabetes.[4, 54, 55, 113, 117, 120] None were specifically designed to investigate harms. Characteristics of three of the trials, already included in KQ 4 or KQ 5,[4, 54, 55, 113, 117] are summarized in **Tables 6** and **8**. The fourth trial, not previously described, reported on harms related to saxagliptin (5 mg daily) as

initial therapy in treatment-naïve adults with newly diagnosed type 2 diabetes.[120] It was a 24-week double-blind placebo-controlled trial of 213 adults recruited from 12 centers across India. Of the four included RCTs, one (described in 2 articles), from the ADDITION-Netherlands trial (n=498), compared an intensive multifactorial intervention among screen-detected type 2 diabetes patients with usual care.[54, 55] The other three trials enrolled patients with recently diagnosed diabetes. One, the UKPDS trial (n=3,867), compared intensive blood-glucose control using sulphonylureas or insulin with conventional treatment,[4] the DESMOND trial (n=824) compared a 6-hour structured group education program with usual care,[113, 117] and one RCT compared saxagliptin with placebo (n=213).[120] Treatment duration ranged from 6 hours to 10 years. Three studies (5 articles) reported on withdrawals for any reason,[54, 55, 113, 117, 120] two reported on treatment-related mortality,[4, 120] two on hypoglycemic events requiring medical attention,[4, 120] and one on general adverse events.[120] Results are summarized in **Appendix E Table 11**.

Withdrawals

Across three trials (described in 5 articles) enrolling 1,535 participants[54, 55, 113, 117, 120] there were a total of 51 withdrawals (for any reason) with no statistically significant differences between the intervention and control group in any trial (**Appendix E Table 11**).

Treatment-Related Mortality

Treatment-related mortality was rarely reported and very uncommon. The UKPDS trial (n=3,867) reported one patient out of 911 in the intervention group receiving insulin who died from hypoglycemia,[4] and in the 24-week trial comparing saxagliptin with placebo (n=213) there were no reported treatment-related deaths.[120]

Hypoglycemic Events Requiring Medical Attention

Serious hypoglycemic events requiring medical attention were reported in two trials and were very rare (**Appendix E Table 11**). The UKPDS trial (n=3,867) compared each of three medication groups (chlorpropamide, glibenclamide, and insulin) with conventional care and found no statistically significant difference between each of the three medication groups and the usual care group. In the intention-to-treat analysis, major hypoglycemic events were reported in 1 percent (6/619) of participants receiving chlorpropamide, 1.4 percent (9/615) of participants receiving glibenclamide, 1.8 percent (16/911) of participants receiving insulin, and 0.7 percent (6/896) of participants in the conventional care group.[4] The 24-week trial comparing saxagliptin as initial therapy with placebo (n=213) reported no hypoglycemic events requiring medical attention in either group.[120]

Serious and Treatment-Related Adverse Events

Only the 24-week trial comparing saxagliptin as initial therapy with placebo (n=213) reported serious and treatment-related adverse events.[120] There was no statistically significant difference between the saxagliptin group and the placebo group in treatment-related adverse events (6 vs. 8; RR, 0.74 [95% CI, 0.27 to 2.07]), and there were no serious adverse events in either group.

Harms of Interventions for Prediabetes

In summary, 21 trials reported on harms associated with interventions for prediabetes (8 assessing a lifestyle intervention and 13 assessing a pharmacologic intervention). Categories and definitions used for adverse events were heterogenous across studies and few trials (k=3) reported adverse events beyond 5-years of followup.[69, 80, 101] Five trials reported rates of hypoglycemia (using various definitions), each comparing a different medication with placebo (liraglutide, sitagliptin, metformin, nateglinide, and rosiglitazone +metformin); event rates were low, and no trial found no difference between groups over followup durations ranging from 8 weeks to 5 years.[52, 69, 97, 101, 108] Twelve studies reported withdrawals due to adverse events associated with a pharmacotherapy intervention. Six trials (2 assessing metformin,[77, 100] and 1 each assessing sitagliptin,[97] nateglinide,[101] valsartan,[102] acarbose,[109] and rosiglitazone plus metformin,[108]) found no increased risk of withdrawals among the intervention group compared with placebo or control, and six found higher rates of withdrawals due to adverse effects associated the pharmacologic intervention than the placebo, including two studies of acarbose,[90, 104] and one study each assessing pioglitazone,[93] ramipril,[94] rosiglitazone,[95] voglibose,[98] and liraglutide.[52] Nine studies of pharmacologic interventions reported on gastrointestinal adverse events; compared with placebo or control, higher rates were seen in studies assessing metformin (k=3),[66, 77, 108] acarbose (k=2), and liraglutide (k=1),[52] and rates were similar among groups in one study each assessing pioglitazone, sitagliptin, nateglinide, and valsartan.[93, 97, 101, 102] Seventeen studies reported other adverse events; types of events reported (and definitions) were heterogeneous and most found no difference between groups. Four studies of lifestyle interventions reported on musculoskeletal-related adverse events, two found no significant difference between groups,[62, 86] and one (the DPP) found higher rates of musculoskeletal symptoms per 100 person-years in the intensive lifestyle intervention group than control group (24.1 vs. 21.1 events per 100 person-years; $p<0.017$) at 2.3 years[66] but no difference between groups for sprains or fractures needing medical attention at 15 years postrandomization.[53]

Study Characteristics

Study characteristics of interventions for prediabetes are described in detail in KQ 4. A subset of these studies (k=21) report on one or more harms, including eight studies (described in 12 publications) assessing a lifestyle intervention[53, 62, 63, 66, 68-71, 77, 79, 84, 86] and 13 studies (described in 16 publications) assessing a pharmacotherapy intervention.[52, 90, 93-95, 97, 98, 100-106, 108, 109] Across all studies, adverse events were reported during followup durations that ranged from 8 weeks to 9 years; few studies (k=3) followed participants 5 years or longer.[69, 80, 101]

Hypoglycemia

Only one study reported rates of severe hypoglycemia requiring third-party assistance and found no events in participants randomized to liraglutide or placebo over 3.3 years.[52] Four studies of pharmacotherapy interventions (sitagliptin, metformin, nateglinide, and rosiglitazone +metformin) reported on any hypoglycemia, or hypoglycemia defined as "non-serious versus serious," "symptomatic," or "mild versus moderate" and found no difference between interventions and placebo over 8 weeks to 5 years.[69, 97, 101, 108]

Withdrawals Due to Adverse Events

Twelve studies reported withdrawals due to adverse events associated with a pharmacotherapy intervention. Six found no withdrawals due to adverse events associated with study treatments, or few withdrawals and no difference between groups over 8 weeks to 5 years among two studies assessing metformin,[77, 100] and one each assessing sitagliptin,[97] nateglinide,[101] valsartan,[102] acarbose,[109] and rosiglitazone plus metformin.[108] Six other studies found higher rates of withdrawals due to adverse effects associated with a pharmacologic intervention than the placebo, including two studies of acarbose (STOP-NIDDM:[90] 19% vs. 5% and the Dutch Acarbose Intervention Trial: 36.7% vs. 13.8%[104]), and one study each assessing pioglitazone (withdrawals due to weight gain, 3% vs. 1.0%),[93] ramipril (medication withdrawals due to cough, 9.7 vs. 1.8%),[94] rosiglitazone (withdrawals due to edema, 4.8% vs. 1.6%),[95] voglibose (withdrawals attributed to study medication, 5% vs. 3%; p=0.01),[98] and liraglutide (withdrawals due to any adverse event, 13% vs. 6%).[52]

Gastrointestinal Adverse Events

Nine studies reported on gastrointestinal adverse events (**Appendix E Table 12**). Three trials found higher rates of gastrointestinal adverse events associated with metformin.[66, 77, 108] Of these, two found higher rates of any gastrointestinal symptoms in the metformin group than a standard lifestyle group, including the DPP (77.8% vs. 30.7%; p<0.017)[66] and the PREVENT-DM trial (28% vs. 0%);[77] one compared metformin plus rosiglitazone with placebo and found higher rates of any gastrointestinal events in the metformin plus rosiglitazone group (37% vs. 19%), as well as higher rates of diarrhea (16% vs. 6%).[108] In the DPPOS, rates of gastrointestinal symptoms declined over time in all groups but continued to be significantly higher in the metformin group through 9 years of followup.[69] Two trials found higher rates of gastrointestinal adverse events among the acarbose group than placebo; one reported higher rates of any gastrointestinal adverse events (85% vs. 60%; p<0.001)[90] and one reported higher rates of specific gastrointestinal symptoms, including flatulence (15.9 vs. 6.1%), diarrhea (13.5% vs. 3.8%), and enlarged abdomen (13.5 vs. 3.8%).[109] In one trial, participants randomized to liraglutide reported higher rates of nausea than placebo (41% vs. 17%) and higher rates of diarrhea (41% vs. 15%); the liraglutide group was associated with more cases of pancreatitis than placebo, although overall rates were low (10 vs. 2 cases; rates per group: 0.6% vs. 0.2%).[52] One trial each assessed pioglitazone, sitagliptin, nateglinide, and valsartan and found similar rates of various gastrointestinal adverse events among medication and placebo groups (**Appendix E Table 12**).[93, 97, 101, 102]

Other Adverse Events

Seventeen studies reported other adverse events; types of events reported (and definitions) were heterogeneous and most found no difference between groups or reported no adverse events were attributed to study interventions (**Appendix E Table 12**). Six studies of pharmacotherapy interventions reported rates of any adverse event per group; rates were generally higher among the pharmacotherapy intervention arm than placebo, including two trials of metformin[77, 93] and one trial each assessing rosiglitazone plus metformin (41% vs. 28%),[108] sitagliptin,[97] liraglutide,[52] and acarbose.[109]

Four studies of lifestyle interventions reported on musculoskeletal events, one found no significant difference between groups for rates of joint sprains/strains or muscle or joint aches over one year,[62] one found few cases of musculoskeletal problems[86] (<1% per group, 6 vs. 3 cases in the intervention vs. control group, respectively), and one (the DPP) found higher rates of musculoskeletal symptoms per 100 person-years in the intensive lifestyle intervention group than control group (24.1 vs. 21.1 events per 100 person-years; p<0.017).[66] In the DPPOS, rates of sprains or fractures needing medical attention were similar across groups at 15 years postrandomization (ranging from 3.7 to 4.3 events per 100 person-years).[53]

KQ 7. Do Interventions for Prediabetes Delay or Prevent Progression to Type 2 Diabetes?

KQ 7a. Does the Effectiveness of These Interventions Differ for Subgroups Defined by Age, Sex, Race/Ethnicity, Socioeconomic Status, or BMI?

In summary, lifestyle interventions were associated with a reduction in the incidence of diabetes (pooled RR, 0.78 [95% CI, 0.69 to 0.88], 23 trials; 12,915 participants) (**Figure 6**). Most trials assessed high-contact lifestyle interventions. Pooled RRs were 0.63 (95% CI, 0.50 to 0.81) for followup less than 1 year, 0.58 (95% CI, 0.41 to 0.82) for followup 1 to 2 years, and 0.81 (95% CI, 0.73 to 0.89) for followup greater than 2 years. For medications, metformin, TZDs, and alpha glucosidase inhibitors were all associated with a reduction in diabetes (pooled RRs [95% CI] 0.73 [0.64, 0.83], 0.50 [0.28, 0.92], and 0.64 [0.43, 0.96], respectively) (**Figure 6**), although results for TZDs and alpha glucosidase inhibitors were limited by imprecision, inconsistency, and risk of bias (for trials of alpha glucosidase inhibitors).

Lifestyle Interventions: Study Characteristics

Twenty-three trials (described in 33 articles) compared lifestyle interventions with controls for delaying or preventing the onset of type 2 diabetes (**Appendix E Table 4**).[47, 49, 51, 53, 62, 63, 66-69, 71-77, 79-89, 110, 121-124] This current report includes data from 16 additional articles assessing lifestyle interventions that were not in the 2015 review for the USPSTF,[49, 51, 62, 63, 71, 74, 75, 77, 86, 88, 89, 110, 121-124] including an update to the DPPOS trial,[53] which extended followup time to 15 years.

Trial start dates ranged from 1986[79] to 2015.[75] No trials had less than 12 months of followup, ten had 12 months to 24 months followup,[49, 62, 71, 72, 74, 75, 77, 88, 89, 121] and 13 had greater than 24 months of followup.[51, 53, 63, 73, 76, 80-87, 110, 123, 124] Six trials were conducted in the United States,[49, 62, 66, 72, 77, 88] four in the United Kingdom,[51, 63, 82, 89] four in Japan,[73, 84-86] three in China,[75, 79-81, 110, 123, 124] two in Sweden,[74, 76] and one each in Denmark,[71] Finland,[47, 87],India,[83] and Thailand.[121] Sample sizes ranged from 52[74] to 3,284.[66] Three trials had a sample size less than 100,[74, 77, 89] 11 had a sample sizes between 100 and 500,[49, 63, 71-73, 75, 76, 82, 85, 88, 123, 124] and nine had sample sizes greater than 500.[51, 62, 66, 79, 83, 84, 86, 87, 121]

Regarding prediabetes ascertainment, studies used a variety of approaches to define participant eligibility, with three focusing on criteria for IFG,[72, 84, 86] nine on IGT,[49, 73, 74, 76, 79, 82, 85, 87, 89] eight on IFG and/or IGT,[51, 63, 66, 75, 83, 88, 121, 123, 124] two on IFG and/or A1c,[71, 77] and one on IFG or IGT or A1c.[62]

In most trials (18 of the 23), the lifestyle interventions focused on both diet/nutrition and physical activity.[51, 62, 63, 66, 72, 73, 75-77, 82-88, 121, 123, 124] In three of the 23 RCTs, the lifestyle interventions were focused on physical activity only.[49, 74, 89]In one of the 23 trials, participants were randomized to one of three treatment groups: diet, exercise, or diet plus exercise,[79] and one RCT did not specify whether the focus of the intervention was diet, exercise, or both.[71]

Most studies (k=18) delivered high-contact (i.e., dose) lifestyle interventions.[51, 62, 63, 66, 71-73, 76, 77, 79-85, 87, 88, 121] Five studies evaluated medium-dose interventions,[49, 75, 86, 89] and two evaluated a low-dose intervention.[74] Lifestyle interventions were administered in a group setting in six trials,[51, 62, 74, 77, 89, 121] individually in eight trials,[49, 66, 71, 73, 75, 84, 87, 88] within individual and group sessions in four trials,[72, 79, 82, 85] by telephone and/or email in two trials,[65, 86], by text messages in one trial,[123, 124] and in sessions that included family members in two trials.[63, 88] Two trials did not specify whether interventions were delivered in individual or group settings.[76, 83] Intervention delivery personnel varied and included physicians, nurse practitioners, dieticians, nurses, community health workers, trained educators, physiotherapists, behavioral medicine clinic staff, public health professionals, case managers, dieticians, and nutritionists. All control groups received a variation of standard care that was minimal and included advice on healthy lifestyle, diabetes, and its management.

Among trials that reported mean or median baseline A1c values, most were less than 6 percent,[49, 65, 74, 75, 77] but some were greater than 6 percent.[51, 62, 66] Mean baseline fasting glucose levels among the trials ranged from 98 to 113 mg/dL. Baseline mean or median ages of participants ranged from 43[88] to 67.[49] Mean or median ages were in the 40s in six trials,[77, 79, 81 , 82, 83, 86, 88] in the 50s in eleven trials,[62, 66, 72, 73, 76, 84, 85, 87, 121, 123, 124] and in the 60s in six trials.[49, 51, 71, 74, 75, 89] Two trials enrolled females only[77, 88] and four enrolled no females[73] or less than 20 percent females.[49, 86, 123, 124] Among the other trials, the proportion of female participants ranged from 34 percent[89] to 71 percent.[62] Eleven trials did not report information on race/ethnicity.[71, 73-76, 79, 82, 84-87] The proportion of nonwhite participants ranged from 25 percent to 100 percent in trials reporting the information.[49, 51, 62, 63, 66, 72, 77, 83, 88, 89] Seven trials enrolled a majority of nonwhite participants.[62, 63, 77, 83, 88, 121, 123, 124] Mean baseline BMI ranged from 24 kg/m^2 [73] to 37 kg/m^2.[62] Baseline mean or median BMIs were below 25 for four trials,[73, 75, 85, 86] in the overweight range (>25 kg/m^2 and <30 kg/m^2) for seven trials,[75, 79, 83, 84, 89, 121, 123, 124] and in the obesity range (≥30 kg/m^2) for 13 studies.[49, 51, 62, 63, 66, 71, 72, 74, 76, 77, 82, 87, 88] Among the trials that reported mean or median systolic blood pressures, they ranged from 123[66] to 148.[51]

Lifestyle Interventions: Results for Delay or Prevention of Progression to Diabetes

Figure 6 provides the pooled estimates from multiple meta-analyses; **Appendix F** includes the complete forest plot for each meta-analysis as well as additional figures showing trial data that were not pooled. Meta-analysis of 23 trials (using the longest available followup from each) found that lifestyle interventions were associated with a reduction in progression to diabetes (pooled RR, 0.78 [95% CI, 0.69-0.88]; 12,915 participants; I^2=47%). Based on this pooled risk, nine people with prediabetes would need to be treated to prevent one case of diabetes after 15 years. For the 18 high-contact interventions, the pooled estimate was nearly the same as for all interventions (pooled RR, 0.79 [95% CI, 0.71 to 0.889]), whereas the meta-analysis for medium contact interventions yielded a very imprecise result and considerable statistical heterogeneity (pooled RR, 0.67 [95% CI, 0.37 to 1.22]; I^2=71%). When stratifying by followup time, the

pooled risk ratios were 0.81 (95% CI, 0.73 to 0.89) for followup greater than 2 years, 0.58 (95% CI, 0.41 to 0.82) for followup 1 to 2 years, and 0.63 (95% CI, 0.50 to 0.81) for followup less than 1 year (**Figure 6**). When stratifying by baseline BMI, the four trials with baseline mean or median BMI less than 25 kg/m^2 yielded a pooled RR of 0.46 (95% CI, 0.21 to 1.01), the six with baseline BMI in the overweight range (>25 kg/m^2 and < 30 kg/m^2) yielded a pooled RR of 0.86 (95% CI, 0.71 to 1.05), and the 13 with baseline BMI in the obese range (>30 kg/m2) yielded a pooled RR of 0.77 (95% CI, 0.65 to 0.91) (**Figure 6**).

Lifestyle Interventions: Subgroups

The DPP, the DPPOS, and the Da Qing study reported eligible subgroup analyses. While these studies were not designed or powered to detect differences in intervention effects for subgroups, a statistically significant benefit favoring lifestyle intervention over control was found for nearly all subgroups. The DPP investigators reported that the lifestyle intervention was effective in all subgroups and treatment effects did not differ by age (25-44, 45-59, ≥60), sex, race or ethnicity (White, African American, Hispanic, American Indian, Asian), or BMI (22 to <30, 30 to <35, ≥35 kg/m^2) after three years of followup, acknowledging that subgroup analyses were post-hoc. The Da Qing study reported subgroup results by baseline BMI after six years of followup, finding that the relative decrease in diabetes incidence was similar for lean (<25 kg/m^2) and overweight (BMI ≥25 kg/m^2) participants. In post-hoc secondary analysis after 23 years, the Da Qing study reported a similar decrease in diabetes incidence for women and men after 23 years (adjusted HR, 0.55 [95% CI, 0.35 to 0.87] vs. 0.56 [95% CI, 0.39 to 0.81], respectively) and after 30 years (adjusted HR, 0.62 [95% CI, 0.42 to 0.92] vs. 0.61 [95% CI, 0.44 to 0.83], respectively).

Pharmacologic Interventions: Study Characteristics

Fifteen trials (reported in 23 articles) evaluated pharmacologic interventions to delay or prevent diabetes.[52, 53, 66-68, 70, 77, 83, 90, 92-95, 98, 100-102, 104-106, 108, 125] Diabetic medications evaluated in the trials included the biguanide metformin,[66, 77, 83, 106] thiazolidinediones,[93, 95, 105] alpha glucosidase inhibitors,[90, 98, 104] liraglutide,[52] nateglinide,[101] a sulfonylurea,[100] a combination of metformin and the thiazolidinedione rosiglitazone,[108] and acarbose or metformin.[100] Two studies also evaluated antihypertensives: valsartan[102] or ramipril.[94] This current report includes data from four additional articles assessing medications that were not in the 2015 USPSTF report.[52, 53, 77, 106]

Trial start dates ranged from 1996[66] to 2013.[77] Followup was 3 years or longer for all but three trials.[77, 93, 98] Four trials were conducted in multiple countries,[52, 90, 94, 101] three in the United States,[66, 77, 93] three in India,[83, 105, 106] and one trial each in Japan,[98] Sweden,[100] and the Netherlands.[104] Sample sizes ranged from 92[77] to 9306.[101] Five trials had a sample size less than 500,[77, 100, 104, 105, 108] three had a sample size between 500 and 1000,[83, 93, 106] and six had a sample size greater than 1,000.[52, 66, 90, 94, 98, 101] Studies used a variety of approaches to define participant eligibility, with two focusing on IFG;[83, 99] three on IFG and IGT;[90, 101, 108] four on IGT;[66, 93, 100, 105] two on IFG and/or IGT;[94, 106] three on A1c, IFG, and IGT;[52, 98, 104] and one on IFG and/or A1c.[77]

Trials that evaluated metformin used doses of 500 mg twice daily[83, 106] or 850 mg twice daily.[66, 77] The three trials evaluating alpha glucosidase inhibitors examined acarbose 50 mg three times daily,[104] acarbose 100 mg three times daily,[90] and voglibose 0.2 mg three times daily.[98] The TZD

trials evaluated pioglitazone 30 mg daily,[105] pioglitazone 45 mg daily,[93] and rosiglitazone 80 mg daily.[95] One study each examined the glucagon-like peptide 1 receptor agonist liraglutide at 3.0 mg daily,[52] the meglitinide nateglinide 60 mg three times daily,[101] the sulfonylurea glimepiride 1 mg daily,[100] a combination of metformin 500 mg and rosiglitazone 2 mg twice daily,[108] and acarbose 50 mg three times daily or metformin 250 mg three times daily.[100]

Control groups received placebo and variations of usual care or minimal intervention including written materials. Usual care or minimal intervention varied and consisted of standard care, diabetes prevention materials, general healthy lifestyle advice, lifestyle counseling focused on diabetes prevention, diabetic education, and sometimes no counseling or educational materials. Four trials did not have a placebo in their control group.[77, 83, 100, 106]

Baseline mean ages of participants ranged from 45 to 64. The percentage of females enrolled ranged from 13 percent[105] to 100 percent,[77] and the percentage of nonwhite participants ranged from 0[77, 83, 105, 106] to 97.[90] Baseline BMIs ranged from 26 kg/m^2 [83, 98] to 39 kg/m^2.[52] Baseline mean or median systolic blood pressure readings were between 118[105] and 142.[99]

Pharmacologic Interventions: Results for Delay or Prevention of Progression to Diabetes

Figure 6 provides the pooled estimates from multiple meta-analyses; **Appendix F** includes the complete forest plot for each meta-analysis as well as additional figures showing trial data that were not pooled. For metformin, meta-analysis of three trials, including 3-year followup data for the DPP, found that it was associated with a reduction in the incidence of diabetes (pooled RR, 0.73 [95% CI, 0.64 to 0.83]) (**Figure 6**); using 15-year followup data from DPPOS (instead of the 3-year DPP data) in the meta-analysis also found that metformin was associated with a reduction in the incidence of diabetes (pooled RR, 0.87 [95% CI, 0.77 to 0.98]). For both TZDs and alpha glucosidase inhibitors, meta-analysis of three trials each found associations with a reduction in the incidence of diabetes (**Figure 6**), but the results were limited by imprecision and inconsistency across trials (**Appendix F)**.

Pharmacologic Interventions: Subgroups

With the caveat that their subgroup analyses were post-hoc and underpowered, the DPP authors noted that after 3 years of followup, the effect of metformin compared with placebo was not statistically significantly different for subgroups defined by age, sex, or race and ethnicity. However, they reported statistically significant effect modification by BMI ($p<0.05$), with greater effect on diabetes incidence for those with higher BMIs (e.g., reduction in diabetes incidence 53% [95% CI, 36% to 65%] for BMI ≥35 kg/m^2 vs. 3% [95% CI, -36% to 30%] for BMI 22 to <30 kg/m^2). After 15 years of followup within DPPOS, the effect of metformin compared with control was not significantly different (i.e., there was no effect modification) between males and females or for those in different categories defined by BMI, age, or race/ethnicity.[125] The Indian Diabetes Prevention Program (IDPP) investigators found that age, sex, and BMI did not independently influence the development of diabetes for the control group compared with any of its three treatment groups, including the metformin only group.

Mixed Interventions and Stepwise Strategies

The CANOE trial[108] randomly assigned participants to receive a combination pill of rosiglitazone and metformin or matching placebo with a median followup of 3.9 years. Participants in both groups also received five 30-minute individually delivered lifestyle intervention sessions during the first year. The incidence of diabetes in the combination pill group was 14% compared with 39% in the placebo group (RR, 0.42 [95% CI, 0.24 to 0.74]; 207 total participants).

Two trials used impaired fasting glucose and impaired glucose tolerance to guide pharmacologic treatment for their intervention groups.[100, 106] One trial was performed in China[100] (n=210) and randomized participants to receive medication with a lifestyle intervention or routine care for 2 years. The group receiving medication with a lifestyle intervention received acarbose if they had isolated impaired fasting glucose and metformin if they had both impaired fasting glucose and impaired glucose tolerance. After 2 years, no subjects in the intervention group and six subjects in the control group developed diabetes based on a per-protocol analysis. The Diabetes Community Lifestyle Improvement Program (D-CLIP)[106] intervention was performed in India and randomized participants to receive a DPP-based lifestyle intervention and then metformin if (after at least 4 months) they had IFG and IGT or IFG and an A1c was at least 5.7 percent. After a followup of 3 years, 26 percent in the intervention group and 35 percent in the control group developed diabetes (RR, 0.79 [95% CI, 0.60 to 1.32]; 578 total participants).

KQ 8. After Interventions for Prediabetes Are Provided, What Is the Magnitude of Change in Health Outcomes That Results From the Reduction in Type 2 Diabetes Incidence?

In summary, most studies had insufficient followup duration to assess long-term health outcomes. Just two trials had longer than 5 years followup, and just one trial (Da Qing) reported a decrease in diabetes incidence. It found an absolute decrease in diabetes incidence of about 24 percent over 6 years (43.6% vs. 67.7% of participants after a 6-year lifestyle intervention vs. control) was associated with 10 percent fewer deaths (46% vs. 56%) and 8 percent fewer cardiovascular deaths (22% vs. 30%) over 30 years.[110] However, the trial was assessed as having at least medium risk of bias (e.g., for unclear methods of randomization and allocation concealment and baseline differences between groups in smoking status) and results were imprecise.[81]

Eight RCTs (described in 17 articles) were eligible.[50-53, 67, 79-81, 90-93, 95, 96, 101, 110, 122] Sample sizes ranged from 576[79-81] to 9,306.[101] Other than prediabetes, participants were not required to have additional cardiovascular risk factors in three studies (reported in 8 articles).[51, 79-81, 95, 96, 110, 122] Participants had elevated BMI in four studies (reported in 8 articles).[50, 52, 53, 67, 90-93] In one study participants had at least one cardiovascular risk factor or CVD.[101] Three studies (reported in 9 articles) investigated lifestyle interventions[50, 51, 53, 67, 79-81, 110, 122] and one study investigated each of the following medications: metformin,[50, 53, 67] acarbose,[90, 91] pioglitazone,[92, 93] rosiglitazone,[94-96] liraglutide,[52] and nateglinide.[101] Total length of followup ranged from 2.2 years[92, 93] to 30 years.[110] Only two included studies (Da Qing and NAVIGATOR)[79-81, 101, 110] had greater than 5 years followup. Six studies analyzed diabetes incidence over the same time period as the health outcome.[50-53, 67, 90-93, 95, 96, 122] One study (Da Qing) analyzed diabetes incidence at 6, 23, and 30

years, and health outcomes at 20, 23, and 30 years,[79-81, 110] and another (NAVIGATOR) analyzed diabetes incidence at 5 years and health outcomes at 6.5 years.[101]

Two studies (described in 5 articles) were conducted in the United States,[50, 53, 67, 92, 93] one (described in 2 articles) was conducted in the United Kingdom,[51, 122] one (described in 4 articles) was conducted in China,[79-81, 110] and four (described in 6 articles) were conducted across multiple countries.[52, 90, 91, 95, 96, 101] Three studies (reported in 7 articles) reported all-cause mortality and cardiovascular mortality.[79-81, 95, 96, 101, 110] Seven studies (reported in 15 articles) reported cardiovascular events (either individually or as composites).[50, 52, 53, 67, 79-81, 90-93, 95, 96, 101, 110] Three studies (reported in 6 articles) reported quality of life outcomes.[50-53, 67, 122] One study[110] reported retinopathy, nephropathy, and neuropathy outcomes and a composite of these.

Main results are summarized in **Figure 7**. Because most of the trials had insufficient duration of followup to adequately assess for long-term benefits for health outcomes after a reduction in diabetes incidence, the text here focuses on the two trials with more than 5 years followup as well as the DPP because of its particular applicability to the U.S. populations. Additional detailed results for the other included trials are provided in **Appendix E**.

The China Da Qing Diabetes Prevention Outcomes Study (CDQDPOS) evaluated a lifestyle intervention with 30 years of followup in China, among people with prediabetes without requiring additional risk factors for diabetes or mortality.[79-81, 110] The Da Qing results indicate that an absolute decrease in diabetes incidence of about 24 percent over 6 years (43.6% vs. 67.7%) of participants for lifestyle intervention vs. control)[79-81] was associated with 10 percent fewer deaths (46% vs. 56%), 8 percent fewer cardiovascular deaths (22% vs. 30%), 11 percent fewer cardiovascular events (48% vs. 59%), and 5 percent fewer microvascular events (19% vs. 24%) over 30 years.[110] Other outcomes are reported in **Appendix E**. However, the risk of bias was at least medium, in part because of unclear randomization and a baseline imbalance in smoking status. Differences in diabetes incidence developed over the first 6 years, then decreased slightly over the 30 years of followup because the majority of participants developed diabetes.[81] At the 20-year followup, differences in all-cause mortality, cardiovascular mortality, and cardiovascular events were not statistically significant.[80]

The NAVIGATOR trial recruited participants with both prediabetes and either cardiovascular risk factors or CVD from multiple countries, with 6.5 years of followup.[101] Nateglinide did not significantly reduce diabetes incidence or improve health outcomes (**Figure 7**).[101]

The DPP evaluated a lifestyle intervention and metformin in people with prediabetes and BMI of 24 or higher in non-Asians and 22 or higher in Asians.[50, 53, 67] The DPP results found an absolute decrease in diabetes incidence of about 15 percent with lifestyle interventions (14.4% vs. 29.7% for lifestyle intervention vs. control) and an absolute decrease in diabetes incidence of about 8 percent with metformin (21.5% vs. 29.7% for metformin vs. control) over about 3 years[53] and no statistically significant change in incidence of composite cardiovascular events (including cardiovascular death, coronary revascularization, artery disease, stroke, cardiac arrhythmia, congestive heart failure, and unstable angina) over the same time period (2.4% lifestyle vs. 1.6% metformin vs. 2.0% control) (**Figure 7**).[67]

KQ 9. Do Interventions for Prediabetes Improve Other Intermediate Outcomes (Blood Pressure, Lipid Levels, BMI, Weight, and Calculated 10-Year Cardiovascular Disease Risk)?

In summary, 38 RCTs (described in 58 articles) were included (**Appendix E Table 4**).[47-53, 62-80, 82, 84-96, 100-108, 110, 121-124, 126-128] Of those, 28 trials (described in 41 articles) evaluated lifestyle interventions and 13 (described in 25 articles) evaluated pharmacotherapy. **Figures 8** through **10** provide the pooled estimates from multiple meta-analyses; **Appendix F** includes the complete forest plot for each meta-analysis as well as additional figures showing trial data that were not pooled. Lifestyle interventions were associated with reduced systolic and diastolic blood pressure (pooled WMD, -1.7 mm hg [95% CI, -2.6 to -0.8] and -1.2 mm hg [95% CI, -2.0 to -0.4], respectively), weight (pooled WMD, -1.15 kg [95% CI, -1.56 to -0.74]), and BMI (pooled WMD, -0.54 kg/m^2 [95% CI, -0.76 to -0.33]) (**Figures 8** and **10**). Most trials evaluating hypoglycemic agents found no statistically significant association with changes in blood pressure or lipids. Trials of some hypoglycemic agents (metformin, acarbose, or liraglutide) reported reductions in weight and BMI, whereas meta-analysis of trials evaluating TZDs found an association with weight gain (pooled WMD, 1.9 kg [95% CI, 0.8 to 3.1]).

Lifestyle Interventions: Study Characteristics

Twenty-eight RCTs (described in 41 articles) evaluated lifestyle interventions.[47-49, 51, 53, 62-68, 70-80, 82, 84-89, 110, 121-124, 126-128] Trials were conducted between 1986 and 2017 and had a mean duration of followup ranging from 6 months to 30 years. Followup duration was less than 12 months in four trials,[65, 78, 126, 127] 12 to 24 months in 13,[48, 49, 62, 71, 72, 74, 75, 77, 86, 88, 89, 121, 128] and more than 24 months in 12.[47, 51, 53, 63, 64, 66-68, 70, 73, 76, 79, 80, 82, 84, 85, 87, 110, 123, 124] Eight trials were conducted in the United States;[49, 53, 62, 65-70, 72, 77, 88, 128] five in the United Kingdom;[51, 63, 64, 78, 82, 89] four in Japan;[73, 84-86] three in China;[75, 79, 80, 110, 123, 124] two each in Sweden[74, 76] and Thailand;[121, 126] and one each in Denmark,[71] Finland,[47, 87] Germany,[48] and India.[127] Sample sizes ranged from 52 to 3,234. In six studies, sample sizes were fewer than 100,[63, 64, 74, 77, 78, 89, 127] in 13 they were 100 to 499,[48, 49, 65, 71-73, 75, 76, 82, 85, 88, 123, 124, 126, 128] in five they were 500 to 1,000,[47, 51, 62, 79, 80, 84, 87, 110] and four studies had sample sizes greater than 1,000.[53, 66-68, 70, 86, 121]

Studies used a variety of approaches to define prediabetes. In six trials, prediabetes was determined by the results of either the fasting glucose or glucose tolerance test.[48, 51, 63, 64, 85, 88, 123, 124] Three studies used A1c results as criteria for prediabetes, with or without results from other tests,[62, 65, 77] two focused on fasting glucose,[72, 86, 128] three focused on OGTT results,[76, 78, 82] and 14 focused on a combination of test results.[47, 49, 53, 66-71, 73-75, 79, 80, 84, 87, 89, 110, 121, 126, 127] Overweight or obesity, as defined by BMI measures, was included as an eligibility criterion in 15 trials, though none required subjects to be obese (BMI >30 kg/m^2).[47-49, 53, 62, 65-68, 70, 72, 76, 82, 84, 87, 89, 121, 126]

The mean age of participants ranged from 44 to 70 years. Two studies enrolled women only,[77, 88] and another only men;[73] among the others, the proportion of female participants ranged from 3 percent (in a veteran population[49]) to 80 percent. The proportion of nonwhite participants ranged from 10 percent to 100 percent in trials reporting the information. Twenty-one trials did not report information on race/ethnicity. Participants' mean fasting plasma glucose levels at baseline ranged from 96 mg/dL to 112 mg/dL (reported in all but 3 studies). In the 15 trials that reported

mean baseline hemoglobin A1c, levels ranged from 5.4 percent to 6.2 percent. Mean baseline BMI ranged from 24 kg/m^2 to 37 kg/m^2, and values were 30 or above (indicating obesity) in 17 studies.[47-49, 51, 53, 62-72, 74, 76-78, 82, 87, 88, 128]

In 23 of the trials, the lifestyle intervention focused on diet/nutrition and physical activity,[47, 48, 51, 53, 62-68, 70-73, 75-78, 82, 84-88, 121, 123, 124, 126-128] while three had physical activity-related interventions only.[49, 74, 89] In one trial, participants were randomized to diet-only, exercise-only, or diet-and-exercise interventions (or to the control group).[79, 80, 110] The specific content of the theory-based health behavior promotion in one study was not described.[71] Most interventions also included material on health behavior topics such as goal setting, self-monitoring/regulation, problem solving, stress management, or relapse prevention. In 14 of the included trials, the lifestyle intervention was administered in small groups,[48, 51, 62, 71, 72, 74-77, 85, 88, 89, 121, 126, 128] in nine trials during individual visits/sessions,[47, 49, 53, 66-68, 70, 73, 78, 82, 84, 87, 127] one of which also provided weekly reminders via standardized short message service (SMS) and monthly phone calls.[127] In one trial, the intervention was delivered in both individual and group sessions.[79, 80, 110] Sessions included family members in one trial.[63, 64] Two trials evaluated the effects of telephone- and/or email-delivered lifestyle interventions,[65, 86] and in another the intervention was provided via SMS messages alone.[123, 124] In trials with multiple group sessions, the number of meetings ranged from 3 to 24 during the intervention period; the number of individual intervention visits ranged from 6 to 34, and the family-centered intervention took place during 15 visits. We identified high-contact interventions (>360 minutes) in 21 studies[47, 48, 51, 53, 62-68, 70-74, 76, 77, 79, 80, 82, 84, 85, 87, 88, 110, 121, 126, 128] and medium (31 to 360 minutes) in seven.[49, 75, 78, 86, 89, 123, 124, 127] One of the studies that evaluated a high-contact intervention had three groups and also evaluated a low-contact intervention.[74] Intervention delivery personnel varied widely and included instructors hired and trained for the trial, health care staff, case managers, public health professionals, and community health care workers. Control groups received some variation of standard care, usually including, on a less intensive basis than the intervention, written and/or verbal information and advice on diabetes and its management.

Effects on systolic blood pressure were assessed in 18 trials.[47, 48, 51, 62-64, 67, 71, 74, 76-78, 80, 84, 87-89, 110, 123, 124, 127, 128] Of those, all but three also reported on diastolic blood pressure.[62, 89, 127] Effects on total cholesterol and HDL levels were assessed in 19 trials[47-49, 62, 64, 67, 71, 74-78, 84, 87-89, 121, 123, 124, 127] and one on total cholesterol alone;[80, 110] 12 assessed effects on low density lipoprotein (LDL) levels.[49, 51, 64, 67, 71, 74, 76-78, 121, 123, 124, 127] Nineteen assessed effects on triglycerides;[47-49, 51, 64, 67, 74-78, 84, 87-89, 121-124, 126-128] two of these also reported HDL outcomes.[126, 128] Twenty-seven trials evaluated effects of lifestyle interventions on continuous measures of weight;[47-49, 51, 53, 62-66, 68, 71-77, 80, 82, 84-89, 121, 123, 124, 126, 127] 10 evaluated binary measures of weight change (e.g., less than vs. more than 5% of baseline body weight,[62, 63, 65, 70-72, 82, 84, 87, 121]) and 20 reported on BMI.[48, 49, 51, 53, 63, 65, 72, 74-80, 84, 85, 88, 110, 121, 123, 124, 126, 127]

Lifestyle Interventions: Results for Blood Pressure

Lifestyle interventions were associated with a reduction in both systolic and diastolic blood pressure (pooled WMD, -1.7 [95% CI, -2.57 to -0.79] and pooled WMD, -1.2 [95% CI, -2.02 to -0.42], respectively) (**Figure 8**). Analyses stratified by duration of followup (i.e., timing of outcome assessment) found similar associations with blood pressure reduction at 12 to 24 months but no association with blood pressure reduction at followups greater than 24 months or

followups shorter than 12 months (**Figure 8)**. Analyses stratified by contact (i.e., dose) and by BMI found an association with reduction in blood pressure for trials evaluating high-contact interventions (but not lower contact) and for studies of participants with baseline BMI of 30 kg/m^2 or higher (but not lower BMI), which represents the vast majority of included trials (**Figure 8**).

Lifestyle Interventions: Results for Lipid Levels

Meta-analyses of all eligible trials (regardless of contact dose, followup, or baseline BMI) found that lifestyle interventions were not associated with improvements in total cholesterol, HDL, LDL, or triglycerides (**Figure 9**). However, analyses stratified by duration of followup found associations with increased HDL at followups greater than 24 months (**Figure 9**). Analyses stratified by contact and BMI found associations with reduced total cholesterol for medium contact interventions and for trials of participants with baseline BMI of 25 to 29.9 kg/m^2. Analyses stratified by BMI found an association with improvement in HDL for trials of participants with baseline BMI of 30 kg/m^2 or higher (but not lower BMI), which represents the vast majority of included trials.

Lifestyle Interventions: Results for Weight and BMI

Lifestyle interventions were associated with a reduction in weight and BMI (pooled WMD, -1.2 kg [95% CI, -1.6 to -0.74] and pooled WMD, -0.54 kg/m^2 [95% CI, -0.76 to -0.33], respectively) (**Figure 10**). Analyses stratified by duration of followup (i.e., timing of outcome assessment) found similar associations with reduction in weight and BMI. The associations remained significant for trials of medium dose and high-contact lifestyle interventions when stratifying by contact dose (**Figure 10**), but one trial of a low-contact lifestyle intervention found no significant association.[74]

Ten studies reported on weight as a binary outcome between 6 months and 15 years (**Appendix F Figures 81** through **84**).[47, 53, 62, 63, 65, 68, 70-72, 82, 84, 87, 121] Nine reported on the proportion achieving some weight loss threshold,[47, 53, 62, 63, 65, 68, 70-72, 84, 87, 121] one on weight gain,[63] and one reported on beneficial changes in weight.[82] Lifestyle interventions were associated with a greater proportion of participants achieving at least 5 percent weight loss compared with controls over 6 months to 3 years (pooled RR, 3.3 [95% CI, 2.6 to 4.2]; $I^2 = 61\%$; 9 trials; 6,658 participants) (**Appendix F Figure 82**). The association remained significant in analyses stratified by medium or high-contact (no low-contact studies were found), duration of followup, and baseline BMI (for 7 trials with baseline BMI ≥30 and 2 with baseline 25 to 29.9; none had baseline BMI <25) (**Appendix F Figures 83** through **84**).

Lifestyle Interventions: Results for 10-Year CVD Risk

One trial (Let's Prevent Diabetes) reported on 10-year CVD risk.[51] The trial (N= 880) found no statistically significant association between the intervention and improvements in CVD risk scores at 6, 12, 24, and 36 months (**Appendix F Figure 95**).

Pharmacological Interventions: Study Characteristics

Thirteen trials (described in 25 articles) evaluated pharmacological interventions.[52, 53, 66-70, 77, 90-96, 100-108] All of these trials were included in KQ 7 also and have been previously described. Briefly, duration of followup ranged from 1 year to 3.9 years. Followup duration was 12 to 24 months in two studies[77, 100] and more than 24 months in 11.[52, 53, 66-70, 90-95, 101-105, 107, 108] Sample sizes ranged from 62 to 9,306. In one study, sample sizes were fewer than 100,[77] in three they were 100 to 499,[100, 104, 105] in two they were 500 to 1,000,[92, 93, 107] and six had sample sizes greater than 1,000.[52, 53, 66-70, 90, 91, 94, 95, 101-103]

Trials used a variety of approaches to define prediabetes. In two trials, prediabetes was determined by the results of either the fasting glucose or glucose tolerance test.[94, 95, 107] Two studies used A1c results as criteria for prediabetes, with or without results from other tests,[52, 77] one focused on fasting glucose,[101-103] one focused on OGTT results,[100] and seven focused on combinations of test results.[53, 66-70, 90-93, 104, 105, 108] Overweight or obesity, as defined by BMI measures, was part of the eligibility criteria in seven trials,[53, 66-70, 90-93, 100, 107, 108] and one required subjects to be obese (BMI ≥30 kg/m).[52] Participants' mean fasting plasma glucose levels at baseline ranged from 96 mg/dL to 118 mg/dL. Baseline measures for hemoglobin A1c, when reported, ranged from 5.5 percent to 6.0 percent. Mean baseline BMI ranged from 26 to 39 kg/m^2, and values were 30 or above (indicating obesity) in nine studies.[52, 53, 66-70, 77, 90-95, 101-103, 108]

Medications evaluated were metformin (4 trials, including 1 using a stepwise strategy with some participants receiving metformin after 4 months),[53, 66-70, 77, 107] liraglutide,[52] pioglitazone (2 trials),[93, 105] acarbose (2 trials),[90, 91, 104] combination therapy with metformin plus rosiglitazone,[108] rosiglitazone,[95] nateglinide,[101] and acarbose 50 mg three times daily or metformin 250 mg three times daily.[100] In the trial that evaluated acarbose or metformin, participants were stratified into three groups (isolated IGT [I-IGT], isolated IFG [I-IFG], and IFG+IGT) before randomization. Subjects with I-IGT received 50 mg acarbose 3 times daily plus lifestyle intervention; those with I-IFG or IFG-IGT received 250 mg metformin three times daily plus lifestyle intervention.[100]

Pharmacological Interventions: Results for Blood Pressure

Ten trials evaluated the effects of pharmacological interventions on blood pressure (**Appendix F Figures 82** and **83**).[52, 66, 67, 77, 90-94, 100-103, 105, 107] Overall, most trials did not find a statistically significant association between hypoglycemic agents and blood pressure reduction (**Appendix F Figures 82** and **83**). For some medications (rosiglitazone, acarbose),[90, 91, 94, 95] a single trial reported a statistically significant reduction in blood pressure, but the finding has not been replicated (there was not another eligible trial evaluating the medication and reporting on blood pressure). For metformin, two trials (PREVENT-DM and DPP) evaluated 850 mg twice daily and reported no significant difference in blood pressure measures between those receiving metformin and those receiving standard care[77] or placebo[67] over 1 to 3 years.

Two trials using a stepwise design initially focusing on lifestyle interventions that incorporated subsequent medications both reported greater reductions in blood pressure for the intervention groups compared with controls after 1 to 2 years.[100, 106, 107] The D-CLIP trial evaluated 4 months of lifestyle intervention followed by the addition of metformin in very high-risk participants compared with standard care and found greater reduction in blood pressure for the intervention

group (mean difference for systolic blood pressure -1.2 mm hg [95% CI, -2.4 to -0.01] for the 150 participants with blood pressure data). In Lu et al., all participants initially entered the study and received lifestyle and health education for 1 year followed by randomization to a control group or intensive intervention with either acarbose or metformin. Results showed a reduction in systolic blood pressure for individuals in the intensive intervention particularly compared with the control group (mean difference for systolic blood pressure -17.3 mm hg [95% CI, -25.8 to -8.7], 210 participants).[100]

Pharmacological Interventions: Results for Lipid Levels

Ten trials reported on lipid outcomes (**Appendix F Figures 84** through **87**).[52, 67, 77, 90, 91, 93, 100, 104, 105, 107, 108] Of these, seven reported total cholesterol levels,[52, 66, 67, 77, 100, 104, 105, 107, 108] seven reported HDL,[52, 66, 67, 77, 93, 100, 107, 108] seven reported LDL,[52, 66, 67, 77, 92, 93, 100, 107, 108] and 10 reported triglycerides.[52, 66, 67, 77, 90, 91, 93, 100, 104, 105, 107, 108] Overall, most trials did not find a statistically significant association between hypoglycemic agents and change in lipid levels (**Appendix F Figures 84** through **87**). For some medications (metformin, pioglitazone, acarbose, liraglutide),[90, 91, 94, 95] a single trial reported a statistically significant improvement in one or two lipid categories, but the findings have not been replicated (either there was not another eligible trial evaluating the medication and reporting on lipids, or a second trial had a null finding). For metformin, the DPP (n=2,155) reported a greater increase in HDL for those receiving metformin compared with those receiving placebo after 3 years (difference between groups 0.40 [95% CI, 0.15 to 0.65]) but no difference between groups for other lipids,[67] whereas the PREVENT-DM study (n=92) found no statistically significant difference between metformin and controls at 1 year.[77]

Pharmacological Interventions: Results for Weight and BMI

Effects of pharmacological interventions on weight or BMI were assessed in 13 trials.[52, 53, 66-70, 77, 83, 90-95, 100-103, 105, 107, 108] All of these reported on continuous measures of weight, many also reported on BMI,[52, 53, 68-70, 77, 90-95, 100-103, 105, 107, 108] and three assessed binary measures of weight change (e.g., achieving weight loss of 5% of body weight).[52, 53, 68-70, 108]

Seven trials reported on the association between change in weight or BMI and monotherapy with metformin (2 trials),[50, 66, 67, 77] acarbose,[90, 91] liraglutide,[52] pioglitazone (2 trials),[93, 105] or rosiglitazone.[95] Overall, trials of metformin, acarbose, and liraglutide generally reported reductions in weight and BMI with medications, whereas meta-analysis of three trials[93, 95, 105] of TZDs (pioglitazone and rosiglitazone) found that they were associated with an increase in weight compared with controls (pooled WMD for TZDs, 1.9 kg [95% CI, 0.8 to 3.1]; 6,278 participants) (**Appendix F Figures 88** through **92**). For metformin, the DPP (n=2,155) reported greater decreases in weight for those receiving metformin compared with those receiving placebo (-2.0 kg [95% CI, -3.2 to -0.8]);[66] in DPPOS, higher percentages of participants in the metformin group achieving 5 percent weight loss (at 1 year, 29% vs. 13%, $p<0.001$; at 2 years, 26% vs. 14%, $p<0.001$),[70] and higher percentages of participants in the metformin group achieving 10 percent weight loss (1 year, 8% vs. 4%, $p<0.001$; 2 years, 10% vs. 5%, $p<0.001$). The PREVENT-DM trial of metformin also found that participants in the intervention group had greater decreases in weight and BMI, but the differences between groups were not statistically

significant and results were imprecise (-1.7 kg [95% CI, -4.7 to 1.3] and -0.7 kg/m^2 [95% CI, -1.9 to 0.5]).[77]

Two trials using a stepwise design initially focusing on lifestyle interventions that incorporated subsequent medications both reported greater reductions in weight or BMI for the intervention groups compared with controls after 1 to 2 years.[100, 106, 107] Among a subgroup of 150 overweight/obese participants from the D-CLIP trial,[107] investigators evaluated 4 months of lifestyle intervention followed by the addition of metformin in very high-risk participants and reported that the intervention of adapted DPP lifestyle classes plus metformin was associated with decreases in weight (-0.60 kg [95% CI, -1.94 to 0.74] and BMI compared with control at 12 months (-0.50 kg/m^2 [95% CI, -0.996 to -0.004]). In an RCT (n=210) of an intensive integrated intervention (lifestyle and health education for 1 year followed by either acarbose or metformin),[100] participants in the intervention group had a decrease in weight (mean difference, -1.43 [95% CI, -2.549 to -0.311]) and BMI (mean difference, -0.58 [95% CI, -1.149 to -0.011] compared with control at 2 years.[100]

Pharmacological Interventions: Results for 10-Year Cardiovascular Disease Risk

No eligible studies reported this outcome.

Chapter 4. Discussion

Summary of Evidence

Table 9 provides a summary of the main findings in this evidence review organized by KQ along with a description of consistency, precision, quality, limitations, strength of evidence, and applicability.

Evidence for Benefit and Harms of Screening

For benefits of screening, two trials (ADDITION-Cambridge and Ely; 25,120 total participants) evaluated invitations to screening for diabetes and found no significant difference between screening and control groups for all-cause or cause-specific mortality at 10 years or self-reported CVD events or quality of life at 7 through 13 years. The data for outcomes other than mortality were limited, because data were missing for most participants, and the duration of followup in both trials may have been too short to detect benefits for health outcomes. Neither trial assessed screening for prediabetes and neither assessed initial screening with A1c or fasting glucose. For harms of screening, no included studies reported on labeling, harms from false-positive results, burden, inconvenience, or unnecessary testing and treatment. The two included trials reported no significant differences between screening and control groups for anxiety, depression, worry, or self-reported health, but one reported short-term increases in anxiety (at 6 weeks) among persons screened and diagnosed with diabetes mellitus versus those not diagnosed with diabetes mellitus.

Compared with the prior evidence review for the USPSTF, one of the included articles is new in this update,[36] and one included in the prior report for harms of screening has been added to KQ 1 in this update (because it reported some data on health outcomes).[39] The former found no significant difference between screening and control groups in cardiovascular morbidity (the proportion reporting heart attack or stroke), self-rated functional status, quality of life, and a variety of health behaviors after 7 years in ADDITION-Cambridge.[36] The latter found no significant difference between screening and control groups in self-reported myocardial infarction or stroke, symptoms of ischemic heart disease, or quality of life in the Ely study for the subgroup of participants not diagnosed with diabetes.[39]

Benefits of Interventions for Screen-Detected or Recently Diagnosed Diabetes

For screen-detected diabetes, one trial (ADDITION-Europe, 3,057 participants) evaluated an intensive multifactorial intervention aimed at controlling glucose, blood pressure, and cholesterol and found no difference over 5 to 10 years in the risk of all-cause mortality, cardiovascular-related mortality, cardiovascular events, or other health outcomes between intervention and routine care groups. Followup may have been too short to detect benefits for health outcomes and results were imprecise. For recently diagnosed (not screen-detected) diabetes, the UKPDS found that long-term health outcomes (all-cause mortality, diabetes-related mortality, and myocardial infarction) were improved with intensive glucose control with sulfonylureas or insulin over 20 years (10-year post-trial assessment) but not at shorter followups. And, for overweight people, intensive glucose control with metformin decreased all-cause mortality,

diabetes-related mortality, and myocardial infarction at the 10-year followup, and benefits were maintained longer term.

Regarding applicability, it is uncertain whether results from trials of people with recently diagnosed diabetes are applicable to those with screen-detected diabetes. Recently diagnosed diabetes was generally clinically detected (e.g., because of symptoms) and may represent a different subset of the diabetes spectrum, possibly with greater condition severity. Further, the evidence of benefits for people with recently diagnosed (not screen-detected) diabetes comes primarily from the UKPDS, conducted among predominantly white participants from 1977 through 1997 when routine care for cardiovascular disease prevention would not have included treatments now considered to be current standard medical therapy (e.g., statins, lower blood pressure targets). The comparison used in the hypertension in diabetes study embedded in UKPDS exemplifies differences from current standard therapy because it compared tighter control of blood pressure by targeting less than 150/85 versus less tight control targeting less than 180/105.

Benefits of Interventions for Prediabetes

For prediabetes interventions, most trials had insufficient duration of followup for long-term health outcomes, reported few events, and found no differences between groups. One trial of a 6-year lifestyle intervention for people with IGT conducted in China (Da Qing, n=576) reported lower all-cause mortality and CVD-related mortality at 23 years and at 30 years but not at earlier followup. The trial was limited by at least medium risk of bias because of unclear randomization and allocation concealment methods and baseline differences likely to bias results in favor of the intervention. The sample size was relatively small, and the original trial was designed to assess diabetes incidence and not long-term health outcomes. Regarding applicability, the trial began in 1986 when (like UKPDS) routine care for cardiovascular disease prevention would not have included treatments now considered to be current standard medical therapy. Participants had IGT and mean baseline BMI was 25.7 kg/m^2; applicability to other categories of prediabetes, U.S. populations, and those in different BMI categories is uncertain.

Meta-analyses found that lifestyle interventions for obese or overweight people with prediabetes were associated with a reduction in the incidence of diabetes in trials ranging from 1 year of followup to 30 years of followup (including 13 trials with at least 3 years of followup). Using the control group event rate from DPPOS, it was estimated that the number of obese or overweight people with prediabetes needed to treat to prevent one person from developing diabetes over 15 years was 9. Lifestyle interventions were also associated with reduced blood pressure (by about 1.7/1.2 mmHg), weight (by 1.2 kg), and BMI (by 0.54 kg/m^2). The clinical significance of these small mean reductions is somewhat uncertain. For blood pressure, for example, some guidelines suggest that reductions of 2 to 3 mmHg could result in significant improvement in cardiovascular outcomes.[129]

Regarding applicability, the findings are applicable to overweight and obese adults, and most trials evaluated high-contact interventions (>360 minutes). For example, the intensive lifestyle modification program evaluated in the DPP comprised a 16-lesson curriculum covering diet, exercise, and behavior modification that was taught one-on-one by case managers. The goals of the lifestyle intervention were to achieve and maintain at least a 7 percent weight reduction

through a low-calorie, low-fat diet, and moderate intensity physical activity for at least 150 minutes per week.

For medications, metformin, TZDs, and AGIs were associated with a reduction in diabetes incidence. Most trials of medications found no significant association between hypoglycemic agents and changes in blood pressure or lipids. The evidence for TZDs and AGIs was limited by imprecision, inconsistency, and risk of bias, but evidence for metformin was consistent, precise, and generally assessed as good quality. Nevertheless, head-to-head trial data demonstrate that lifestyle interventions are superior to metformin. The DPP compared an intensive lifestyle modification program with metformin and placebo, finding a greater reduction in diabetes incidence over about 3 years with a lifestyle program than with metformin, as compared with placebo (58% vs. 31% reduction in diabetes incidence).[66] The authors estimated that about seven people would need to be treated with the lifestyle intervention or about 14 with metformin to prevent one case of diabetes over about 3 years.[66] Longer followup over a mean of 15 years reported by the DPPOS also found greater reduction for the lifestyle program than for metformin, although it found a declining between-group difference (27% vs. 18% reduction in diabetes incidence).[53]

Limitations

This review has limitations. The limitations of the included studies are discussed above in Results and Discussion. Here we focus on limitations of this review. We excluded non-English language articles. For studies of recently diagnosed diabetes, we excluded studies of persons who had diabetes for more than 1 year or with more advanced diabetes, aiming to identify the studies with good applicability to a screen-detected population. This review did not evaluate studies of weight loss medications or bariatric surgery to treat diabetes. FDA has approved one short-term (phentermine) and several long-term medications or medication combinations (orlistat, lorcaserin, phentermine/topiramate, naltrexone/bupropion, and liraglutide) for weight loss. Except for liraglutide, none of these medications is approved to treat diabetes. Instead, FDA has approved these weight-loss medications for individuals with a BMI greater than 27 kg/m^2 with one or more obesity-related comorbid conditions, including type 2 diabetes, or those with a BMI greater than 30.[130] NICE recommends orlistat, along with a low-fat diet, to prevent the onset of diabetes among individuals at high risk for developing diabetes who are unable to achieve weight loss through lifestyle changes.[21]

Future Research Needs

Screening trials of sufficient duration and sample size that focus on health outcomes (e.g., mortality, CVD events) are needed, as are studies on potential harms of screening such as labeling, harms from false-positive results, burden, inconvenience, or unnecessary testing and treatment. Neither of the existing screening trials assessed screening for prediabetes, and neither assessed initial screening with A1c or fasting glucose, tests that might be more likely used in the United States if screening is performed. Longer followup of participants from trials is needed. For example, longer followup of participants with screen-detected diabetes from the ADDITION-Europe trial and followup for more than 20 years from trials evaluating lifestyle interventions for prediabetes (to replicate or refute the Da Qing results) would be helpful. Some

of the key evidence has uncertain applicability to current U.S. adult populations (e.g., evidence from China or the United Kingdom from trials beginning 30 to 40 years ago), and trials conducted in the United States would be informative. For example, the prevalence of undiagnosed diabetes in U.S. adults might be higher (given the higher prevalence of obesity).

Conclusion

Trials of screening for diabetes found no mortality benefit at 10 years but had insufficient data to assess other health outcomes. Evidence on harms of screening was scant. For people with screen-detected diabetes, one trial found no improvement in health outcomes over 5 to 10 years. For people with recently diagnosed (not screen-detected) diabetes, interventions improved health outcomes over 10 to 20 years. For obese or overweight people with prediabetes, interventions were associated with reduced incidence of diabetes and improvement in other intermediate outcomes, and limited evidence suggests that very high-contact lifestyle interventions improve health outcomes after more than 20 years.

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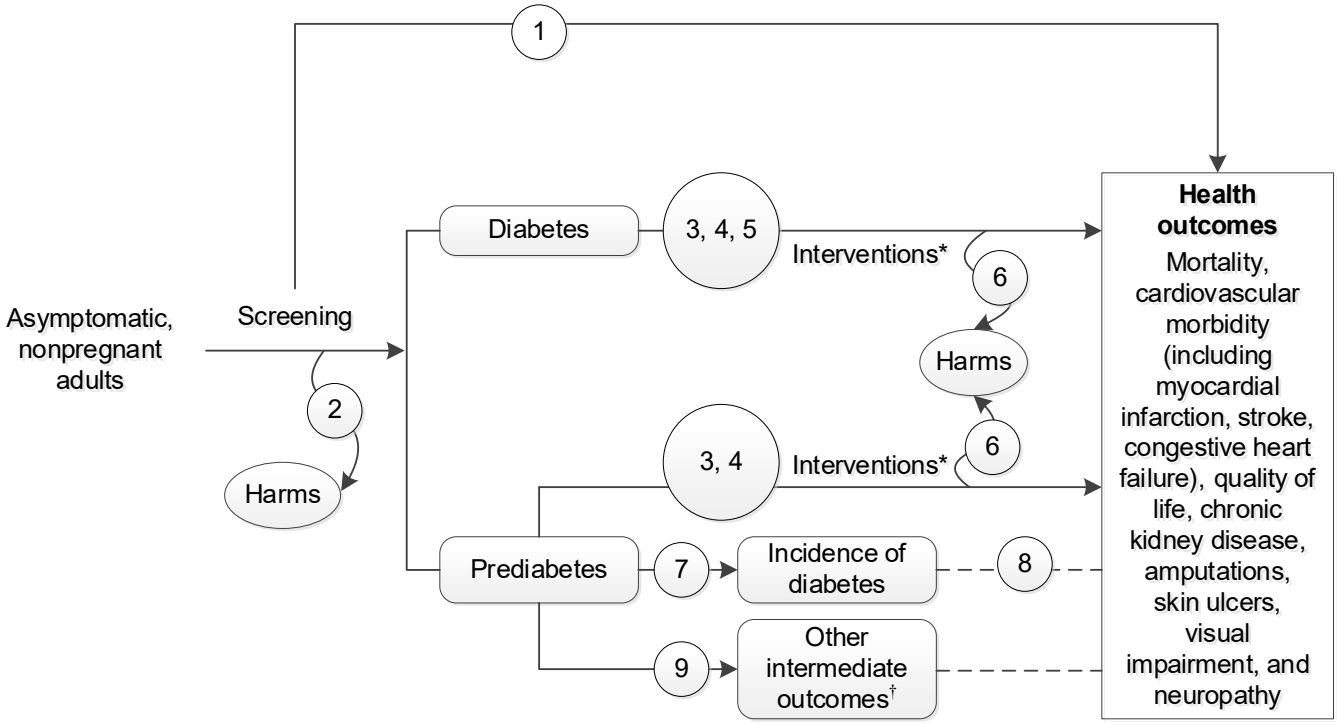
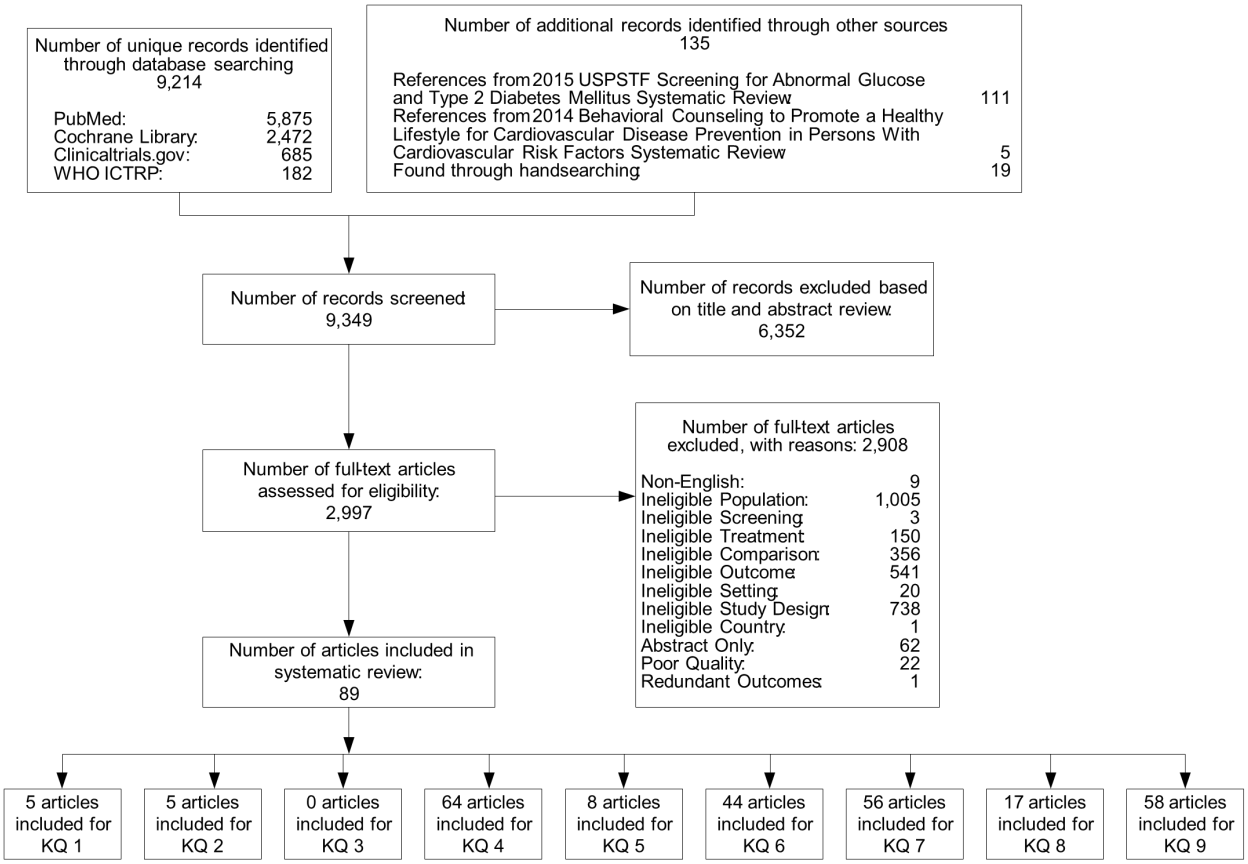
Figure 1. Analytic Framework



* Eligible interventions include pharmacotherapy and primary care–relevant behavioral counseling focused on healthy diet and nutrition, physical activity, or both.
† Other intermediate outcomes include blood pressure, lipid levels, BMI, weight, and calculated 10-year cardiovascular disease risk.

Abbreviations: BMI=body mass index.

Figure 2. Summary of Evidence Search and Selection



Note: The sum of the number of articles per KQ exceeds the total number of articles because some articles were applicable to multiple KQs.

Abbreviations: ICTRP=International Clinical Trials Registry Platform; KQ=key question; USPSTF=U.S. Preventive Services Task Force; WHO=World Health Organization.

Figure 3. All-Cause Mortality in Trials of Interventions for People With Recently Diagnosed Type 2 Diabetes (KQ 5)

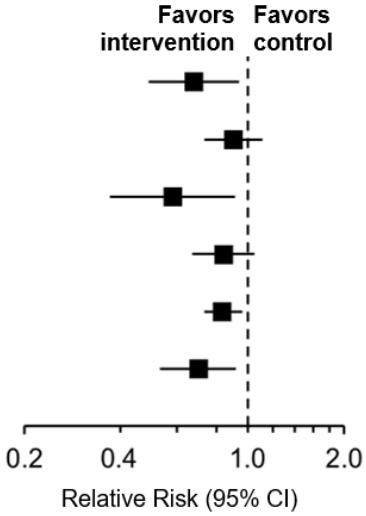
			Intervention Group		Control Group		
Source	Treatment	Duration of F/U, y	Persons With Event, No.	Persons Without Event, No.	Persons With Event, No.	Persons Without Event, No.	Relative Risk (95% CI)
Davies et al., 2003[113]	Group education*	1	2	435	5	382	0.35 (0.07, 1.82)
Khunti et al., 2012[117]	Group education*	3	15	422	11	376	1.21 (0.56, 2.60)
Holman et al., 2008[116]	BP control†	9	134	624	83	307	0.82 (0.63, 1.08)
UKPDS Group, 1998[4]	Glucose control‡	10	489	2240	213	925	0.94 (0.80, 1.10)
UKPDS Group, 1998[119]	Weight control§	10	50	292	89	322	0.64 (0.45, 0.91)
Holman et al., 2008[115]	BP control†	10 post-trial	373	385	211	179	0.89 (0.75, 1.06)
Holman et al., 2008[114]	Glucose control‡	10 post-trial	1,162	1,567	537	601	0.87 (0.79, 0.96)
Holman et al., 2008[114]	Weight control§	10 post-trial	152	190	217	294	0.73 (0.59, 0.89)

* Group education in the DESMOND trial.
† BP control=Tighter blood pressure control (<150/85 vs. <180/105) in the hypertension in diabetes study embedded in UKPDS.
‡ Glucose control=Intensive therapy with sulfonylureas or insulin in UKPDS.
§ Weight control=Metformin for overweight substudy UKPDS group.

Abbreviations: BP=blood pressure; CI=confidence interval; DESMOND=Diabetes Education and Self Management for Ongoing and Newly Diagnosed; F/U=followup; KQ=key question; UKPDS=United Kingdom Prospective Diabetes Study; vs.=versus.

Figure 4. Diabetes-Related Mortality in Trials of Interventions for People With Recently Diagnosed Type 2 Diabetes (KQ 5)

Source	Treatment	Duration of F/U, y	Intervention Group: Persons With Event, No.	Intervention Group: Persons Without Event, No.	Control Group: Persons With Event, No.	Control Group: Persons Without Event, No.	Relative Risk (95% CI)
Holman et al., 2008[116]	BP control*	9	82	676	62	328	0.68 (0.49, 0.94)
UKPDS Group, 1998[4]	Glucose control†	10	285	2444	129	1009	0.90 (0.73, 1.11)
UKPDS Group, 1998[119]	Weight control‡	10	28	314	55	356	0.58 (0.37, 0.91)
Holman et al., 2008[115]	BP control*	10 post-trial	203	555	122	268	0.84 (0.67, 1.05)
Holman et al., 2008[114]	Glucose control†	10 post-trial	618	2,111	297	841	0.83 (0.73, 0.96)
Holman et al., 2008[114]	Weight control‡	10 post-trial	81	261	120	291	0.70 (0.53, 0.92)

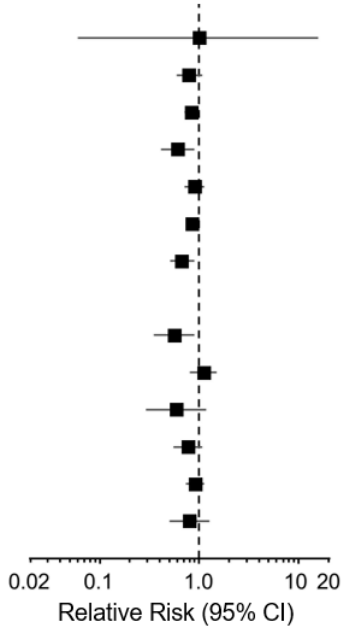


* BP control=Tighter blood pressure control (<150/85 vs. <180/105) in the hypertension in diabetes study embedded in UKPDS.
† Glucose control=Intensive therapy with sulfonylureas or insulin in UKPDS.
‡ Weight control=Metformin for overweight substudy UKPDS group.

Abbreviations: BP=blood pressure; CI=confidence interval; F/U=followup; KQ=key question; UKPDS=United Kingdom Prospective Diabetes Study; vs.=versus.

Figure 5. Myocardial Infarction and Stroke Outcomes in Trials of Interventions for People With Recently Diagnosed Type 2 Diabetes (KQ 5)

			Intervention Group		Control Group		
Source	Treatment	Duration of F/U, y	Persons With Event, No.	Persons Without Event, No.	Persons With Event, No.	Persons Without Event, No.	Relative Risk (95% CI)
Myocardial Infarction							
Yang et al., 2013[118]	Multifactorial*	7	1	74	1	74	1.00 (0.06, 15.7)
Holman et al., 2008[116]	BP control†	9	107	651	69	321	0.79 (0.59, 1.07)
UKPDS Group, 1998[4]	Glucose control‡	10	387	2342	186	952	0.84 (0.71, 1.00)
UKPDS Group, 1998[119]	Weight control§	10	39	303	73	338	0.61 (0.41, 0.89)
Holman et al., 2008[115]	BP control†	10 post-trial	205	553	115	275	0.90 (0.71, 1.13)
Holman et al., 2008[114]	Glucose control‡	10 post-trial	678	2,051	319	819	0.85 (0.74, 0.97)
Holman et al., 2008[114]	Weight control§	10 post-trial	81	261	126	285	0.67 (0.51, 0.89)
Stroke							
Holman et al., 2008[116]	BP control†	9	38	720	34	356	0.56 (0.35, 0.89)
UKPDS Group, 1998[4]	Glucose control‡	10	148	2,581	55	1083	1.11 (0.81, 1.51)
UKPDS Group, 1998[119]	Weight control§	10	12	330	23	388	0.59 (0.29, 1.18)
Holman et al., 2008[115]	BP control†	10 post-trial	90	668	58	332	0.77 (0.55, 1.07)
Holman et al., 2008[114]	Glucose control‡	10 post-trial	260	2,469	116	1022	0.91 (0.73, 1.13)
Holman et al., 2008[114]	Weight control§	10 post-trial	34	308	42	369	0.80 (0.50, 1.27)

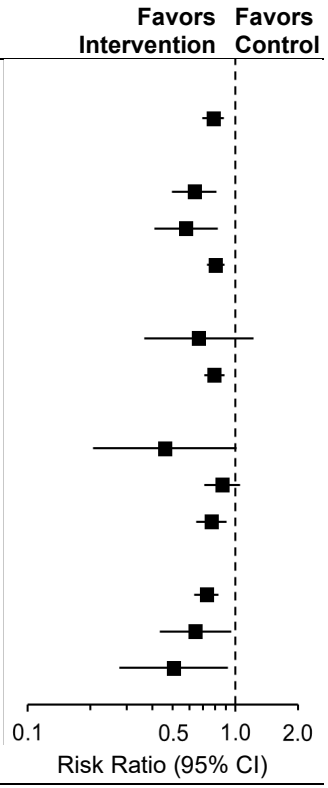


* Multifactorial=Multifactorial intensive therapy.
† BP control=Tighter blood pressure control (<150/85 vs. <180/105) in the hypertension in diabetes study embedded in UKPDS.
‡ Glucose control=Intensive therapy with sulfonylureas or insulin in UKPDS.
§ Weight control=Metformin for overweight substudy UKPDS group.

Abbreviations: BP=blood pressure; CI=confidence interval; F/U=followup; KQ=key question; UKPDS=United Kingdom Prospective Diabetes Study; vs.=versus.

Figure 6. Delaying or Preventing Progression to Diabetes: Results of Meta-Analyses of Trials Evaluating Interventions for People With Prediabetes (KQ 7)

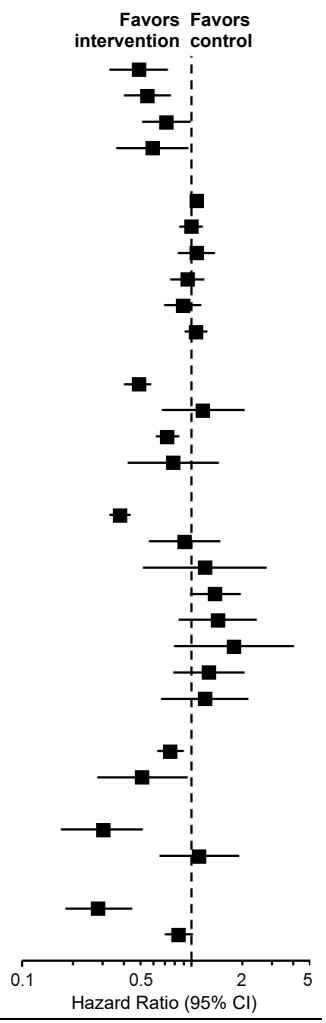
Category	K	Total N	RR (95% CI)	I^2
Lifestyle Intervention				
All (longest f/u)	23	12,915	0.78 (0.69, 0.88)	46.76
Time Point				
<12 months	4	3,518	0.63 (0.50, 0.81)	0.00
12-24 months	15	5,946	0.58 (0.41, 0.82)	55.70
>24 months	13	8,947	0.81 (0.73, 0.89)	40.56
Contact dose				
Medium	5	3,579	0.67 (0.37, 1.22)	70.70
High	18	9,303	0.79 (0.71, 0.89)	36.62
BMI (kg/m^2)				
<25	4	3,803	0.46 (0.21, 1.02)	82.92
25-29.5	6	3,575	0.86 (0.71, 1.05)	44.21
≥30	13	5,503	0.77 (0.65, 0.91)	20.13
Pharmacological Intervention				
Metformin	3	2,181	0.73 (0.64, 0.83)	0.00
Acarbose or voglibose	3	3,264	0.64 (0.43, 0.96)	76.27
Pioglitazone or rosiglitazone	3	6,238	0.50 (0.28, 0.92)	91.86



Abbreviations: BMI=body mass index; CI=confidence interval; f/u=followup; K=number of studies; KQ=key question; N=number; RR=relative risk.

Figure 7. Main Results of Studies Reporting Both Diabetes Incidence and Health Outcomes After Interventions for Prediabetes (KQ 8)

Source	Intervention	Outcome	F/Y, y	Intervention Group		Control Group		Hazard Ratio (95% CI)
				No. with Event	No. without Event	No. with Event	No. without Event	
CDQPDPOS	Combination	T2DM incidence	6	173	224	90	43	0.49 (0.33-0.73)
			23	312	118	124	14	0.55 (0.40, 0.76)
		All-cause mortality	23	121	309	53	85	0.71 (0.51, 0.99)
		CV mortality	23	51	379	27	111	0.59 (0.36, 0.96)
NAVIGATOR	Nateglinide	T2DM incidence	5	1674	2971	1580	3081	1.07 (1.00, 1.15)
		All-cause mortality	6.5	310	4335	312	4023	1.00 (0.85, 1.17)
		CV mortality	6.5	126	4519	118	4543	1.07 (0.83, 1.38)
		MI	6.4	135	4510	143	4518	0.95 (0.75, 1.20)
		Stroke	6.4	111	4534	126	4535	0.89 (0.69, 1.15)
		Revascularization	6.3	332	4313	315	4346	1.06 (0.91, 1.24)
DPP	Lifestyle	T2DM incidence	3	132	783	278	657	0.49 (0.40, 0.58)*
		CV event	3	26	1063	22	1060	1.17 (0.67, 2.06)*
	Metformin	T2DM incidence	3	199	727	278	657	0.72 (0.62, 0.85)*
		CV event	3	17	1056	22	1060	0.78 (0.42, 1.46)*
DREAM	Rosiglitazone	T2DM incidence	3	280	2355	658	1976	0.38 (0.33, 0.44)
		All-cause mortality	3	30	2605	33	2601	0.91 (0.56, 1.49)
		CV mortality	3	12	2623	10	2624	1.20 (0.52, 2.77)
		CV event 1	3	77	2558	56	2578	1.38 (0.98, 1.95)
		CV event 2	3	33	2602	23	2611	1.43 (0.84, 2.44)
		MI	3	16	2619	9	2625	1.78 (0.79, 4.03)
		Revascularization	3	37	2598	29	2605	1.27 (0.78, 2.07)
		New angina	3	24	2635	20	2634	1.20 (0.66, 2.17)
STOP-NIDDM	Acarbose	T2DM incidence	3.3	221	461	285	401	0.75 (0.63, 0.90)
		Major CV event	3.3	15	667	32	654	0.51 (0.28, 0.95)
ACT NOW	Pioglitazone	T2DM incidence	2.2	15	288	50	249	0.30 (0.17, 0.52)*
		CV event	2.2	26	277	23	276	1.1 (0.65, 1.91)*
SCALE	Liraglutide	T2DM incidence	3.1	26	1479	46	703	0.28 (0.18, 0.45)*
		CV event	3.1	242	1263	142	607	0.84 (0.70, 1.02)*

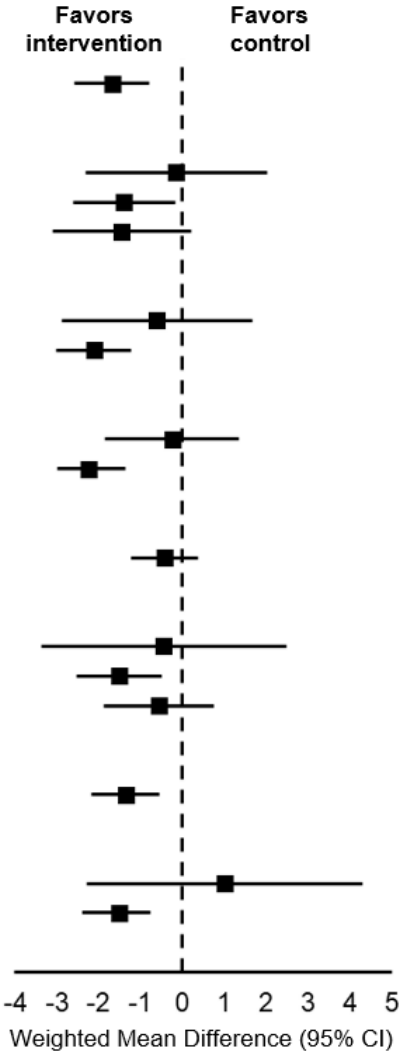


* Calculated RR and 95% CI from number of events; study did not report HR.

Abbreviations: CDQDPOS=China Da Qing Diabetes Prevention Outcomes Study; CI=confidence interval; CV=cardiovascular; DPP=Diabetes Prevention Program; F/U=followup; HR=hazard ratio; KQ=key question; NAVIGATOR=Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; RR=relative risk; STOP-NIDDM=Study TO Prevent Noninsulin-Dependent Diabetes Mellitus; T2DM=type 2 diabetes mellitus; y=years.

Figure 8. Blood Pressure: Results of Meta-Analyses of Trials Evaluating Lifestyle Interventions for People With Prediabetes (KQ 9)

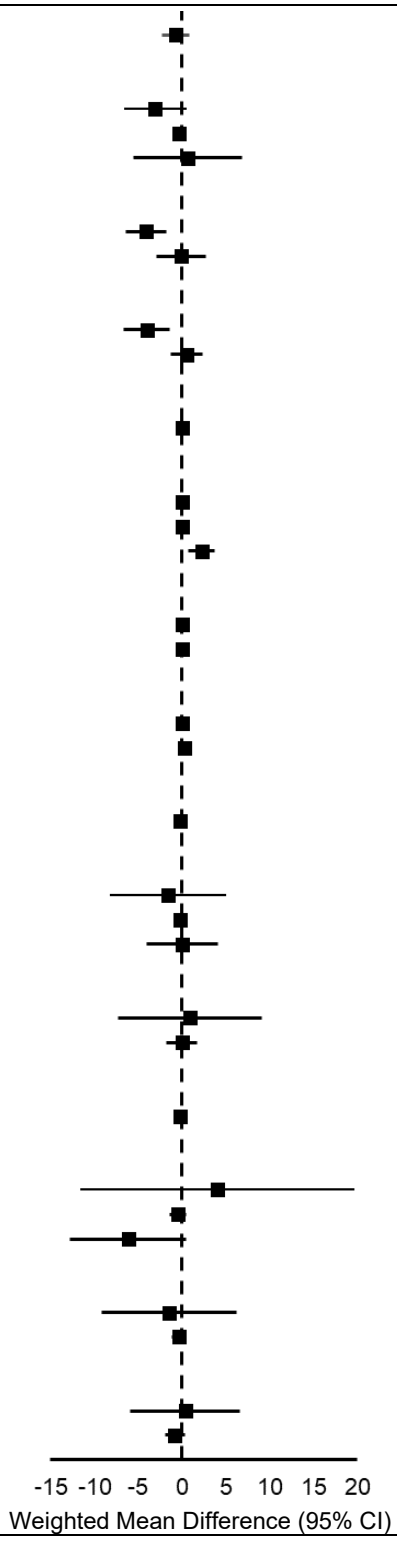
Outcome	Category	K	Total N	WMD (95% CI)	I^2
SBP	**All (longest f/u)**	18	6880	-1.68 (-2.57, -0.79)	11.43
	Time point				
	<12 months	5	1262	-0.15 (-2.31, 2.01)	33.17
	12-24 months	14	5987	-1.39 (-2.60, -0.17)	64.56
	>24 months	6	4060	-1.44 (-3.08, 0.21)	25.97
	Contact dose				
	Medium	5	1023	-0.60 (-2.86, 1.67)	24.30
	High	13	5824	-2.11 (-3.01, -1.21)	1.53
	BMI (kg/m²)				
	25-29.5	5	1521	-0.24 (-1.84, 1.36)	0.00
	≥30	13	5359	-2.23 (-3.11, -1.36)	0.00
DBP	**All (longest f/u)**	15	6171	-1.22 (-2.02, -0.42)	31.62
	Time point				
	<12 months	3	1062	-0.44 (-3.36, 2.48)	67.18
	12-24 months	12	5346	-1.51 (-2.52, -0.49)	63.22
	>24 months	6	4060	-0.55 (-1.86, 0.76)	51.82
	Contact dose				
	High	12	5289	-1.35 (-2.17, -0.54)	25.84
	BMI (kg/m²)				
	25-29.5	3	1321	1.01 (-2.26, 4.29)	52.75
	≥30	12	4850	-1.52 (-2.27, -0.76)	18.12



Abbreviations: BMI=body mass index; CI=confidence interval; DBP=diastolic blood pressure; f/u=followup; KQ=key question; K=number of studies; N=number; SBP=systolic blood pressure; WMD=weighted mean difference.

Figure 9. Lipids: Summary of Meta-Analysis Results for Trials Evaluating Lifestyle Interventions for People With Prediabetes (KQ 9)

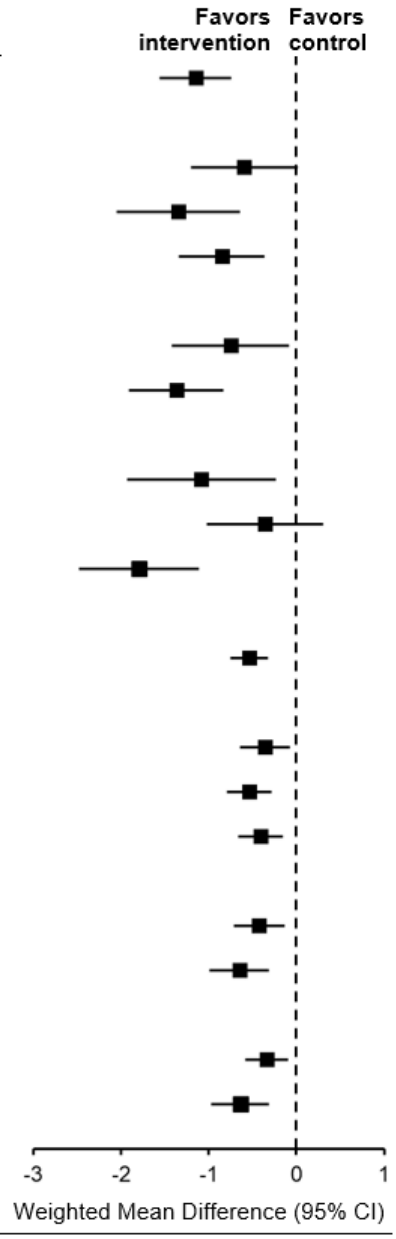
Outcome	Category	K	Total N	WMD (95% CI)	I^2
TC	**All (longest f/u)**	19	7,044	-0.69 (-2.23, 0.86)	83.17
	Time Point				
	<12 months	4	1,158	-3.03 (-6.62, 0.57)	0.00
	12-24 months	14	4,253	-0.27 (-0.60, 0.06)	16.11
	>24 months	6	3,797	0.66 (-5.57, 6.90)	84.76
	Contact dose				
	Medium	7	1,759	-4.10 (-6.43, -1.77)	0.00
	High	12	5,252	-0.07 (-2.84, 2.70)	88.60
	BMI (kg/m^2)				
	25-29.5	6	3,419	-3.98 (-6.60, -1.36)	0.00
	≥30	12	3,128	0.56 (-1.21, 2.32)	87.97
HDL	**All (longest f/u)**	21	9,062	0.00 (-0.004, 0.004)	58.80
	Time Point				
	<12 months	5	1,283	0.00 (0.00, 0.00)	0.00
	12-24 months	15	4,562	0.00 (-0.01, 0.01)	34.16
	>24 months	7	5,682	2.25 (0.74, 3.77)	57.96
	Contact dose				
	Medium	7	1,759	0.00 (0.00, 0.00)	0.00
	High	14	7,270	0.00 (-0.01, 0.01)	72.80
	BMI (kg/m^2)				
	25-29.5	6	2,973	0.00 (0.00, 0.00)	59.16
	≥30	14	5,655	0.30 (0.05, 0.55)	63.20
LDL	**All (longest f/u)**	12	4,061	-0.18 (-0.52, 0.17)	4.94
	Time Point				
	<12 months	3	1,026	-1.58 (-8.22, 5.06)	37.31
	12-24 months	8	1,841	-0.25 (-0.66, 0.16)	12.98
	>24 months	5	3,226	0.10 (-3.97, 4.16)	52.58
	Contact dose				
	Medium	4	552	0.98 (-7.22, 9.18)	0.00
	High	8	3,476	0.01 (-1.72, 1.74)	27.74
Tri	**All (longest f/u)**	19	8,432	-0.21 (-0.71, 0.28)	61.95
	Time Point				
	<12 months	5	1,283	4.06 (-11.54, 19.66)	47.19
	12-24 months	13	3,926	-0.41 (-1.34, 0.52)	59.54
	>24 months	7	5,688	-6.13 (-12.73, 0.47)	67.87
	Contact dose				
	Medium	7	1,759	-1.42 (-9.13, 6.29)	30.53
	High	12	6,640	-0.33 (-1.12, 0.47)	71.85
	BMI (kg/m^2)				
	25-29.5	6	2,973	0.42 (-5.84, 6.68)	26.90
	≥30	12	5,025	-0.77 (-1.89, 0.34)	71.39



Abbreviations: BMI=body mass index; CI=confidence interval; HDL=high density lipoprotein; f/u=followup; KQ=key question; K=number of studies; LDL= low density lipoprotein; N=number; WMD=weighted mean difference.

Figure 10. Weight and BMI: Summary of Meta-Analysis Results for Trials Evaluating Lifestyle Interventions for People With Prediabetes (KQ 9)

Outcome	Category	K	Total N	WMD (95% CI)	I^2
Weight (kg)	**All (longest f/u)**	27	13 454	-1.15 (-1.56, -0.74)	80.84
	Time point				
	<12 months	7	1726	-0.59 (-1.20, 0.01)	70.44
	12-24 months	18	7838	-1.35 (-2.05, -0.65)	89.56
	>24 months	12	10 155	-0.85 (-1.34, -0.36)	82.05
	Contact dose				
	Medium	7	4234	-0.75 (-1.42, -0.08)	85.26
	High	20	9187	-1.37 (-1.91, -0.84)	77.12
	BMI (kg/m²)				
	<25	4	3803	-1.09 (-1.93, -0.24)	79.00
	25-29.5	6	2973	-0.36 (-1.02, 0.30)	78.34
	≥30	16	6102	-1.79 (-2.48, -1.11)	76.53
BMI	**All (longest f/u)**	19	6836	-0.54 (-0.76, -0.33)	70.50
	Time point				
	<12 months	6	1594	-0.36 (-0.64, -0.07)	63.57
	12-24 months	12	3446	-0.54 (-0.80, -0.28)	74.69
	>24 months	8	4407	-0.41 (-0.67, -0.16)	63.13
	Contact dose				
	Medium	8	3371	-0.43 (-0.72, -0.14)	66.96
	High	12	4872	-0.65 (-0.99, -0.31)	72.53
	BMI (kg/m²)				
	25-29.5	6	3417	-0.34 (-0.58, -0.10)	47.91
	≥30	11	2681	-0.64 (-0.97, -0.32)	73.64



Abbreviations: BMI=body mass index; CI=confidence interval; f/u=followup; KQ=key question; K=number of studies; N=number; WMD=weighted mean difference.

Table 1. Classification of Diabetes*

Category	Definition/Etiology
Type 1 diabetes	Diabetes due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency
Type 2 diabetes	Diabetes due to a progressive loss of β-cell insulin secretion frequently on the background of insulin resistance
Gestational diabetes mellitus	Diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation
Diabetes due to other causes	Includes specific types of diabetes attributable to the following: monogenic diabetes syndromes (e.g., maturity-onset diabetes of the young), diseases of the exocrine pancreas (e.g., pancreatitis), and drug- or chemical-induced diabetes (e.g., glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)

* Adapted from 2018 American Diabetes Association guidelines[1]

Abbreviation: HIV/AIDS=human immunodeficiency virus/acquired immunodeficiency syndrome.

Table 2. Criteria for the Diagnosis of Type 2 Diabetes and Prediabetes*

Diagnosis	A1c†	Fasting‡ Plasma Glucose	OGTT†,§	Other
Type 2 diabetes	≥6.5% (48 mmol/mol) §	≥126 mg/dL (7.0 mmol/L)	≥200 mg/dL (11.1 mmol/L)	Random plasma glucose ≥200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia or hyperglycemia crisis
Prediabetes‖	5.7 to 6.4% (39-47 mmol/mol)	IFG: 100 to 125 mg/dL (5.6-6.9 mmol/L)	IGT: 140 to 199 mg/dL (7.8-11.0 mmol/L)	NA

* Adapted from 2018 American Diabetes Association guidelines.[1]
† The ADA guidelines note this test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.
‡ Fasting is defined as no caloric intake for at least 8 hours.
§ Refers to values measured 2 hours post-load on the 75 g OGTT. Per the ADA recommendations, the test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75-gram anhydrous glucose dissolved in water.
‖ ADA guidelines note that for all three tests the risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

Abbreviations: A1c=glycated hemoglobin; ADA=American Diabetes Association; DCCT=Diabetes Control and Complications Trial; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; NA=not applicable; NGSP=National Glycohemoglobin Standardization Program; OGTT=oral glucose tolerance test.

Table 3. Characteristics of Included Trials Evaluating Screening for Type 2 Diabetes (KQ 1 and KQ 2)*

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup	Age, Mean (SD or IQR), Years	No. (%) F	No. (%) Non-white	Diabetes Risk Score, Median (IQR)	BMI, Mean (kg/m^2)	Prescribed Antihyper-tensive Medications, No. (%)	Quality
Eborall, 2007[42] Paddison, 2011[43] ADDITION-Cambridge	Substudy of an RCT involving 15 practices in the United Kingdom	Adults at high risk of having undiagnosed type 2 DM	G1: Invited for screening (6,416, 10 practices) G2: Non-Invited controls (964, 5 practices)	12-15 months	G1: 57.6 (7.9) G2: 58.6 (7.8)	G1: 2,220 (34.6) G2: 343 (35.6)	NR	NR	G1: 30.5 (4.7) G2: 30.6 (4.9)	G1: 2,992 (46.6) G2: 472 (49.0)	Fair
Echouffo-Tcheugui, 2015[36] ADDITION-Cambridge, 7 year followup	Cluster RCT; 33 practices in the United Kingdom	In trial and completed 7-year followup question-naire	G1: Invited to stepwise screening and returned questionnaires at 7 year followup (27 practices; 1,373) G2: No screening and returned questionnaires at 7-year followup (5 practices; 572)	7 years	Median G1: 60 (54-65) G2: 60 (54-65)	G1: 534 (38.9) G2: 212 (37.1)	NR (1)	0.36 (0.25-0.52) vs. 0.38 (0.25-0.56)	G1: 29.4 (27.7-32.3) G2: 29.6 (27.8-32.2)	654 (47.6) 298 (52.1)	Fair
Rahman, 2012[38]† Ely	Subgroup analysis of an RCT; 1 general practice in the United Kingdom	Invited for screening in Phase 1 or Phase 2; diagnosed with DM	G1: Invited to screening in Phase 1 (1990-1999) and diagnosed with DM (116 invited; 92 attended health assessment) G2: Unscreened in Phase 1 and invited to screening in Phase 2 and diagnosed with DM (83 invited; 60 attended health assessment)	12 years (Mean 11.6 years)	G1: 68.3 (7.0) G2: 66.4 (6.6)	G1: 31 (47.4) G2: 15 (45.8)	NR	NR	G1: 30.4 (SD 5.0) G2: 29.7 (SD 4.5)	G1: 46 (50.5) G2: 37 (59.7)	Fair
Rahman, 2012[39]‡ Ely	Subgroup analysis of an RCT; 1 general practice in the United Kingdom	Invited for screening in Phase 1 or 2 and attended a health assessment; not diagnosed with DM	G1: Invited for screening in Phase 1 and not diagnosed with DM (1,696 invited; 731 attended health assessment) G2: Not initially invited to screening, but invited 10 years later, in Phase 2, and not diagnosed with DM (1,694 invited; 711 attended health assessment)	13 years (mean 12.5 years)	G1: 63.5 (7.7) G2: 61.9 (7.0)	G1:423 (57.9) G2: 353 (49.6)	NR	NR	G1: 26.9 (SD 4.4) G2: 27.4 (SD 4.8)	G1: 230 (25.1) G2: 197 (25.1)	Fair
Simmons 2012[35] ADDITION-Cambridge	Cluster RCT; 33 practices in the United Kingdom	High risk of diabetes (risk score ≥0.17) and without known DM	G1: Invited to screening with random capillary blood glucose and HbA1c§ (27 practices; 16,047 eligible, 15,089 invited) G1-a: Attended: 11,737, 78% G1-b: Did not attend: 3,352, 22% G2: No screening (5 practices; 4,137)	Median 9.6 years	G1: 58.2 (7.7) G2: 57.9 (7.8)	G1: 5,787 (36.1) G2: 1,496 (36.1)	NR (NR)	G1: 0.35 (0.24-0.52) G2: 0.34 (0.24-0.51)	G1: 30.5 (SD 4.6) G2: 30.6 (SD 4.6)	G1: 7,372 (45.9) G2: 1,853 (44.8)	Good

Table 3. Characteristics of Included Trials Evaluating Screening for Type 2 Diabetes (KQ 1 and KQ 2)*

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup	Age, Mean (SD or IQR), Years	No. (%) F	No. (%) Non-white	Diabetes Risk Score, Median (IQR)	BMI, Mean (kg/m^2)	Prescribed Antihyper-tensive Medications, No. (%)	Quality
Simmons, 2011[37] Ely	RCT; 1 general practice in the United Kingdom	Free of known diabetes	*Phase 1 (1990-1999)* G1: Invited to screening every 5 years with OGTT and for CVD risk (cholesterol, BP) (1,705) G1-a: Attended screening (1,157/1,705; 68%) G1-b: Did not attend (548/1,705; 32%) G2: No screening (3,231) *Phase 2 (2000-2008)*[‖] G1: Invited to screening G1-a: Attended screening (714/1,577; 45%) G1-b: Did not attend (863/1,577; 55%) G2: No screening (1,425)	10 years 8 y	G1: 53 G2: 51	G1: 936 (54.9) G2: 1,592 (49.3)	NR	NR	NR	NR	Fair
Park, 2008[41] ADDITION pilot phase	RCT; 2 practices in the United Kingdom	Without known diabetes, high risk of having DM	G1: Invited to screening (116) G2: Not invited to screening (238)	Mean: 6 weeks	G1: 58.3 (7.3) G2: 58.9 (7.2)	G1: 40 (34.5) G2: 89 (37.4)	NR	NR	G1: 31.8 (4.5) G2: 31.3 (4.1)	G1: 42 (36.2) G2: 91 (38.2)	Fair

* None of the included studies reported baseline data for screened and unscreened groups for fasting plasma glucose, HbA1c, blood pressure, or smoking. The 12-year followup of the Ely study reported mean (SD) HbA1c for the subset of participants who were diagnosed with diabetes and attended a health assessment: for those invited to screening in Phase 1 versus those unscreened in Phase 1 and invited to screening in Phase 2 (7.0 [1.7] vs. 7.4 [1.6], p=0.22).[38] The 13-year followup of the Ely study reported mean (SD) HbA1c for the subset of participants who were not diagnosed with diabetes and attended a health assessment between 2000-2003: for those invited to screening in Phase 1 versus those unscreened in Phase 1 and invited to screening in Phase 2 (5.4 [0.5] vs. 5.5 [0.7], p=0.002).[39] It also reported mean (SD) systolic (132 [16] vs. 132 [17]) and diastolic (79 [10] vs. 79 [10]) blood pressure and the number (%) of current smokers at the 2000-2003 health assessment (97 [10.6] vs. 92 [11.7]).

† Data for participant characteristics (age, %F, etc.) are from the health assessment conducted in 2000-2003 (not from the time of enrollment/baseline of the trial).

‡ Data for participant characteristics (age, %F, etc.) are from the health assessment conducted in 2000-2003 (not from the time of enrollment/baseline of the trial).

§ After the random capillary blood glucose, participants were determined to have no diabetes if result was <5.5 mmol/L (100 mg/dL). If the random capillary blood glucose was 5.5 to 11.0 mmol/L (100 to 196 mg/dL), they went on to have a fasting capillary blood glucose test (if the result was <5.5 mmol/L they were determined to have no diabetes; if the fasting glucose was 5.5-6.0 [100-106 mg/dL] and capillary HbA1c of 6.1% or higher, they went on to have a standard 75 g OGTT; if the result was 6.1 [110 mg/dL] or higher, the went on to have a standard 75 g OGTT). If the initial random capillary blood glucose was 11.1 [200 mg/dL] or higher, participants went on to have a standard 75 g OGTT.

‖ Participants not invited to screening in Phase 1 were randomized to screening invitations vs. no invitations in Phase 2.

Abbreviations: ADDITION=Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care; BMI=body mass index; BP=blood pressure; CVD=cardiovascular disease; DM=diabetes mellitus; F=female; G=group; IQR=interquartile range; HbA1c=hemoglobin A1c (or glycated hemoglobin); KQ=key question; No.=number; NR=not reported; OGTT=oral glucose tolerance test; RCT=randomized, controlled trial; SD=standard deviation; vs.=versus.

Table 4. Main Results of Studies Evaluating Screening for Diabetes That Reported Health Outcomes (KQ 1)*

Author, Year Trial Name Diagnosis of DM, No.	Mortality G1 vs. G2; HR (95% CI)	CVD Events G1 vs. G2; OR, or RR, (95% CI)	Quality of Life G1 vs. G2
Echouffo-Tcheugui, 2015[36] ADDITION-Cambridge, 7-year followup G1: 466 G2: NR	NR	7 years CVD events (MI or stroke), self-reported: 142 (12.4%) vs. 67 (13.5%), OR, 0.90 (0.71 to 1.15)	SF-8 physical health summary score,† mean (SD): 47.8 (9.8) vs. 47.8 (10.3). Beta‡ -0.33 (95% CI, -1.80 to 1.14) SF-8 mental health summary score,† mean (SD): 51.8 (8.6) vs. 52.2 (8.1). Beta‡ -0.38 (95% CI, -1.33 to 0.57) EQ-5D score,† mean (SD): 0.87 (0.16) vs. 0.87 (0.15). Beta‡ 0.002 (95% CI, -0.02 to 0.02) EuroQol visual acuity score,† mean (SD): 74.5 (16.5) vs. 73.7 (17.2). Beta‡ 0.80 (95% CI, -1.28 to 2.87)
Rahman, 2012[38] Ely, diabetic subgroup Total: 199 G1: 116 (108 screen detected) G2: 83 (26 screen detected).	G1: 0 G2: 0 Evaluation was limited to those diagnosed with diabetes who attended health assessment	Self-reported MI: 7/92 vs. 8/60, p=0.29; RR, 0.57 (0.22 to 1.49) Self-reported stroke: 3/92 vs. 5/60, p=0.19; RR, 0.39 (0.10 to 1.58) Clinical ischemic heart disease:‖ 18/92 vs. 8/60, p=0.32 ECG-confirmed ischemic heart disease:¶ 30/92 vs. 28/60, p=0.11; RR, 0.70 (0.47 to 1.04) Peripheral vascular disease:# 5/92 vs. 2/60, p=0.55; RR, 1.63 (0.33 to 8.13)	Mean SF-36§ physical function score: 67.2 (SD, 29.4) vs. 69.6 (SD 30.7); p=0.64 Mean SF-36 mental health score: 77.8 (SD, 16.5) vs. 79.7 (SD, 16.1); p=0.47 Mean EQ-5D visual analog scale (95% CI): 78 (65 to 85) vs. 79.5 (60 to 88), p=0.68
Rahman, 2012[39] Ely, nondiabetic subgroup G1: 0 G2: 0	G1: 0 G2: 0 Evaluation was limited to those not diagnosed with diabetes who attended health assessment	Self-reported MI: 28/731 vs. 29/711, p=0.9 Self-reported stroke: 13/731 vs. 12/711, p=0.7 Clinical ischemic heart disease:‖ 78/731 vs. 53/711, p=0.2	Median (IQR) SF-36** physical function score: 90 (75-95) vs. 90 (75-95); p=0.4 Median (IQR) SF-36 mental health score: 84 (68-92) vs. 84 (68-92); p=0.8 Mean EQ-5D visual analog scale (95% CI): 78.3 (77.2 to 79.4) vs. 77.7 (76.5 to 79.0), p=0.9
Simmons 2012[35] ADDITION-Cambridge G1: 466 G2: NR	10 years All-cause mortality: 1,532 vs. 377; 1.06 (0.90 to 1.25)†† Cardiovascular mortality: 482 vs. 124; 1.02 (0.75 to 1.38) Cancer mortality: 697 vs. 169; 1.08 (0.90 to 1.30) Other mortality: 353 vs. 84; 1.10 (0.87 to 1.39) Diabetes-related mortality: 75 vs. 16; 1.26 (0.75 to 2.10)	NR	NR

Table 4. Main Results of Studies Evaluating Screening for Diabetes That Reported Health Outcomes (KQ 1)*

Author, Year Trial Name Diagnosis of DM, No.	Mortality G1 vs. G2; HR (95% CI)	CVD Events G1 vs. G2; OR, or RR, (95% CI)	Quality of Life G1 vs. G2
Simmons, 2011[37] Ely G1: 51, 26, and 31 in first, second, and third rounds of screening, respectively G2: NR	*Phase 1:* 345 total deaths from 1991 to 1999, median 10-year followup (47,854 person-years) All-cause mortality: 116 vs. 229, 0.96 (0.77 to 1.20); adjusted‡‡ 0.79 (0.63 to 1.00)§§ Cancer-related mortality: 52 vs. 107; CVD mortality 41 vs. 74; other mortality 23 vs. 48 *Phase 2:* 291 total deaths from 2000 to 2008, median 8.1 y (23,144 person-years) All-cause mortality: 165 vs. 126, 1.20 (0.95 to 1.51); adjusted‡‡ 1.18 (0.93 to 1.51) §§ Cancer-related mortality 44 vs. 47; CVD mortality 68 vs. 43; other mortality 53 vs. 36	NR	NR

* None of the included studies reported on amputations, skin ulcers, visual impairment, or periodontitis.
† SF-8 scale ranges from 0 to 100 for each summary score.
ǂ Beta coefficients represent the mean difference between groups.
§ Medical Outcomes Study Short Form Health Survey, scale 0-100. Higher scores indicate better function.
ǁ Based on Rose angina questionnaire score >3.
¶ Defined by Minnesota coding of ECG.
# Defined as ABPI <0.9, for which the article reports 90% sensitivity and specificity among in symptomatic disease. The article did not report whether any of these persons had symptoms of PVD.
** Medical Outcomes Study Short Form Health Survey, scale 0-100. Higher scores indicate better function.
†† Among G1 (the screening group), nonattenders had higher all-cause mortality than attenders: HR 2.01 (1.74 to 2.32) and were younger, more obese, more likely to be men, and less likely to be taking antihypertensive medications.
‡‡ Adjusted for age, sex, and deprivation (determined using the Townsend Index, which was calculated using postcodes to determine material deprivation based on four factors derived from the 1991 UK census: unemployment, overcrowding, car ownership, and home ownership).
§§ For phase 1, comparing those who attended screening vs. controls (G1-a vs. G2), the HR for all-cause mortality was 0.64 (0.47 to 0.86) and the adjusted HR was 0.54 (0.40 to 0.74). Comparing those who did not attend screening vs. controls (G1-b vs. G2), the HR for all-cause mortality was 1.68 (1.27 to 2.22) and the adjusted HR was 1.36 (1.01 to 1.82). For phase 2, comparing those who attended screening vs. controls (G1-a vs. G2), the HR for all-cause mortality was 0.46 (0.31 to 0.69) and the adjusted HR was 0.52 (0.35 to 0.78). Comparing those who did not attend screening vs. controls (G1-b vs. G2), the HR for all-cause mortality was 1.85 (1.45 to 2.36) and the adjusted HR 1.73 (1.34 to 2.24).

Abbreviations: ABPI=Ankle-brachial pressure index; ADDITION=Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care; CI=confidence interval; CVD=cardiovascular disease; DM=diabetes mellitus; ECG=electrocardiogram; EQ-5D=EuroQol Research Foundation and LimeSurvey; G=group; HR=hazard ratio; IQR=interquartile range; KQ=key question; MI=myocardial infarction; No.=number; NR=not reported; OR=odds ratio; PVD=peripheral vascular disease; RR=relative risk; SD=standard deviation; SF-8=Short Form-8 questionnaire; SF-36=Short Form-36 questionnaire; U.K.=United Kingdom; vs.=versus.

Table 5. Results of Studies That Reported Harms of Screening for Diabetes (KQ 2)*

Author, Year Trial Name	Anxiety	Depression	Other Adverse Events
Eborall, 2007; Paddison, 2011[42, 43] ADDITION-Cambridge substudy (15 practices)	*Between group differences (95% CI) for G1 vs. G2* State Anxiety:† Initial time point:‡ -0.53 (-2.60 to 1.54), p=0.62 3-6 months: 1.51 (-0.17 to 3.20), p=0.10 12-15 months: 0.57 (-1.11 to 2.24), p=0.52 HADS anxiety:‖ Initial time point: -0.46 (-0.99 to 0.07), p=0.12 3-6 months: -0.12 (-0.55 to 0.32), p=0.61 12-15 months: -0.01 (-0.47 to 0.45), p=0.98 *G1 who screened positive for DM vs. G1 who screened negative* Met threshold for anxiety disorder (HADS anxiety score of 11 or higher) at 12-15 months: 14.3% vs. 11.3%, p=NS§	*Between group differences (95% CI) for G1 vs. G2* HADS depression:‖ Initial time point: -0.37 (-0.93 to 0.18), p=0.21 3-6 months: 0.01 (-0.51 to 0.54), p=0.96 12-15 months: 0.22 (-0.31 to 0.74), p=0.44 *G1 who screened positive for DM vs. G1 who screened negative* Met threshold for depressive disorder (HADS depression score of 11 or higher) at 12-15 months: 6.4% vs. 5.5%, p=NS§	*Between group differences (95% CI) for G1 vs. G2* Self-reported health (scale range 1-5): Initial time point: -0.02 (-0.18 to 0.14), p=0.81 3-6 months: 0.02 (-0.13 to 0.18), p=0.78 12-15 months: -0.03 (-0.20 to 0.13), p=0.70 Worry about diabetes:¶ Initial time point: 0.03 (-0.36 to 0.42), p=0.90 3-6 months: -0.11 (-0.42 to 0.19), p=0.48 12-15 months: -0.33 (-0.67 to 0.01), p=0.08
Park, 2008[41] ADDITION-Cambridge (pilot phase)	STAI anxiety score (scale range 20-80; higher score indicates more anxiety), mean (SD) G1 vs. G2 after 6 weeks 37.6 (12.2) vs. 34.1 (12.1); p=0.015 G1 diagnosed with DM (n=6) vs. G1 not diagnosed with DM: 46.7 vs. 37.0; p=0.031	NR	Self-perceived health score (scale range 1-5; higher score indicates better perceived health), mean (SD), G1 vs. G2: 2.97 (0.86) vs. 2.95 (0.87); p=0.82 Illness representation subscales: no between group difference for any measure
Rahman, 2012[38, 39] Ely	Prescribed anxiolytic drugs, n (%) *Among those without DM, 13-year followup:* G1: 5 (0.5) vs. G2: 5 (0.6), p=0.8 *Among those with DM, 12-year followup:* G1: 1 (1.1) vs. G2: 1 (1.6), p=0.78	Prescribed antidepressants, n (%) *Among those without DM, 13-year followup:* G1: 52 (5.7) vs. G2: 38 (4.8), p=0.4 *Among those with DM, 12-year followup:* G1: 4 (4.4) vs. G2: 2 (3.2), p=0.71	NR (self-reported MI, self-reported stroke, SF-36 and EQ-5D data are with the health outcomes, KQ 1)

* None of the included studies reported on harms from labeling, false-positive results, burden or inconvenience, or unnecessary testing or treatment.
† Scale range 20-80.
‡ Immediately after initial (random blood glucose) test for screening attenders, first contact for control participants.
§ Actual p value not reported but article noted that chi-square analysis showed no significant difference.
‖ Scale range 0-21.
¶ Scale range 6-24.

Abbreviations: ADDITION=Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care; CI=confidence interval; DM=diabetes mellitus; EQ-5D=EuroQol Research Foundation and LimeSurvey; G=group; HADS=Hospital Anxiety and Depression Scale; KQ=key question; MI=myocardial infarction; n=number; NR=not reported; NS=not statistically significant; SD=standard deviation; SF-36=Short Form-36 questionnaire; STAI=Short-form Spielberger State Anxiety Inventory vs.=versus.

Table 6. Characteristics of Included ADDITION-Europe Studies Evaluating Interventions for Screen-Detected Type 2 Diabetes (KQ 4)

Author, Year Trial Name Country	Group (No. Participants)	Duration of Followup, Years	Age, Mean (Range or SD), Years	No. (%) F	No. (%) Nonwhite	HbA1c Mean (%)(SD)*	BMI, Mean (kg/m^2)	Mean (SD), SBP (mmHg) DBP (mmHg); No. (%) Smokers	Quality
Charles, 2011[57] ADDITION-Denmark Denmark	G1: Intensive multifactorial treatment using medication and promotion of healthy lifestyle† (702) G2 Routine care: standard level of diabetes care according to Danish national recommendations (459)	Mean (SD) G1: 5.9 (1.6) G2: 5.8 (1.5)	G1: 59.6 (6.9) G2: 59.9 (6.8)	G1: 281 (40) G2: 190 (41)	NR	G1: 6.4 (6.0; 7.0) G2: 6.4 (6.0; 7.0)	G1: F: 31.5 (6.5); M: 30.4 (3.4) G2: F: 31.2 (6.0); M: 30.4 (4.4)	G1: 147.0 (19.1) G2: 149.8 (19.3) G1: 87.3 (10.6) G2: 88.3 (11.3) Daily G1: 215 (31) G2: 134 (30) <Daily: G1: 271 (39) G2: 169 (37)	Fair
Griffin, 2011[56] Simmons, 2012[58] van den Donk, 2013[59] Simmons, 2016[60] Griffin, 2019[61] ADDITION-Europe Denmark, U.K., the Netherlands	G1: Intensive multifactorial treatment with medications and healthy lifestyle education† (1,678) G2: Routine care according to recommendations applicable to each center (1,379)	Mean followup 5.3 (±1.6) years in main trial; 9.6 (±2.99) in posttrial followup	G1: 60.3 (6.9) G2: 60.2 (6.8)	G1: 697 (41.5) G2: 589 (42.7)	G1: 68 (4.2) G2: 88 (6.6)	G1: 7.0 (1.6) G2: 7.0 (1.5)	G1: 31.6 (5.6) G2: 31.6 (5.6)	G1: 148.5 (22.1) G2: 149.8 (21.3) G1: 86.1 (11.1) G2: 86.5 (11.3) G1: 444 (27.0) G2: 375 (27.8)	Fair
van den Donk, 2010[55] Janssen, 2009[54] ADDITION-Netherlands Netherlands	G1: 3-4 years of intensified multi-factorial treatment with medications and healthy lifestyle education† (255) G2: routine care based on national guidelines (243)	4.5 (3 for the SF-36 and the EQ-5D)	G1: 60.1 (5.4) G2: 59.9 (5.1)	G1:123 (48) G2:107 (44)	G1: 5 (2.0) G2: 3 (1.3)	G1: 7.3 (1.6) G2: 7.4 (1.7)	G1: 31.2 (5.1) G2: 30.4 (4.6)	G1: 166 (23) G2: 163 (23) G1: 90 (11) G2: 89 (10) G1: 67 (26.3) G2: 52 (21.4)	Fair

*Baseline fasting plasma glucose was not reported for ADDITION-Europe. It was only reported for ADDITION-Netherlands; for those participants, it was 8.0 Mmol/L (144 mg/dL).[54]

† Intensive Treatment Targets: HbA1c <7.0%; blood pressure ≤135/85 mmHg; total cholesterol <5.0 mmol/L (<193 mg/dL) in patients with no history of CVD; <4.5 mmol/L in patients with history of CVD.

Abbreviations: ADDITION=Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care; BMI=body mass index; CVD=cardiovascular disease; DBP=diastolic blood pressure; EQ-5D=EuroQol-5D; F=female; G=group; HbA1c=hemoglobin A1c (or glycated hemoglobin); KQ=key question; M=male; No.=number; NR=not reported; SBP=systolic blood pressure; SD=standard deviation; SF-36=Short Form 36 questionnaire; U.K.=United Kingdom.

Table 7. Results for Mortality and Cardiovascular Events From Trials Evaluating Interventions for Screen-Detected Type 2 Diabetes (KQ 4)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality G1 vs. G2; HR (95% CI)	CVD Events G1 vs. G2; HR (95% CI)
Griffin, 2011[56] Simmons, 2012[58] van den Donk, 2013[59] Simmons, 2016[60] Griffin, 2019[61] ADDITION-Europe	G1: Intensive multifactorial treatment (1,678) G2: Routine care (1,379)	**G1 vs. G2** Mean 5.3-year followup **All-cause mortality combined across countries** 104/1,678 (6.2%) vs. 92/1,377 (6.7%) HR (95% CI) 0.91 (0.69,1.21) **All-cause mortality U.K.** HR (95% CI) 0.59 (0.35,0.98) **All-cause mortality Denmark** HR (95% CI) 1.15 (0.80,1.66) **All-cause mortality Netherlands** HR (95% CI) 0.85 (0.35,2.06) **Cardiovascular-related death** 26/1,678 (1.5%) vs. 22/12,77 (1.6%) HR (95% CI) 0.88 (0.51,1.51) **Cardiovascular-related death as first CV event** 26/121 (21%) vs. 22/117 (19%) HR (95% CI) 0.83 (0.64, 1.07) **Cardiovascular-related death as second CV event** 5/33 (15%) vs. 3/38 (8%) HR (95% CI) 0.70 (0.43, 1.12) Mean 9.6-year followup **All-cause mortality combined across countries** 246/1,678 vs. 219/1,379 HR (95% CI) 0.90 (0.76, 1.07) **Cardiovascular death** 60/1,678 (3.6%) vs. 47/1,379 (3.4%) HR (95% CI) 0.97 (0.69, 1.37)	**G1 vs. G2** Mean 5.3-year followup **Composite of first cardiovascular event*** 121/1,678 (7.2%) vs. 117/1,377 (8.5%) HR (95% CI) 0.83 (0.65,1.05) P=0.12 *Subgroups* Patients <60 years: HR (95% CI) 1.12 (0.70,1.79) Patients ≥60 years: HR (95% CI) 0.70 (0.52,0.95) P>0.1 **Myocardial infarction** 29/1,678 (1.7%) vs. 32/1,377 (2.3%) HR (95% CI) 0.70 (0.41,1.21) **Stroke** 22/1,678 (1.3%) vs. 19/1,377 (1.4%) HR (95% CI) 0.98 (0.57,1.71) **Revascularization** 44/1,678 (2.6%) vs. 44/13,77 (3.2%) HR (95% CI) 0.79 (0.53,1.18) **Risk of having one CV event per 1,000 person-years** HR (95% CI) 0.83 (0.64, 1.07) **Risk of having two CV events per 1,000 person-years** HR (95% CI) 0.70 (0.43, 1.12) **Risk of having any CVD event per 1,000 person-years** HR (95% CI) 0.77 (0.58, 1.02) **Amputations with CV events** With 1st CV event: G1 (0) G2 (0); with 2nd CV event G1 (0) G2 (1); with 3rd CV event G1 (1) G2 (0) Mean 9.6-year followup **Composite of first cardiovascular event*** 232/1,678 (13.8%) vs. 211/1,379 (15.3%) HR (95% CI) 0.87 (0.73, 1.04) p=0.14 *Subgroups* Patients <60 years: HR (95% CI) 1.19 (0.86, 1.65) Patients ≥60 years: HR (95% CI) 0.74 (0.59, 0.93) p=0.046 **Myocardial infarction** 48/1,678 (2.9%) vs. 48/1,379 (3.5%) HR (95% CI) 0.72 (0.48, 1.08)

Table 7. Results for Mortality and Cardiovascular Events From Trials Evaluating Interventions for Screen-Detected Type 2 Diabetes (KQ 4)

First Author, Year Trial Name	G1 (N) G2 (N)	Mortality G1 vs. G2; HR (95% CI)	CVD Events G1 vs. G2; HR (95% CI)
			Stroke 38/1,678 (2.3%) vs. 43/1,379 (3.1%) HR (95% CI) 0.74 (0.48, 1.16) **Revascularization** 80/1,678 (4.8%) vs. 73/1,379 (5.3%) HR (95% CI) 0.87 (0.64, 1.17) **Amputations** 6/1,678 (0.4%) vs. 0/1,379 (0%) HR (95% CI) NA

*Primary outcome: Any of cardiovascular death, myocardial Infarction, stroke, revascularization, and amputation.

Abbreviations: ADDITION=Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care; CI=confidence interval; CV=cardiovascular; CVD=cardiovascular disease; G=group; HR=hazard ratio; KQ=key question; N=number; U.K.=United Kingdom.

Table 8. Characteristics of Included Trials of Interventions for Individuals With Recently Diagnosed Type 2 Diabetes (KQ 5)

Author, Year Trial Name Country	Group (No. Participants)	Followup	Duration of Diabetes, Mean (Range or SD)	Age, Mean (Range or SD), Years	No. (%) F	No. (%) Nonwhite	HbA1C Mean (%)(SD)	FPG Mean	BMI, Mean (kg/m^2)	Mean (SD), SBP (mmHg) DBP (mmHg); No. (%) Smokers	Quality
Davies, 2008[113] Khunti, 2012[117] DESMOND U.K.	G1: 6-hour group education session (delivered in 1-day or 2 half-days) focusing on lifestyle, food, physical activity and cardiovascular risk factors (437) G2: Usual care (including some form of access to diabetes education) (387)	1 y	≤12 weeks	G1: 59.0 (28-87) G2: 60.0 (29-87)	G1: 204 (47) G2: 168 (43)	G1: 39 (9) G2: 60 (15.5)	G1: 8.3 (2.2) G2: 7.9 (2.0)	NR	G1: 32.3 (6.1) G2: 32.4 (6.5)	G1: 141.1 (18.5) G2: 140.0 (16.6) G1: 82.4 (10.5) G2: 81.0 (10.5) G1: 57 (14) G2: 53 (16)	Fair
Yang, 2013[118] China*	G1: Intensive multifactorial intervention including medications and healthy lifestyle, advice (n=75). **Targets:** HbA1c <7%, FBG <7.0 mmol/L; BP 130/85; total cholesterol <4.66 mmol/L G2: Conventional therapy (n=75) outpatient management without targets	7 years	G1: 0.24 (.21) years G2: 0.26 (0.22) years	G1: 49.5 (7.8) G2: 50.3 (7.2)	G1: 39 (52) G2: 35 (47)	NR	G1: 8.8 (1.6) G2: 8.6 (1.7)	Mmol/L G1: 9.98 (2.81) G2: 9.95 (0.74)	G1: 24.8(2.1) G2: 23.3(1.9)	G1: 129.1(15.2) G2: 128.8 (11.3) G1: 79.8 (11.8) G2: 76.9 (6.4) G1: 24 (34) G2: 33 (48)	Fair
Holman, 2008†[114] UKPDS U.K.	G1: Intensive therapy with sulfonylurea or insulin (2,729) G2: Intensive therapy with metformin (342) G3: Conventional therapy primarily with diet for normal weight (1,138) G4: Conventional therapy primarily with diet for overweight group (411)	10-yr post-trial monitoring	Reported as newly diagnosed	G1: 63 (9) G2: 64 (9) G3 normal weight: 63 (9) G4 overweight: 64 (9)	G1: 870 (41.1) G2: 152 (54.5) G3 normal weight: 348 (39.5) G4 overweight: 167 (54.0)	G1: 401 (18.9) G2: 44 (15.8) G3 normal weight: 170 (19.3) G4 overweight: 47 (15.2)	Median (IQR) G1: 7.9 (6.8-9.2) G2: 8.4 (7.2-9.7) G3: 8.5 (7.3-9.7) G4 t: 8.9 (7.5-10.0) G1 V G3: p<0.001	Mg/dl G1: 161 (61) G2: 177 (64) G3: 178 (58) G4 : 182 (55) G1 vs. G3: p<0.001	G1: 29.3 (5.5) G2: 31.7 (5.4) G3: 28.7 (5.6) G4: 32.2 (5.7) G1 vs. G3: p<0.005	G1: 139 (20) G2: 141 (18) G3: 138 (21) G4 : 139 (22) G1: 77 (10) G2: 78 (10) G3: 77 (10) G4: 77 (10) NR	Good

Table 8. Characteristics of Included Trials of Interventions for Individuals With Recently Diagnosed Type 2 Diabetes (KQ 5)

Author, Year Trial Name Country	Group (No. Participants)	Followup	Duration of Diabetes, Mean (Range or SD)	Age, Mean (Range or SD), Years	No. (%) F	No. (%) Nonwhite	HbA1C Mean (%)(SD)	FPG Mean	BMI, Mean (kg/m^2)	Mean (SD), SBP (mmHg) DBP (mmHg); No. (%) Smokers	Quality
Holman, 2008[115] UKPDS, 2008[116] Hypertension in diabetes Study, embedded in UKPDS‡	G1: Tight BP control; BP target <150/85 mmHg, main treatment (758): ACE inhibitor, captopril (400); beta-blocker, atenolol (358) G2: Less-tight BP control, target <180/105 mmHg (without use of ACE inhibitors or beta-blockers) (390) 10-year, post-trial followup (n=884)	Median 8.4	Mean years (IQR) G1: 2.7 (1.0-4.2) G2: 2.5 (1.0-4.4)	G1: 56.4 (8.1) G2: 56.5 (8.1)	G1: 348 (46) G2: 163 (42)	G1: 107 (14) G2: 46 (12)	G1: 6.9 (1.7) G2: 6.8 (1.5)	Median (IQR) mmol/L G1: 7.4 (6.1-9.2) G2: 7.4 (6.2-9.8)	G1: 29.8 (5.5) G2: 29.3 (5.5)	G1: 159 (20) G2: 160 (22) G1: 94 (10) G2: 94 (9) Current smoker G1: 171 (23) G2: 85 (22)	Good
UKPDS Group 1998[4] UKPDS† U.K.	G1: 23 centers: Intensive glucose control with sulphonylureas§ or insulin (2,729) G2: 1st 15 centers: Intensive glucose control with chlorpropamide (100-500 mg/d) (619) G3: 1st 15 centers: Intensive glucose control with glibenclamide (2.5-20 mg/d) (615) G4: 1st 5 centers: Intensive blood glucose control with insulin (911) G5a: Conventional care vs. G1, diet alone (1,138) G5b: Conventional care vs. G2, G3, G4 diet alone (896)	Median 10 years	Reported as newly diagnosed	G1: 53.2 (8.6) G2: 54 (9) G3: 54 (8) G4: 54 (8) G5a: 53.4 (8.6) G5b: 54 (9)	G1: 1075 (39.3) G2: 260 (42.0) G3: 234 (38.0) G4: 346 (38.0) G5a: 433 (38.0) G5b: 341 (38.0)	G1: 519 (19) G2: 130 (21) G3: 98 (16) G4: 164 (18) G5a: 216 (19) G5b:152 (17)	G1: 7.09 (1.54) G2: 6.3 (1.4) G3: 6.3 (1.3) G4: 6.1 (1.1) G5a: 7.05 (1.42) G5b: 6.2 (1.2)	Mmol/L Median (IQR) G1: 8.1 (7.1-9.8) G2: 8.0 (7.1-9.7) G3: 8.0 (7.2-9.6) G4: 8.1 (7.1-9.9) G5a: 8.0 (7.1-9.6) G5b: 7.9 (7.1-9.4)	G1: 27.5 (5.1) G2: 27.0 (4.9) G3: 27.4 (5.0) G4: 27.0 (4.8) G5a: 27.8 (5.5) G5b: 27.5 (5.3)	G1: 135 (20) G2: 136 (19) G3: 136 (19) G4: 136 (20) G5a: 135 (19 G5b: 136 (19) G1: 83 (10) G2: 83 (10) G3: 83 (10) G4: 83 (11) G5a: 82 (10) G5b: 83 (10) Current G1: 30% G2: 31% G2: 30% G3: 30% G5a: 31% G5b: 32%	**Good**

Table 8. Characteristics of Included Trials of Interventions for Individuals With Recently Diagnosed Type 2 Diabetes (KQ 5)

Author, Year Trial Name Country	Group (No. Participants)	Followup	Duration of Diabetes, Mean (Range or SD)	Age, Mean (Range or SD), Years	No. (%) F	No. (%) Nonwhite	HbA1C Mean (%)(SD)	FPG Mean	BMI, Mean (kg/m^2)	Mean (SD), SBP (mmHg) DBP (mmHg); No. (%) Smokers	Quality
UKPDS group, 1998[119] UKPDS[†] (Metformin for overweight substudy) U.K.	G1: Intensive blood glucose control with metformin (glucose target FPG <6 mmol/l) (342) G2: Conventional care with diet alone (411)	Median 10.7 years	Reported as newly diagnosed	G1: 53 (8) G2: 53 (9)	G1: 185 (54.1) G2: 218 (53.0)	G1: 51 (14.9) G2: 57 (13.9)	G1: 7.3 (1.5) G2: 7.1 (1.5)	G1: 8.1 (7.2-9.8) G2: 8.0 (7.1-9.3)	G1: 31.6 (4.8) G2: 31.8 (4.9)	G1: 140 (18) G2: 140 (18) G1: 85 (9) G2: 86 (10) Current G1: 85 (25) G2: 103 (25)	Good

[a] Stepped approach to glucose medication treatment: metformin for patients with BMI≥24 kg/m^2; glipizide for patients with BMI< BMI≥24 kg/m^2 ; followed by a combination of these; followed by acarbose, followed by insulin. For BP control: Captopril followed by addition of calcium antagonist, followed by addition of diuretics or B-blockers Lipids: Statins or Chinese herb complex, aspirin.

[†] Unable to determine duration of diabetes for the UKPDS reported as all patients were newly diagnosed with type 2 diabetes.

[‡] Included the hypertension in diabetes study (embedded in the UKPDS) because participants were newly diagnosed with diabetes at the time of entry into the UKPDS study (even though they had a mean duration of diabetes of 2.6 years at the time of randomization in the hypertension study).

[§] Chlorpropamide, glibenclamide, or glipizide.

Abbreviations: ACE=angiotensin-converting enzyme; BMI=body mass index; BP=blood pressure; DBP=diastolic blood pressure; F=female; FBG=fasting blood glucose; FPG=fasting plasma glucose; G=group; HbA1c=hemoglobin A1c (or glycated hemoglobin); IQR=interquartile range; KQ=key question; No.=number; NR=not reported; SBP=systolic blood pressure; SD=standard deviation; U.K.=United Kingdom; UKPDS=United Kingdom Prospective Diabetes Study; vs.=versus.

Table 9. Summary of Evidence on Screening for Abnormal Glucose and Diabetes

Key Question and Topic	No. of Studies (k), No. of Observations (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 1. Benefits of screening	k=2 RCTs (5 publications), 25,120 participants	For invitations to screening with a stepwise approach (starting with random glucose) or OGTT every 5 years compared with controls, no significant difference between groups for all-cause or cause-specific mortality at 10 years, or self-reported CVD events or quality of life at 7-13 years.	Consistency unknown (the 2 trials evaluated different screening approaches); imprecise	1 Good 1 Fair	Duration of followup may be too short; for outcomes other than mortality, missing data from most participants; reporting bias not detected.	*Low* for no benefit for mortality. *Insufficient* for all other outcomes.	Asymptomatic adults 40-69; trials evaluated invitations to screening for DM; neither assessed screening for prediabetes or focused on fasting glucose or A1c as the initial test; neither reported race/ethnicity; mean BMI was 30-31 (NR in 1 trial).
KQ 2. Harms of screening	k=3 RCTs (5 publications), 9,328 participants*	No significant differences between screening and control groups for anxiety, depression, worry, or self-reported health. Possible short-term increases in anxiety (at 6 weeks) among persons screened and diagnosed with DM vs. those not diagnosed with DM (STAI scores: 46.7 vs. 37.0; p=0.031). No trials reported on labeling, harms from false-positive results, burden, inconvenience, or unnecessary testing and treatment.	Consistency unknown (no 2 studies used similar measures at similar timepoints); imprecise	Fair (at least medium risk of bias)	Missing data from many participants; heterogeneity of measures used and timing of assessments; reporting bias not detected.	*Low* for anxiety, depression, worry, or self-reported health. *Insufficient* for other outcomes†	Asymptomatic adults 40-69 at high risk of diabetes

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Key Question and Topic	No. of Studies (k), No. of Observations (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 3. Intervening at time of screen-detection vs. later	k=0, 0	No eligible studies	NA	NA	NA	Insufficient	NA
KQ 4. Benefits of interventions for screen-detected DM	k=1 RCT (8 publications), 3,057 participants	ADDITION-Europe found no difference over 5 to 10 years between an intensive multifactorial intervention aimed at controlling glucose, blood pressure and cholesterol and routine care in the risk of all-cause mortality, cardiovascular-related mortality, cardiovascular events, quality of life, nephropathy, retinopathy, or neuropathy.	Consistency unknown (single study); imprecise	Fair	Followup may have been too short; decisions about medication choices were made by individual physicians and patients; reporting bias not detected	Low for no benefit	Adults age 40 to 69 years with screen-detected DM; mean baseline HbA1C 7.0% (median 6.5%); mean BMI 31.5; participants were predominantly white; screening risk questionnaire followed by random glucose or invitation to have OGTT.

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Key Question and Topic	No. of Studies (k), No. of Observations (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 4. Benefits of interventions for prediabetes	k=38 (56 publications), 36,393 participants	Most trials reported mortality or CVD events after ≤6 years and reported few events with no difference between groups. Two trials had ≥10 years of followup: Finnish DPP (n=505) found no statistically significant difference between groups for mortality or composite CVD events over 10 years[‡] and Da Qing (n=576) found no statistically significant difference between lifestyle and control groups at 20 years,[§] but rates were lower in the combined intervention groups at 23 years for all-cause mortality (28.1% vs. 38.4%; HR 0.71 [95% CI, 0.51 to 0.99]) and CVD-related mortality (11.9% vs. 19.6%; HR 0.59 [95% CI, 0.36 to 0.96]); rates remained lower at 30-year followup. For QOL, 5 trials suggested no clinically meaningful benefit.	Reasonably consistent for CVD events, mortality, and QOL; consistency unknown for aggregate microvascular outcome (single study); imprecise	Fair	Followup duration too short in most studies; at least medium risk of bias in the Da Qing trial,[‖] and relatively few participants; heterogeneity of measures used to assess QOL; reporting bias not detected	Low for long-term mortality benefit after 20 years	Adults with prediabetes; the trial reporting reduction in CVD events associated with acarbose included a population at high risk of CVD; the Da Qing trial showing long-term mortality benefit associated with a lifestyle intervention was conducted in China and used a 6-year lifestyle intervention.

Table 9. Summary of Evidence on Screening for Abnormal Glucose and Diabetes

Key Question and Topic	No. of Studies (k), No. of Observations (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 5. Benefits of interventions for recently diagnosed DM	k=5 RCTs[¶] (8 publications), 5,138 participants	Intensive glucose control with sulfonylureas or insulin decreased the risk for all-cause mortality (RR, 0.87 [95% CI, 0.79 to 0.96]), diabetes-related mortality (RR, 0.83 [95% CI, 0.73 to 0.96]) and myocardial infarction (RR, 0.85 [95% CI, 0.74 to 0.97]) over 20 years (10-year post-trial assessment) but not at shorter followup. For overweight people, intensive glucose control with metformin decreased the risk for all-cause mortality (RR, 0.64 [95% CI, 0.45 to 0.91]), diabetes-related mortality [RR, 0.58 [95% CI, 0.37 to 0.91]) and myocardial infarction (RR, 0.61 [95% CI, 0.41 to 0.89]) at 10-year followup, and benefits were maintained longer term.[#]	Consistency unknown;[**] precise for mortality and CVD outcomes; imprecise for other outcomes	Good	The longer-term results presented were from 10-year post-trial monitoring. Only one lifestyle intervention was included with followup for only 3 years and few clinical events. Reporting bias was not detected. Duration of diabetes at baseline was NR in the UKPDS.	Moderate for improved long-term health outcomes	Most of the data is from UKPDS, conducted from 1977-1997; 4 of the included studies were from the U.K.; participants were predominantly white

Table 9. Summary of Evidence on Screening for Abnormal Glucose and Diabetes

Key Question and Topic	No. of Studies (k), No. of Observations (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 6. Harms of interventions for diabetes	k=4 RCTs (6 publications), 5,402 participants	Overall, harms were generally sparsely reported, rare, and (when reported) not significantly different between groups. UKPDS reported major hypoglycemic events in 1%-1.8% of participants receiving sulfonylureas or insulin (vs. 0.7% in the conventional care group)	Unknown consistency; imprecise	Fair	Included studies all assessed different interventions; reporting bias not detected	Low	Screen-detected or newly diagnosed type 2 diabetes

Table 9. Summary of Evidence on Screening for Abnormal Glucose and Diabetes

Key Question and Topic	No. of Studies (k), No. of Observations (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 6. Harms of interventions for prediabetes	k=21 RCTs (38 publications), 32,468 participants	Lifestyle interventions: 2 studies found no or few musculoskeletal adverse events; DPP found higher rates of musculoskeletal symptoms among the intensive lifestyle intervention group. Medications: no increased risk of hypoglycemic events vs. placebo in 5 trials assessing 5 different medications (liraglutide, sitagliptin, metformin, nateglinide, and rosiglitazone+ metformin). Six pharmacologic trials found higher rates of GI adverse events vs. controls: metformin (k=3), and acarbose (k=2), and liraglutide (k=1).	Lifestyle interventions: inconsistent, imprecise Pharmacologic interventions: reasonably consistent; imprecise	Fair	Sparse reporting of harms (of 38 studies of interventions for prediabetes, 21 reported on harms)	Low	Adults with screen-detected or newly diagnosed prediabetes; most studies reporting harms assessed pharmacologic interventions

Table 9. Summary of Evidence on Screening for Abnormal Glucose and Diabetes

Key Question and Topic	No. of Studies (k), No. of Observations (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 7. Interventions for prediabetes to delay or prevent progression to diabetes	Lifestyle: k=23 RCTs (33 publications), 12,915 participants Pharmacologic: k=15 RCTs (23 publications), 24,295 participants	Lifestyle interventions associated with reduction in diabetes (k=23, pooled RR, 0.78 [95% CI, 0.69 to 0.88]).[††] Pooled RRs 0.63 (95% CI, 0.50 to 0.81) for followup <1 year, 0.58 (95% CI, 0.41 to 0.82) for followup 1-2 years, and 0.81 (95% CI, 0.73 to 0.89) for followup >2 years. For medications, metformin, TZDs, and AGIs were all associated with a reduction in diabetes (pooled RRs 0.73 [0.64, 0.83], 0.50 [0.28, 0.92], and 0.64 [0.43, 0.96], respectively.[‡‡]	Reasonably consistent (except for TZDs and AGIs); precise for lifestyle interventions and metformin, imprecise for TZDs and AGIs	Good: 6 Fair: 30	Heterogeneity in approaches to defining prediabetes; higher rates of dropout or nonadherence in studies of alpha glucosidase inhibitors; reporting bias not detected	High for lifestyle interventions and metformin (for benefit) Low for other medications[§§] (for benefit)	Asymptomatic adults age 40s to 60s years; most trials evaluated high contact lifestyle interventions; mean baseline BMI ranged from 24 to 39 kg/m^2

Table 9. Summary of Evidence on Screening for Abnormal Glucose and Diabetes

Key Question and Topic	No. of Studies (k), No. of Observations (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 8. Change in health outcomes that results from reduction in DM incidence after interventions for prediabetes	k=8 (17 publications), 23,489 participants	Two trials had >5-year followup and 1 had >10-year followup. 1 trial (Da Qing, n=576) reported reduction in both diabetes incidence and long-term adverse health outcomes with more than 5 years followup, finding that a 6-year lifestyle intervention yielded an absolute decrease in diabetes incidence of 24% (over 6 years) and was associated with 10% fewer deaths and 8% fewer cardiovascular deaths over 30 years.	Consistency unknown (single study with adequate long-term followup); imprecise	Fair	Most trials had insufficient followup to assess long-term health outcomes; at least medium risk of bias in the Da Qing trial;[III] and relatively few participants	Low	Trials in U.S. and other highly developed countries had insufficient followup; Da Qing trial was conducted in China

Table 9. Summary of Evidence on Screening for Abnormal Glucose and Diabetes

Key Question and Topic	No. of Studies (k), No. of Observations (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 9. Interventions for prediabetes and other intermediate outcomes	Lifestyle: k=28 (41 publications), 14,671 participants Pharmacologic: k=13 (25 publications), 26,619 participants	Lifestyle interventions: associated with reduced SBP and DBP (pooled WMD -1.7 mmHg [95% CI, -2.6 to -0.8] and -1.2 mmHg [95% CI, -2.0 to -0.4], respectively), weight (pooled WMD -1.2 kg [95% CI, -1.6 to -0.7]), and BMI (pooled WMD -0.54 kg/m^2 [95% CI, -0.76 to -0.33]). Medications: most trials found no statistically significant association between hypoglycemic agents and changes in blood pressure or lipids,¶¶ but found reduction in weight and BMI## (except TZDs were associated with weight gain: pooled WMD 1.9 kg [95% CI, 0.8 to 3.1]).	Lifestyle: reasonably consistent; precise Hypoglycemic medications: inconsistent or consistency unknown (depending on the medication); imprecise	Good: 5 Fair: 33	Outcomes were often among many secondary outcomes and not the primary focus of trials; Substantial or considerable statistical heterogeneity in some meta-analyses for weight, BMI, and lipids; reporting bias not detected	Lifestyle: High for benefit*** Medications: Low for no benefit for blood pressure and lipids; moderate for weight loss with metformin and weight gain with TZDs	Asymptomatic adults age 40s to 60s years; most trials evaluated high-contact lifestyle interventions; mean baseline BMI ranged from 24 to 39 kg/m^2 (and was >30 in most)

***** Comprising 7,380 participants surveyed from all 5 control practices and 10 intervention practices in ADDITION-Cambridge (although the number responding for any given timepoint and outcome measure ranged from 2,667 to 3,654), 1,594 from Ely (1442 without and 152 with diabetes), and 354 from the ADDITION-Cambridge pilot.

† Including labeling, harms from false-positive results, burden, inconvenience, or unnecessary testing and treatment.

ǂ The Finnish DPP (n=505) found no statistically significant difference between groups for all-cause mortality (2.2 vs. 3.8 deaths per 1,000 person-years; HR, 0.57 [95% CI, 0.21 to 1.58]) or composite CVD events (incident fatal and nonfatal acute coronary events, coronary heart disease, stroke, and hypertensive disease) (22.9 vs. 22.0 events per 1,000 person-years; HR, 1.04 [95% CI, 0.72 to 1.51]) over 10 years of followup.[47]

§ Da Qing trial found no significant difference between lifestyle groups and control for all-cause mortality (25.0% vs. 29.3%; HR, 0.96 [95% CI, 0.65 to 1.41]) or CVD-related mortality (12% vs. 17%; HR, 0.83 [95% CI, 0.48 to 1.40]) at 20 years, but rates were significantly lower in the combined intervention group at 23 years for all-cause mortality (28.1% vs. 38.4%; HR, 0.71 [95% CI, 0.51 to 0.99]) and CVD-related mortality (11.9% vs. 19.6%; HR, 0.59 [95% CI, 0.36 to 0.96]).

ǁ Unclear randomization and allocation concealment methods; baseline differences for smoking that bias results in favor of intervention.

Table 9. Summary of Evidence on Screening for Abnormal Glucose and Diabetes

¶ Three of the trials were related to the U.K. Prospective Diabetes Study (UKPDS), which was a randomized multicenter trial that ran for 20 years (from 1977 to 1997) in 23 sites across the United Kingdom.
# Tighter control of BP vs. less tight control (<150/85 vs. <180/105) decreased the risk of diabetes-related mortality (RR, 0.68 [95% CI, 0.49-0.94]) and stroke (RR, 0.56 [95% CI, 0.35–0.89]) at 9 years followup but the benefits were not maintained over longer term followup.
** Single study for each intervention and outcome, with most evidence of benefit coming from UKPDS trials.
†† Estimated number needed to treat (NNT) of 9 over 15 years.
‡ Estimated NNTs were 13 over 3 years and 8 over 15 years for metformin.
§§ Downgrading for imprecision and inconsistency for TZDs and alpha glucosidase inhibitors and for risk of bias for alpha glucosidase inhibitors.
‖ Unclear randomization and allocation concealment methods; baseline differences for smoking that bias results in favor of intervention.
¶¶ For some medications (rosiglitazone, acarbose) a single trial reported a statistically significant reduction in blood pressure, but the finding has not been replicated.
Trials reporting reduction in weight or BMI assessed metformin, acarbose, or liraglutide.
*** Presence of dose response increased the strength of evidence for some outcomes (i.e., greater improvement with high contact interventions).

Abbreviations: ADDITION=Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care; AGI=alpha glucosidase inhibitor; BMI=body mass index; BP=blood pressure; CI=confidence interval; CVD=cardiovascular disease; DBP=systolic blood pressure; DM=diabetes mellitus; G=group; HR=hazard ratio; k=number; KQ=key question; n=number; NA=not applicable; NNT=number needed to treat; NR=not reported; OGTT=oral glucose tolerance test; QOL=quality of life; RCT=randomized, controlled trial; RR=relative risk; SBP=systolic blood pressure; STAI=State-Trait Anxiety Inventory; TZD=thiazolidinedione; U.K.=United Kingdom; UKPDS=United Kingdom Prospective Diabetes Study; U.S.=United States; WMD=weighted mean difference.

Appendix A Table 1. Incidence of Diabetes-Related Conditions in the UKPDS Conventional Care Arm[1]

Outcome	n With Outcome (total N=1,138)	Absolute Risk, Events per 1,000 Patient-Years
All-cause mortality	213	18.9
Diabetes-related deaths	129	11.5
Myocardial infarction	188	17.4
Stroke	55	5.0
Amputation for health from PVD	18	1.6
Death from renal disease	2	0.2
Renal failure	9	0.8
Blind in one eye	38	3.5

Abbreviations: n/N=sample size; PVD=peripheral vascular disease; UKPDS=United Kingdom Prospective Diabetes Study.

Appendix A Table 2. Screening Recommendations of Other Groups

Organization, Year	Screening Recommendation	Risk Factors Considered	Frequency of Screening
American Diabetes Association (ADA), 2018[2]	Screen all asymptomatic adults for DM risk. Universal blood sugar screening for all adults ≥45 years of age regardless of risk factors. Regardless of age, screen overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) adults with ≥1 risk factor.	Close relative with DM, high-risk race/ethnicity, history (Hx) of CVD, hypertension, HDL cholesterol level <35 mg/dL (0.90 mmol/L), triglyceride level >250 mg/dL (2.82 mmol/L), POS, physical inactivity, other clinical conditions associated with insulin resistance	If normal, repeat at a minimum of 3-year intervals. Annual screening for patients with prediabetes. Screen women with a Hx of GDM at ≤3-year intervals
International Diabetes Federation (IDF), 2017[3]	No universal blood sugar screening. Screen people above 40 to 45 years of age and/or with high-risk factors using a locally validated screening test such as the FINDRISC score. If unavailable, use fasting blood glucose.	Family Hx of diabetes, obesity, increased waist circumference, and hypertension	If normal, repeat at ≤3 year
The Royal Australian College of General Practitioners (RACGP), 2016-2018[4]	No universal blood sugar screening. Screen for risk with AUSDRISK at age ≥40. Risk assessment should begin from 18 years of age in Aboriginal and Torres Strait Islander peoples. Screen individuals with ≥1 risk factors.	AUSDRISK score of ≥12, history of previous cardiovascular event, history of GDM, polycystic ovary syndrome, on antipsychotic drugs	Repeat screening every 3 years regardless of age, individuals at high risk with IGT or IFG should be screened annually
American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE), 2015[5]	Universal blood sugar screening for adults aged ≥45 regardless of risk factors. Screening for high-risk groups	CVD or family Hx of type 2 DM; all obese adults; overweight with additional risk factors; sedentary lifestyle; at-risk racial/ethnic groups; HDL <35 mg/dL (0.90 mmol/L) and/or TG >250 mg/dL (2.82 mmol/L); IGT or IFG and/or metabolic syndrome; POS, acanthosis nigricans, or nonalcoholic fatty liver disease; hypertension; Hx of GDM or baby >9 lbs; antipsychotic therapy; chronic glucocorticoid exposure; sleep disorders in the presence of glucose intolerance	Repeat screening every 3 years with annual screening for individuals with ≥2 risk factors
Institute for Clinical Systems Improvement (ICSI), 2014[6]	No universal blood sugar screening. Screen people with a BMI ≥25 kg/m^2 and ≥1 risk factor regardless of age. Regardless of age, screen asymptomatic patients with increased cardiovascular risk	High-risk race/ethnicity; Hx GDM or baby >9 lbs; POS; prediabetes as defined by IFG, IGT or A1c on previous testing; Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans); Hx of close relative with DM	At least annual monitoring for the development of diabetes in those with prediabetes

Appendix A Table 2. Screening Recommendations of Other Groups

Organization, Year	Screening Recommendation	Risk Factors Considered	Frequency of Screening
Canadian Diabetes Association, 2013[7]	Annual DM risk assessment; universal blood sugar screening for adults aged ≥ 40 regardless of risk factors and those at high risk using a risk calculator. More frequent and/or earlier screening for those at very high risk or in people with additional risk factors	Close relative with type 2 DM; high-risk racial/ethnic group; Hx of prediabetes, GDM, delivery of a macrosomic infant; presence of end organ damage complications associated with diabetes, vascular risk factors; POS; acanthosis nigricans; obstructive sleep apnea; psychiatric disorders; HIV; use of drugs associated with diabetes; other secondary causes	Screen every 3 years for adults ages ≥40 years regardless of risk factors and for those at high risk. More frequent and/or earlier screening for those at very high risk using a risk calculator or in people with additional risk factors.
The European Society of Cardiology (ESC), 2013[8]	No universal blood sugar screening. Screen for DM risk using a diabetes risk score (e.g., the FINDRISC) followed by diagnosis testing. In CVD patients, no diabetes risk score is needed but an OGTT is indicated if HbA1c and/or FPG are inconclusive.	NA	NR
Canadian Task Force on Preventive Health Care, 2012[9]	No universal blood sugar screening. Screen for DM risk using the FINDRISC or the CANRISK.	NA	For adults at high risk, screen every 3-5 years with HbA1c. For adults at very high risk screen annually with HBA1c.
National Institute for Health and Care Excellence (NICE), 2012[10] (intensive lifestyle-change programs and metformin sections updated in 2017) and U.K. National Screening Committee (UKNSC), 2013[11]	No universal blood sugar screening (UKNSC). Use a validated computer-based risk assessment (or a validated self-assessment questionnaire) to identify people at high risk of type 2 DM (NICE). Individuals identified as high risk should be screened. Screen those age 25 years or older of South Asian or Chinese descent whose BMI is >23 kg/m^2.	NA	Repeat screening every 5 years for those at low risk, every 3 years for those at moderate risk (a high-risk score, but with a fasting plasma glucose <5.5 mmol/l [<99 mg/dL], or HBA1c <42 mmol/mol). Annual screening for those at high risk (a high-risk score and fasting plasma glucose of 5.5-6.9 mmol/l [99-125], or HbA1c of 42-47 mmol/mol).

Abbreviations: A1c=glycated hemoglobin; AACE/ACE=American Association of Clinical Endocrinologists and American College of Endocrinology; ADA=American Diabetes Association; AUSDRISK=Australian Type 2 Diabetes Risk Assessment Tool; BMI=body mass index; CANRISK=Canadian Diabetes Risk Assessment Questionnaire; CVD=cardiovascular disease; DM=diabetes mellitus; ESC=European Society of Cardiology; FINDRISC=Finnish Diabetes Risk Score; FPG=fasting plasma glucose; GDM=gestational diabetes mellitus; HbA1c/HBA1c=hemoglobin A1c; HDL=high-density lipoproteins; HIV=human immunodeficiency virus; HIV=human immunodeficiency virus; Hx=history; ICSI=Institute for Clinical Systems Improvement;

Appendix A Table 2. Screening Recommendations of Other Groups

IDF=International Diabetes Federation; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; NA=not applicable; NICE=National Institute for Health and Care Excellence; NR=not reported; OGTT=oral glucose tolerance test; POS=polycystic ovary syndrome; RACGP=The Royal Australian College of General Practitioners; TG=triglycerides; UKNSC=U.K. National Screening Committee.

Additional Background

Other treatments to reduce CVD risk and microvascular complications. Because patients with prediabetes and diabetes are at higher risk for CVD and microvascular complications, screening and treating for conditions such as hyperlipidemia, hypertension, and tobacco abuse are recommended.[12] Treatments to decrease cardiovascular risk can include antihypertensives, statins, and aspirin. Management to decrease microvascular complications includes routine eye exams for retinopathy, urinary albumin excretion for nephropathy, and foot exams for neuropathy.[6]

Aspirin therapy. The ADA recommends that aspirin (75 to 162 mg daily) may be considered for primary prevention in people with diabetes who are at increased cardiovascular risk after a discussion on the benefits versus increased risk of bleeding.[13] The American Academy of Family Practice (AAFP) endorses the USPSTF's recommendation to initiate aspirin therapy for individuals between the ages of 50 and 59 years with at least a 10 percent 10-year risk (calculated using the pooled cohort equations) of CVD.[14] The 10-year risk calculation incorporates presence or absence of diabetes.

Hypertension treatment. Initial antihypertensive therapy for diabetics with hypertension includes diuretics, calcium channel blockers, and an angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB). Either an ACE inhibitor or an ARB is recommended for diabetic patients with microalbuminuria.[12] There is disagreement, however, about optimal blood pressure targets for hypertensive patients, a controversy that is important for individuals newly diagnosed with diabetes through screening whose 10-year risk of developing CVD is at least 10 percent only because of their new diabetes diagnosis.

In 2017, the American Heart Association and American College of Cardiology jointly published blood pressure targets that were lower than those of most other organizations.[15] The two professional organizations recommended that hypertensive individuals with CVD or a 10-year atherosclerotic CVD (ASCVD) risk of at least 10 percent should have a blood pressure target of less than 130/80 and lower risk individuals should have a blood pressure goal below 140/90. In response, the ACP and the AAFP jointly recommended less aggressive blood pressure targets for people with hypertension age 60 years or older based on the results of a systematic review they performed.[16, 17] The ACP and AAFP recommended a systolic blood pressure goal of 150 for those with lower CVD risk and a systolic blood pressure goal of less than 140 for those with a history of stroke, history of transient ischemic attack, or high cardiovascular risk. The ADA now recommends that blood pressure targets be individualized through a shared decision making process that addresses CVD risk, potential adverse effects of antihypertension medications, and patient preferences.[13] They note that a target of <130/80 may be appropriate for those with diabetes and higher CVD risk (10-year ASCVD risk >15%) and recommend to treat to a target of <140/90 for those with lower 10-year risk.[13]

For individuals with a 10-year ASCVD risk of at least 10 percent prior to being screened for diabetes, screening results would not alter blood pressure targets because they are already over the threshold for lower targets. However, for individuals for whom a diabetes diagnosis could increase their 10-year risk (to above 10%), the screening results can potentially alter blood pressure targets.

Contextual Questions

CQ 1. Are there risk assessment tools that are feasible for use in primary care settings, accurately predict the risk of prediabetes or type 2 diabetes, and have been externally validated in U.S. populations?

Several risk prediction models have been developed or validated using U.S. populations to assess the risk of developing prediabetes[18] or diabetes.[19-21] These models vary in complexity, and most have not been validated in diverse populations.[19] They also differ in country of origin of the samples used in development and validation, the number and type of variables used to estimate risk, and whether they were basic or extended models. Briefly, basic models were calculated using values collected noninvasively, and extended models required the collection of biomarkers such as HbA1c, glucose, and lipid values. Models that do not require blood testing[22-24] were similar to the Diabetes Risk Test recommended by the ADA, which includes age, sex, history of gestational diabetes, family history of diabetes among first-degree relatives, hypertension, physical activity, and BMI category (not overweight or obese, overweight, obese, or extremely obese).[25] The ADA risk score was developed using NHANES data from 1999 to 2004 and validated using NHANES data from 2005 to 2006.[26] When used to predict either prediabetes (fasting plasma glucose 100-125 mg/dL) or diabetes (fasting plasma glucose ≥126 mg/dL) with fasting plasma glucose as the reference standard, it had an AUROC of 0.72. When HbA1c of 6.5 or greater was used as the reference standard, the AUROC was 0.78.

A 2014 systematic review[18] identified risk assessment tools to detect patients with prediabetes defined as IFG and/or IGT using OGTT(1998 WHO criteria[27]) or HbA1c using any recommended definition. Studies were required to have at least two or more risk factors, could not include genetic factors, and had to be developed using a population-based sample or volunteers/opportunist sample. Eighteen risk prediction tools (in 12 articles) were identified including the Tool to Assess likelihood of fasting Glucose ImpairmentT (TAG-IT[28]), the TAG-IT for Adolescents (TAG-IT-A),[29] the Leicester risk assessment score,[30] the Diabetes Risk Calculator,[31] eCANRISK,[32] pCANRISK,[32] and the Diabetes Classifier,[33] and 11 tools did not have official names.[34-39] The number of risk factors for each tool ranged from 6 to 26, and the number of outcome events ranged from 244 to 2,156 (median of 644). Of these 18 risk tools, seven (reported in 6 articles) were developed using samples from the United States. These seven included three unnamed risk tools, TAG-IT-A,[40] Diabetes Risk Calculator,[41] TAG-IT,[42] and the Diabetes Classifier.[43] Three of the seven risk scores were developed using a sample from the United States with NHANES data and externally validated using an NHANES sample from a different year (TAG-IT-A, TAG-IT, and the Diabetes Risk Calculator). All three risk scores were simple diabetes risk scores. TAG-IT-A and TAG-IT used a definition of prediabetes that would also include those with diabetes (i.e., fasting blood glucose ≥100 mg/dL), while the Diabetes Risk Calculator used fasting plasma glucose 100 to 125 mg/dL and/or 2-hour OGTT 140 to 199 mg/dL without diabetic values for either. TAG-IT-A included age, BMI, gender, and resting heart rate and had a reported AUROC of 0.61. TAG-IT included age, BMI, family history of type 2 diabetes, gender, hypertension, and resting heart rate and had an AUROC of 0.74. The Diabetes Risk Calculator included age, family history of type 2 diabetes, and waist circumference and had an AUROC of 0.70.

A 2011 review included studies that derived and/or validated a statistically weighted risk model for type 2 diabetes in a population not preselected for known risk factors or disease and that could be applied to another population.[20] It described three diabetes risk models (Framingham Offspring, San Antonio, and Atherosclerosis Risk in Communities [ARIC] risk scores)[22, 44, 45] that have been validated in U.S. populations[46] with the high potential for use in clinical practice (i.e., were externally validated by a

separate research team on a different population, had statistically significant calibration, discrimination value greater than 0.70, and 10 or fewer components). The three risk prediction models were a subset of seven models (ARIC, AUSDRISK, Cambridge risk score, FINDRISC, Framingham Offspring, San Antonio risk score, and QDScore) that the authors classified as having high potential for use in practice (i.e., were externally validated by a separate research team on a different population, had statistically significant calibration, had a discrimination value greater than 0.70, and had 10 or fewer components). The Framingham Offspring[22] and San Antonio[45] risk scores were developed and validated using samples from the United States, and ARIC[44] was developed in Germany and validated using a U.S. sample. The Framingham Offspring risk score included fasting plasma glucose, BMI, HDL, parental history of diabetes, triglyceride level, and blood pressure and had a development AUROC of 0.85 and a validation AUROC of 0.78.[46] The San Antonio risk score included age, sex, ethnicity, fasting plasma glucose, systolic blood pressure, HDL, BMI, and family history of diabetes in a first-degree relative and had a development AUROC of 0.84 (0.82 to 0.87) and a validation AUROC of 0.83. The ARIC used age, ethnicity, waist circumference, height, systolic blood pressure, family history of diabetes, fasting plasma glucose, triglyceride level, and HDL and had a development AUROC of 0.80;[44] and a validation AUROC of 0.84. For assessing discrimination of all three risk models (Framingham Offspring, San Antonio, and ARIC), incident diabetes was determined using data collected during three in-person MESA followup examinations and was defined as self-reported use of oral hypoglycemic drugs or insulin or had a fasting serum glucose level greater than or equal to 126 mg/dL.

Another systematic review published in 2011 by Buijsse et al. included studies of diabetes risk assessment tools that used prospective cohort studies involving the general adult population for their derivation or validation and evaluated at least three risk factors.[21] This review found two diabetes risk models that were developed or validated in samples from the United States that were not included among the seven diabetes risk models that Nobel et al. determined had a high potential for use in clinical practice, the Epidemiological Study on the Insulin Resistance Syndrome Diabetes Risk Score[24] and the Rancho Bernardo Diabetes Risk Score.[47] Developed in France, the Epidemiological Study on the Insulin Resistance Syndrome Risk Score[24] included waist circumference, hypertension, current smoking (for men), and family history of diabetes (for women) and had a poor validation discrimination of 0.66 in a U.S. population.[48] The Rancho Bernardo Diabetes Risk Score[47] was developed and validated using a sample from the United States and included sex, age, fasting glucose, and triglycerides and had an adequate validation discrimination of 0.71.[47] Notably, the review by Buijsse et al. reported a lower discrimination value (of 0.70) for the ARIC risk score than reported in the Noble et al. systematic review when waist circumference, triglycerides, HDL cholesterol, hypertension, fasting glucose, and BMI were included in the validation score with a different U.S. sample. Similarly, the Buijsse systematic review also reported Framingham Offspring Diabetes Risk score discrimination values that were not reported in the Noble study. These scores ranged from the 0.66 to 0.86 in validation studies performed using samples from different countries and different simple and extended forms of the Framingham Offspring Diabetes risk score.[21]

A 2012 systematic review and external validation study identified 25 prediction models; 12 were categorized as basic models that can be assessed noninvasively (e.g., using demographics, family history, measures of obesity, lifestyle factors), and 13 were categorized as extended because of the inclusion of data on one or more biomarkers (e.g., A1c, lipid levels, uric acid, and others).[19] The authors applied all 25 models to the Dutch cohort of the European Prospective Investigation into Cancer and Nutrition cohort study over 10 years of followup and found that most basic models perform similarly well in identifying individuals at high and low risk of developing diabetes (C-statistics ranged from 0.74 [95% CI, 0.73 to

0.75] to 0.84 [95% CI, 0.82 to 0.85] for risk at 7.5 years). Models including biomarkers classified cases slightly better (C-statistics ranged from 0.81 [95% CI, 0.80 to 0.83] to 0.93 [95% CI, 0.92 to 0.94]) than basic ones; however, most models overestimated the actual risk of diabetes, particularly at higher observed rates. After adjusting models for differences in incidence, calibration improved, but significant deviations between predicted and observed risks remained for most models.[19]

CQ 2. What is the frequency of agreement among screening tests (HbA1c, fasting plasma glucose, and 2-hour glucose tolerance test) for prediabetes and diabetes?

A recent systematic review summarized the prevalence of prediabetes that would be identified by various screening tests.[49] The review identified five studies (17,108 total adult participants from the United States, Italy, China, Spain, and the United Kingdom) that reported on the prevalence of prediabetes for all three tests (HbA1c, fasting plasma glucose, and 2-hour glucose tolerance test) and found generally low agreement between the three tests for which people were classified as having prediabetes. Using the criteria of the International Expert Committee (IEC) and World Health Organization (WHO), the prevalence of prediabetes by any one of the tests was 27 percent. Of those, 5 percent had isolated IFG (6.0-6.9 mmol/L, 106-125 mg/dl), 24 percent had isolated IGT (7-11.1 mmol/L, 126-200 mg/dl), 48 percent had isolated HbA1c criteria (6.0-6.4%), 3 percent had IFG and IGT, 4 percent had IFG and HbA1c criteria, 12 percent had IGT and HbA1c criteria, and 4 percent had all three.

If ADA criteria for HbA1c (5.7-6.4%) are applied to the same cohort, the prevalence of prediabetes by any test was 49 percent. Use of the ADA criteria for both the oral glucose tolerance test and HbA1c increased the prevalence of prediabetes to 54 percent. Of those, 25 percent had isolated IFG (fasting plasma glucose 5.6-6.9 mmol/L, 100-125 mg/dl), 6 percent isolated IGT (OGTT 2 hour result 140-199 mg/dl), 22 percent isolated HbA1c criteria, 7 percent IFG and IGT, 27 percent IFG and HbA1c criteria, 4 percent IGT and HBA1c criteria, and 9 percent had all three.

CQ 3. Which of these screening tests (HbA1c, fasting plasma glucose, and 2-hour glucose tolerance test) best predicts future adverse health outcomes associated with type 2 diabetes?

Overall there is no clear evidence that either HbA1c, OGTT, or FPG is better at predicting health outcomes. When considering the evidence on the value of the tests, four previous reviews (ADA, WHO, Canadian Task Force for Preventive Medicine, and U.K. National Screening Committee)[50-54] all concluded that all three tests were appropriate for diagnosing diabetes.

Study Design and Interpretation

Much of the evidence comparing diabetes tests is cross-sectional and has a high risk of bias to address prediction of future outcomes. Therefore, the focus here is on cohort studies from within the identified reviews. Unlike randomized, controlled trials (RCTs), these studies typically do not give associations between test results and outcomes with and without treatment. A strong association between positive test results and adverse health outcomes may indicate that the test is accurate at detecting people at higher risk, but in the presence of treatment it may indicate the test detects people who do not respond well to treatment (or perhaps that a treatment was harmful). Many of the cohort studies available only reported one or two out of the three tests in the same population. Further, there is heterogeneity across studies, particularly in test thresholds used, methods of outcome ascertainment, and methods of reporting results.

There was some evidence of a J-shaped association between glycemic score and all-cause mortality.[55, 56] If such an association is present, the relative risk of mortality in diabetic and nondiabetic subjects depends on the spectrum of scores in the population, with, for example, inclusion of more participants with very low glycemic scores biasing relative risk estimates toward the null. Results are reported using the ADA 2019 thresholds when available (FPG≥126mg/dl, 2hr PG200mg/dl, HbA1c≥6.5 percent).

Reviews Comparing Screening Tests

A 2011 systematic review commissioned by the WHO[51, 52] recommended using HbA1c as a diagnostic test for diabetes providing there is stringent quality assurance in place. The question they addressed was how does HbA1c perform in the diagnosis of type 2 diabetes based on the detection and prediction of microvascular complications? They did not consider macrovascular complications. The GRADE assessment for quality of evidence was moderate, but this was based on cross-sectional studies of prevalent retinopathy, rather than incident retinopathy where the quality of evidence was low because of the low number of studies. They describe four longitudinal studies reporting the association between HbA1c and incident retinopathy.[57-60] These are described alongside studies from the other reviews in **Appendix A Table 3**. Of the four studies in this review, one gave sufficient information to allow calculation of the relative risk of incident retinopathy in participants with and without diabetes on each test. For the Hoorn study,[59] reviewers combined normoglycemic and prediabetic categories to give unadjusted relative risks. The relative risk of developing retinopathy in those with HbA1c above 5.8 in comparison to below is 3.1 (95% CI, 1.5 to 6.5). The relative risk of developing retinopathy in those who are diabetic according to WHO 1999 criteria in comparison to normoglycemic or prediabetic is 1.8 (0.9 to 3.7). Microvascular complications (retinopathy and nephropathy) in Pima Indians[60] were considered in their review but not reported further because data from the HbA1 and HbA1c tests were combined.

A more recent systematic review (2016) compared HbA1c and FPG in accuracy to detect retinopathy.[61]They included 11 studies, of which only one provided any longitudinal data; the remainder were cross-sectional. They concluded the diagnostic odds ratio for diagnosing retinopathy was higher for HbA1c (16.3 [95% CI, 13.9 to 19.2]) than for FPG (4.9 [95% CI, 4.4 to 5.4]). There was more limited data for OGTT (four studies), but the diagnostic odds ratio was described as similar to that of HbA1c. They included a range of thresholds, which makes results more complex to interpret.

The guidance from the ADA suggests that, generally, FPG, 2-h PG during 75-g OGTT and A1C are equally appropriate for diagnostic testing for diabetes,[62] while acknowledging that the three tests do not necessarily detect the same people (see CQ 2). Similarly, the WHO added HbA1c to FPG and OGTT as an appropriate diabetes test after a systematic review in 2011.[51, 52] The latest Canadian Task Force recommendations on this topic cite the WHO 2011 review.[53]

The U.K. National Screening Committee systematically reviewed the evidence for whether to screen for type 2 diabetes in 2019.[54] They compared accuracy of the three tests (HbA1c, OGTT, and FPG) in predicting mortality, microvascular complications, and macrovascular complications. To reduce spectrum bias, they only included studies that compared all three tests in the same population and did not include evidence from studies examining one or two of the tests. They concluded that there was consistent evidence for an association between higher blood glucose levels and some of the complications of diabetes (i.e., mortality, retinopathy, and nephropathy) for all three tests, but they found no evidence that any one test was a better predictor of these complications. They identified seven relevant cohort studies (**Appendix A Table 3**).[55, 56, 63-66] Sample sizes ranged from 593[65] to 31,148.[64] Two were from the United

States[60, 66] and one from each of Australia,[56] Finland,[65] Netherlands,[63] Germany,[55] and New Zealand.[64] Four studies reported on all-cause mortality;[55, 56, 63, 64] two of them also reported cardiovascular mortality.[56, 63] One study[63] reported mortality outcomes by diabetic status on all three tests using ADA 2019 thresholds. An additional three studies reported mortality outcomes by diabetic status on all three tests but using a different threshold for diabetes for at least one of the tests (see **Appendix A Table 3**).[55, 56, 64] In summary, few studies report mortality outcomes for all three tests, and within them there is heterogeneity in test thresholds. All four included studies showed some evidence of a trend toward OGTT outperforming FPG, but the differences were small and none of them were tested statistically. There were no consistent trends between studies in comparisons between FPG and HbA1c and between HbA1c and OGTT. There was no clear evidence of advantage of one test over another for microvascular or macrovascular outcomes.

The single study that reported mortality outcomes at ADA thresholds was a prospective cohort of 1,484 people from the Netherlands with 8 years of followup.[63] Relative risk for all-cause mortality for diabetics in comparison to nondiabetics was 2.8 (95% CI, 1.8 to 4.4) using HbA1c, 2.5 (95% CI, 1.6 to 3.8) for OGTT and 2.1 (95% CI, 1.4 to 3.3) for FPG. Relative risk for cardiovascular mortality for diabetics compared with nondiabetics was 3.5 (1.9 to 6.3) using HbA1c, 2.6 (95% CI, 1.4 to 4.7) using OGTT, and 2.4 (95% CI, 1.3 to 4.3) using FPG. While the authors did not statistically compare the three tests, they suggested that high glycemic variables, especially OGTT concentrations and to a lesser extent HbA1c values, may be indicators of increased risk of CVD mortality.

Three studies reported macrovascular complications in cohorts with results on all three tests at baseline, but none use the same thresholds as ADA 2019 for all tests.[64-66] Two studies followed up participants to incident retinopathy and neuropathy,[60, 64] and one study followed up participants to development of nephropathy.[64] They are described in **Appendix A Table 3**.

CQ 4. What is the yield (i.e., incidence of prediabetes or diabetes) of rescreening at different intervals in adults with an initial normal screening test (HbA1c, fasting plasma glucose, and 2-hour glucose tolerance test) result?

Overall, the four studies directly addressing this question found yields of rescreening persons for diabetes who had an initial normal test that ranged from 1.3 percent to 4.4 percent over 3 to 12 years. Some of the studies highlighted that those with lower HbA1c at baseline or lower calculated risk (using a risk prediction model) had lower yield of rescreening than those with higher HbA1c or higher calculated risk.

A study of adults screened for diabetes with HbA1c at the Cleveland Clinic evaluated persons with an initial HbA1c less than 6.5 percent in 2008 and at least one subsequent HbA1c over the following 5 years.[67] Of 2,281 people with a normal HbA1c, 100 (4.4%) developed diabetes within 5 years. Of 2,803 people with prediabetes, 772 (27.5%) developed diabetes within 5 years. The authors concluded that screening intervals could be informed by a risk prediction model (including HbA1c, family history, smoking, triglycerides, alanine aminotransferase, BMI, age, and HDL) to determine screening intervals of less than a year for those at highest risk and 3 to 5 years for those at lowest risk.

In the Ely study (described in KQ 1 of the systematic review), participants with initial normal screening tests (OGTT) were rescreened every 5 years. At initial screening, 1,157 people attended and 51 had screen-detected diabetes. Of the 1,106 with initial normal screening results, 1,071 were invited for rescreening at 5 years, yielding 26 additional screen-detected cases (yield 2.4% of those invited), and 994 were invited for rescreening at 10 years, yielding 31 additional screen-detected cases (yield 3.1% of those

invited). Number of persons invited who attended screening at each 5-year interval was not reported; thus, the yield calculated is out of the number invited (yield out of number screened would be somewhat higher).

A cohort study of healthy adults older than age 65 years conducted in New Mexico screened annually with fasting serum glucose for up to 18 years (mean 12 years).[68] Of 299 persons with normal fasting serum glucose (<126 mg/dl) at baseline, four (1.3%) subsequently met criteria for the diagnosis of diabetes. The authors noted that fasting glucose decreased for most participants. None of the participants who passed age 75 developed diabetes or a significant upward slope of fasting glucoses plotted over time.

A retrospective cohort study of over 16,000 Japanese adults with mean BMI 22.5 kg/m^2 without diabetes at baseline reported a yield of 3.2 percent for annual screening over three consecutive years.[69] The study also found that the yield was much lower for those with HbA1c less than 5.5 percent at baseline and those with HbA1c 5.5 to 5.9 percent at baseline than for those with HbA1c 6.0 to 6.4 percent at baseline (0.5% vs. 1.2% vs. 20%).

CQ 5. What is the utility of recently published modeling studies that assess screening for type 2 diabetes and prediabetes (vs. no screening) in examining health outcomes?

The prior report for the USPSTF described four recently published (at that time; from 2007 to 2012) modeling studies that estimated the cost-effectiveness of various screening strategies for diabetes, IFG, or IGT in the United States, United Kingdom, or Canada.[70-74] The modeling studies evaluated screening with capillary blood glucose, fasting plasma glucose, and OGTT; none evaluated screening with HbA1c. One study evaluated one-time screening,[72] and the other three modeled rescreening at various intervals (e.g., every 3 years with fasting plasma glucose[71] or rescreening every 1, 3, or 5 years with annual screening for those with IFG or IGT[73]). All of them were conducted prior to the publication of the ADDITION-Europe and ADDITION-Cambridge trials (described in KQs 1 and 4). All of them found incremental cost-effectiveness ratios less than $15,000 per quality-adjusted life-year for screening strategies beginning at age 40 or 45. Three of the four modeled screening followed by treatment of diabetes, IFG, or IGT; one modeled screening and treatment of diabetes (but not prediabetes/IFG/IGT[71]). The two models that reported on the timing of benefits estimated that they accrued over 10[73] to 30[72] years.

One of the modeling studies in the prior report that was conducted in the United States used the Archimedes model, that has been shown to have good calibration (with clinical and epidemiologic studies) for its assumptions regarding rates of diabetes progression and outcomes.[71] The study compared eight simulated screening strategies with the most optimal incremental cost-effectiveness ratios for strategies starting between the ages of 30 and 45 with rescreening every 3 to 5 years. Beginning screening at age 45 with fasting plasma glucose every 3 years was associated with an incremental cost-effectiveness ratio of less than $10,000 per quality-adjusted life-year. The estimated benefits for health outcomes include an estimated two to five deaths, three to nine myocardial infarctions, and three to nine microvascular complications prevented per 1,000 people screened. Sensitivity analyses found that the results for costs per quality-adjusted life-year were sensitive to the disutility estimated for the state of having diabetes with or without symptoms. Citing this study, the ADA notes that screening beginning at age 30 or 45 (independent of risk factors) may be cost-effective.[13]

Three more recent modeling studies were identified for this update, all using some data from ADDITION.[75-77] One used data from ADDITION-Europe and the Michigan Model for Type 2 Diabetes to estimate the benefits of screening and intensive treatment, screening and routine treatment, and no

screening (with associated 3- or 6-year delay in diagnosis) and routine treatment of diabetes and CVD risk factors.[75] The computer simulation models accurately predicted the results of the ADDITION-Europe trial (for intensive vs. routine treatment of those with screen-detected diabetes) and estimated greater benefits at 5 years with screening, early diagnosis, and routine treatment compared with a 3- or 6-year delay in diagnosis (no screening) followed by routine treatment. The authors estimated an absolute risk reduction of 3.3 percent for cardiovascular events compared with a 3-year delay in diagnosis and 4.9 percent compared with a 6-year delay. The authors concluded that screening for diabetes to reduce the lead time between diabetes onset and diagnosis is warranted to allow for prompt multifactorial treatment.

A cost-effectiveness analysis from the ADDITION-Europe investigators conducted along with the ADDITION-Europe trial reported that the cost of the intervention was 981 pounds per patient and was not cost-effective (but that it might be if delivered at a reduced cost).[76] The economic analyses estimated costs and quality-adjusted life-years from the U.K. National Health Service (NHS) perspective and used 2009-2010 U.K. costs and extrapolated data to 30 years using the UKPDS outcomes model.

Finally, and most recently, an updated cost-effectiveness analysis from the perspective of the U.K. NHS estimated the cost-effectiveness of intensive treatment for those with screen-detected diabetes in the ADDITION-UK trial.[77] It found over 10-, 20-, and 30-year time horizons, incremental cost-effectiveness ratios of about 71,000, 28,000, and 27,500 pounds per quality-adjusted life-year, respectively. The authors concluded that intensive treatment for screen-detected diabetes is of borderline cost-effectiveness over 20 years or more for U.K. willingness-to-pay thresholds.

Appendix A Table 3. Studies Reporting Followup to Health Outcomes After HbA1c, FPG, and OGTT Tests, From Recent Systematic Reviews.

Study Reference Country (Source)	Participants	Followup	Relative Risk of Outcome in Diabetic vs. Nondiabetic Subjects*
Barr[56] Australia (UKNSC review)	10,026	Median 6 years	**All-cause mortality+** HbA1c RR, 2.2 (1.8 to 2.8) (threshold lower at 6.1%, biasing RR downward) OGTT RR, 3.6 (2.6 to 4.9) FPG RR, 2.1 (1.2 to 3.4) **CVD mortality+** HbA1c RR, 2.5 (1.6 to 3.9) (threshold lower at 6.1%, biasing RR downward) OGTT RR, 5.1 (2.8 to 9.1) FPG RR, 3.7 (1.8 to 8.0)
Cederberg[65] Finland (UKNSC review)	593	Mean 9.7 years	**RR of cardiovascular disease (women)** HbA1c RR, 2.99 (2.5 to 3.6) [>6% vs. <5.6%, middle category excluded] OGTT RR, 2.0 (1.2 to 3.4) [>200mg/dl vs. <139mg/dl, middle category excluded] FPG RR, 1.4 (0.9 to 2.5) [>110mg/dl vs. <99mg/dl, middle category excluded] **RR of cardiovascular disease (men)** HbA1c RR, 0.62 (0.11 to 3.42) [>6% vs. <5.6%] OGTT RR, 0.60 (0.22 to 1.62) [>200mg/dl vs <139mg/dl] FPG RR, 1.25 (0.75 to 2.07) [>110mg/dl vs <99mg/dl]
de Vegt[63] Netherlands (UKNSC review)	2,484	8 years	**All-cause mortality+** HbA1c RR, 2.8 (1.8 to 4.4) OGTT RR, 2.5 (1.6 to 3.8) FPG RR, 2.1 (1.4 to 3.3) **CVD mortality+** HbA1c RR, 3.5 (1.9 to 6.3) OGTT RR, 2.6 (1.4 to 4.7) FPG RR, 2.4 (1.3 to 4.3)
Kalogeropoulos[66] USA (UKNSC review)	2,386	Median 7.2 years	**Heart failure (hazard ratio per SD, unadjusted)** HbA1c: HR, 1.26 (95% CI, 1.13 to 1.41) OGTT: HR, 1.22 (95% CI, 1.07 to 1.39) FPG: HR, 1.22 (95% CI, 1.10 to 1.35) **Heart failure (hazard ratio per SD, adjusted for BMI and FPG)** HbA1c: HR, 1.08 (95% CI, 0.90 to 1.28) OGTT: HR, 1.01 (95% CI, 0.83 to 1.23)
Kowall[55] Germany (UKNSC review)	1,653	Median 8.8 years	**All-cause mortality (HR adjusted for age and sex)** HbA1c5.2%: HR, 2.0 (1.04 to 3.9) 5.4/5.5%: HR 1 (ref) ≥6.1%: HR 2.5 (1.4 to 4.5) OGTT<79: HR, 1.8 (0.8 to 4.2) ≥79, <94: HR 1 (ref) ≥176: HR 3.8 (1.9 to 7.9) FPG <88: HR, 1.9 (0.8 to 4.6) ≥88, <94: HR 1 (ref) ≥115: HR 3.6 (1.7 to 7.5)
Massin DESIR study[57] France WHO review	700	10 years	**Test accuracy to predict retinopathy** HbA1c: sensitivity 9%, specificity 98% FPG: sensitivity 19%, specificity 97% (FPG threshold lower at 115, biasing sensitivity upward and specificity downward)
McCance[60] USA (UKNSC review)	960, but varied by analysis	Mean 4.5 years	**Retinopathy+** HbA1c RR 20.9 (9.8 to 44.8) (threshold 9.4%) OGTT RR 266 (16 to 4,344) (threshold 227) FPG RR 14.1 (6.7 to 29.7) (threshold 167) **Nephropathy+**

Appendix A Table 3. Studies Reporting Followup to Health Outcomes After HbA1c, FPG, and OGTT Tests, From Recent Systematic Reviews.

Study Reference Country (Source)	Participants	Followup	Relative Risk of Outcome in Diabetic vs. Nondiabetic Subjects*	
			HbA1c RR 2.4 (0.7 to 8.4) (threshold 9.4%) OGTT RR 3.0 (1.1 to 8.2) (threshold 227) FPG RR 2.8 (0.9 to 8.8) (threshold 167)	
Metcalf[64] New Zealand	31,148	Median 4 years	Thresholds used were higher than ADA 2019 for HbA1c (6.8%) and OGTT (220) but lower for FPG (122).	
(UKNSC review)			**All-cause mortality+** HbA1c RR, 1.5 (1.3 to 1.8) OGTT RR, 1.5 (1.3 to 1.8) FPG RR, 1.3 (1.1 to 1.6) **Cardiovascular Disease+** HbA1c RR, 1.1 (1.003 to 1.2) OGTT RR, 1.2 (1.1 to 1.3 FPG RR, 1.2 (1.1 to 1.3) **Coronary Heart Disease+** HbA1c RR, 1.1 (0.96 to 1.2) OGTT RR, 1.2 (1.04 to 1.4) FPG RR, 1.2 (1.03 to 1.3)	**Retinopathy+** HbA1c RR, 3.4 (2.9 to 3.9) OGTT RR, 3.8 (3.3 to 4.4) FPG RR, 3.1 (2.7 to 3.6) **Nephropathy+** HbA1c RR, 3.4 (2.9 to 4.0) OGTT RR, 3.1 (2.6 to 3.7) FPG RR, 3.4 (2.9 to 4.0) **Neuropathy+** HbA1c RR, 2.7 (1.9 to 3.8) OGTT RR, 4.0 (2.8 to 5.7) FPG RR, 3.6 (2.6 to 5.2)
Tapp, AusDiab study[58] Australia (WHO review)	1,192	5 years	**Retinopathy** FPG (18 mg/dl increase) OR, 1.52 (1.30 to 1.77) adjusted for age A1C (1% increase) OR, 2.29 (1.75 to 3.02) adjusted for age	
Van Leiden Hoorn study[59] Netherlands (WHO Review)	233	average 9.4 years	**Retinopathy** HbA1c 3.1 (95% CI, 1.5 to 6.5)+, (threshold lower at 5.8%). WHO 1999 criteria RR, 1.8 (0.9 to 3.7)+. HbA1c OR, 3.3 (95% CI, 1.1 to 9.7, HbA1c.>5.8 in comparison to <5.2, adjusted for sex hypertension age and glycemic category according to WHO 1999 criteria) WHO 1999 OR, 1.91 (95% CI, 0.7 to 5.4, WHO diabetic vs. WHO normoglycemic, prediabetics excluded, adjusted for sex and hypertension age and HbA1c category)	

Note: Units for FPG and OGTT are in mg/dL and HbA1c in percent.

*Above in comparison to below the ADA threshold or nearest available threshold unless otherwise stated.

+ Unadjusted and not reported by the article (but calculated from data reported in the article).

Abbreviations: A1c=glycated hemoglobin; CI=confidence interval; CVD=cardiovascular disease; DESIR=Data From an Epidemiological Study on the Insulin Resistance Syndrome; FPG=fasting plasma glucose; HbA1c/HBA1c=hemoglobin A1c; OGTT=oral glucose tolerance test; OR=odds ratio; RR=relative risk; UKNSC=U.K. National Screening Committee; USA=United States of America; vs.=versus; WHO=World Health Organization.

Appendix B1. Original Search Strategies

Screening Searches
PubMed, 6-27-2018

Search	Query	Items Found
#1	Search (“Diabetes Mellitus, Type 2”[Mesh] OR “Glucose Tolerance”[Mesh] OR “glucose tolerance”[All Fields] OR “impaired glucose tolerance”[All Fields] OR IGT OR “impaired fasting glucose” OR IFG OR “Glucose Intolerance”[MeSH] OR “glucose intolerance”[All Fields] OR “Prediabetic State”[MeSH] OR “prediabetic state”[All Fields] OR prediabet* OR “pre diabetes”[All Fields] OR “diabetes mellitus type 2”[All Fields] OR “type 2 diabetes mellitus”[All Fields])	183989
#2	Search (“Blood Glucose”[Mesh] OR “blood glucose”[tiab] OR “Glucose Tolerance Test”[Mesh] OR OGTT[tiab] OR “glucose tolerance test”[ti] OR "Glycated Hemoglobin A"[Mesh] OR “hemoglobin A1c” OR HbA1c OR “fasting plasma glucose”[tiab])	224814
#3	Search (((“HbA(1c)”[tiab] or HbA1[tiab] or HbA1c[tiab] or “HbA 1c”[tiab] or ((glycosylated[tiab] or glycated[tiab]) AND hemoglobin[tiab])))	40212
#4	Search (#2 or #3)	228775
#5	Search (#1 and #4)	84503
#6	Search ("Mass Screening"[Mesh] OR screen*[tiab])	681189
#7	Search (#5 and #6)	5301
#8	Search (#7 NOT (gestation* OR Pregnancy[Mesh]))	3904
#9	Search (#7 NOT (gestation* OR Pregnancy[Mesh])) Filters: English	3536
#10	Search (#7 NOT (gestation* OR Pregnancy[Mesh])) Filters: English; Adult: 19+ years	2353
#11	Search ((#10 AND humans[mesh:noexp]) OR (#10 NOT animals[mesh:noexp]))	2353
#12	Search ((#10 AND humans[mesh:noexp]) OR (#10 NOT animals[mesh:noexp])) Filters: Publication date from 2014/01/01 to 2018/12/31	651
#13	Search (("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields] OR “meta synthesis”[ti] OR “systematic literature review”[ti] OR “this systematic review”[tw] OR “cochrane database syst rev”[ta])	244004
#14	Search (#12 and #13)	12
#15	Search (((randomized[tiab] OR randomised[tiab]) AND controlled[tiab] AND trial[tiab]) OR (controlled[tiab] AND trial[tiab]) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	713625
#16	Search (#12 and #15)	87
#17	Search ("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Epidemiologic Studies"[MeSH] OR "Cross-Sectional Studies"[MeSH] OR "Organizational Case Studies"[MeSH] OR "Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Seroepidemiologic Studies"[MeSH] OR "Evaluation Studies"[Publication Type] OR “observational study” OR “observational studies”)	2458093
#18	Search (#12 and #17)	387

Appendix B1. Original Search Strategies

Cochrane Library, 6-27-2018

ID	Search	Hits
#1	[mh "Diabetes Mellitus, Type 2"] or [mh "Glucose Tolerance"] or "glucose tolerance" or "impaired glucose tolerance" or IGT or "impaired fasting glucose" or IFG or [mh "Glucose Intolerance"] or "glucose intolerance" or [mh "Prediabetic State"] or "prediabetic state" or prediabet* or "pre diabetes" or "diabetes mellitus type 2" or "type 2 diabetes mellitus"	25233
#2	[mh "Blood Glucose"] or "blood glucose":ti,ab or [mh "Glucose Tolerance Test"] or OGTT:ti,ab or "glucose tolerance test":ti or [mh "Glycated Hemoglobin A"] or "hemoglobin A1c" or HbA1c or "fasting plasma glucose":ti,ab	30959
#3	("HbA(1c)":ti,ab or HbA1:ti,ab or HbA1c:ti,ab or "HbA 1c":ti,ab or ((glycosylated:ti,ab or glycated:ti,ab) and hemoglobin:ti,ab))	11067
#4	#2 or #3	31609
#5	#1 and #4	13452
#6	[mh "Mass Screening"] or screen*:ti,ab	39953
#7	#5 and #6	639
#8	#7 not (gestation* or [mh Pregnancy])	522
#9	Adult*	522081
#10	#8 and #9	323
#11	(#10 and [mh ^humans]) or (#10 not [mh ^animals])	323
#12	#11 Publication Year from 2014 to 2018	133

Appendix B1. Original Search Strategies

Intervention Searches
PubMed, 6-27-2018

Search	Query	Items Found
#1	Search (“Diabetes Mellitus, Type 2”[Mesh] OR “impaired glucose tolerance”[All Fields] OR IGT OR “impaired fasting glucose” OR IFG OR “Glucose Intolerance”[MeSH] OR “glucose intolerance”[All Fields] OR “Prediabetic State”[MeSH] OR “prediabetic state”[All Fields] OR prediabet* OR “pre diabetes”[All Fields] OR “diabetes mellitus type 2”[All Fields] OR “type 2 diabetes mellitus”[All Fields])	152417
#2	Search (“ACE inhibitor”[tiab] OR “ACE inhibitors”[tiab] OR "Acebutolol"[Mesh] OR Acebutolol[tiab] OR “Adalat CC”[tiab] OR "Adrenergic beta-Antagonists" [Pharmacological Action] OR “Adrenergic beta-Antagonists“[tiab] OR Altoprev[tiab] OR “Afeditab CR”[tiab] OR "Amlodipine"[Mesh] OR "Amlodipine, Valsartan Drug Combination"[Mesh] OR "Amlodipine Besylate, Olmesartan Medoxomil Drug Combination"[Mesh] OR "amlodipine, perindopril drug combination"[Supplementary Concept] OR Amlodipine[tiab] OR “Adrenergic beta-Antagonists"[Mesh] OR “Adrenergic beta-Antagonists”[tiab] OR “angiotensin II receptor blocker”[tiab] OR “angiotensin II receptor blockers”[tiab] OR "Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR “Angiotensin-converting enzyme inhibitor”[tiab] OR “angiotensin-converting enzyme inhibitors”[tiab] OR "Angiotensin-Converting Enzyme Inhibitors"[Pharmacological Action] OR "Angiotensin Receptor Antagonists"[Mesh] OR "Angiotensin Receptor Antagonists"[Pharmacological Action] OR “Angiotensin Receptor Antagonists”[tiab] OR "Antihypertensive Agents"[Mesh] OR "Antihypertensive Agents"[Pharmacological Action] OR “antihypertensive agent”[tiab] OR “antihypertensive agents”[tiab] OR Aspirin[Mesh] OR aspirin[tiab] OR Atenolol[Mesh] OR Atenolol[tiab] OR "Atorvastatin Calcium"[Mesh] OR Atorvastatin[tiab] OR azilsartan [Supplementary Concept] OR "azilsartan medoxomil"[Supplementary Concept] OR azilsartan[tiab] OR benazepril[Supplementary Concept] OR benazepril[tiab] OR “beta blocker”[tiab] OR “beta blockers”[tiab] OR Betapace[tiab] OR Betaxolol[Mesh] OR Betaxolol[tiab] OR "Bezafibrate"[Mesh] OR Bezafibrate[tiab] OR Bisoprolol[Mesh] OR "bisoprolol, hydrochlorothiazide drug combination"[Supplementary Concept] OR Bisoprolol[tiab] OR Bystolic[tiab] OR Calan[tiab] OR "Calcium Channel Blockers"[Mesh] OR "Calcium Channel Blockers"[Pharmacological Action] OR “calcium channel blockers”[tiab] OR candesartan[Supplementary Concept] OR candesartan[tiab] OR Captopril[MeSH] OR Captopril[tiab] OR Cardizem[tiab] OR carvedilol[Supplementary Concept] OR carvedilol[tiab] OR Chlorothiazide[Mesh] OR Chlorothiazide[tiab] OR Chlorthalidone[Mesh] OR Chlorthalidone[tiab] OR Clofenapate[Mesh] OR clofenapate[tiab] OR "Clofibric Acid"[Mesh] OR "Clofibric Acid"[tiab] OR Coreg[tiab] OR Corgard[tiab] OR Crestor[tiab] OR Diltiazem[Mesh] OR Diltiazem[tiab] OR Diuretics[Mesh] OR Diuretics[Pharmacological Action] OR diuretics[tiab] OR Diuril[tiab] OR Enalapril[Mesh] OR Elanapril[tiab] OR Enduron[tiab] OR eprosartan[Supplementary Concept] OR eprosartan[tiab] OR Esidrix[tiab] OR Felodipine[Mesh] OR Felodipine[tiab] OR Fenofibrate[Mesh] OR Fenofibrate[tiab] OR Fosinopril[Mesh] OR fosinopril[tiab] OR fluvastatin[Supplementary Concept] OR fluvastatin[tiab] OR Gemfibrozil[Mesh] OR Gemfibrozil[tiab] OR HCTZ[tiab] OR Hydrochlorothiazide[Mesh] OR Hydrochlorothiazide[tiab] OR Hydrodiuril[tiab] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh] OR Hygroton[tiab] OR "Hypolipidemic Agents"[Mesh] OR "Hypolipidemic Agents" [Pharmacological Action] OR “hypolipidemic agents”[tiab] OR Indapamide[Mesh] OR Indapamide[tiab] OR “Inderal LA”[tiab] OR “Inderal XL”[tiab] OR irbesartan[Supplementary Concept] OR irbesartan[tiab] OR Isradipine[Mesh] OR Isradipine[tiab] OR Kerlone[tiab] OR Labetalol[Mesh] OR labetalol[tiab] OR Lescol[tiab] OR “Lescol XL”[tiab] OR Levatol[tiab] OR Lipitor[tiab] OR Lisinopril[Mesh] OR Lisinopril[tiab] OR Livalo[tiab] OR Lopressor[tiab] OR Losartan[Mesh] OR Losartan[tiab] OR Lovastatin[MeSH] OR lovastatin[tiab] OR Lozol[tiab] OR Methyclothiazide[Mesh] OR Methyclothiazide[tiab] OR Metoprolol[Mesh] OR Metoprolol[tiab] OR Mevacor[tiab] OR Microzide[tiab] OR moexipril[Supplementary Concept] OR moexipril[tiab] OR Nadolol[Mesh] OR nadolol[tiab] OR Nebivolol[Mesh] OR nebivolol[tiab] OR Nicardipine[Mesh] OR	664232

Appendix B1. Original Search Strategies

Search	Query	Items Found
#2 continued	Nicardipine[tiab] OR Nifedipine[Mesh] OR Nifedipine[tiab] OR Nisoldipine[Mesh] OR Nisoldipine[tiab] OR Norvasc[tiab] OR "Olmesartan Medoxomil"[Mesh] OR olmesartan[Supplementary Concept] OR olmesartan[tiab] OR Penbutolol[Mesh] OR penbutolol[tiab] OR Perindopril[Mesh] OR Perindopril[tiab] OR Pindolol[Mesh] OR pindolol[tiab] OR pitavastatin[Supplementary Concept] OR pitavastatin[tiab] OR Pravachol[tiab] OR Pravastatin[MeSH] OR pravastatin[tiab] OR Procardia[tiab] OR Propranolol[Mesh] OR Propranolol[tiab] OR quinapril[Supplementary Concept] OR quinapril[tiab] OR Ramipril[Mesh] OR Ramipril[tiab] OR "Rosuvastatin Calcium"[MeSH Terms] OR rosuvastatin[tiab] OR Sectral[tiab] OR Simvastatin[Mesh] OR simvastatin[tiab] OR Sotalol[Mesh] OR sotalol[tiab] OR statins[tiab] OR Sular[tiab] OR telmisartan[Supplementary Concept] OR telmisartan[tiab] OR Tenormin[tiab] OR Tiazac[tiab] OR Timolol[Mesh] OR timolol[tiab] OR “Toprol XL”[tiab] OR ToprolXL[tiab] OR Trandate[tiab] OR trandolapril[Supplementary Concept] OR trandolapril[tiab] OR Valsartan[Mesh] OR valsartan[tiab] OR Verapamil[Mesh] OR Verapamil[tiab] OR Verelan[tiab] OR Visken[tiab] OR Zebeta[tiab] OR Ziac[tiab] OR Zocor[tiab])	
#3	Search (#1 and #2)	9778
#4	Search (Actos[tiab] OR Albiglutide[tiab] OR Amaryl[tiab] OR “antidyslipidemic agent”[tiab] OR “antidyslipidemic agents”[tiab] OR Avandia[tiab] OR “beta blocker”[tiab] “beta blockers”[tiab] OR Biguanides[Mesh] OR Biguanides[tiab] OR Bydureon[tiab] OR Byetta[tiab] OR DiaBeta[tiab] OR "Dipeptidyl-Peptidase IV Inhibitors"[Mesh] OR "Dipeptidyl-Peptidase IV Inhibitors"[Pharmacological Action] OR “Dipeptidyl peptidase IV inhibitor”[tiab] OR “Dipeptidyl peptidase IV inhibitors”[tiab] OR dulaglutide[Supplementary Concept] OR dulaglutide[tiab] OR exenatide[Supplementary Concept] OR Exenatide[tiab] OR Ezetimibe[Mesh] OR "Ezetimibe, Simvastatin Drug Combination"[Mesh] OR Ezetimibe[tiab] OR Fortamet[tiab] OR Gliclazide[Mesh] OR Gliclazide[tiab] OR glimepiride[tiab] OR Glipizide[Mesh] OR glipizide[tiab] OR “GLP-1 receptor agonist”[tiab] OR “GLP-1 receptor agonists”[tiab] OR “Glucagon-like peptide-1 receptor agonist”[tiab] OR “Glucagon-like peptide-1 receptor agonists”[tiab] OR Glucophage[tiab] OR Glucotrol[tiab] OR “Glucotrol XL”[tiab] OR Glumetza[tiab] OR Glyburide[Mesh] OR glyburide[tiab] OR “Glynase PresTab”[tiab] OR Linagliptin[Mesh] OR Linagliptin[tiab] OR Liraglutide[Mesh] OR liraglutide[tiab] OR lixisenatide[Supplementary Concept] OR lixisenatide[tiab] OR Lyxumia[tiab] OR Meglitinides[tiab] OR Metformin[Mesh] OR Metformin[tiab] OR Micronase[tiab] OR nateglinide[Supplementary Concept] OR Nateglinide[tiab] OR Niacin[Mesh] OR niacin[tiab] OR Ozempic[tiab] OR pioglitazone[Supplementary Concept] OR Pioglitazone[tiab] OR Prandin[tiab] OR Repaglinide[tiab] OR rosiglitazone[Supplementary Concept] OR Rosiglitazone[tiab] OR Saxagliptin[tiab] OR semaglutide[Supplementary Concept] OR semaglutide[tiab] OR Sitagliptin[tiab] OR "Sitagliptin Phosphate"[Mesh] OR "Sitagliptin Phosphate, Metformin Hydrochloride Drug Combination"[Mesh] OR "Sulfonylurea Compounds"[Mesh] OR Starlix[tiab] OR Sulfonylureas[tiab] OR Tanzeum[tiab] OR Thiazolidinediones[Mesh] OR Thiazolidinediones[tiab] OR Tolazamide[Mesh] OR Tolazamide[tiab] OR Tolbutamide[Mesh] OR tolbutamide[tiab] OR Trulicity[tiab] OR TZDs[tiab] OR Victoza[tiab] OR vildagliptin[Supplementary Concept] OR vildagliptin[tiab])	88394
#5	Search (#1 and #4)	18217
#6	Search (advice[tiab] OR “Behavior Therapy”[Mesh] OR “behavior therapy”[tiab] OR (behavior*[tiab] AND therap*[tiab]) OR (behavior*[tiab] AND chang*[tiab]) OR (behavior*[tiab] AND modification*[tiab]) OR “Caloric Restriction”[Mesh] OR Counseling[Mesh] OR counsel*[tiab] OR “Diabetes Prevention Program”[tiab] OR “Diabetes Prevention Programme”[tiab] OR DPP[tiab] OR (“Diabetes Prevention”[tiab] AND (program*[tiab] OR stud*[tiab] OR trial*[tiab])) OR diet[ti] OR “Diet, Carbohydrate-Restricted”[Mesh] OR “Diet, Fat-Restricted”[Mesh] OR “Diet, Mediterranean”[Mesh] OR “Diet, Reducing”[Mesh] OR “Diet Therapy”[Mesh] OR dietary[ti] OR “Directive Counseling”[Mesh] OR Exercise[Mesh] OR exercise[ti] OR “Exercise Therapy”[Mesh] OR “Feedback, Psychological”[Mesh] OR "Health Behavior"[Majr] OR “health behavior”[tiab] OR “health behaviors”[tiab] OR “health behavioral”[tiab] "health behaviours"[tiab] OR "health behaviour"[tiab] OR “Health	415785

Appendix B1. Original Search Strategies

Search	Query	Items Found
#6 continued	Education”[Mesh] OR “Health Education as Topic”[Mesh] OR “health education”[tiab] OR “Health Promotion”[Majr] OR “health promotion”[tiab] OR “Life Style”[Mesh] OR lifestyle[tiab] OR “life style”[tiab] OR “Lifestyle Intervention”[Mesh] OR “Motivational Interviewing”[Mesh] OR “motivational interviewing”[tiab] OR “non pharmacologic intervention”[tiab] OR “nonpharmacologic intervention”[tiab] OR "Patient Education as Topic"[Mesh] OR “patient education”[tiab] OR “physical activity”[ti] OR “physically active”[ti] OR “psychological feedback”[tiab] OR “Risk Reduction Behavior”[Mesh] OR “Risk Reduction Behavior”[tiab])	
#7	Search (#1 and #6)	13211
#8	Search (#3 or #5 or #7)	38015
#9	Search (#3 or #5 or #7) Filters: English	34169
#10	Search (#3 or #5 or #7) Filters: Publication date from 2014/01/01 to 2018/12/31; English	10761
#11	Search ((#10 and Humans[Mesh:NOEXP]) OR (#10 not Animals[Mesh:NOEXP]))	10146
#12	Search ((#10 and Humans[Mesh:NOEXP]) OR (#10 not Animals[Mesh:NOEXP])) Filters: Adult: 19+ years	5194
#13	Search (letter[pt] OR newspaper article[pt] OR editorial[pt] OR comment[pt] OR case reports[pt])	3341617
#14	Search (#12 not #13)	4961
#15	Search (("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields])	239210
#16	Search (#14 and #15)	174
#17	Search ((randomized[tiab] OR randomised[tiab]) AND controlled[tiab] AND trial[tiab]) OR (controlled[tiab] AND trial[tiab]) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH]	713625
#18	Search (#14 and #17)	1703
#19	Search "Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Cross-Sectional Studies"[MeSH] OR "Organizational Case Studies"[MeSH] OR "Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Seroepidemiologic Studies"[MeSH] OR "Evaluation Studies"[Publication Type] OR “observational study”[tw] OR “observational studies”[tw] OR cohort[tw] OR compared[tw] OR groups[tw] OR "case control"[tw] OR “cross sectional”[tw] OR multivariate[tw] OR (first[Tiab] AND episode[Tiab]) OR cohort[Tiab]))	6211555
#20	Search (#14 and #17)	4037
#21	Search (#20 not (#18 or #16))	2518

Appendix B1. Original Search Strategies

Cochrane Library, 6-27-2018

ID	Search	Hits
#1	[mh "Diabetes Mellitus, Type 2"] or "impaired glucose tolerance" or IGT or "impaired fasting glucose" or IFG or [mh "Glucose Intolerance"] or "glucose intolerance" or [mh "Prediabetic State"] or "prediabetic state" or prediabet* or "pre diabetes" or "diabetes mellitus type 2" or "type 2 diabetes mellitus"	22234
#2	"ACE inhibitor":ti,ab or "ACE inhibitors":ti,ab or [mh Acebutolol] or Acebutolol:ti,ab or "Adalat CC":ti,ab or "Adrenergic beta-Antagonists":ti,ab or Altoprev:ti,ab or "Afeditab CR":ti,ab or [mh Amlodipine] or [mh "Amlodipine, Valsartan Drug Combination"] or [mh "Amlodipine Besylate, Olmesartan Medoxomil Drug Combination"] or Amlodipine:ti,ab or [mh "Adrenergic beta-Antagonists"] or "Adrenergic beta-Antagonists":ti,ab or "angiotensin II receptor blocker":ti,ab or "angiotensin II receptor blockers":ti,ab or [mh "Angiotensin-Converting Enzyme Inhibitors"] or "Angiotensin-converting enzyme inhibitor":ti,ab or "angiotensin-converting enzyme inhibitors":ti,ab or [mh "Angiotensin Receptor Antagonists"] or "Angiotensin Receptor Antagonists":ti,ab or [mh "Antihypertensive Agents"] or "antihypertensive agent":ti,ab or "antihypertensive agents":ti,ab or [mh Aspirin] or aspirin:ti,ab or [mh Atenolol] or Atenolol:ti,ab or [mh "Atorvastatin Calcium"] or Atorvastatin:ti,ab or azilsartan:ti,ab or benazepril:ti,ab or "beta blocker":ti,ab or "beta blockers":ti,ab or Betapace:ti,ab or [mh Betaxolol] or Betaxolol:ti,ab or [mh Bezafibrate] or Bezafibrate:ti,ab or [mh Bisoprolol] or Bisoprolol:ti,ab or Bystolic:ti,ab or Calan:ti,ab or [mh "Calcium Channel Blockers"] or "calcium channel blockers":ti,ab or candesartan:ti,ab or [mh Captopril] or Captopril:ti,ab or Cardizem:ti,ab or carvedilol:ti,ab or [mh Chlorothiazide] or Chlorothiazide:ti,ab or [mh Chlorthalidone] or Chlorthalidone:ti,ab or [mh Clofenapate] or clofenapate:ti,ab or [mh "Clofibric Acid"] or "Clofibric Acid":ti,ab or Coreg:ti,ab or Corgard:ti,ab or Crestor:ti,ab or [mh Diltiazem] or Diltiazem:ti,ab or [mh Diuretics] or diuretics:ti,ab or Diuril:ti,ab or [mh Enalapril] or Elanapril:ti,ab or Enduron:ti,ab or eprosartan:ti,ab or Esidrix:ti,ab or [mh Felodipine] or Felodipine:ti,ab or [mh Fenofibrate] or Fenofibrate:ti,ab or [mh Fosinopril] or fosinopril:ti,ab or fluvastatin:ti,ab or [mh Gemfibrozil] or Gemfibrozil:ti,ab or HCTZ:ti,ab or [mh Hydrochlorothiazide] or Hydrochlorothiazide:ti,ab or Hydrodiuril:ti,ab or [mh "Hydroxymethylglutaryl-CoA Reductase Inhibitors"] or Hygroton:ti,ab or [mh "Hypolipidemic Agents"] or "hypolipidemic agents":ti,ab or [mh Indapamide] or Indapamide:ti,ab or "Inderal LA":ti,ab or "Inderal XL":ti,ab or irbesartan:ti,ab or [mh Isradipine] or Isradipine:ti,ab or Kerlone:ti,ab or [mh Labetalol] or labetalol:ti,ab or Lescol:ti,ab or "Lescol XL":ti,ab or Levatol:ti,ab or Lipitor:ti,ab or [mh Lisinopril] or Lisinopril:ti,ab or Livalo:ti,ab or Lopressor:ti,ab or [mh Losartan] or Losartan:ti,ab or [mh Lovastatin] or lovastatin:ti,ab or Lozol:ti,ab or [mh Methyclothiazide] or Methyclothiazide:ti,ab or [mh Metoprolol] or Metoprolol:ti,ab or Mevacor:ti,ab or Microzide:ti,ab or moexipril:ti,ab or [mh Nadolol] or nadolol:ti,ab or [mh Nebivolol] or nebivolol:ti,ab or [mh Nicardipine] or Nicardipine:ti,ab or [mh Nifedipine] or Nifedipine:ti,ab or [mh Nisoldipine] or Nisoldipine:ti,ab or Norvasc:ti,ab or [mh "Olmesartan Medoxomil"] or olmesartan:ti,ab or [mh Penbutolol] or penbutolol:ti,ab or [mh Perindopril] or Perindopril:ti,ab or [mh Pindolol] or pindolol:ti,ab or pitavastatin:ti,ab or Pravachol:ti,ab or [mh Pravastatin] or pravastatin:ti,ab or Procardia:ti,ab or [mh Propranolol] or Propranolol:ti,ab or quinapril:ti,ab or [mh Ramipril] or Ramipril:ti,ab or [mh "Rosuvastatin Calcium"] or rosuvastatin:ti,ab or Sectral:ti,ab or [mh Simvastatin] or simvastatin:ti,ab or [mh Sotalol] or sotalol:ti,ab or statins:ti,ab or Sular:ti,ab or telmisartan:ti,ab or Tenormin:ti,ab or Tiazac:ti,ab or [mh Timolol] or timolol:ti,ab or "Toprol XL":ti,ab or ToprolXL:ti,ab or Trandate:ti,ab or trandolapril:ti,ab or [mh Valsartan] or valsartan:ti,ab or [mh Verapamil] or Verapamil:ti,ab or Verelan:ti,ab or Visken:ti,ab or Zebeta:ti,ab or Ziac:ti,ab or Zocor:ti,ab	68414
#3	#1 and #2	2557
#4	Actos:ti,ab or Albiglutide:ti,ab or Amaryl:ti,ab or "antidyslipidemic agent":ti,ab or "antidyslipidemic agents":ti,ab or Avandia:ti,ab or "beta blocker":ti,ab "beta blockers":ti,ab or [mh Biguanides] or Biguanides:ti,ab or Bydureon:ti,ab or Byetta:ti,ab or DiaBeta:ti,ab or [mh "Dipeptidyl-Peptidase IV Inhibitors"] or "Dipeptidyl peptidase IV inhibitor":ti,ab or "Dipeptidyl peptidase IV inhibitors":ti,ab or dulaglutide:ti,ab or Exenatide:ti,ab or [mh Ezetimibe] or [mh "Ezetimibe, Simvastatin Drug Combination"] or Ezetimibe:ti,ab or Fortamet:ti,ab or [mh Gliclazide] or Gliclazide:ti,ab or glimepiride:ti,ab or [mh Glipizide] or glipizide:ti,ab or "GLP-1 receptor agonist":ti,ab or "GLP-1 receptor agonists":ti,ab or "Glucagon-like peptide-1 receptor agonist":ti,ab or "Glucagon-like peptide-1 receptor	17545

Appendix B1. Original Search Strategies

ID	Search	Hits
#4 continued	agonists":ti,ab or Glucophage:ti,ab or Glucotrol:ti,ab or "Glucotrol XL":ti,ab or Glumetza:ti,ab or [mh Glyburide] or glyburide:ti,ab or "Glynase PresTab":ti,ab or [mh Linagliptin] or Linagliptin:ti,ab or [mh Liraglutide] or liraglutide:ti,ab or lixisenatide:ti,ab or Lyxumia:ti,ab or Meglitinides:ti,ab or [mh Metformin] or Metformin:ti,ab or Micronase:ti,ab or Nateglinide:ti,ab or [mh Niacin] or niacin:ti,ab or Ozempic:ti,ab or Pioglitazone:ti,ab or Prandin:ti,ab or Repaglinide:ti,ab or Rosiglitazone:ti,ab or Saxagliptin:ti,ab or semaglutide:ti,ab or Sitagliptin:ti,ab or [mh "Sitagliptin Phosphate"] or [mh "Sitagliptin Phosphate, Metformin Hydrochloride Drug Combination"] or [mh "Sulfonylurea Compounds"] or Starlix:ti,ab or Sulfonylureas:ti,ab or Tanzeum:ti,ab or [mh Thiazolidinediones] or Thiazolidinediones:ti,ab or [mh Tolazamide] or Tolazamide:ti,ab or [mh Tolbutamide] or tolbutamide:ti,ab or Trulicity:ti,ab or TZDs:ti,ab or Victoza:ti,ab or vildagliptin:ti,ab	
#5	#1 and #4	6201
#6	advice:ti,ab or [mh "Behavior Therapy"] or "behavior therapy":ti,ab or (behavior*:ti,ab and therap*:ti,ab) or (behavior*:ti,ab and chang*:ti,ab) or (behavior*:ti,ab and modification*:ti,ab) or [mh "Caloric Restriction"] or [mh Counseling] or counsel*:ti,ab or "Diabetes Prevention Program":ti,ab or "Diabetes Prevention Programme":ti,ab or DPP:ti,ab or ("Diabetes Prevention":ti,ab and (program*:ti,ab or stud*:ti,ab or trial*:ti,ab)) or diet:ti or [mh "Diet, Carbohydrate-Restricted"] or [mh "Diet, Fat-Restricted"] or [mh "Diet, Mediterranean"] or [mh "Diet, Reducing"] or [mh "Diet Therapy"] or dietary:ti or [mh "Directive Counseling"] or [mh Exercise] or exercise:ti or [mh "Exercise Therapy"] or [mh "Feedback, Psychological"] or [mh "Health Behavior" [mj]] or "health behavior":ti,ab or "health behaviors":ti,ab or "health behavioral":ti,ab "health behaviours":ti,ab or "health behaviour":ti,ab or [mh "Health Education"] or [mh "Health Education as Topic"] or "health education":ti,ab or [mh "Health Promotion" [mj]] or "health promotion":ti,ab or [mh "Life Style"] or lifestyle:ti,ab or "life style":ti,ab or [mh "Lifestyle Intervention"] or [mh "Motivational Interviewing"] or "motivational interviewing":ti,ab or "non pharmacologic intervention":ti,ab or "nonpharmacologic intervention":ti,ab or [mh "Patient Education as Topic"] or "patient education":ti,ab or "physical activity":ti or "physically active":ti or "psychological feedback":ti,ab or [mh "Risk Reduction Behavior"] or "Risk Reduction Behavior":ti,ab	130176
#7	#1 and #6	5373
#8	#3 or #5 or #7	12588
#9	#8 Publication Year from 2014 to 2018	4299
#10	(#9 and [mh ^Humans]) or (#9 not [mh ^Animal])	4299
#11	#10 not (letter:pt or newspaper article:pt or editorial:pt or comment:pt or "case reports":pt)	4269
#12	#11 and adult* (All Cochrane Library results)	2288

Appendix B1. Original Search Strategies

Prediabetes Search
Cochrane Library, 6-27-2018

ID	Search	Hits
#1	[mh "Prediabetic State"] or prediabet* or "pre diabetes" in Cochrane Reviews and Other Reviews	60

Risk Prediction Systematic Review Search
PubMed, 6-27-2018

Search	Query	Items Found
#1	Search (“ARIC diabetes risk score” OR “ARIC diabetes risk calculator” OR “Australian Type 2 Diabetes Risk Assessment Tool” OR AUSDRISK OR QDiabetes OR QDScore OR “Cambridge diabetes risk score”[all fields] OR “Cambridge risk score” OR (“Canadian Diabetes Risk Assessment” AND Questionnaire) OR CANRISK OR “Finnish Diabetes Risk Score” OR FINDRISC OR “Leicester Practice Risk Score” OR “QRISK 2”[all fields] OR QRISK2)	408
#2	Search (“Diabetes Mellitus, Type 2”[Mesh] OR “Type 2 Diabetes”[ALL FIELDS] OR “Prediabetic State”[MeSH] OR “prediabetic state”[All Fields] OR prediabet* OR “pre diabetes”[All Fields] OR “diabetes mellitus type 2”[All Fields] OR “type 2 diabetes mellitus”[All Fields] OR (“diabetes” AND “mellitus” AND “type 2”))	163235
#3	Search (#1 and #2)	249
#4	Search "Risk Assessment"[Mesh] OR “risk assessment”[all fields] OR “risk assessments”[all fields] OR “risk score”[all fields] OR “risk scores”[all fields] “risk identification”[all Fields] OR “risk reduction”[all fields] OR “Know Your Risk”[all fields] OR (risk* and (calculator* OR calculation*))	39878
#5	Search (#2 and #4)	2029
#6	Search (#3 or #5)	2243
#7	Search (#3 or #5) Filters: English	2111
#8	Search (#3 or #5) Filters: English; Adult: 19+ years	1104
#9	Search (#3 or #5) Filters: Publication date from 2008/06/27 to 2018/12/31; English; Adult: 19+ years	902
#10	Search (#9 AND Humans[Mesh:NOEXP]) OR (#9 NOT Animals[Mesh:NOEXP])	902
#11	Search ("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]	239210
#12	Search (#10 and #11)	36

Appendix B1. Original Search Strategies

Risk Prediction Search
Cochrane Library, 6-28-2018

ID	Search	Hits
#1	"ARIC diabetes risk score" or "ARIC diabetes risk calculator" or "Australian Type 2 Diabetes Risk Assessment Tool" or AUSDRISK or QDiabetes or QDScore or "Cambridge Diabetes Risk Score" or "Cambridge risk score" or ("Canadian Diabetes Risk Assessment" and Questionnaire) or CANRISK or "Finnish Diabetes Risk Score" or FINDRISC or "Leicester Practice Risk Score" or "QRISK 2" or QRISK2	57
#2	[mh "Diabetes Mellitus, Type 2"] or "Type 2 Diabetes" or [mh "Prediabetic State"] or "prediabetic state" or prediabet* or "pre diabetes" or "diabetes mellitus type 2" or "type 2 diabetes mellitus" or ("diabetes" and "mellitus" and "type 2")	28001
#3	#1 and #2	44
#4	[mh "Risk Assessment"] or "risk assessment" or "risk assessments" or "risk score" or "risk scores" "risk identification" or "risk reduction" or "Know Your Risk" or (risk* and (calculator* or calculation*))	35040
#5	#2 and #4	1832
#6	#3 or #5	1844
#7	#6 Publication Year from 2008 to 2018	1536
#8	(#7 and [mh ^Humans]) or (#7 not [mh ^Animals])	1536
#9	#8 and Adult*	1003
#10	#9 in Cochrane Reviews (Reviews and Protocols) and Other Reviews	318

Screening Searches
PubMed, 9-10-2019

Search	Query	Items Found
#1	Search (“Diabetes Mellitus, Type 2”[Mesh] OR “Glucose Tolerance”[Mesh] OR “glucose tolerance”[All Fields] OR “impaired glucose tolerance”[All Fields] OR IGT OR “impaired fasting glucose” OR IFG OR “Glucose Intolerance”[MeSH] OR “glucose intolerance”[All Fields] OR “Prediabetic State”[MeSH] OR “prediabetic state”[All Fields] OR prediabet* OR “pre diabetes”[All Fields] OR “diabetes mellitus type 2”[All Fields] OR “type 2 diabetes mellitus”[All Fields])	200064
#2	Search (“Blood Glucose”[Mesh] OR “blood glucose”[tiab] OR “Glucose Tolerance Test”[Mesh] OR OGTT[tiab] OR “glucose tolerance test”[ti] OR "Glycated Hemoglobin A"[Mesh] OR “hemoglobin A1c” OR HbA1c OR “fasting plasma glucose”[tiab])	239252
#3	Search (((“HbA(1c)”[tiab] or HbA1[tiab] or HbA1c[tiab] or “HbA 1c”[tiab] or ((glycosylated[tiab] or glycated[tiab]) AND hemoglobin[tiab]))))	44994
#4	Search (#2 OR #3)	243499
#5	Search (#1 AND #4)	90906
#6	Search ("Mass Screening"[Mesh] OR screen*[tiab])	743905
#7	Search (#5 AND #6)	5788
#8	Search (#7 NOT (gestation* OR Pregnancy[Mesh]))	4275
#9	Search (#7 NOT (gestation* OR Pregnancy[Mesh])) Filters: English	3903
#10	Search (#7 NOT (gestation* OR Pregnancy[Mesh])) Filters: English; Adult: 19+ years	2575
#11	Search ((#10 AND humans[mesh:noexp]) OR (#10 NOT animals[mesh:noexp]))	2575
#12	Search ((#10 AND humans[mesh:noexp]) OR (#10 NOT animals[mesh:noexp])) Filters: Publication date from 2018/01/01 to 2019/12/31	206
#13	Search (("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields] OR “meta synthesis”[ti] OR “systematic literature review”[ti] OR “this systematic review”[tw] OR “cochrane database syst rev”[ta])	286249
#14	Search (#12 AND #13)	6
#15	Search (((randomized[tiab] OR randomised[tiab]) AND controlled[tiab] AND trial[tiab]) OR (controlled[tiab] AND trial[tiab]) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	757903
#16	Search (#12 AND #15)	35

Appendix B1. Original Search Strategies

Search	Query	Items Found
#17	Search ("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Epidemiologic Studies"[MeSH] OR "Cross-Sectional Studies"[MeSH] OR "Organizational Case Studies"[MeSH] OR "Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Seroepidemiologic Studies"[MeSH] OR "Evaluation Studies"[Publication Type] OR "observational study" OR "observational studies")	2664953
#18	Search (#12 NOT #17)	89
#19	Search (#11 AND ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Duplicate Publication [PT] OR Erratum[All Fields]))	1

Cochrane Library, 9-10-2019

ID	Search	Hits
#1	[mh "Diabetes Mellitus, Type 2"] or [mh "Glucose Tolerance"] or "glucose tolerance" or "impaired glucose tolerance" or IGT or "impaired fasting glucose" or IFG or [mh "Glucose Intolerance"] or "glucose intolerance" or [mh "Prediabetic State"] or "prediabetic state" or prediabet* or "pre diabetes" or "diabetes mellitus type 2" or "type 2 diabetes mellitus"	30591
#2	[mh "Blood Glucose"] or "blood glucose":ti,ab or [mh "Glucose Tolerance Test"] or OGTT:ti,ab or "glucose tolerance test":ti or [mh "Glycated Hemoglobin A"] or "hemoglobin A1c" or HbA1c or "fasting plasma glucose":ti,ab	41937
#3	("HbA(1c)":ti,ab or HbA1:ti,ab or HbA1c:ti,ab or "HbA 1c":ti,ab or ((glycosylated:ti,ab or glycated:ti,ab) and hemoglobin:ti,ab))	19541
#4	#2 or #3	43118
#5	#1 and #4	17573
#6	[mh "Mass Screening"] or screen*:ti,ab	61933
#7	#5 and #6	1486
#8	#7 not (gestation* or [mh Pregnancy])	1337
#9	Adult*	609506
#10	#8 and #9	609
#11	(#10 and [mh ^humans]) or (#10 not [mh ^animals])	609
#12	#11 Publication Year from 2018 to 2019	336

Intervention Searches
PubMed, 9-10-2019

Search	Query	Items Found
#1	Search ("Diabetes Mellitus, Type 2"[Mesh] OR "impaired glucose tolerance"[All Fields] OR IGT OR "impaired fasting glucose" OR IFG OR "Glucose Intolerance"[MeSH] OR "glucose intolerance"[All Fields] OR "Prediabetic State"[MeSH] OR "prediabetic state"[All Fields] OR prediabet* OR "pre diabetes"[All Fields] OR "diabetes mellitus type 2"[All Fields] OR "type 2 diabetes mellitus"[All Fields])	166921
#2	Search "ACE inhibitor"[tiab] OR "ACE inhibitors"[tiab] OR "Acebutolol"[Mesh] OR Acebutolol[tiab] OR "Adalat CC"[tiab] OR "Adrenergic beta-Antagonists" [Pharmacological Action] OR "Adrenergic beta-Antagonists"[tiab] OR Altoprev[tiab] OR "Afeditab CR"[tiab] OR "Amlodipine"[Mesh] OR "Amlodipine, Valsartan Drug Combination"[Mesh] OR "Amlodipine Besylate, Olmesartan Medoxomil Drug Combination"[Mesh] OR "amlodipine, perindopril drug combination"[Supplementary Concept] OR Amlodipine[tiab] OR "Adrenergic beta-Antagonists"[Mesh] OR "Adrenergic beta-Antagonists"[tiab] OR "angiotensin II receptor blocker"[tiab] OR "angiotensin II receptor blockers"[tiab] OR "Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR "Angiotensin-converting enzyme inhibitor"[tiab] OR "angiotensin-converting enzyme inhibitors"[tiab] OR "Angiotensin-Converting Enzyme Inhibitors"[Pharmacological Action] OR "Angiotensin Receptor Antagonists"[Mesh] OR "Angiotensin Receptor Antagonists"[Pharmacological Action] OR "Angiotensin Receptor Antagonists"[tiab] OR "Antihypertensive Agents"[Mesh] OR "Antihypertensive Agents"[Pharmacological Action] OR "antihypertensive agent"[tiab] OR "antihypertensive agents"[tiab] OR Aspirin[Mesh] OR aspirin[tiab] OR Atenolol[Mesh] OR Atenolol[tiab] OR "Atorvastatin Calcium"[Mesh] OR Atorvastatin[tiab] OR azilsartan [Supplementary Concept] OR "azilsartan medoxomil"[Supplementary Concept] OR azilsartan[tiab] OR	685376

Appendix B1. Original Search Strategies

Search	Query	Items Found
	benazepril[Supplementary Concept] OR benazepril[tiab] OR “beta blocker”[tiab] OR “beta blockers”[tiab] OR Betapace[tiab] OR Betaxolol[Mesh] OR Betaxolol[tiab] OR "Bezafibrate"[Mesh] OR Bezafibrate[tiab] OR Bisoprolol[Mesh] OR "bisoprolol, hydrochlorothiazide drug combination"[Supplementary Concept] OR Bisoprolol[tiab] OR Bystolic[tiab] OR Calan[tiab] OR "Calcium Channel Blockers"[Mesh] OR "Calcium Channel Blockers"[Pharmacological Action] OR “calcium channel blockers”[tiab] OR candesartan[Supplementary Concept] OR candesartan[tiab] OR Captopril[MeSH] OR Captopril[tiab] OR Cardizem[tiab] OR carvedilol[Supplementary Concept] OR carvedilol[tiab] OR Chlorothiazide[Mesh] OR Chlorothiazide[tiab] OR Chlorthalidone[Mesh] OR Chlorthalidone[tiab] OR Clofenapate[Mesh] OR clofenapate[tiab] OR "Clofibric Acid"[Mesh] OR "Clofibric Acid"[tiab] OR Coreg[tiab] OR Corgard[tiab] OR Crestor[tiab] OR Diltiazem[Mesh] OR Diltiazem[tiab] OR Diuretics[Mesh] OR Diuretics[Pharmacological Action] OR diuretics[tiab] OR Diuril[tiab] OR Enalapril[Mesh] OR Elanapril[tiab] OR Enduron[tiab] OR eprosartan[Supplementary Concept] OR eprosartan[tiab] OR Esidrix[tiab] OR Felodipine[Mesh] OR Felodipine[tiab] OR Fenofibrate[Mesh] OR Fenofibrate[tiab] OR Fosinopril[Mesh] OR fosinopril[tiab] OR fluvastatin[Supplementary Concept] OR fluvastatin[tiab] OR Gemfibrozil[Mesh] OR Gemfibrozil[tiab] OR HCTZ[tiab] OR Hydrochlorothiazide[Mesh] OR Hydrochlorothiazide[tiab] OR Hydrodiuril[tiab] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh] OR Hygroton[tiab] OR "Hypolipidemic Agents"[Mesh] OR "Hypolipidemic Agents" [Pharmacological Action] OR “hypolipidemic agents”[tiab] OR Indapamide[Mesh] OR Indapamide[tiab] OR “Inderal LA”[tiab] OR “Inderal XL”[tiab] OR irbesartan[Supplementary Concept] OR irbesartan[tiab] OR Isradipine[Mesh] OR Isradipine[tiab] OR Kerlone[tiab] OR Labetalol[Mesh] OR labetalol[tiab] OR Lescol[tiab] OR “Lescol XL”[tiab] OR Levatol[tiab] OR Lipitor[tiab] OR Lisinopril[Mesh] OR Lisinopril[tiab] OR Livalo[tiab] OR Lopressor[tiab] OR Losartan[Mesh] OR Losartan[tiab] OR Lovastatin[MeSH] OR lovastatin[tiab] OR Lozol[tiab] OR Methyclothiazide[Mesh] OR Methyclothiazide[tiab] OR Metoprolol[Mesh] OR Metoprolol[tiab] OR Mevacor[tiab] OR Microzide[tiab] OR moexipril[Supplementary Concept] OR moexipril[tiab] OR Nadolol[Mesh] OR nadolol[tiab] OR Nebivolol[Mesh] OR nebivolol[tiab] OR Nicardipine[Mesh] OR Nicardipine[tiab] OR Nifedipine[Mesh] OR Nifedipine[tiab] OR Nisoldipine[Mesh] OR Nisoldipine[tiab] OR Norvasc[tiab] OR "Olmesartan Medoxomil"[Mesh] OR olmesartan[Supplementary Concept] OR olmesartan[tiab] OR Penbutolol[Mesh] OR penbutolol[tiab] OR Perindopril[Mesh] OR Perindopril[tiab] OR Pindolol[Mesh] OR pindolol[tiab] OR pitavastatin[Supplementary Concept] OR pitavastatin[tiab] OR Pravachol[tiab] OR Pravastatin[MeSH] OR pravastatin[tiab] OR Procardia[tiab] OR Propranolol[Mesh] OR Propranolol[tiab] OR quinapril[Supplementary Concept] OR quinapril[tiab] OR Ramipril[Mesh] OR Ramipril[tiab] OR "Rosuvastatin Calcium"[MeSH Terms] OR rosuvastatin[tiab] OR Sectral[tiab] OR Simvastatin[Mesh] OR simvastatin[tiab] OR Sotalol[Mesh] OR sotalol[tiab] OR statins[tiab] OR Sular[tiab] OR telmisartan[Supplementary Concept] OR telmisartan[tiab] OR Tenormin[tiab] OR Tiazac[tiab] OR Timolol[Mesh] OR timolol[tiab] OR “Toprol XL”[tiab] OR ToprolXL[tiab] OR Trandate[tiab] OR trandolapril[Supplementary Concept] OR trandolapril[tiab] OR Valsartan[Mesh] OR valsartan[tiab] OR Verapamil[Mesh] OR Verapamil[tiab] OR Verelan[tiab] OR Visken[tiab] OR Zebeta[tiab] OR Ziac[tiab] OR Zocor[tiab]	
#3	Search (#1 AND #2)	10308
#4	Search (Actos[tiab] OR Albiglutide[tiab] OR Amaryl[tiab] OR “antidyslipidemic agent”[tiab] OR “antidyslipidemic agents”[tiab] OR Avandia[tiab] OR “beta blocker”[tiab] “beta blockers”[tiab] OR Biguanides[Mesh] OR Biguanides[tiab] OR Bydureon[tiab] OR Byetta[tiab] OR DiaBeta[tiab] OR "Dipeptidyl-Peptidase IV Inhibitors"[Mesh] OR "Dipeptidyl-Peptidase IV Inhibitors"[Pharmacological Action] OR “Dipeptidyl peptidase IV inhibitor”[tiab] OR “Dipeptidyl peptidase IV inhibitors”[tiab] OR dulaglutide[Supplementary Concept] OR dulaglutide[tiab] OR exenatide[Supplementary Concept] OR Exenatide[tiab] OR Ezetimibe[Mesh] OR "Ezetimibe, Simvastatin Drug Combination"[Mesh] OR Ezetimibe[tiab] OR Fortamet[tiab] OR Gliclazide[Mesh] OR Gliclazide[tiab] OR glimepiride[tiab] OR Glipizide[Mesh] OR glipizide[tiab] OR “GLP-1 receptor agonist”[tiab] OR “GLP-1 receptor agonists”[tiab] OR “Glucagon-like peptide-1 receptor agonist”[tiab] OR “Glucagon-like peptide-1 receptor agonists”[tiab] OR Glucophage[tiab] OR Glucotrol[tiab] OR “Glucotrol XL”[tiab] OR Glumetza[tiab] OR Glyburide[Mesh] OR glyburide[tiab] OR “Glynase PresTab”[tiab] OR Linagliptin[Mesh] OR Linagliptin[tiab] OR Liraglutide[Mesh] OR liraglutide[tiab] OR lixisenatide[Supplementary Concept] OR lixisenatide[tiab] OR	94774

Appendix B1. Original Search Strategies

Search	Query	Items Found
	Lyxumia[tiab] OR Meglitinides[tiab] OR Metformin[Mesh] OR Metformin[tiab] OR Micronase[tiab] OR nateglinide[Supplementary Concept] OR Nateglinide[tiab] OR Niacin[Mesh] OR niacin[tiab] OR Ozempic[tiab] OR pioglitazone[Supplementary Concept] OR Pioglitazone[tiab] OR Prandin[tiab] OR Repaglinide[tiab] OR rosiglitazone[Supplementary Concept] OR Rosiglitazone[tiab] OR Saxagliptin[tiab] OR semaglutide[Supplementary Concept] OR semaglutide[tiab] OR Sitagliptin[tiab] OR "Sitagliptin Phosphate"[Mesh] OR "Sitagliptin Phosphate, Metformin Hydrochloride Drug Combination"[Mesh] OR "Sulfonylurea Compounds"[Mesh] OR Starlix[tiab] OR Sulfonylureas[tiab] OR Tanzeum[tiab] OR Thiazolidinediones[Mesh] OR Thiazolidinediones[tiab] OR Tolazamide[Mesh] OR Tolazamide[tiab] OR Tolbutamide[Mesh] OR tolbutamide[tiab] OR Trulicity[tiab] OR TZDs[tiab] OR Victoza[tiab] OR vildagliptin[Supplementary Concept] OR vildagliptin[tiab])	
#5	Search (#1 AND #4)	20097
#6	Search (advice[tiab] OR “Behavior Therapy”[Mesh] OR “behavior therapy”[tiab] OR (behavior*[tiab] AND therap*[tiab]) OR (behavior*[tiab] AND chang*[tiab]) OR (behavior*[tiab] AND modification*[tiab]) OR “Caloric Restriction”[Mesh] OR Counseling[Mesh] OR counsel*[tiab] OR “Diabetes Prevention Program”[tiab] OR “Diabetes Prevention Programme”[tiab] OR DPP[tiab] OR (“Diabetes Prevention”[tiab] AND (program*[tiab] OR stud*[tiab] OR trial*[tiab])) OR diet[ti] OR “Diet, Carbohydrate-Restricted”[Mesh] OR “Diet, Fat-Restricted”[Mesh] OR “Diet, Mediterranean”[Mesh] OR “Diet, Reducing”[Mesh] OR “Diet Therapy”[Mesh] OR dietary[ti] OR “Directive Counseling”[Mesh] OR Exercise[Mesh] OR exercise[ti] OR “Exercise Therapy”[Mesh] OR “Feedback, Psychological”[Mesh] OR "Health Behavior"[Majr] OR “health behavior”[tiab] OR “health behaviors”[tiab] OR “health behavioral”[tiab] "health behaviours"[tiab] OR "health behaviour"[tiab] OR “Health Education”[Mesh] OR “Health Education as Topic”[Mesh] OR “health education”[tiab] OR “Health Promotion”[Majr] OR “health promotion”[tiab] OR “Life Style”[Mesh] OR lifestyle[tiab] OR “life style”[tiab] OR “Lifestyle Intervention”[Mesh] OR “Motivational Interviewing”[Mesh] OR “motivational interviewing”[tiab] OR “non pharmacologic intervention”[tiab] OR “nonpharmacologic intervention”[tiab] OR "Patient Education as Topic"[Mesh] OR “patient education”[tiab] OR “physical activity”[ti] OR “physically active”[ti] OR “psychological feedback”[tiab] OR “Risk Reduction Behavior”[Mesh] OR “Risk Reduction Behavior”[tiab])	445942
#7	Search (#1 AND #6)	14598
#8	Search (#3 OR #5 OR #7)	41546
#9	Search (#3 OR #5 OR #7) Filters: English	37550
#10	Search (#3 OR #5 OR #7) Filters: Publication date from 2018/01/01 to 2019/12/31; English	3822
#11	Search ((#10 and Humans[Mesh:NOEXP]) OR (#10 not Animals[Mesh:NOEXP]))	3619
#12	Search ((#10 and Humans[Mesh:NOEXP]) OR (#10 not Animals[Mesh:NOEXP])) Filters: Adult: 19+ years	1449
#13	Search (letter[pt] OR newspaper article[pt] OR editorial[pt] OR comment[pt] OR case reports[pt])	3613181
#14	Search (#12 NOT #13)	1379
#15	Search (("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields])	285477
#16	Search (#14 AND #15)	60
#17	Search ((randomized[tiab] OR randomised[tiab]) AND controlled[tiab] AND trial[tiab]) OR (controlled[tiab] AND trial[tiab]) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH]	757903
#18	Search (#14 AND #17)	418
#19	Search ("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Cross-Sectional Studies"[MeSH] OR "Organizational Case Studies"[MeSH] OR "Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Seroepidemiologic Studies"[MeSH] OR "Evaluation Studies"[Publication Type] OR “observational study”[tw] OR “observational studies”[tw] OR cohort[tw] OR compared[tw] OR groups[tw] OR "case control"[tw] OR “cross sectional”[tw] OR multivariate[tw] OR (first[Tiab] AND episode[Tiab]) OR cohort[Tiab]))	6724215
#20	Search (#14 AND #19)	1097
#21	Search (#20 NOT (#18 OR #16))	717

Appendix B1. Original Search Strategies

Search	Query	Items Found
#22	Search (#9 AND ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Duplicate Publication [PT] OR Erratum[All Fields]))	27
#23	Search (((#22 and Humans[Mesh:NOEXP]) OR (#22 not Animals[Mesh:NOEXP])))	25
#24	Search ((#21 OR #18 OR #16) AND #23) One retraction was among new update search results Jung 2018	1

Cochrane Library, 9-10-2019

ID	Search	Hits
#1	[mh "Diabetes Mellitus, Type 2"] or "impaired glucose tolerance" or IGT or "impaired fasting glucose" or IFG or [mh "Glucose Intolerance"] or "glucose intolerance" or [mh "Prediabetic State"] or "prediabetic state" or prediabet* or "pre diabetes" or "diabetes mellitus type 2" or "type 2 diabetes mellitus"	26772
#2	"ACE inhibitor":ti,ab or "ACE inhibitors":ti,ab or [mh Acebutolol] or Acebutolol:ti,ab or "Adalat CC":ti,ab or "Adrenergic beta-Antagonists":ti,ab or Altoprev:ti,ab or "Afeditab CR":ti,ab or [mh Amlodipine] or [mh "Amlodipine, Valsartan Drug Combination"] or [mh "Amlodipine Besylate, Olmesartan Medoxomil Drug Combination"] or Amlodipine:ti,ab or [mh "Adrenergic beta-Antagonists"] or "Adrenergic beta-Antagonists":ti,ab or "angiotensin II receptor blocker":ti,ab or "angiotensin II receptor blockers":ti,ab or [mh "Angiotensin-Converting Enzyme Inhibitors"] or "Angiotensin-converting enzyme inhibitor":ti,ab or "angiotensin-converting enzyme inhibitors":ti,ab or [mh "Angiotensin Receptor Antagonists"] or "Angiotensin Receptor Antagonists":ti,ab or [mh "Antihypertensive Agents"] or "antihypertensive agent":ti,ab or "antihypertensive agents":ti,ab or [mh Aspirin] or aspirin:ti,ab or [mh Atenolol] or Atenolol:ti,ab or [mh "Atorvastatin Calcium"] or Atorvastatin:ti,ab or azilsartan:ti,ab or benazepril:ti,ab or "beta blocker":ti,ab or "beta blockers":ti,ab or Betapace:ti,ab or [mh Betaxolol] or Betaxolol:ti,ab or [mh Bezafibrate] or Bezafibrate:ti,ab or [mh Bisoprolol] or Bisoprolol:ti,ab or Bystolic:ti,ab or Calan:ti,ab or [mh "Calcium Channel Blockers"] or "calcium channel blockers":ti,ab or candesartan:ti,ab or [mh Captopril] or Captopril:ti,ab or Cardizem:ti,ab or carvedilol:ti,ab or [mh Chlorothiazide] or Chlorothiazide:ti,ab or [mh Chlorthalidone] or Chlorthalidone:ti,ab or [mh Clofenapate] or clofenapate:ti,ab or [mh "Clofibric Acid"] or "Clofibric Acid":ti,ab or Coreg:ti,ab or Corgard:ti,ab or Crestor:ti,ab or [mh Diltiazem] or Diltiazem:ti,ab or [mh Diuretics] or diuretics:ti,ab or Diuril:ti,ab or [mh Enalapril] or Elanapril:ti,ab or Enduron:ti,ab or eprosartan:ti,ab or Esidrix:ti,ab or [mh Felodipine] or Felodipine:ti,ab or [mh Fenofibrate] or Fenofibrate:ti,ab or [mh Fosinopril] or fosinopril:ti,ab or fluvastatin:ti,ab or [mh Gemfibrozil] or Gemfibrozil:ti,ab or HCTZ:ti,ab or [mh Hydrochlorothiazide] or Hydrochlorothiazide:ti,ab or Hydrodiuril:ti,ab or [mh "Hydroxymethylglutaryl-CoA Reductase Inhibitors"] or Hygroton:ti,ab or [mh "Hypolipidemic Agents"] or "hypolipidemic agents":ti,ab or [mh Indapamide] or Indapamide:ti,ab or "Inderal LA":ti,ab or "Inderal XL":ti,ab or irbesartan:ti,ab or [mh Isradipine] or Isradipine:ti,ab or Kerlone:ti,ab or [mh Labetalol] or labetalol:ti,ab or Lescol:ti,ab or "Lescol XL":ti,ab or Levatol:ti,ab or Lipitor:ti,ab or [mh Lisinopril] or Lisinopril:ti,ab or Livalo:ti,ab or Lopressor:ti,ab or [mh Losartan] or Losartan:ti,ab or [mh Lovastatin] or lovastatin:ti,ab or Lozol:ti,ab or [mh Methyclothiazide] or Methyclothiazide:ti,ab or [mh Metoprolol] or Metoprolol:ti,ab or Mevacor:ti,ab or Microzide:ti,ab or moexipril:ti,ab or [mh Nadolol] or nadolol:ti,ab or [mh Nebivolol] or nebivolol:ti,ab or [mh Nicardipine] or Nicardipine:ti,ab or [mh Nifedipine] or Nifedipine:ti,ab or [mh Nisoldipine] or Nisoldipine:ti,ab or Norvasc:ti,ab or [mh "Olmesartan Medoxomil"] or olmesartan:ti,ab or [mh Penbutolol] or penbutolol:ti,ab or [mh Perindopril] or Perindopril:ti,ab or [mh Pindolol] or pindolol:ti,ab or pitavastatin:ti,ab or Pravachol:ti,ab or [mh Pravastatin] or pravastatin:ti,ab or Procardia:ti,ab or [mh Propranolol] or Propranolol:ti,ab or quinapril:ti,ab or [mh Ramipril] or Ramipril:ti,ab or [mh "Rosuvastatin Calcium"] or rosuvastatin:ti,ab or Sectral:ti,ab or [mh Simvastatin] or simvastatin:ti,ab or [mh Sotalol] or sotalol:ti,ab or statins:ti,ab or Sular:ti,ab or telmisartan:ti,ab or Tenormin:ti,ab or Tiazac:ti,ab or [mh Timolol] or timolol:ti,ab or "Toprol XL":ti,ab or ToprolXL:ti,ab or Trandate:ti,ab or trandolapril:ti,ab or [mh Valsartan] or valsartan:ti,ab or [mh Verapamil] or Verapamil:ti,ab or Verelan:ti,ab or Visken:ti,ab or Zebeta:ti,ab or Ziac:ti,ab or Zocor:ti,ab	77302
#3	#1 and #2	2871
#4	Actos:ti,ab or Albiglutide:ti,ab or Amaryl:ti,ab or "antidyslipidemic agent":ti,ab or "antidyslipidemic agents":ti,ab or Avandia:ti,ab or "beta blocker":ti,ab "beta blockers":ti,ab or [mh Biguanides] or Biguanides:ti,ab or Bydureon:ti,ab or Byetta:ti,ab or DiaBeta:ti,ab or [mh "Dipeptidyl-Peptidase IV Inhibitors"] or "Dipeptidyl peptidase IV inhibitor":ti,ab or "Dipeptidyl	22875

Appendix B1. Original Search Strategies

ID	Search	Hits
	peptidase IV inhibitors":ti,ab or dulaglutide:ti,ab or Exenatide:ti,ab or [mh Ezetimibe] or [mh "Ezetimibe, Simvastatin Drug Combination"] or Ezetimibe:ti,ab or Fortamet:ti,ab or [mh Gliclazide] or Gliclazide:ti,ab or glimepiride:ti,ab or [mh Glipizide] or glipizide:ti,ab or "GLP-1 receptor agonist":ti,ab or "GLP-1 receptor agonists":ti,ab or "Glucagon-like peptide-1 receptor agonist":ti,ab or "Glucagon-like peptide-1 receptor agonists":ti,ab or Glucophage:ti,ab or Glucotrol:ti,ab or "Glucotrol XL":ti,ab or Glumetza:ti,ab or [mh Glyburide] or glyburide:ti,ab or "Glynase PresTab":ti,ab or [mh Linagliptin] or Linagliptin:ti,ab or [mh Liraglutide] or liraglutide:ti,ab or lixisenatide:ti,ab or Lyxumia:ti,ab or Meglitinides:ti,ab or [mh Metformin] or Metformin:ti,ab or Micronase:ti,ab or Nateglinide:ti,ab or [mh Niacin] or niacin:ti,ab or Ozempic:ti,ab or Pioglitazone:ti,ab or Prandin:ti,ab or Repaglinide:ti,ab or Rosiglitazone:ti,ab or Saxagliptin:ti,ab or semaglutide:ti,ab or Sitagliptin:ti,ab or [mh "Sitagliptin Phosphate"] or [mh "Sitagliptin Phosphate, Metformin Hydrochloride Drug Combination"] or [mh "Sulfonylurea Compounds"] or Starlix:ti,ab or Sulfonylureas:ti,ab or Tanzeum:ti,ab or [mh Thiazolidinediones] or Thiazolidinediones:ti,ab or [mh Tolazamide] or Tolazamide:ti,ab or [mh Tolbutamide] or tolbutamide:ti,ab or Trulicity:ti,ab or TZDs:ti,ab or Victoza:ti,ab or vildagliptin:ti,ab	
#5	#1 and #4	7823
#6	advice:ti,ab or [mh "Behavior Therapy"] or "behavior therapy":ti,ab or (behavior*:ti,ab and therap*:ti,ab) or (behavior*:ti,ab and chang*:ti,ab) or (behavior*:ti,ab and modification*:ti,ab) or [mh "Caloric Restriction"] or [mh Counseling] or counsel*:ti,ab or "Diabetes Prevention Program":ti,ab or "Diabetes Prevention Programme":ti,ab or DPP:ti,ab or ("Diabetes Prevention":ti,ab and (program*:ti,ab or stud*:ti,ab or trial*:ti,ab)) or diet:ti or [mh "Diet, Carbohydrate-Restricted"] or [mh "Diet, Fat-Restricted"] or [mh "Diet, Mediterranean"] or [mh "Diet, Reducing"] or [mh "Diet Therapy"] or dietary:ti or [mh "Directive Counseling"] or [mh Exercise] or exercise:ti or [mh "Exercise Therapy"] or [mh "Feedback, Psychological"] or [mh "Health Behavior" [mj]] or "health behavior":ti,ab or "health behaviors":ti,ab or "health behavioral":ti,ab "health behaviours":ti,ab or "health behaviour":ti,ab or [mh "Health Education"] or [mh "Health Education as Topic"] or "health education":ti,ab or [mh "Health Promotion" [mj]] or "health promotion":ti,ab or [mh "Life Style"] or lifestyle:ti,ab or "life style":ti,ab or [mh "Lifestyle Intervention"] or [mh "Motivational Interviewing"] or "motivational interviewing":ti,ab or "non pharmacologic intervention":ti,ab or "nonpharmacologic intervention":ti,ab or [mh "Patient Education as Topic"] or "patient education":ti,ab or "physical activity":ti or "physically active":ti or "psychological feedback":ti,ab or [mh "Risk Reduction Behavior"] or "Risk Reduction Behavior":ti,ab	159258
#7	#1 and #6	6747
#8	#3 or #5 or #7	15322
#9	#8 Publication date from Jan 2018 to Dec 2019	5789
#10	(#9 and [mh ^Humans]) or (#9 not [mh ^Animal])	5789
#11	#10 not (letter:pt or newspaper article:pt or editorial:pt or comment:pt or "case reports":pt)	5776
#12	#11 and Adult* (All Cochrane Library results)	1915

Gray Literature

ClinicalTrials.gov, 8-7-2018
ClinicalTrials.gov Screening:

74 Studies found for: screen OR screening | "Diabetes Mellitus, Type 2" OR "Glucose Tolerance" OR "glucose tolerance" OR "impaired glucose tolerance" OR IGT OR "impaired fasting glucose" OR IFG OR "Glucose Intolerance" OR "glucose intolerance" OR "Prediabetic State" OR "prediabetic state" OR prediabet* OR "pre diabetes" OR "diabetes mellitus type 2" OR "type 2 diabetes mellitus" | "Blood Glucose" OR "Glucose Tolerance Test" OR OGTT OR "glucose tolerance test" OR "Glycated Hemoglobin A" OR "hemoglobin A1c" OR HbA1c OR "fasting plasma glucose" OR "HbA(1c)" OR HbA1 OR HbA1c OR "HbA 1c" OR "glycosylated hemoglobin" OR "glycated hemoglobin" | Adult, Older Adult | Last update posted from 01/01/2014 to 12/31/2018

ClinicalTrials.gov and ICTRP Interventions: too big 3000-4000 results, not saved, we will rely on Cochrane Trials results for Interventions

ClinicalTrials.gov Prediabetes:

577 Studies found for: "Prediabetic State" OR prediabetes OR prediabetic OR "pre diabetes" | Adult, Older Adult | Last update posted from 01/01/2014 to 12/31/2018

The system automatically also searched for **Glucose Intolerance**, **Pre diabetics**, **Prediabetes**.

WHO ICTRP, 8-9-2018
WHO ICTRP - Screening

97 trials,

Advanced search:

In Title box: screen or screening

Condition box:

glucose tolerance OR impaired glucose tolerance OR IGT OR impaired fasting glucose OR IFG OR Glucose Intolerance OR diabetes mellitus type 2 OR type 2 diabetes mellitus

Recruitment status: ALL
Date of registration between 01/01/2014 and 12/31/2018
WHO ICTRP - Prediabetes

137 trials,

In Title box:

Prediabetic State OR prediabet* OR pre diabetes

Recruitment status: ALL
Date of registration between 01/01/2014 and 12/31/2018

ClinicalTrials.gov, 9-11-2019
ClinicalTrials.gov Screening:

67 Studies found for: ("Blood Glucose" OR "Glucose Tolerance Test" OR OGTT OR "glucose tolerance test" OR "Glycated Hemoglobin A" OR "hemoglobin A1c" OR HbA1c OR "fasting plasma glucose" OR "HbA(1c)" OR HbA1 OR HbA1c OR "HbA 1c" OR "glycosylated hemoglobin" OR "glycated hemoglobin") AND ("Diabetes Mellitus, Type 2" OR "Glucose Tolerance" OR "glucose tolerance" OR "impaired glucose tolerance" OR IGT OR "impaired fasting glucose" OR IFG OR "Glucose Intolerance" OR "glucose intolerance" OR "Prediabetic State" OR "prediabetic state" OR prediabet* OR "pre diabetes" OR "diabetes mellitus type 2" OR "type 2 diabetes mellitus") | screen OR screening | Adult, Older Adult | Last update posted from 06/01/2018 to 09/11/2019

Team relying on Cochrane Library Trials results for the interventions search.
WHO ICTRP, 9-11-2019
WHO ICTRP - Screening

42 trials,

Advanced search:

In Title box: screen or screening

Condition box:

glucose tolerance OR impaired glucose tolerance OR IGT OR impaired fasting glucose OR IFG OR Glucose Intolerance OR diabetes mellitus type 2 OR type 2 diabetes mellitus

Recruitment status: ALL
Date of registration between 06/01/2014 and 9/11/2019

Appendix B2. Eligibility Criteria

	Include	Exclude
Populations	All KQs: Studies of participants without obvious symptoms of diabetes (e.g., for KQ 1, studies of unselected populations that may include some participants with unrecognized symptoms of diabetes such as fatigue); nonpregnant women with a history of gestational diabetes (if they are >1 year postpartum) KQs 1, 2: Asymptomatic, nonpregnant adults KQs 3, 4: Asymptomatic, nonpregnant adults with screen-detected prediabetes or type 2 diabetes KQ 5: Asymptomatic, nonpregnant adults with recently diagnosed type 2 diabetes KQ 6: Asymptomatic, nonpregnant adults with screen-detected prediabetes or type 2 diabetes; nonpregnant adults with recently diagnosed type 2 diabetes KQs 7-9: Asymptomatic, nonpregnant adults with screen-detected prediabetes	KQs 1-9: Studies limited to or predominately comprising children, adolescents, and pregnant women; persons with symptomatic prediabetes or type 2 diabetes (e.g., weight loss, polyuria, blurred vision, headache); persons with a recent hospitalization; persons with a recent myocardial infarction; persons taking antipsychotics or glucocorticoids; persons with known cardiovascular disease or severe chronic kidney disease; persons living in an institution; other persons with medical conditions limiting their applicability to primary care–based populations (e.g., those with acute illness) KQ 5: Studies limited to or predominately comprising persons who have had diabetes for more than 1 year or with more advanced diabetes (e.g., persons already taking insulin or other medications; persons with proliferative retinopathy, nephropathy)
Screening	KQs 1, 2: Screening (targeted or universal) for prediabetes* or diabetes; tests include hemoglobin A1c, fasting plasma glucose, and the oral glucose tolerance test	All other tests, such as genetic testing for the risk of prediabetes or diabetes or testing for autoantibodies, which may be used for further evaluation after a diabetes diagnosis (e.g., to assess for type 1 or type 2 diabetes)
Interventions	All KQs: Behavioral counseling interventions can be provided alone or as part of a larger multicomponent intervention on diet and nutrition, physical activity, sedentary behavior, or a combination thereof, including but not limited to assessment with feedback, advice, collaborative goal setting, assistance, exercise prescriptions (referral to exercise facility or program), or arranging of further contacts. Interventions may be delivered via face-to-face contact, telephone, print materials, or technology (e.g., computer based, text messages, remote video feed) and can be delivered by a number of potential interventionists, including but not limited to clinicians, nurses, exercise specialists, dietitians, nutritionists, and behavioral health specialists. Dietary counseling may involve: Increased consumption of fruits, vegetables, whole grains, fat-free or low-fat dairy, and/or lean proteins Limited consumption of sodium, saturated fat, trans fat, and/or sugar-sweetened food and beverages Physical activity counseling may involve: Aerobic activities that involve repeated use of large muscles, such as walking, cycling, and swimming Resistance training designed to improve physical strength Reduction of sedentary behaviors	Counseling interventions aimed at falls prevention, balance, flexibility, gait, depression, or cognitive functioning Prenatal or postnatal dietary counseling Counseling interventions with components that are not feasible for implementation in health care settings (e.g., occupational/worksite-, church-, or school-based interventions conducted within existing social networks) Social marketing (e.g., media campaigns) Policy (e.g., local or state public/health policy) Stress management interventions (e.g., meditation, yoga, tai chi) Use of incentives (e.g., paying persons to lose weight) Supervised exercise with the goal of assessing effects of exercise Dietary counseling solely focused on increasing intake of specific vitamins, micronutrients, herbal supplements, spices (e.g., ginger, cinnamon), or antioxidants through dietary change or supplementation, or counseling on alcohol moderation Surgery

Appendix B2. Eligibility Criteria

	Include	Exclude
Interventions (continued)	Optional or access to guided physical activity or exercise classes Limited guided physical activity (i.e., 1 to 2 sessions) or provision of food samples is allowed if intention is to teach or demonstrate healthy lifestyle principles KQs 3-6: Primary care–relevant behavioral counseling or pharmacotherapy interventions for glycemic control or for more intensive risk reduction of atherosclerotic cardiovascular disease, including more intensive blood pressure control, lipid control, or aspirin KQs 7-9: Primary care–relevant behavioral counseling or pharmacotherapy interventions for glycemic control	
Comparisons	KQs 1, 2: No screening or alternative screening strategies KQ 3: Comparison based on timing; sooner vs. later intervention (i.e., starting intervention upon detection by screening vs. starting later based on clinical diagnosis); clinical diagnosis refers to any approach based on development of symptoms (e.g., polyuria, polydipsia, paresthesia) or monitoring of biomarkers (e.g., increase in hemoglobin A1c above a certain threshold) KQs 4, 5: No intervention, placebo, usual care (can include minimal intervention), different treatment targets (e.g., glucose or blood pressure targets), waitlist, or attention control (for lifestyle interventions) KQ 6: All comparisons eligible for KQs 3-5 KQs 7-9: Sooner vs. later intervention, no intervention, placebo, usual care, waitlist, or attention control (for lifestyle interventions)	Comparative effectiveness (head-to-head) trials of medications or behavioral counseling without another eligible control group
Outcomes	KQs 1, 3-5, 8: Mortality, cardiovascular morbidity (including myocardial infarction, stroke, congestive heart failure), chronic kidney disease, amputation, skin ulcers, visual impairment (including blindness), periodontitis (including tooth loss), moderate to severe neuropathy, and quality of life KQ 2: Labeling, anxiety, harms from false-positive results, burden, inconvenience, depression, and unnecessary testing and treatment KQ 6: Serious side effects from treatment, including mortality, myocardial infarction, stroke, cancer, and hypoglycemic events requiring medical attention, burden and inconvenience KQ 7: Development of type 2 diabetes KQ 9: Blood pressure; total, low-density lipoprotein, and high-density lipoprotein cholesterol; BMI, weight; calculated 10-year cardiovascular disease risk	KQs 1, 3-5, 7–9: Studies with less than 6 months of followup
Study Designs	All KQs: Controlled clinical trials KQs 2, 6: Controlled prospective cohort studies and case-control studies are also eligible KQ 8: Controlled prospective cohort studies are also eligible	Modeling studies, systematic reviews,** case series, case reports, uncontrolled observational studies, retrospective cohort studies, editorials, and all other study designs not mentioned
Settings	Studies conducted in or recruited from primary care settings or settings otherwise applicable to primary care (i.e., screening/interventions that could feasibly be implemented in or referred from primary care)	Settings not generalizable to primary care (e.g., inpatient hospital units, emergency departments, nursing home and other institutional settings, school-based programs, occupational settings)

Appendix B2. Eligibility Criteria

	Include	Exclude
Countries	Studies conducted in countries categorized as "Medium" or higher on the 2016 Human Development Index (as defined by the United Nations Development Programme)	Studies conducted in countries that are not categorized as "Medium" or higher on the 2016 Human Development Index
Language	English language	Languages other than English
Study quality	Good or fair quality	Poor quality (according to design-specific USPSTF criteria)

* Prediabetes includes persons who meet criteria for impaired fasting glucose or impaired glucose tolerance and persons with an A1c level of 5.7 percent to 6.4 percent.

** Systematic reviews were excluded from the evidence review; however, separate searches were conducted to identify relevant systematic reviews, and the citations of all studies included in those systematic reviews were reviewed to ensure that the database searches captured all relevant primary studies.

Randomized, Controlled Trials and Cohort Studies

Criteria

- Initial assembly of comparable groups
- Randomized, controlled trials (RCTs)—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements that are equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: Adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of Ratings Based on Above Criteria

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention is given to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair: Studies will be graded "fair" if any or all of the following problems occur without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains on whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is lacking for RCTs.

Poor: Studies will be graded "poor" if any of the following major limitations exist: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Sources: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force, Procedure Manual, Appendix VI. Rockville, MD: U.S. Preventive Services Task Force; 2015[78]

Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of Ratings Based on Above Criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (greater than 100) of broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.

Poor: Has a fatal flaw, such as uses inappropriate reference standard; improperly administers screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients.

Source: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force, Procedure Manual, Appendix VI. Rockville, MD: U.S. Preventive Services Task Force; 2015[78]

Appendix B4. Supplemental Questions

To address the supplemental questions, we used an approach similar to that used for contextual questions with targeted searches and streamlined methods (e.g., less comprehensive electronic literature searches were conducted, dual risk-of-bias assessment of studies was not conducted). The methods used included identifying relevant information from within the evidence review and from currently included studies (at a minimum) for each question. We conducted targeted supplemental literature searches of PubMed/MEDLINE. The additional searches (focused mainly on Questions 4 through 8) for these questions yielded 1,489 citations that we reviewed. The reference lists of relevant articles were also reviewed to supplement the electronic searches. To answer the supplemental questions, we used a best-evidence approach when possible (e.g., if we identified a recent, good-quality systematic review for a question, we focused on it).

Supplemental Question 1. What is the evidence on the magnitude of the marginal benefit of starting metformin in the prediabetes state (i.e., A1c=5.7) vs. when diagnosed with diabetes (i.e., A1c=6.5)?

No randomized, controlled trials (RCTs) were directly designed to answer this question: No trials directly answer this question by randomizing persons to be treated at an A1c around 5.7 versus waiting until their A1c is around 6.5. If there were, they would fall within the current scope of the review and we would include them. We continue to look for evidence on this question in our literature surveillance, and we have not identified any new trials. The Diabetes Prevention Program (DPP) and other trials of metformin (and other interventions) for prediabetes enrolled persons with prediabetes (often defined by their oral glucose tolerance test [OGTT] or fasting plasma glucose [FPG], rather than defined by A1c 5.7 to 6.4) and were designed to assess the outcome of progression to diabetes (as defined by OGTT, FPG, A1c, or some combination of those). They did not include a comparison of starting metformin at a lower versus higher A1c and subsequently follow persons for the development of the health outcomes listed in the analytic framework (e.g., microvascular outcomes, cardiovascular events).

Subgroup analyses for the aggregate microvascular outcome from the Diabetes Prevention Program Outcomes Study (DPPOS) are potentially relevant: DPPOS (intensive lifestyle intervention [ILI] vs. metformin vs. placebo) reported an aggregate microvascular outcome that combined intermediate outcomes and health outcomes (e.g., nephropathy includes urine microalbumin as well as renal failure/dialysis/transplant) for the comparison of ILI versus metformin vs. placebo. At 15-year followup, the metformin group had the highest percentage of participants with that adverse health outcome, although there was no statistically significant difference between groups (ILI 11.3% vs. metformin 13.0% vs. placebo 12.4%). As described in the evidence review, DPPOS was not focused on a comparison based on treating at different A1c thresholds (recall that it invited all DPP participants to continue into DPPOS; all participants were offered the ILI in a group format during the 1-year bridge between DPP and DPPOS; placebo was discontinued; metformin became unmasked; the ILI group was offered supplementary group programs and lifestyle check-ins).

Subgroup analyses from DPPOS showed that higher baseline A1c was associated with higher prevalence of the aggregate microvascular outcome, and the raw numbers showed higher percentages for metformin than for placebo in the lower A1c categories, but the interaction across A1c subgroups was not significant for the metformin vs. placebo comparison (for metformin vs. placebo: baseline A1c 3.2 to 5.7, RR 1.19 [0.84, 1.67]; baseline A1c 5.7 to 6.0, RR 1.17 [0.87-1.57]; baseline A1c 6.0 to 8.5, RR 0.96 [0.78, 1.19]; p=0.44) (shown in Table 2 of the 15-year followup paper[79] and on backup slide 127 from the October 2019 in-person U.S. Preventive Services Task Force (USPSTF) meeting presentation). Figure 4 of the 15-

year DPPOS followup paper shows an inflection point for increased risk of the aggregate microvascular endpoint around an A1c of 6.2.[79]

Subgroup analyses from DPP were highlighted by the DPP authors as post hoc, and they emphasized that DPP was not designed or powered to assess subgroups. DPPOS reported that it prespecified subgroup analyses for sex, age, race/ethnic origin, and glycemia (although it is possibly a stretch to consider these as prespecified by DPPOS considering how DPP describes its design and subgroups approach and given that DPPOS is an extension of a subset of DPP participants).

Supplemental Question 2. Does the effectiveness of metformin vary by subpopulation, such as age, body mass index (BMI), gender, race/ethnicity, or baseline A1c?

Baseline A1c: The answer to Supplemental Question 1 above addresses what we found for baseline A1c (no significant effect modification) and comes from DPPOS for that aggregate microvascular outcome. We found no other eligible studies that reported on health outcomes in our analytic framework. For the outcome of diabetes incidence, the main DPP paper does not include baseline A1c among its subgroup analyses, although it does have baseline FPG and OGTT results (in Table 2 of the paper[80]), and it found no statistically significant effect modification for OGTT for metformin versus placebo but found a statistically significant effect modification for baseline FPG for metformin vs. placebo for the outcome of diabetes incidence (relative reduction of 48% [33% to 60%] for FPG 110 to 125 vs. 15% [-12% to 36%] for FPG 95 to 109 $p<0.05$). A publication focused on the subgroups that benefited most over 15 years of DPP/DPPOS for the outcome of diabetes incidence compared metformin with placebo groups.[81] The study reported that metformin was more effective in subjects with higher baseline A1c levels (6.0% to 6.4% vs. <6.0%), higher baseline fasting glucose levels, and women with a history of gestational diabetes mellitus. There were no significant interactions with baseline age, BMI, sex, or race/ethnicity.[81]

Age, BMI, gender, race/ethnicity: DPPOS reported no significant effect modifications by age, BMI, sex, or race/ethnicity[79] (table shown on backup slide 127 from the October 2019 in-person USPSTF meeting presentation). We found no other eligible studies that reported on health outcomes in our analytic framework. For the outcome of diabetes incidence, Table 2 of the primary DPP article provides the main results[80] (shown on backup slide 120 from the slide deck used at the in-person October 2019 USPSTF meeting). We had included this information in the evidence review (key question [KQ] 7 section on pharmacologic interventions: subgroups), specifically stating the following:

> With the caveat that their subgroup analyses were post hoc and underpowered, the DPP authors noted that after 3 years of followup, the effect of metformin compared with placebo was not statistically significantly different for subgroups defined by age, sex, or race and ethnicity. However, they reported statistically significant effect modification by BMI ($p<0.05$), with greater effect on diabetes incidence for those with higher BMIs (e.g., reduction in diabetes incidence 53% [95% CI 36% to 65%] for BMI ≥35 kg/m^2 vs. 3% [95% CI -36% to 30%] for BMI 22 to <30 kg/m^2). After 15 years of followup within DPPOS, the effect of metformin compared with control was not significantly different between males and females. The Indian Diabetes Prevention Program investigators found that age, sex, and BMI did not independently influence the development of diabetes for the control group compared with any of its three treatment groups, including the metformin only group.

Comparative effectiveness of metformin vs. ILI: We note that the head-to-head comparison of metformin and ILI does not directly address Supplemental Question 2 (because the question is about the effectiveness of metformin, and not comparative effectiveness), but DPPOS and DPP both reported on this comparison; therefore, we include it here. DPPOS reported no statistically significant effect modification for ILI vs. metformin for the aggregate microvascular outcome by baseline A1c, age, sex, BMI, and race or ethnicity[79] (table shown on backup slide 127 from the October 2019 in-person USPSTF meeting presentation). For the outcome of diabetes incidence, Table 2 from the main DPP publication shows that the advantage of ILI over metformin was greater in older persons (than younger persons, ages 25 to 44 years) and those with lower BMI (than higher BMI ≥35).[80] DPP authors noted that their subgroup analyses were post hoc and underpowered, and they tested many comparisons.

Supplemental Question 3. What is the natural history of prediabetes, as currently defined?

Levels of glucose and glycemia in the prediabetes range are associated with an increased risk of adverse health outcomes. The introduction to the evidence review (Etiology and Natural History section) and Supplemental Questions 7 and 9 have information about the risk of mortality and adverse health outcomes associated with prediabetic glucose and glycemic levels. Various studies have demonstrated that increasing glucose and glycemia levels are associated with a continuously increasing risk of adverse health outcomes without a clear inflection point (i.e., without a clear threshold/value at which the risk escalates).

Data from control groups of randomized trials included in the Evidence-based Practice Center evidence review: The randomized trials included in KQ 7 of the evidence review (on interventions for prediabetes to delay or prevent progression to diabetes) provided control group data to inform this question. Those trials, including the DPP and DPPOS, described rates of progression from prediabetes to diabetes (defined by FPG, OGTT, or A1c). These data were in the review and presented at the in-person October 2019 USPSTF meeting (some of the data are shown on backup slide 76 from the in-person presentation). Overall, the studies show a wide range of rates of progression from prediabetes to type 2 diabetes mellitus, perhaps due to heterogeneity of prediabetes itself, differences in enrolled populations, and variation in followup duration and measures.

Looking at all the trials of lifestyle interventions compared with controls that were included in the evidence review, we see that control group event rates indicate that an average of 20 percent of persons (range across trials: 3.3% at 1 year to 90% at 23 years) progress from prediabetes to diabetes (defined by FPG, OGTT, or A1c) over a broad range of followup periods from 1 to 23 years. When limiting to studies with 1 year of followup (k=8), the mean was 9 percent (range 3.3% to 20%) of persons progressing to incident diabetes. The breakdown by control group event rate is as follows; we include the number of studies (k) for each event rate and the followup duration of those studies:

<5%: k=3 (all 1 year)

5% to <10%: k=6 (3 were 1 year and 1 study each of 2, 4, and 5.5 years)

10% to <20%: k=5 (4 studies of 3 years; 1 study of 1 year)

20% to <30%: k=4 (all different durations: 1 year, 3 years, 5 years, and 6 years)

≥30%: k=3 (55% in the IDDP at 3 years, 52% in DPPOS at 15 years, and 90% in Da Qing at 23 years)

If we focus on the placebo arm of the DPP, we see that 29 to 30 percent progressed to type 2 diabetes mellitus over 3 years. In the DPPOS, 52 percent of those in the placebo group progressed to type 2 diabetes mellitus over 15 years (raw data shown in the figures in **Appendix F**).

Data from other studies that used current definitions of prediabetes: Three cohort studies that used current definitions were identified in targeted searches.[82-84] Briefly, a cohort study of over 77,000 Kaiser Foundation Health Plan members with prediabetes (based on A1c) reported that the 2-year risk of incident diabetes varied widely by A1c and BMI.[82] A small subset (5.2% of the population) had a very high risk (18.0% probability) of developing type 2 diabetes mellitus within 2 years, about 13 percent of the population had a moderate 2-year risk (8.2% probability), and most (81.5%) of the population was at much lower risk (1.6% probability). The authors developed a simple stratification scheme based on A1c and BMI to estimate the risk of developing type 2 diabetes mellitus. The high-risk group comprised 4,001 of the 77,107 persons and generally had baseline A1c 6.3 to 6.4%. The risk of developing diabetes increased with increasing A1c and with increasing BMI.

A longitudinal cohort study of American Indians reported on incident type 2 diabetes mellitus over 10 years.[83] The study included 2,005 adults. Of those, 168 had prediabetes (based on A1c 5.7 to 6.4%) at baseline and their mean age was 30 years and mean BMI was 39. Over a median followup of 4.6 years (total person-years of followup were 11,520), the incidence rate was about 100 type 2 diabetes mellitus cases per 1,000 person-years for men and about 114 cases per 1,000 person-years for women (data reported in the figure only).

The third cohort study assessed 406 persons of Asian ethnicity with prediabetes and followed them every 3 to 6 months for up to 9 years.[84] About 20 percent (n=81) were diagnosed with type 2 diabetes mellitus over a median followup of 46 months. The study showed variation in rates of progression to type 2 diabetes mellitus by the prediabetes category/definition, with the highest rates for persons with combined glucose intolerance (i.e., those with both impaired fasting glucose [IFG] and impaired glucose tolerance [IGT]) (31.9%) or isolated IGT (18.5%) than for those with isolated IFG (15.2%) or isolated elevated A1c (10.9%).

Supplemental Question 4. What is the amount of overdiagnosis and overtreatment in prediabetes and diabetes?

Supplemental Question 4a. What percentage of patients with prediabetes, by today's definitions (e.g., A1c=5.7 to 6.4), progress to diabetes, remain prediabetic, or return to normal glucose tolerance (without intervention), and over what time frame? How does this differ by baseline A1C?

Data from control groups of randomized trials included in the EPC evidence review: Supplemental Question 3 addresses how many people with prediabetes progress to type 2 diabetes mellitus. Among DPP participants in the placebo arm, after 3 years, 40.7 percent remained prediabetic and 24 percent were reported to have at least one episode of return to normal glucose tolerance without intervention. The study did not report on how long normal glucose tolerance was maintained. It is unclear in the other studies that

we identified whether individuals who did not progress to diabetes remained prediabetic or returned to normal glucose tolerance.

Data from other studies that used current definitions of prediabetes: The Supplemental Question 3 response provides information from such studies on how many people with prediabetes progress to type 2 diabetes mellitus. No additional studies were identified that report how many people with prediabetes remained prediabetic or returned to normal glucose tolerance.

Difference by baseline A1c: Six studies reported progression to diabetes by baseline A1c.[64, 82, 85-88] Overall, these studies show an increasing risk of progression to T2DM with increasing baseline A1c and show that people with both IFG and IGT have an increased risk of progression to diabetes than those with only IFG or IGT or isolated elevated A1c.

A cohort study with more than 77,000 participants, described in Supplemental Question 3, reported increased risk of diabetes progression for individuals as their A1c increased.[82] Persons in the low-risk category (with an A1c of 6.0% or less or 6.1-6.2% if their BMI was less than 30) had a much lower risk of progressing to diabetes than individuals in the highest risk category (A1c 6.2-6.4% with BMI 25 or more) (1.6% vs. 18.0% progressed to diabetes over 2 years).

A cohort study in New Zealand followed 18,728 individuals with elevated A1c in the prediabetes range for a median of 4 years.[64] Participants were categorized by baseline A1c into three categories: A1c 5.8-6.0%, 6.1-6.2%, and 6.3-6.7%. Progression to diabetes increased as baseline A1c increased (progression to T2DM occurred in 9.9% vs. 11.1% vs. 28.8% of participants, respectively).

The Singapore Chinese Health Study reported incident diabetes in men and women among participants (n=2,191) who were categorized by baseline A1c (5.7 or less, 5.8-5.9, 6.0-6.1, 6.2-6.4, and 6.5 or greater).[88] Over a mean followup of 5.2 years, progression to diabetes for participants in A1c categories that meet criteria for prediabetes (A1c 5.8-5.9, 6.0-6.1, and 6.2-6.4) were 14 percent, 11 percent, and 10 percent, respectively. Using a standardized incidence rate, progression to diabetes was calculated at 243, 366, and 579 per 100,000 person-years for participants with baseline A1c of 5.8-5.9, 6.0-6.1, and 6.2-6.4, respectively.

Another cohort study, based in the United States, followed 4,714 middle-aged adults without diabetes for a median of 14 years.[85] Individuals were categorized by baseline A1c of less than 5.0 percent, 5 to less than 5.5 percent, 5.5 to less than 6.0 percent, 6.0 to less than 6.5 percent, and 6.5 percent or greater. Cumulative incidence for progression to diabetes was reported as 21 percent for individuals with baseline A1c of 5.5 percent to less than 6.0 percent compared with 44 percent for individuals with a baseline A1c of 6.0 percent to less than 6.5 percent.

One additional cohort study of 406 adults[84] and two randomized controlled trials[86, 87] addressed progression to diabetes by examining subgroups of patients with IFG, IGT, or a combination of both. All three studies found higher rates of progression for participants with combined IFG and IGT (31.3-32.9% over 36-46 months) than for those with only IFG or only IGT (5-15.2% for IFG; 11.2-18.5% for IGT). Two studies also differentiated participants who had isolated elevated HbA1c and found lower progression rates (10.9-15.2% over 36-46 months) than for those with combined IFG and IGT.[84, 86]

Supplemental Question 4b. What percentage of patients with early-stage diabetes progress to complications with current medical therapy?

We aimed to identify evidence for people with early stage T2DM diabetes who were on no more than 1 hypoglycemic agent (and did not use insulin), had an A1c of less than 9.0 percent, and were diagnosed with T2DM within 5 years. Key Question 4 (KQ 4) in the evidence review provides information relevant to this supplemental question. Targeted searches identified a cost-effectiveness analysis and two additional cohort studies that provide additional information regarding progression to complications for early-stage diabetes, although neither cohort study provided details on the medical therapies received over the course of followup.[89-91]

Data from randomized trials included in the evidence report: Key Question (KQ 5) of the evidence report included two studies relevant to this question.[1, 92-94] In summary, UKPDS reported outcomes for participants in two different trials with early-stage diabetes on one of two sulphonylureas (chlorpropamide or glibenclamide) or metformin during a 10-year followup with additional 10-year post-trial monitoring period. The DESMOND trial reported outcomes for an education-based program during a 3-year period. All-cause mortality was variable in these studies (3.9-44%, highest noted for metformin in post-trial monitoring and lowest for group education). UKPDS reported lower rates of diabetes-related death, MI, and stroke for participants in the metformin group than participants in either sulphonylurea group during the initial 10 years of followup. During the post-trial monitoring, rates for metformin surpassed those of the sulphonylurea group. Progression to chronic kidney disease, amputations, and blindness were all low (less than 5%), with retinal photocoagulation slightly higher (7.3-8.9%).

Data from other studies that included participants with early-stage diabetes: Two additional cohort studies were identified in a targeted search. Data from the studies were uncertain, however, because the participants did not have an identified medical therapy. A cost-effectiveness analysis modeled complications from early-stage diabetes using UKPDS data.[89, 90]

In a cohort study from New Zealand, 62,002 patients with type 2 diabetes and a mean duration of disease of 3-4 years were followed for a median of slightly more than 7 years. It is unclear what medical therapy participants were using in this cohort study. Participants were followed for progression to lower limb amputations, which was calculated at 2.11 amputations per 1,000 person-years (based on a total of 892 lower limb amputations).[89]

Another cohort study used data from the Nurses' Health study for women and the Health Professionals Follow-Up Study for men, following participants with newly diagnosed diabetes for an average of 13.3 years.[90] Outcomes for this study were cardiovascular disease incidence and mortality, which included fatal and nonfatal coronary heart disease (including myocardial infarction, fatal and nonfatal stroke, and coronary artery bypass graft surgery). Among the 8,970 women and 2,557 men enrolled, there were 2,311 adverse cardiovascular events (20.0%). These included 498 fatal and nonfatal strokes (4.3%) and 1,844 instances of nonfatal coronary heart disease (16.0%). There were also 858 deaths from cardiovascular disease (7.4%). The study did not comment on current medical therapy or how these therapies may have changed during the followup period.

A cost-effectiveness analysis focused on lifestyle modification or metformin in preventing diabetes in adults with IGT estimated that incidence of complications in a 10-year period from diagnosis was very

low.[88] Specifically, mimicking UKPDS data, it estimated an incidence of 6.5 percent for microalbuminuria and 3.3 percent for peripheral neuropathy (and zero for retinopathy).

Supplemental Question 4c. What percentage of the diabetes prevented in the DPPOS represents overdiagnosed diabetes?

i. Were microvascular complications prevented by metformin in DPPOS? Was uncontrolled diabetes (A1c>9) prevented by metformin in DPPOS?

Published studies did not report on how much of the diabetes in DPPOS represents overdiagnosed diabetes, but information related to microvascular complications and uncontrolled diabetes may inform discussions about that question. Overall, data from DPPOS did not indicate that metformin prevented adverse microvascular outcomes when compared with placebo, and the data suggest that metformin is less effective than lifestyle interventions.

One of the primary outcomes for DPPOS was the prevalence of an aggregate microvascular outcome (retinopathy, nephropathy, and neuropathy), as described in the evidence review. The aggregate outcome combined intermediate outcomes and health outcomes (e.g., the nephropathy component included urine microalbumin as well as renal failure/dialysis/transplant). At 15-year followup, prevalence of the aggregate microvascular outcome was not statistically significantly different between trial arms (ILI 11.3% vs. metformin 13.0% vs. placebo 12.4%).[79] As detailed in the evidence review, there were no significant differences in treatment effects among subgroups defined by age at DPP enrollment, but sex-specific analyses found a significant interaction between sex and intervention, with a benefit only in women. Among women (n=1,887), the lifestyle intervention was associated with a lower prevalence than the placebo group (8.7% vs. 11.0%; $p<0.05$) or the metformin group (8.7% vs. 11.2%; $p<0.05$); rates were similar among women in the metformin and placebo groups (11.2% vs. 11.0%).[79] Among men, rates were similar for those in the placebo group (15.1%), metformin group (16.8%), and lifestyle intervention group (16.6%). A post hoc analysis among participants whose most-recent HbA1c was 6.5 percent or greater (n=607, approximately 26% of the DPPOS cohort) found lower rates of retinopathy (RR 0.61 [95% CI, 0.37 to 1.01]) and neuropathy (RR 0.38 [95% CI, 0.19 to 0.75]) for the intensive lifestyle group than placebo; there were no significant differences between the metformin and placebo groups.

We did not identify any DPPOS studies that specifically reported information regarding prevention of uncontrolled diabetes, defined by A1c greater than 9 percent. The DPPOS 15-year followup study reported that the mean A1cs for participants who developed T2DM in three trial arms were 6.7 (SD 1.4) for placebo, 6.5 (SD 1.3) for metformin, and 6.7 (SD 1.4) for lifestyle intervention (at DPPOS end in year 2013).[79] Among all participants (any study group) who developed T2DM (n=1550), the mean A1c was 6.6 percent (SD 1.4). The corresponding data for the DPP end (year 2001) were 6.5 (SD 0.9) for placebo, 6.3 (SD 0.7) for metformin, and 6.4 (SD 0.7) for lifestyle intervention. Although standard deviations are reported, there is uncertainty about the distribution of the data (i.e., uncertainty about whether the data were normally distributed). Therefore, it is not possible to reliably estimate how many participants in any group had an A1c greater than 9 percent.

Supplemental Question 4d. Prepare an outcomes table on the benefits and harms (including overdiagnosis and overtreatment of prediabetes) of metformin as a preventive medication in a hypothetical cohort of 10,000 unscreened asymptomatic adults. (Consider including "opportunity costs" [i.e. not receiving benefits of diet/physical activity because metformin is prescribed instead of diet/physical activity].)

Table 1 provides projected 10-year outcomes of treating 10,000 adults with prediabetes, comparing intensive lifestyle intervention versus metformin started at the time of prediabetes diagnosis versus metformin started (later) at the time of diabetes diagnosis. Overall, we did not identify reliable inputs for many cells in the outcomes table, precluding our ability to provide reliable total estimates for benefits and for harms under each scenario.

Supplemental Question 5. What is the distribution of disutilities of having diabetes, screen-detected or early diabetes (precomplications), or prediabetes?

Eight studies (4 RCTs and 4 cross sectional studies) using data from across 13 articles provided health utility data for individuals with screen-detected or uncomplicated early diabetes or prediabetes.[76, 86, 95-105] The findings represent individuals not on metformin or making intensive lifestyle changes. Four articles from the ADDITION-Europe trial provided health utility values for a population with screen-detected diabetes,[76, 95, 98, 102] two studies provided health utilities for a population with uncomplicated early diabetes (diagnosed within the previous 5 years),[96, 101] and 10 articles from eight studies provided health utilities for populations with prediabetes.[86, 96-101, 103-105] RCT data reflected either baseline or control group results. **Appendix B5** provides additional details on measures of utilities used in studies addressing this Supplemental Question.

Studies included populations with a mean or median age between 44 and 67 years and with sample sizes varying widely from 47 to 7,632. Of the eight included studies, six (represented in nine articles) were conducted in Europe[76, 86, 95, 98, 100-102, 104, 105] and two (represented in four articles) were conducted in the United States.[76, 96, 97, 99, 103] Multiple instruments were used to measure health utilities, including the EQ-5D, used in three studies (described in five articles);[76, 95, 98, 102, 104] the SF-6D, used in four studies (described in five articles);[97, 99-101, 103] the HRQOL 15-D, used in two studies;[101, 105] and the QWB-SA, used in 1 study.[96] Because health utility instruments differ in several ways, including what aspects of psychological health and well-being are measured, ceiling effects, and the processes by which index values and summary scores are calculated, comparisons cannot simply be made across instruments.[106] Furthermore, these general health utilities instruments may not be very sensitive to particular health issues that are important to those with diabetes and prediabetes.[107]

Table 2 presents the reported health utility values and corresponding disutility associated with having diabetes (screen-detected or uncomplicated early T2DM) or prediabetes. Disutilities were derived from reported health utility values as 1 minus the utility index score. It is important to note that uncertainty around health state utility values is usually underreported and that frequently, only mean values are used in decision-analytic models.[108] Disutilities were generally found to be reported without a distribution (i.e., without reported measures of statistical dispersion such as standard deviation, 95% CI, or interquartile

range). For cross-sectional studies comparing a group with diabetes or prediabetes to a group without diabetes, disutility values are presented for both groups and provide a within-study comparison to determine whether having uncomplicated diabetes or prediabetes results in a disutility greater than that reported by individuals without diabetes/prediabetes. For all studies, including trials without a "no diabetes/prediabetes" comparison, we report population norm disutilities for each utility measure. Because population norm disutilities reflect disutilities reported by individuals representative of the entire population (both healthy and with chronic diseases), they may be less useful than within-study comparators but provide an anchor for interpreting the reported disutilities associated with having diabetes/prediabetes. To determine whether the disutility findings reflect differences that may meet criteria for a minimal clinically important difference (MCID), **Table 2** also presents suggested MCIDs for each health utility measure.

Overall, for screen-detected or early diabetes (precomplications) or prediabetes, the range of estimated disutilities varied widely, from 0.12 to 0.33. There is some limited evidence suggesting that living with screen-detected or uncomplicated early diabetes (without taking metformin or making intensive lifestyle changes or on other therapies) results in greater health disutilities compared with individuals without diabetes. However, results were inconsistent with some evidence suggesting better health (lower disutilities) among individuals with recently diagnosed T2DM when compared with population norms. Among those with prediabetes, most studies reported health disutilities slightly greater than or the same as individuals without prediabetes with no clear evidence that having prediabetes results in health disutilities that are meaningfully greater than disutilities reported by individuals without prediabetes or by the general population.

For screen-detected T2DM, four sites (Leicester and Cambridge in the UK, Denmark, and the Netherlands) involved in the ADDITION-Europe trial reported disutilities ranging from 0.15 to 0.21. The publications did not include data for a "no diabetes" comparator group, so we were unable to determine whether disutilities would differ among similar individuals without diabetes. Compared with estimated population norms for the EQ-5D in the included countries, individuals in the ADDITION-Europe trial living with screen-detected T2DM reported greater disutility compared with the general population, but the reported disutilities did not meet criteria for a MCID in all cases. If the lower bound of the range of a MCID (i.e., 0.04) is used, then the disutility reported among individuals with screen-detected T2DM meets MCID criteria in five of eight reported datasets (with greater disutility for those with screen-detected T2DM compared with norms for the general population). However, if the upper bound of the range of a suggested MCID (i.e., 0.08) is used, the reported disutility from just one site, Leicester, meets criteria for a MCID.

For early diabetes without complications, reported disutilities ranged from 0.12 to 0.33. There was some evidence from one study conducted in Finland (n=920) that early diabetes without complications may result in a disutility that is greater than that of those without diabetes, although the difference between those with and without diabetes was just at the lower range of an estimated MCID.[101] The study reported a disutility of 0.25 using the SF-6D and 0.12 using the HRQOL 15-D among individuals with uncomplicated T2DM compared with disutilities of 0.22 on the SF-6D and 0.09 on the HRQOL 15-D for those without diabetes.[101] Results from 155 individuals enrolled in the placebo arm (so not receiving an intervention) of the DPP/DPPOS and diagnosed with T2DM during the study were more difficult to interpret because there was no within-study comparison with a nondiabetic population. There was, however, no difference in the disutility values (using the QWB-SA) reported by those in the placebo arm who developed diabetes within 2-years of enrollment in the DPP/DPPOS and those who remained

prediabetic (both groups reported a disutility of 0.32).[96] The DPP/DPPOS measured health utilities for each year of the study and reported a mean disutility of 0.33 among those in the placebo arm who developed diabetes throughout any of the remaining years of the study, compared with a mean disutility of 0.32 for those who remained prediabetic. These findings are lower than the disutility of 0.36 reported for QWB-SA among individuals in the general population suggesting, better health among those in the DPPOS placebo arm than in the general population even after developing diabetes.[96]

Among eight studies of people with **prediabetes**, reported disutilities ranged from 0.08 to 0.33. Four of the eight were cross-sectional studies comparing a population living with prediabetes to a population without prediabetes.[100, 101, 103, 105] As outlined in **Table 2** below, studies generally reported a disutility slightly greater than or the same as individuals without prediabetes; just one study reported a greater disutility for those living with prediabetes that was considered to just barely meet criteria for a MCID (0.25 vs. 0.22 on the SF-6D and 0.11 versus 0.09 on the HRQOL-Q15D).[101] DiBonaventura and colleagues stratified health utilities (using the SF-6D) by weight and found increased obesity levels resulted in more disutility among those with prediabetes as well as among those with normal glucose tolerance. Statistical differences between the prediabetes and normal glucose groups were not performed, but the observed difference did not meet criteria for a MCID. This suggests that obesity, rather than prediabetes, was responsible for the increased disutility. All groups (even the normal weight groups) reported greater disutility than the population norm of 0.21 for the SF-6D.

Control group results from four prediabetes intervention studies, including two articles from the DPP/DPPOS trial, employed different health utility measures and reported mixed findings (**Table 2**).[86, 96, 98, 99, 104] One UK-based study, which used the EQ-5D measure, found greater disutility over time, ranging from a disutility of 0.18 at baseline to 0.22 at 36 months. These were all greater than the UK population norm for the EQ-5D-3L of 0.14, meeting criteria for MCIDs.[104] Results from the control arm of the IGT group in the ADDITION-Denmark study also reported a disutility greater than the population norm (0.16 vs. the population norm of 0.13 for the EQ-5D), but this did not meet criteria for a MCID.[98] In contrast, results from the DPP/DPPOS study, which included two separate measures of health utilities (the SF-6D and the QWB-SA), found no added disutility of having prediabetes compared with population norms.[96, 99] In fact, using both measures, individuals with prediabetes reported better health (i.e., lower disutilities) than the population norm of 0.36 for the QWB-SA. Similarly, results from the usual care group of the Let's Prevent Diabetes Lifestyle trial in the UK reported disutilities at baseline (0.09) and at 36 months (0.11) that are lower than the population norm of 0.14 for the HRQOL 15-D.[86]

Supplemental Question 5a. What is the distribution of disutilities of taking metformin and of making intensive lifestyle changes?

Disutility of Taking Metformin

We found no studies, meeting inclusion criteria, that reported disutilities for individuals with screen-detected diabetes and taking metformin. Two articles from the DPP/DPPOS provided health utility data specific to individuals taking metformin who had prediabetes or who developed T2DM during the study.[96, 99] **Table 3** presents the distribution of reported disutilities for individuals in the DPP/DPPOS with uncomplicated early diabetes or prediabetes and taking metformin, and reports the corresponding disutilities for those taking a placebo. The data capture the disutility related to the side effects of taking metformin. Because both groups are taking a pill, however, the data do not capture the disutility related to taking a pill in and of itself. **Table 3** also provides population norm disutilities for each measure.

Evidence from the DPP/DPPOS should be considered in the context of the study over 10 years. The initial 3 years represent the randomized controlled trial phase of the study with individuals in the metformin arm prescribed 850 mg of metformin daily for the first month, which was increased to 850 mg twice daily afterwards (if tolerated). At the end of the randomized controlled phase, participants in both the metformin and placebo arms were offered a 16-session lifestyle intervention, and those on metformin were encouraged to maintain (open label) metformin treatment. Thereafter, participants entered the followup observational study phase, during which all participants received the healthy lifestyle intervention and participants in the metformin arm were once again encouraged to maintain metformin treatment. In all, 58 percent of metformin participants also attended at least one lifestyle session during the followup phase. Of the original 3,234 participants enrolled in the RCT, 924 of 1073 from the metformin arm and 932 of 1082 from the placebo participated in the DPPOS phase. Very few participants in the placebo arm (3%) took metformin prescribed outside the study. With this in mind, and noting the lack of distributions around the reported estimates, the findings largely suggest no difference in reported disutilities between individuals taking metformin and those taking placebo (e.g., the mean disutility over 10 years was virtually identical, 0.32 vs. 0.33).[96]

Early uncomplicated T2DM: Among individuals who developed T2DM during the randomized phase of the DPP, those taking placebo report greater disutility (just meeting criteria for a MCID) than those taking metformin, although confidence intervals were not provided and statistical comparison of the disutilities was not conducted by the study. However, in year 2 of the RCT and for all followup years, participants reported identical or similar disutilities whether they were taking metformin or taking a placebo. Over all 10 years of the DPP/DPPOS, the mean disutility was 0.32 for those on metformin versus 0.33 for those taking a placebo.[96]

Prediabetes: Similar results were observed for individuals with prediabetes taking metformin compared with those taking placebo. Using the SF-6D, Marrero and colleagues reported disutilities of 0.22, 0.22, 0.24, 0.26, and 0.28 at years 2, 3, 4, 5, and 6 of the DPPOS, respectively. The corresponding scores for individuals in the placebo arm (not assigned to metformin) were 0.21, 0.22, 0.24, 0.26, and 0.27.[99] Results using the QWB-SA, which include the randomized phase of the DPP, also suggest that there is no added disutility associated with taking metformin compared with taking placebo, with almost identical disutilities reported across each year of the study (see **Table 3**).

Disutility of Making Intensive Lifestyle Changes

Table 4 presents the distribution of reported disutilities from 5 studies (6 articles)[86, 96, 98, 99, 102, 104] for individuals with screen-detected or uncomplicated early diabetes or prediabetes and making intensive lifestyle changes and compares them to reported disutilities from those not making lifestyle changes (where provided) and to population norm disutilities for each health utility measure. Overall, among individuals with screen-detected or complicated early diabetes or prediabetes, there is no clear evidence that making intensive lifestyle changes results in health disutilities greater than that experienced by those not making lifestyle changes. Across studies and measures, individuals making intensive lifestyle changes largely reported almost identical disutilities to those not making lifestyle changes and by some measures reported slightly better health (lower disutilities) than those not making lifestyle changes. This finding should be considered with the caveat that studies did not generally provide a distribution around health utility estimates or statistical comparison of utility estimates between groups, and several studies did not have a within-study comparison.

Screen-detected T2DM: Two studies used the EQ-5D to measure disutilities among individuals with screen-detected T2DM enrolled in the ADDITION-Denmark and ADDITION-Cambridge trials and reported disutilities of 0.16 and 0.15, respectively.[98, 102] Neither study compared results to a group not making lifestyle changes. However, compared with population norms for the EQ-5D in each country (0.13 in Denmark and 0.14 in the UK), the reported disutilities do not suggest significant disutility associated with having diabetes while making intensive lifestyle changes.

Early uncomplicated T2DM: Using the QWB-SA, individuals enrolled in the DPP/DPPOS who were assigned to the intensive lifestyle group and who developed diabetes within 2 years of enrollment (n=51) reported a disutility of 0.36 compared with a reported disutility of 0.32 among those in the placebo group who also developed diabetes within 2 years of enrollment (n=155). This difference of 0.04 is considered a MCID for the QWB-SA, suggesting that making intensive lifestyle changes may have resulted in an added meaningful disutility.[96] However, this result was not emulated across any other year of either the DPP or the DPPOS. In fact, individuals making intensive lifestyle changes regularly reported slightly better overall health (i.e., lower disutilities) than those in the placebo arm (**Table 4**). It should be noted that during the DPPOS (i.e., the follow-on observational study from year 3/4 through year 10), participants in the placebo arm were offered a healthy lifestyle program and 58 percent of the placebo arm attended at least one session during the initial 16-session program.[96] It is therefore possible that participants in the placebo arm of the DPPOS were benefiting from making some lifestyle changes.

Prediabetes: Overall, reported disutilities for individuals with prediabetes and making intensive lifestyle changes were not greater than disutilities reported by those not making intensive lifestyle changes. Results from two studies using the EQ-5D reported disutilities that were greater than the reported population norms for each country,[98, 104] but when compared with study participants not making intensive lifestyle changes, the slightly higher disutility reported by Leal and colleagues for the Let's Prevent Diabetes Lifestyle trial in the UK did not meet criteria for a MCID[104] (**Table 4**). Results among participants in the DPP/DPPOS differed depending on the health utility measure employed. Marrero and colleagues reported slightly higher disutilities among those with prediabetes and making intensive lifestyle changes compared with those with prediabetes not making intensive lifestyle changes, but the results did not meet criteria for a MCID.[99] When the QWB-SA was employed as the health utility measure, participants with prediabetes making intensive lifestyle changes reported slightly better health (i.e., lower disutilities) than participants with prediabetes not making intensive lifestyle changes, suggesting no added disutility related to making intensive lifestyle changes. Similarly, results from the usual care group of the Let's Prevent Diabetes Lifestyle trial in the UK reported disutilities at baseline (0.10) and at 36 months (0.09) that are lower than the population norm of 0.14 for the HRQOL 15-D.[86]

Participants in the DPP/DPPOS with prediabetes (IGT) who did not develop diabetes showed little decline in SF-D utility scores over the first 3 years of participation in the DPPOS whether they were in the placebo arm, on metformin, or making intensive lifestyle changes.[99] From year 3, participants in all treatment groups (including the placebo arm) that remained diabetes-free showed a progressive decline in SF-6D scores. For those on Metformin or making intensive lifestyle changes, reported disutility values on the SF-6D increased from 0.20 at baseline to 0.28 after 6 years of participating in the DPPOS. Similarly, for those in the placebo arm, disutility values on the SF-6D scores increased from 0.20 at baseline to 0.27 after 6 years. These suggest that treatment-specific burden was not responsible for the observed decline in health status and that it was due to other factors (e.g., aging, other additional health problems, study participation).

Supplemental Question 5b. Would the disutility of having prediabetes be similar to diabetes if a patient with prediabetes is taking metformin or is making intensive lifestyle changes?

Table 5 compares the reported disutility of having prediabetes with the reported disutility of having screen-detected or early uncomplicated diabetes among people taking metformin (top row) or making intensive lifestyle changes (bottom two rows). Three studies provided data comparing relevant groups across similar measures.[96, 98, 102] Overall, one study (the DPP/DPPOS) suggested that disutilities were similar for persons with prediabetes and those with early uncomplicated diabetes who were taking metformin.[96] For intensive lifestyle changes, results from the ADDITION-Denmark and ADDITION-Cambridge studies suggest similar disutilities for those with prediabetes and those with screen-detected or early uncomplicated diabetes.[98, 102, 104] However, there is some suggestion from the randomized phase of the DPP/DPPOS that those with prediabetes making lifestyle changes may experience less disutility than those with early uncomplicated T2DM making lifestyle changes.

Using the QWB-SA, the DPP/DPPOS measured participant health utilities for each year from enrollment in the program through 7-years of followup (10 years of data). For those on metformin, the reported mean disutility over 10 years of measurement was the same for those with prediabetes (0.32, SD 0.004) as it was for those with uncomplicated early diabetes (0.32, SD 0.02).[96]

For those making intensive lifestyle changes, the results from three studies were mixed. In the DPP/DPPOS, the reported mean disutility (using the QWB-SA) over 10 years of measurement was greater for those with uncomplicated early diabetes (0.33, SD 0.01) than it was for those with prediabetes (0.31, SD 0.01),[96] although this was beneath the threshold considered a MCID. However, a closer look at the DPP phase of the DPP/DPPOS data (years 1-3) shows that participants with diabetes making intensive lifestyle changes consistently reported meaningfully greater disutilities than those with prediabetes. Two studies from ADDITION-Europe used the EQ-5D to measure health utility. Both reported no meaningful difference between those with prediabetes and those with screen-detected diabetes—the ADDITION-Denmark study reported a disutility of 0.17 for those with prediabetes and 0.16 for those with screen-detected diabetes,[98] and the ADDITION-Cambridge study reported a disutility of 0.15 for those with screen-detected diabetes.[102]

Supplemental Question 6. What is the distribution of health impacts of diabetes without complications and prediabetes, measured using patient-reported, non-disease-specific health status measures?

Eleven studies (5 cross-sectional, 5 interventional, 1 longitudinal) provided QOL data relevant to SQ6 (**Table 6**). One provided data for individuals with screen-detected T2DM,[76] three provided data for individuals with early uncomplicated T2DM,[109-111] and nine provided data for those with prediabetes.[99, 103, 110-116] The mean age of included populations ranged from 44 to 64, with sample sizes varying widely, from 19 to 7,632. Of the 11 included studies, 6 were conducted in Europe,[76, 109-112, 116] 2 in the United States,[99, 103] 1 in Canada,[113] 1 in Malaysia,[114] and 1 across 27 countries worldwide.[115] Of seven RCTs providing QOL data for the main evidence review, including data from the ADDITION-Europe trial,[76, 95, 117] the Let's Prevent Diabetes trial,[86, 118] the DPP,[80, 97, 119] the PREDIAS trial,[112] the Enhancing Fitness in Older Overweight Veterans with Impaired Glucose Tolerance trial,[120] the SCALE trial,[115] and the DESMOND trial,[93, 94] one (The Let's Prevent Diabetes trial) provided a health utility index score and is included in SQ5, four (ADDITION-Europe, DPP, PREDIAS, and SCALE trials) are included in SQ6, and

two (the DESMOND trial and the Enhancing Fitness in Older Overweight Veterans with Impaired Glucose Tolerance trial) provided QOL scores from one or more sub-scales but did not provide a summary or total score and were therefore excluded from SQ6.[93, 120] **Appendix A** provides additional details on measures of health status and quality of life used in studies addressing this Supplemental Question.

The distributions of QOL findings for those with screen-detected diabetes, early uncomplicated diabetes, and prediabetes are provided in **Table 7**. Overall, among studies that included a within-study comparison to a "no diabetes" group, screen-detected, early diabetes without complications, and prediabetes QOL scores were similar to populations without diabetes (with just one exception). Among studies that could only be compared with population norms (k=7, n=6,189) estimates suggest that individuals with screen-detected T2DM and early uncomplicated T2DM may have slightly lower QOL with respect to physical health but perhaps slightly greater QOL with respect to mental health, although differences were not compared statistically, differences were not greater than the upper bound of the range for a MCID, and distributions around the estimates were not always reported.

For screen-detected T2DM, we found no study comparing individuals with screen-detected T2DM with a group without diabetes. QOL scores from all four sites of the ADDITION-Europe trial reported SF-36 PCS scores ranging from 43.4 (10.5) to 47.0 (10.5), SF-36 MCS scores ranging from 52.2 (7.4) to 54.9 (8.5), and EQ-5D VAS scores ranging from 74.8 (18.4) to 78.4 (16.4).[76] Comparing the results to the population norm, mean PCS scores were lower than the population norm of 50 points for the PCS summary scores, but higher than the population norm of 50 points for the MCS summary scores, suggesting lower QOL with respect to physical health but greater QOL with respect to mental health. Compared with each country's population norm, individuals with screen-detected T2DM scored lower on the EQ-5D VAS, but the difference did not meet suggested criteria (7-8 points difference) for a minimally important difference.

For early diabetes without complications, two population-based studies (a cross-sectional and longitudinal study) compared individuals with newly diagnosed diabetes to a population without diabetes and found no difference in QOL scores between groups.[110, 111] Both studies reported similar mean SF-12/SF-36 PCS and MCS summary scores with PCS scores in the mid-40s and each with an MCS score of 52 (SD 9.3 in one study, NR in the other).[110, 111] A German study investigating the longer-term effects of a 12-week self-monitoring of blood glucose intervention reported much higher baseline scores on both the SF-36 PCS (65.2, SD NR) and the SF-36 MCS (68.0, SD NR).[109] The study did not have a within-study "no diabetes" group, but the scores were significantly higher than the population norm of 50 for the PCS and MCS, suggesting that study participants were healthier than the general population.

For prediabetes, nine studies (5 cross-sectional, 3 intervention, 1 longitudinal) provided QOL data,[99, 103, 110-116] with just four providing a within-study "no diabetes" group comparator.[103, 110, 111, 116] Although somewhat mixed, overall, most studies reported similar QOL using patient-reported, non-disease-specific health status measures for those with prediabetes compared with those without diabetes.

Of the four studies that included a within-study "no diabetes" comparator group, 2 reported no difference in SF-12/SF-36 QOL PCS and MCS summary scores between participants with prediabetes and those with normal glucose tolerance;[110, 111] one reported greater QOL scores among Polish men with normal glucose tolerance compared with those with prediabetes, although the reported scores were well above the population norm for the SF-36;[116] and one study, which stratified results by BMI, reported significantly lower QOL scores with increasing levels of obesity but did not investigate whether the prediabetic group

differed from the normal glucose group.[103] Differences were not compared statistically, differences were not greater than the upper bound of the range for a MCID for each estimate, and distributions were not reported. However, the reported estimates from the study suggest that compared with participants without diabetes, those with prediabetes had lower scores for physical health but higher scores for mental health.[103]

Of the studies that did not have a within-study "no diabetes" comparator group, three reported summary PCS and MCS scores using the SF-12 or SF-36.[99, 114, 115] Two of these reported scores largely similar to population norms,[99, 115] while one reported PCS and MCS scores far higher than the population norm of 50 for both the SF-36 PCS and MCS summary scores.[114] Among other QOL measures employed, a cross-sectional study of 232 Canadians using the RAND-12 instrument to measure QOL reported a mean (SD) physical health composite score of 46.6 (9.9) and a mean (SD) mental health composite score of 45.2 (9.7),[113] and Kulzer and colleagues reported a baseline mean QOL score (multiplied by 4 to provide a result on the 0-100 scale) of 57.2 (20) using the WHO-5 well-being index instrument.[112] Because neither study had a within-study "normal glucose tolerance" comparison group and no other studies meeting eligibility criteria employed these instruments, the results can only be compared with population norms for each instrument (50 for the RAND-12 and 54-70 for the WHO-5) suggesting similar QOL scores for participants with prediabetes compared with the general population.

Supplemental Question 7. What is the distribution of the health impact of diabetes without complications and prediabetes on length of life?

Prediabetes

Overall, results from both a recent systematic review and meta-analysis and some older observational studies consistently reported evidence of a significant association between prediabetes and increased risk of mortality.

A recent systematic review and meta-analysis (with 129 studies involving 10,069,955 persons) assessed the evidence regarding risk of mortality associated with prediabetes.[121] Among 87 comparisons included, the meta-analysis estimated an increased relative risk of all-cause mortality of 1.13 (95% CI, 1.10 to 1.17) for individuals with prediabetes compared with those without prediabetes or diabetes over a median followup of 9.8 years. This relative risk of all-cause mortality translates to an absolute increase of 9.59 deaths per 10,000 person-years (95% CI, 7.36 to 12.51) for persons with prediabetes.

Meta-analyses identified some differences in estimates by criteria for prediabetes and by analysis subgroups.[121] Meta-analyses of five of the nine definitions of prediabetes were associated with increased risk of all-cause mortality, including the three most frequent definitions (IFG criteria of the American Diabetes Association; IFG criteria of the World Health Organization; and IGT representing 20, 19, and 15 comparisons, respectively). In addition, studies found an increased risk of all-cause mortality in individuals with prediabetes compared with individuals with normal glucose/glycemia in analyses with an average participant age of 60 years or younger (RR, 1.16; 95% CI, 1.12 to 1.20) and in analyses with an average participant age of 60 years or older (RR, 1.08; 95% CI, 1.03 to 1.14). The estimates for the relative risk of mortality associated with prediabetes compared with normal glucose/glycemia were not significantly different for analyses considering Asian or non-Asian populations, men or women, sample size below or above 5,000, length of followup below or above 10 years, or adequacy of adjustment for confounding characteristics. Studies were considered to be adequately adjusted if they included at least

five of the following six covariates: sex; age; hypertension, blood pressure, or antihypertensive treatment; BMI or other measure of overweight or obesity status; cholesterol; and smoking.

Several individual older studies also assessed the relationship between IGT and mortality, although thresholds and study designs varied. These studies generally provided age- or age- and sex-adjusted mortality rates by baseline glucose tolerance classification, but the analyses often did not adjust for other factors. Although these classifications of glucose tolerance do not always align with current thresholds used to define prediabetes, they often overlap and reflect a similar construct.

A study of 18,403 middle-aged male civil servants from London (the Whitehall study) estimated age-adjusted mortality rates for coronary heart disease (CHD) and all causes for two IGT groups relative to those with normal glucose tolerance; however, statistical comparisons of these were not conducted.[122] Moderate IGT was defined as 2-hour blood glucose after 50-g oral load of 96 to 199 mg/dL, while "borderline diabetics" with more severe IGT was classified as 110 to 199 mg/dL. Seven-and-a-half-year age-adjusted CHD mortality was similar for moderate IGT and borderline diabetics at 49.1 and 49.0 per 1,000, respectively, compared with 23.5 per 1,000 for those with no IGT (we assumed the data were per 1,000 persons rather than per 1,000 person-years, although the article did not specify; also, no CIs were provided and no statistical comparisons were conducted). Similarly, all-cause mortality was similar among the two IGT groups at 94.5 and 94.3 per 1,000 for moderate and severe IGT, respectively, while the rate for those with no IGT was 59.4 per 1,000.

A more recent followup of the Whitehall study estimated differences in mortality by IGT and attributed differences in risk.[123] This study found greater relative risks of stroke and CHD mortality for those in the IGT group compared with those in the normoglycemic group after adjusting for age, smoking status, cigarettes per day, work type, systolic blood pressure, cholesterol, BMI, electrocardiographic abnormality, and treatment for hypertension (approximately triple and double the relative risk, respectively; actual estimates and CIs not reported; data shown in bar graph only). Although some of this difference in risk of mortality was explained by characteristics they considered (i.e., age and systolic blood pressure), greater than 60 percent of the difference in risk of stroke and CHD mortality between the IGT and normoglycemic groups remained unexplained.

A similar study of male civil servants in Paris (the Paris Prospective Study) assessed differences in mortality by baseline IGT classification.[124] They also found significant differences in CHD mortality incidence by baseline IGT classification with 1.9 times higher incidence of mortality for those with IGT compared with individuals with normal glucose tolerance (CHD mortality rates of 2.7 vs. 1.4 per 1,000, CIs not reported).

In a population study of nearly 27,000 individuals from Sweden, age- and sex-adjusted mortality rates for individuals with IGT were higher than for individuals with normal glucose tolerance (53.6 deaths/1,000 person-years; 95% CI, 45.4 to 61.9 vs. 37.9 deaths/1,000 person-years; 95% CI, 34.2 to 41.5).[125]

Diabetes Without Complications

Most of the evidence surrounding the relationship between diabetes without complications and mortality stems from a collection of cohort studies that focused on the association between "asymptomatic" hyperglycemia and cardiovascular disease and mortality as part of the International Collaborative Group (ICG).[126, 127] ICG included 15 studies from the 1960s to 1970s of middle-aged men from various countries

with an established focus on asymptomatic diabetes, 11 of which were prospective studies with at least 4 years of followup.

These cohort studies generally followed similar designs and presented similar analyses.[126, 127] Although often parts of larger studies, analyses presented as part of the ICG focused on males generally ages 40 to 59 years at baseline (**Table 6**). Samples were often based on employer or insurer. Examples of populations include men in Chicago employed by Peoples Gas Company and Western Electric Co,[128] policemen from Helsinki,[129] and civil servants in Paris.[130] At the beginning of the study, eligible participants completed health surveys and physical exams, including various measures of blood glucose. Based on these results, participants were classified into various categories often including normoglycemia, IGT, asymptomatic hyperglycemia, and known diabetes. Some studies excluded individuals with known diabetes, while others included them. Asymptomatic hyperglycemia was used to describe participants who reported no known diabetes at baseline but then whose blood sugar was above the respective threshold for diabetes during the initial screening. Because different studies used different measures of blood glucose, different thresholds and categorizations were also defined.[126] Other common exclusion criteria were known cardiovascular disease, history of myocardial infarction, and use of antihypertensive medications.

These studies include a variety of analyses such as differences in mortality by decile, quartile, and quintile of blood glucose; differences in mortality by normoglycemia, impaired glucose tolerance, and hyperglycemia; and multivariate regressions of associations between blood glucose and mortality often controlling for age, systolic blood pressure, BMI, cholesterol, and smoking status or cigarette use. Importantly, these studies considered baseline blood glucose and the association with subsequent mortality.

Overall, although these studies often reported higher age-adjusted mortality rates among groups with the highest blood glucose, adjusted analyses presented limited and inconsistent evidence of the specific association between asymptomatic hyperglycemia and all-cause, cardiovascular-related, or CHD-related mortality (**Table 8)**.[126] Even though a positive relationship between blood sugar among those initially considered to have asymptomatic hyperglycemia and various types of mortality was sometimes found, many studies found no such relationship, and one study found a negative association.[127]

These studies have several important limitations. First, they focused on a narrow population of middle-aged men, often employed, and often white. Findings from these studies may not be generalizable to other populations. Second, those identified as not having been previously diagnosed with diabetes (as being "asymptomatic diabetics") may not perfectly capture those who had diabetes without complications. Third, these studies varied in terms of their population, measure of blood glucose, thresholds for different categorizations, length of followup, exclusion criteria, and analyses. It has been suggested that these differences may be contributing to differences in results. Fourth, some of these studies had relatively small samples with few deaths, making it difficult to detect differences in rates of mortality. Finally, although these studies often controlled for a variety of known confounding variables, other characteristics may not have been considered, and many of the findings related to mortality are not from controlled regression analyses. The studies did not consider interventions received over the course of followup (e.g., lifestyle or weight loss interventions) or changes in weight or BMI over time.

Similar but more recent cohort studies have assessed the relationship between newly diagnosed diabetes and mortality. Mortality for a Danish population of 1,323 individuals with diabetes identified between 1989 and 1992 was assessed 16 years later compared with the general Danish population.[131] This study

found an increased risk of all-cause mortality in the followup period after diagnosis of diabetes compared with the general Danish population for both males and females and across the age groups considered. For example, in males ages 60 to 64 years, the hazard ratio (HR) for all-cause mortality for those with diabetes was 39.4 (95% CI, 29.4 to 52.8), and the HR for the general population using 2001 to 2005 mortality tables was 14.2 and using 1991-1995 mortality tables was 19.2. For females ages 60 to 64 years, the same HR was 15.3 compared with 9.2 and was 12.3 in the 2001 to 2005 and 1991 to 1995 life tables. The increased risk of mortality seemed to be greater among males. Even though this study adds more recent data than the ICG studies add and provides data for both males and females, it is not without important limitations. First, these measures were unadjusted; important potential confounders were not considered. Second, this study was part of a randomized trial. The intervention, referred to as "structured care," included quarterly followup with their general practitioner to discuss treatment goals and progress and annual screenings for complications.[132] The intervention was found to have no effect on mortality, so this study included individuals in both the intervention and comparison groups.[131] Third, the comparison group is the general Danish population, not those without diabetes or prediabetes specifically. Finally, this study assessed differences in risk of mortality in the 16 years after incident diabetes diagnosis and was not specifically limited to persons who have diabetes without complications, although 30.4% had cardiovascular disease, 19.3% had peripheral neuropathy, and 4.8% had diabetic retinopathy at baseline.

A cohort study with matched controls (187,968 participants with diabetes, 908,016 matched controls) in the United Kingdom considered life expectancy for those with an incident diabetes diagnosis from 1998 to 2015 compared with the matched control group.[133] In this study, they found a greater risk of all-cause mortality for those with type 2 diabetes mellitus compared with those without type 2 diabetes mellitus when controlling for gender, age ethnicity, deprivation index, and calendar year (adjusted HR, 2.19 [95% CI, 2.16 to 2.21]). This study also found greater risk of all other causes of mortality considered (except for suicide) for those with type 2 diabetes mellitus compared with those without.

Supplemental Question 8. When informed patients with prediabetes are offered intensive lifestyle modification and/or metformin for diabetes prevention, what is the uptake and adherence with each strategy over time?

For this question, we adopted a two-pronged approach. First, we examined uptake and adherence in the trials that were included for KQ 7 of the evidence review (i.e., Do interventions for prediabetes delay or prevent progression to type 2 diabetes?). We note that our data on uptake and adherence from controlled trials may be limited by differences in characteristics between participants of trials and people initiating real-world interventions,[134] differences in settings and locations between research and real-world settings,[135] differences in recruitment between pragmatic observational research and randomized, controlled trials,[135] and volunteer bias.[136] Second, we searched for studies not eligible for the evidence review that describe uptake and adherence (e.g., observational studies of real-world uptake that should have good applicability) because KQ 7 of the evidence review included only controlled trials.

We defined uptake as the initiation of (or the decision to initiate) a lifestyle intervention or medication to prevent diabetes. Adherence for lifestyle interventions was defined as the percentage of participants who attended a given number of intervention sessions for studies with combined exercise and weight loss goals similar to the DPP (i.e., individual and group classes promoting 7% weight loss, 150 minutes/week of physical activity).[80] For studies that primarily focused on exercise interventions, we defined adherence as the percentage of participants who met an exercise goal. Adherence within studies that assessed

metformin was defined as the percentage of metformin doses taken. Eligible study designs included cross-sectional studies, longitudinal studies, and clinical trials. We required studies to include at least 100 participants. To focus on the most applicable evidence, we required observational studies to be conducted in the United States, although trials from KQ 7 were not limited to those conducted in the United States (they could be from any country with a very high Human Development Index).

Trials of Lifestyle Interventions Included in KQ 7

Among the lifestyle interventions for delaying or preventing the onset of type 2 diabetes mellitus, we identified relevant adherence data in 14 trials (**Table 9**).[36, 80, 86, 87, 118, 120, 137-146]

Three trials primarily focused on exercise.[120, 137, 138] In one trial, the authors reported that the percentage of the intervention group that met the activity goal of 150 minutes of endurance exercise increased from 16 percent to 42 percent between baseline and the 12-month followup.[120] In another trial, the authors reported that the intervention groups assigned to receive a group-based exercise condition with and without a pedometer increased their daily step count by an average of 708 and 421 steps, respectively, from baseline to 12 months.[138] In the third exercise-based intervention, 25.0 percent of the lifestyle intervention group exercised 1 or more times a week at baseline compared with 42.9 percent at the 5-year followup.[137]

Among 10 trials that defined adherence as a percentage of counseling or educational sessions attended by participants,[36, 86, 87, 139-145] attendance ranged from 40 percent[139] to 92.4 percent,[87] with most studies reporting adherence greater than 50 percent (**Table 9**).

The DPP reported the proportion of participants who met the goal of at least 150 minutes of physical activity per week (assessed using logs kept by the participants).[80] At 24 weeks, 74 percent of participants met the goal. At the most recent visit (over a mean 2.8 years followup) 58 percent met the goal.[80] Regarding attendance at lifestyle intervention sessions, the DPP authors reported that the average percentage of participants who attended the quarterly lifestyle sessions offered between the original DPP and followup DPPOS study were 18 percent, 15 percent, and 14 percent in the groups originally randomized to lifestyle, metformin, and placebo, respectively.[146] Additionally, the percentage who attended at least some of these sessions were 40 percent, 58 percent, and 57 percent for the lifestyle, metformin, and placebo groups, respectively.[146]

Trials of Metformin Included in KQ 7

Two trials reported uptake or adherence to metformin, both of which used metformin 850 mg twice daily (**Table 10**).[79, 142, 147] PREVENT-DM randomized 29 adults to the metformin group and uptake was high, with 89 percent (26 participants) taking at least one dose of medication, but adherence was comparatively low, with 37 percent (11 participants) taking at least 80 percent of dispensed doses.[142] During the median 3.2 years of followup for the DPP, 89.2 percent (909 participants) took at least some portion of pills, and 71 percent (724 participants) took at least 80 percent of their dispensed doses.[147] During the DPPOS, 49 percent of participants originally randomized to the metformin group took at least 80 percent of their metformin doses.[79] The DPP reported that 84 percent of those taking metformin were given the full dose of 850 mg twice a day; the remainder were given one tablet a day to limit side effects.[80]

Studies Not in the Draft Evidence Review That Describe Uptake or Adherence

We found six studies in our new, targeted literature searches (**Table 10**).[148-153] Of those six, one trial (the Prediabetes Informed Decision and Education [PRIDE] trial) invited adults with prediabetes to participate in a shared decision making visit with a pharmacist where they were offered DPP-based ILI, metformin, or both;[148] four trials offered DPP-based ILI;[149, 151-153] and one trial promoted resistance training.[150]

PRIDE was the only trial that offered shared decision making about both ILI and medication interventions to prevent diabetes.[148] Twenty primary care clinics at UCLA Health were randomized to be intervention sites or not. Within the 10 intervention clinics, eligible patients with prediabetes were invited to schedule a visit with a pharmacist to learn about prediabetes and options for diabetes prevention. Propensity score matching was used to identify control patients from 10 usual care clinics. Pharmacists in the intervention arm of this study used a shared decision making aid developed by Healthwise, "Prediabetes: Which Treatment Should I Use."[154] The decision aid provided four possible options: ILI alone (the DPP lifestyle intervention), metformin alone, ILI plus metformin, or usual primary care. The decision aid included the absolute risk of developing diabetes at 3, 10, and 15 years' followup in patients who underwent major lifestyle change, metformin plus information about lifestyle changes, or a placebo pill, and it presented the smallest risk of developing diabetes for the major lifestyle change condition at 3 and 10 years, but similar absolute risks of developing diabetes for major lifestyle change and for metformin at 15 years. Uptake of the lifestyle intervention or metformin (the study's primary outcome) was higher among participants who received shared decision making than among controls at 4 months (38% vs. 2%). Among the 351 participants who completed the pharmacist-administered shared decision-making process, 23.4 percent (82 participants) completed at least one DPP lifestyle intervention session, 18.8 percent (65 participants) used any metformin, and 38.2 percent (134 participants) attended at least one DPP lifestyle session or used any metformin. About 74 percent (260 participants) among the shared decision-making group selected the DPP lifestyle intervention with or without metformin, and of these 260 participants, 32 percent (83 participants) adhered to this therapy by attending at least nine sessions.

The four trials that offered DPP-based ILI recruited participants only through advertisements,[149, 151] referrals,[152] and testing events.[153] In the only worksite-based intervention, uptake was low, with roughly 10 percent (217 participants) expressing an interest to participant in the program, and only 5 percent (117 participants) enrolling.[149] In the Prevent trial, 85 percent (187 participants) completed at least four sessions of the initial intervention, and 65 percent (144 participants) completed at least four sessions of the initial intervention and one or more maintenance sessions.[151] Adults with prediabetes or metabolic syndrome were referred by their primary care physician or self-referred to the Group Lifestyle Balance intervention and attended fewer meetings over time, reaching 52 percent (364 participants) by the fourth meeting.[152] Adherence was higher in another study in which participants were recruited largely through community- and employer-based testing, with 89 percent (2,104 participants) completing more than four of 16 initial group sessions, and 73 percent (1,723 participants) attending more than nine of 16 initial group sessions.[153]

Resist Diabetes used newspaper, workplace, and church advertisements to recruit participants into a supervised resistance training trial.[150] Prediabetic participants in this trial first underwent a 3-month run-in period, after which only participants who attended at least 17 of the 24 supervised training sessions were randomized to two different levels of supervised resistance training. During the 3-month run-in, 91 percent (154 participants) went to 22 of 24 supervised training sessions. Seventy-eight percent of the

higher supervised group (61 participants) and 72 percent of the lower supervision group (57 participants) completed at least two resistance training sessions per week by month 9. By month 15, 53 percent of both groups (41 participants and 42 participants, respectively) completed at least two resistance training sessions per week.

Our criteria for selecting studies for this supplemental question had some limitations. First, we excluded studies with fewer than 100 participants. This resulted in exclusion of a study that assessed the intention to participate in ILI or use metformin to prevent diabetes.[155] The study recruited 40 participants with prediabetes from a community health center and reported on the intention to participate before and after using a prediabetes decision aid pamphlet that communicated the absolute risk of developing diabetes for patients who used an intensive lifestyle intervention, metformin, or no treatment.[155] The decision aid emphasized that ILI had greater efficacy than metformin in preventing diabetes using data from the DPP.[156] The proportion of participants who expressed an intention to participate in ILI increased from 70 percent (28 participants) to 88 percent (35 participants) after using the pamphlet. The proportion of participants who expressed an intention to use metformin slightly decreased after using the pamphlet, from 25 percent (10 participants) to 23% (9 participants). Second, we excluded studies from countries other than the United States. This led to the exclusion of a very large study assessing uptake of and adherence to an ILI performed by the National Health Service (NHS) in the United Kingdom, the NHS DPP.[157] In that study, 324,699 patients were referred to the NHS DPP, 46 percent (152,294 participants) attended the initial introductory nonintervention assessment, and 29 percent (96,442 participants) attended one or more group-based intervention sessions. At the time of the publication reporting the results of the assessment, enough time had elapsed for 32,665 of the 96,442 participants who had attended one or more group-based intervention sessions to complete the program, and 52 percent (17,252 participants) had attended at least 60 percent of the sessions.

Supplemental Question 9. What is the association (from observational studies or others) between changes in fasting glucose levels or A1c levels and changes in risk for target organ damage?

Overall, the included studies consistently reported significant associations between baseline glucose or glycemic levels and risk for future target organ damage. Three studies were identified that examined the associations between glycemic or glucose levels as a continuous measure and risk for target organ damage,[66, 89, 158] and six studies were identified that examined the effect of various baseline glucose or glycemia categories on risk for target organ damage (**Table 12**).[85, 122, 159-162] Two of the studies reported only unadjusted data,[158, 161] three adjusted for some potential confounders,[122, 159, 160] and four adjusted for at least five of the following six variables: sex; age; hypertension, blood pressure, or antihypertensive treatment; body mass index or other measure of overweight or obesity status; cholesterol; and smoking.[66, 85, 89, 162]

The three studies that examined the association between glycemic or glucose levels as a continuous measure and risk for target organ damage included two conducted in the United States[66, 158] and one conducted in New Zealand.[89] Data included within these studies were collected in the 1990s[66, 158] and the 2000s.[89] The U.S.-based ABC Study (n=2,386) reported that higher fasting glucose, A1c, and 2-h glucose were associated with increased risk of heart failure and adjusted for BMI, age, history of coronary artery disease and smoking, SBP and heart rate, left ventricular hypertrophy on electrocardiogram, and creatinine and albumin levels.[66] The U.S.-based DPP study[158] (n=2,476) reported that a higher baseline glucose level and 1-year effect size (1-year change in glucose) were associated with incident CVD, but

the results were limited because only unadjusted data were included. Similar associations were found in a large New Zealand study[89] (n=62,002) that reported that higher HbA1c levels were associated with increased risk of lower limb amputations when adjusting for gender, diabetes history, age at onset, smoking status, height, systolic blood pressure, and TC/HDL ratio.[89]

Six studies examined the effect of various baseline glucose or glycemia categories on risk for target organ damage. Two studies were conducted in the United States,[85, 160] one was conducted in New Zealand,[159] and three were conducted in the United Kingdom.[122, 161, 162] One study used data collected before 1980,[122] two included data collected in the late 1980s and early 1990s,[85, 161] one collected data in the late 1990s through early 2000s,[160] and two studies collected data during the 2000s.[159, 162]

In a U.S.-based sample (n=26,111),[160] complications of cardiovascular disease, microvascular complications, and macrovascular complications were significantly lower in those with normoglycemia compared with those with isolated IFG, isolated IGT, and IFG/IGT. However, data were only adjusted for age and sex. The study also found that participants with normoglycemia had a significantly lower prevalence of stroke than those with isolated IGT, but the findings were limited because of only adjusting for age and sex and not controlling for smoking, hypertension, cholesterol, and other important risk factors. In the U.S.-based Atherosclerosis Risk in Communities (ARIC) study (n=11,092),[85] baseline fasting glucose levels above 100mg/dL were significantly associated with increased risk of coronary heart disease, stroke, and all-cause mortality when adjusted for age, sex, and race/ethnicity, but significance was lost after controlling for other risk factors (e.g., age, sex, race/ethnicity, LDL, HDL, triglyceride level, BMI, waist-to-hip ratio, hypertension, family history of diabetes, education, alcohol use, physical activity index score, smoking status, and glycated hemoglobin value) (**Table 12**).

The Whitehall Study, which included male civil servants (n=18, 403),[122] found that the degree of glucose intolerance was associated with mortality rates. Within the study, males within the normo-glycemic group (2-h glucose <96 mg/dL) had lower rates of mortality at 7.5 years compared with men in the impaired glucose tolerance group (2-h glucose 96-199mg/dL), those newly diagnosed with diabetes (2 h glucose $\geq$200 mg/dL), and those with known diabetes (both insulin and non-insulin dependent). The mortality rate was the highest among those with a 2-hour glucose >200 mg/dL. The results of the Whitehall study were limited because of only adjusting for age and not conducting statistical comparisons. The Whitehall II Study (n=5,427),[162] which included a similar population, reported that men with normal glycemia had lower rates of CVD events or cardiovascular disease than those who had higher HbA1c and FPG at 11.5 years when adjusting for age, sex, ethnicity, previous CVD, smoking, total cholesterol, HDL cholesterol, systolic blood pressure, and antihypertensive treatment (**Table 12**).

In the U.K. Diabetes Prospective Study (n=5,088),[161] participants with lower FPG (<140 mg/dL[<7.8 mmol/l]) reported fewer adverse health outcomes (e.g., peripheral vascular disease, myocardial infarction, microvascular disease, diabetes-related deaths, and all-cause mortality) than those with intermediate (<180 mg/dL[<7.8 mmol/l to <10.0 mmol/l]) or high (>180 mg/dL[>10.0 mmol/l]) FPG. There was not a significant difference for strokes. Participants with intermediate FPG, compared with those with high FPG, had a lower risk of all complications except myocardial infarction and stroke. Participants with lower and intermediate FPG also were at a lower risk for progression of retinopathy. The results of the study were based on unadjusted data.

Last, a study conducted in New Zealand (n=31,148) also reported an association between baseline glucose levels and risk of organ damage and reported that participants with higher fasting glucose levels, higher 2-h glucose, and higher HbA1c had an increased risk of retinopathy, renal complications,

neuropathy, and circulatory complications. Results were adjusted for age, sex, ethnicity, smoking history, and other glucose measures.[159]

Appendix B4 Table 1. Projected 10-Year Outcomes of Treating 10,000 Adults With Prediabetes With Metformin Compared With Intensive Lifestyle Interventions or No Intervention

	Intensive Lifestyle Intervention	Metformin—Start at Prediabetes Diagnosis	Metformin—Start at Diabetes Diagnosis	Usual Care or No Intervention
Benefits				
All-cause deaths	Uncertain*	Unknown	Unknown†	Uncertain*
CVD deaths	Uncertain*	Unknown	Unknown	Uncertain*
CVD events	Uncertain*	Unknown	Unknown	Uncertain*
Myocardial infarction	Unknown	Unknown	Unknown†	Unknown
Heart failure	Unknown	Unknown	Unknown	Unknown
Stroke	Unknown	Unknown	Unknown†	Unknown
Aggregate microvascular outcomes (from DPP; this aggregate combines some intermediate outcomes with some health outcomes)	753 (based on extrapolation from 11.3% [10.1-12.7] during DPPOS 15-year followup)‡	867 (based on extrapolation from 13.0% [11.7-14.5] during DPPOS 15-year followup)‡	Unknown	827 (based on extrapolation from 12.4% [11.1-13.8] during DPPOS 15-year followup)‡
ESRD	Uncertain‡	Uncertain‡	Unknown	Uncertain‡
Visual impairment (including blindness)	Uncertain‡	Uncertain‡	Unknown†	Uncertain‡
Moderate to severe neuropathy	Uncertain‡	Uncertain‡	Unknown	Uncertain‡
Amputations	Unknown	Unknown	Unknown†	Unknown
Skin ulcers	Unknown	Unknown	Unknown	Unknown
Harms				
Psychological distress due to labeling or requirement to take medication	Unknown	Unknown	Uncertain§	Unknown
Side effects of intervention (e.g., for metformin—nausea, diarrhea, etc.; for lifestyle intervention—joint pain)	Any GI adverse events (diarrhea, flatulence, nausea, vomiting): 1,290‖ Sprains or fractures: 2,867¶	Any GI adverse events (diarrhea, flatulence, nausea, vomiting): 7,780‖ Sprains or fractures: 2,733¶	Any GI adverse events (diarrhea, flatulence, nausea, vomiting): 3,890‖ Sprains or fractures: 2,733¶	Any GI adverse events (diarrhea, flatulence, nausea, vomiting): 3,070‖ Sprains or fractures: 2,467¶
Opportunity costs (e.g., time for more physician visits because of being on a med; time for intensive lifestyle intervention)	16 sessions (30-60 minutes) for ILI used in DPP over 24 weeks; ongoing maintenance sessions; 150 minutes of exercise weekly	Average of 2 additional office visits per year[79, 163]; potentially additional trips or calls if having adverse effects (e.g., GI adverse events); calls or trips to the pharmacy to obtain medication	Average of 2 additional office visits per year after starting metformin[79, 163]; potentially additional trips or calls if having adverse effects (e.g., GI adverse events); calls or trips to the pharmacy to obtain medication	No increased opportunity cost

Appendix B4 Table 1. Projected 10-Year Outcomes of Treating 10,000 Adults With Prediabetes With Metformin Compared With Intensive Lifestyle Interventions or No Intervention

	Intensive Lifestyle Intervention	Metformin—Start at Prediabetes Diagnosis	Metformin—Start at Diabetes Diagnosis	Usual Care or No Intervention
Overdiagnosis	Estimated 5,000 people would have remained prediabetic or returned to normal without treatment over 10 years[#]	Estimated 5,000 people would have remained prediabetic or returned to normal without treatment over 10 years[#]	Estimated 5,000 people would have remained prediabetic or returned to normal without treatment over 10 years[#]	None (if not tested or labeled with prediabetes); estimated 5,000 if they were tested and labeled[#]
Overtreatment	Uncertain; one might consider that there is no overtreatment because people should be following a similar healthy lifestyle for the overall health benefits	Uncertain, but at least 5,000 people (if that many were treated with metformin and would not have progressed to diabetes without treatment)	Uncertain; estimated as no overtreatment because this scenario assumes waiting until they have diabetes before treating, which is routine care (although some people will be treated without benefit)	None, not treated (assuming they were not tested or labeled)
Adherence to metformin and to counseling for lifestyle change	58-74% in DPP**	72% during DPP during 3-year followup and 49% DPPOS during 15-year followup**	Likely similar to metformin adherence estimates from DPPOS during 15-year followup	Not applicable

[*] Finnish Diabetes Prevention Study (FDPS) and Da Qing provided estimates for all-cause deaths in lifestyle intervention groups. Evidence remains uncertain because the estimates have wide confidence intervals (CIs) and there is a higher risk of bias with these trials. After 10 years, all-cause mortality in FDPS was 2.2 deaths per 1,000 person-years for intensive lifestyle intervention vs. 3.8 deaths per 1,000 person-years in control group (hazard ratio [HR], 0.57 [95% CI, 0.21 to 1.58]). Compositive CVD events were 22.9 vs. 22.0 events per 1,000 person-years (HR, 1.04 [95% CI, 0.72 to 1.51]). All-cause mortality in the Da Qing Diabetes Prevention Outcomes Study was not found to be reduced over 10 years. After 23 years in Da Qing, all-cause mortality was 28.1% for intensive lifestyle intervention vs. 38.4% for control (HR, 0.71 [95% CI, 0.51 to 0.99]). CVD-related mortality was 11.9% vs. 19.6% (HR, 0.59 [95% CI, 0.36 to 0.96]). KQ 4 of the evidence report has further details. The evidence from a different USPSTF topic, Behavioral Counseling Interventions to Promote a Healthy Diet and Physical Activity for CVD in Adults With CV Risk Factors (currently a draft report), includes the following in the abstract: behavioral counseling interventions were associated with a lower risk of cardiovascular events (pooled relative risk [RR]=0.80 [95% CI, 0.73 to 0.87]; 9 RCTs [n=12,551]; I2=0%), myocardial infarction (MI) (pooled RR=0.85 [95% CI, 0.70 to 1.02]; 6 RCTs [n=10,375]; I2=0%) and stroke (RR=0.52 [95% CI, 0.25 to 1.10]; 4 RCTs [n=9,800]; I2=0%), although the pooled effect was not statistically significant for stroke or MI.

[†] The UKPDS metformin for overweight substudy provided 10-year followup data, but those data are not starting from the time of diagnosis of prediabetes; they are from shortly after the time of diagnosis of diabetes. So, we do not have 10-year estimates for outcomes if we were to wait to treat with metformin for those whose A1c increased to 6.5 or higher. The data from the UKPDS metformin for overweight substudy could be considered for bounding, but those data would overestimate an upper bound. The study reported all-cause deaths in 50/342 (14.6%), myocardial infarction in 39/342 (11.4%), stroke in 12/342 (3.5%), risk of blindness in one eye in 3.5% (12/342), and amputation in 1.8% (6/342) over 10-year followup.

[‡] To convert 15-year data to 10-year estimates, we multiplied by two thirds. DPPOS provides information on nephropathy, neuropathy, and retinopathy as an aggregate microvascular events outcome, without reporting specific data by trial arm for each of the individual components of the aggregate outcome separately. The aggregate outcome included intermediate outcomes such as albuminuria on two consecutive spot urine samples and reduced GFR for nephropathy.

[§] Multiple studies were identified that evaluated diabetes-related distress. However, most of those included many participants taking insulin with complications of diabetes such as neuropathy or who have had long-standing diabetes.[164-168] One cross-sectional study conducted in Northern India assessed diabetes distress using the Diabetes Distress Scale (DDS) in a population with more recently diagnosed diabetes (n=410). Medical therapy is not described in this study, so it is unclear how many participants were on insulin. Further, it did not report how many participants had complications of diabetes such as neuropathy. It found that the prevalence of diabetes distress was 18% and that the major predictors for high diabetes distress scores were low education level, retinopathy, neuropathy, and hypertension (but it did not report the number of participants with each of those). Distress was not found to differ based on duration of diabetes (distress present had mean duration of 6.64 years compared with distress absent of 3.53 years).[169]

[‖] Data for any GI adverse events are based on extrapolation from 12.9 events per 100 person-years in DPP for ILI, 77.8 events per 100 person-years for metformin, and 30.7 events per 100 person-years for placebo. For the third column (Metformin–start at diabetes diagnosis), GI adverse events were based on the adverse event rate from the DPP (77.8 events per 100 person-years) and assuming that 50% progressed to diabetes over 10 years, using the rate of progression from 15-year DPPOS figures.

Appendix B4 Table 1. Projected 10-Year Outcomes of Treating 10,000 Adults With Prediabetes With Metformin Compared With Intensive Lifestyle Interventions or No Intervention

¶ Data for sprains or fractures are based on extrapolation from 15-year DPPOS data (4.3 events per 100 person-years for ILI, 4.1 events per 100 person-years for metformin, and 3.7 events per 100 person-years for placebo) and multiplying by two thirds.
# The estimate of 5,000 over 10 years was based on DPPOS 15-year figures (52% progressed to diabetes over 15 years, but figures in the publication indicate that it was already around 50% by 10 years). Overdiagnosis estimates are based on the assumption that a person who would have remained prediabetic or returned to normal glycemia/glucose was overdiagnosed.
** In the DPP, adherence for metformin was defined as taking medication 80% of the time. Lifestyle intervention: 74% met goal of 150 minutes of physical activity per week over 24 weeks and 58% at most recent visit at trial closure (over 3 years).

Note about QALYs: We had estimates for QALYs in an earlier version of this table but removed them because they were annual estimates, and we would need to multiply them by 10 to extrapolate over 10 years; however, that would assume that QALYs remain consistent each year (and they likely may not) and would neglect discounting over time. A modeling study[91] estimated the QALYs of living with diabetes for 1 year of 0.7491 vs. 0.7302 for ILI and metformin, respectively.

Abbreviations: CI=confidence interval; CVD=cardiovascular disease; DDS=Diabetes Distress Scale; DPP=Diabetes Prevention Program; DPPOS=Diabetes Prevention Program Outcomes Study; ESRD=end-stage renal disease; FDPS=Finnish Diabetes Prevention Study; GI=gastrointestinal; GFR=glomerular filtration rate; HR=hazard ratio; ILI=intensive lifestyle intervention; KQ=key question; MI=myocardial infarction; QALY=quality-adjusted life-year; RCT=randomized, controlled trial; RR=relative risk; UKPDS=United Kingdom Prospective Diabetes Study; USPSTF=U.S. Preventive Services Task Force.

Appendix B4 Table 2. Health Utilities and Resulting Disutilities of Having Screen-Detected or Early T2DM Without Complications or Prediabetes

Study Author, Year	Study Description	Sample Size	Health Utility Index Score Mean (SD)	Disutility of Having the Condition (1-Utility Index Score)	Disutility of Not Having the Condition	Population Norm Disutility
Screen-detected T2DM						
EQ-5D: Mean (SD) population norm utility index score=0.86 (0.50) for the U.S. and UK, 0.87 (NR) for Denmark, 0.89 for Netherlands, MCID=0.04-0.08						
van den Donk, 2010[95] Maindal, 2014[98] Simmons, 2016[76] Black, 2015[102]	ADDITION-Europe Routine Care Group	156 463 852 312 85 157 157 144	0.83 (NR) Denmark (3 years) 0.84 (0.22) Denmark (5 years) 0.85§ (NR) UK Cambridge (baseline) 0.83 (0.22) UK Cambridge (5 years) 0.79 (0.23) UK Leicester (5 years) 0.81 (0.25)^ Netherlands (baseline) 0.82 (0.25)^ Netherlands (3 years) 0.82 (0.26)^ Netherlands (5 years)	0.17 0.16 0.15 0.17 0.21 0.19 0.18 0.18	NA	0.13* 0.13 0.14 0.14 0.14* 0.11* 0.11* 0.11*
Early T2DM (Precomplications)						
SF-6D: Mean (SD) population norm utility index score=0.79 (0.50), MID=0.03-0.04						
Vaatainen, 2014[101]	Cross-sectional, Finland	47	0.75 (0.17)^	0.25	0.22*	0.21*
HRQOL 15-D: Mean (SD) population norm utility index score=0.86 (0.12), MID=0.015-0.03						
Vaatainen, 2014[101]	Cross-sectional, Finland	47	0.88 (0.12)^	0.12	0.09*	(0.14)*
QWB-SA: Mean (SD) population norm utility index score=0.64 (0.50), MID=0.03						
DPP/DPPOS, 2012[96]	DPP/DPPOS, placebo group, developed T2DM within 2 years of enrollment and anytime over the 10-year study period	155: 2 years 439: 10 years	0.68 (NR) 0.67 (0.01)^	0.32 0.33	NA	(0.36)* (0.36)*
Prediabetes						
EQ-5D-3L: Mean (SD) population norm utility index score=0.86 (0.50) for the U.S. and UK, 0.8 (NR)7 for Denmark, MID=0.04-0.08						
Maindal, 2014[98]	ADDITION-Denmark control IGT Group	156	0.84 (NR)	0.16	NA	0.13
Leal, 2017[104]	RCT, UK, Standard Care group	433	0.82 (0.01) baseline 0.81 (0.01) 6 months 0.82 (0.01) 12 months 0.80 (0.01) 24 months 0.78 (0.01) 36 months	0.18 0.19 0.18 0.20 0.22	NA	0.14* 0.14* 0.14* 0.14* 0.14*
SF-6D: Mean (SD) population norm utility index score=0.79 (0.50), MID=0.03-0.04						
Vaatainen, 2014[101]	Cross-sectional, Finland, IFG group	75: IFG 122: IGT	0.77 (0.22)^ 0.75 (0.17)^	0.23 0.25	0.22 0.22*	0.21 0.21*

Appendix B4 Table 2. Health Utilities and Resulting Disutilities of Having Screen-Detected or Early T2DM Without Complications or Prediabetes

Study Author, Year	Study Description	Sample Size	Health Utility Index Score Mean (SD)	Disutility of Having the Condition (1-Utility Index Score)	Disutility of Not Having the Condition	Population Norm Disutility
Marrero, 2014[99] Florez, 2012[97]	DPPOS	3,210	0.80 (0.10)	0.20	NA	(0.21)
Neumann, 2014[100]	Cross-sectional, Sweden	5,275: IFG 2,261: IGT 1,122: IFG & IGT	0.76 (0.11) 0.75 (0.11) 0.75 (0.11)	0.24 0.25 0.25	0.23 0.23 0.23	0.21* 0.21* 0.21*
DiBonaventura, 2015[103]	Cross-sectional, U.S.	1,441: Normal weight 7,632: Overweight. 6,087: Obese I 2,421: Obese II 2,331: Obese III	0.75 (NR) 0.75 (NR) 0.73 (NR) 0.70 (NR) 0.68 (NR)	0.25 0.25 0.27 0.30 0.32	0.25 (0.27) (0.28) 0.30 (0.31)	0.21* 0.21* 0.21* 0.21* 0.21*
HRQOL 15-D: Mean (SD) population norm utility index score=0.86 (0.12), MID=0.015-0.03						
Vaatainen, 2014[101]	Cross-sectional, Finland, IFG group	75: IFG 122: IGT	0.92 (0.09)^ 0.89 (0.11)^	0.08 0.11	(0.09) 0.09*	(0.14)* (0.14)*
Makrilakis, 2018[105]	Cross-sectional, Greece	172	0.90 (NR)	0.10	0.09	(0.14)*
Davies, 2016[86]	Let's Prevent Diabetes Lifestyle trial, UK, usual care group	433	Median (IQR) 0.91 (0.84, 0.96) Baseline 0.89 (0.82, 0.95) 36 months	0.09 0.11	NA	(0.14)* (0.14)*
QWB-SA: Mean (SD) population norm utility index score=0.64 (0.50), MID=0.03						
DPP/DPPOS, 2012[96]	DPP/DPPOS, U.S., placebo group (mean over 10 years)	1,082	0.68 (0.01)^	0.32	NA	(0.36)*

Disutilities in parenthesis represent findings where the disutility of having diabetes/prediabetes was lower than that of not having diabetes/prediabetes or lower than the population norm disutility; ^SD that was calculated using other information in the publication(s); §represents a median rather than a mean value; *represents a disutility that meets suggested criteria for a minimally important difference compared with the diabetes/prediabetes group.

Abbreviations: DPP=Diabetes Prevention Program; DPPOS=Diabetes Prevention Program Outcomes Study; HRQOL=health-related quality of life; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; IQR=interquartile ratio; MCID=minimally clinically important difference; MID=minimally important difference; NA=not applicable; NR=not reported; QWB-SA=quality of well-being self-administered; SD=standard deviation; T2DM=type 2 diabetes mellitus; UK=United Kingdom; U.S.=United States.

Appendix B4 Table 3. Distribution of Disutilities Associated with Taking Metformin

Study Author, Year	Study Description	Sample Size (metformin/placebo)	Health Utility Index for Those Taking Metformin	Disutility for Those Taking Metformin (1-Utility Index Score)	Disutility for Those Taking Placebo	Population Norm Disutility
Early T2DM (Precomplications)						
QWB-SA: Mean (SD) population norm utility index score=0.64 (0.50), MID=0.03						
DPP/DPPOS, 2012[96]	DPP/DPPOS, Participants who developed T2DM		0.68 (0.02)^ mean over 10 years	0.32	0.33	(0.36)*
		11/39	0.72 (NR) 1 year	0.28	(0.31)*	(0.36)*
		98/155	0.68 (NR) 2 years	0.32	0.32	(0.36)*
		175/255	0.69 (NR) 3 years	0.31	(0.34)*	(0.36)*
		247/311	0.68 (NR) 4 years	0.32	(0.33)	(0.36)*
		278/341	0.67 (NR) 5 years	0.33	0.33	(0.36)*
		287/356	0.67 (NR) 6 years	0.33	(0.34)	(0.36)*
		314/379	0.67 (NR) 7 years	0.33	0.33	(0.36)*
		341/401	0.67 (NR) 8 years	0.33	0.33	(0.36)*
		363/423	0.66 (NR) 9 years	0.34	0.34	(0.36)*
		377/439	0.67 (NR) 10 years	0.33	(0.34)	(0.36)*
Prediabetes						
SF-6D: Mean (SD) population norm utility index score=0.79 (0.50), MID=0.03-0.04						
Marrero, 2014[99]	DPPOS prediabetes group	327/389	0.80 (NR) baseline	0.20	0.20	0.21
		318/379	0.78 (NR) 2 years	0.22	0.21	0.21
		231/302	0.78 (NR) 3 years	0.22	0.22	0.21
		231/302	0.76 (NR) 4 years	0.24	0.24	0.21*
		141/157	0.74 (NR) 5 years	0.26	0.26	0.21*
		141/157	0.72 (NR) 6 years	0.28	0.27	0.21*
QWB-SA: Mean (SD) population norm utility index score=0.64 (0.50), MID=0.03						
DPP/DPPOS, 2012[96]	DPP/DPPOS prediabetes group by year	1,062/1,043	0.69 (NR) 1 year	0.32	0.31	(0.36)*
		944/889	0.68 (NR) 2 years	0.31	(0.32)	(0.36)*
		837/772	0.68 (NR) 3 years	0.32	0.32	(0.36)*
		736/679	0.68 (NR) 4 years	0.32	0.32	(0.36)*
		663/605	0.68 (NR) 5 years	0.32	0.32	(0.36)*
		619/567	0.68 (NR) 6 years	0.32	0.32	(0.36)*
		576/524	0.69 (NR) 7 years	0.32	0.32	(0.36)*
		536/491	0.68 (NR) 8 years	0.31	0.32	(0.36)*
		500/451	0.68 (NR) 9 years	0.32	(0.33)	(0.36)*
		466/416	0.68 (NR) 10 years	0.32	0.32	(0.36)*

Disutilities in parenthesis represent findings where the disutility of taking metformin was lower than that of taking placebo or lower than the population norm disutility; ^SD that was calculated using other information in the publication(s); *represents a disutility that meets criteria for a suggested MCID compared with the group taking metformin.

Abbreviations: DPP=Diabetes Prevention Program; DPPOS=Diabetes Prevention Program Outcomes Study; MID=minimally important difference; NR=not reported; QWB-SA=quality of well-being self-administered; SD=standard deviation; SF-6D=Short Form Health Survey; T2DM=type 2 diabetes mellitus.

Appendix B4 Table 4. Distribution of Disutilities Associated With Making Intensive Lifestyle Changes

Study Author, Year	Study Description	Sample Size (Lifestyle/ Placebo or Usual Care)	Health Utility Index for Those Making Intensive Lifestyle Changes	Disutility for Those Making Intensive Lifestyle Changes (1-Utility Index Score)	Disutility for Those Not Making Intensive Lifestyle Changes	Population Norm Disutility
Screen-detected T2DM						
EQ-5D: Mean (SD) population norm utility index score=0.86 (0.50) for the U.S. and UK 0.8 (NR)7 for Denmark, MID=0.04-0.08						
Maindal, 2014[98]	Addition Denmark screen-detected T2DM group at 3 years	NR	0.84	0.16	NA	0.13
Black, 2015[102]	Addition Cambridge, screen-detected T2DM group	739 663	0.85 3 years 0.85 5 years	0.15 0.15	NA	0.14 0.14
Early T2DM (Precomplications)						
QWB-SA: Mean (SD) population norm utility index score=0.64 (0.50), MID=0.03						
DPP/DPPOS, 2012[96]	DPPOS, placebo group who developed T2DM	 10/39 51/155 103/255 151/311 186/341 227/356 263/379 288/401 302/423 322/439	0.67 (0.01)^ Mean over 10 years 0.67 (NR) 1 year 0.64 (NR) 2 years 0.67 (NR) 3 years 0.65 (NR) 4 years 0.66 (NR) 5 years 0.68 (NR) 6 years 0.68 (NR) 7 years 0.67 (NR) 8 years 0.68 (NR) 9 years 0.68 (NR) 10 years	0.33 0.33 0.36 0.33 0.35 0.34 0.32 0.32 0.33 0.32 0.32	0.33 0.31 0.32* (0.34) 0.33 0.33 (0.34) (0.33) 0.33 (0.34) (0.34)	(0.36)* 0.36 (0.36)* (0.36) (0.36) (0.36)* (0.36)* (0.36)* (0.36)* (0.36)*
Prediabetes						
EQ-5D: Mean (SD) population norm utility index score=0.86 (0.50) for the U.S. and UK 0.8 (NR)7 for Denmark, MID=0.04-0.08						
Leal, 2017[104]	Let's Prevent Diabetes Intensive lifestyle intervention, UK, prediabetes group	477/433	0.80 (0.01) 6 months 0.80 (0.01) 12 months 0.78 (0.01) 24 months 0.77 (0.01) 36 months	0.20 0.20 0.22 0.23	0.19 0.18 0.20 0.22	0.14* 0.14* 0.14* 0.14*
Maindal, 2014[98]	Addition Denmark IGT group at 3 years	NR	0.83 (NR)	0.17	NA	0.13*
SF-6D: Mean (SD) population norm utility index score=0.79 (0.50), MID=0.03-0.04						
Marrero, 2014[99]	DPP/DPPOS prediabetes group	327/389 318/379 231/302 231/302 141/157 141/157	0.80 (NR) baseline 0.78 (NR) 2 years 0.78 (NR) 3 years 0.76 (NR) 4 years 0.74 (NR) 5 years 0.72 (NR) 6 years	0.20 0.22 0.22 0.24 0.26 0.28	0.20 0.21 0.22 0.24 0.26 0.27	0.21 0.21 0.21 0.21* 0.21* 0.21*

Appendix B4 Table 4. Distribution of Disutilities Associated With Making Intensive Lifestyle Changes

Study Author, Year	Study Description	Sample Size (Lifestyle/ Placebo or Usual Care)	Health Utility Index for Those Making Intensive Lifestyle Changes	Disutility for Those Making Intensive Lifestyle Changes (1-Utility Index Score)	Disutility for Those Not Making Intensive Lifestyle Changes	Population Norm Disutility
QWB-SA: Mean (SD) population norm utility index score=0.64 (0.50), MID=0.03						
DPP/DPPOS, 2012[96]	DPP/DPPOS prediabetes group by year	1,069/1,043	0.70 (NR) 1 year	0.30	(0.31)	(0.36)*
		988/889	0.70 (NR) 2 years	0.30	(0.32)	(0.36)*
		917/772	0.70 (NR) 3 years	0.30	(0.32)	(0.36)*
		827/679	0.70 (NR) 4 years	0.30	(0.32)	(0.36)*
		747/605	0.69 (NR) 5 years	0.31	(0.32)	(0.36)*
		674/567	0.69 (NR) 6 years	0.31	(0.32)	(0.36)*
		620/524	0.69 (NR) 7 years	0.31	(0.32)	(0.36)*
		585/491	0.69 (NR) 8 years	0.31	(0.32)	(0.36)*
		553/451	0.69 (NR) 9 years	0.31	(0.33)	(0.36)*
		511/411	0.69 (NR) 10 years	0.31	(0.32)	(0.36)*
HRQOL 15-D: Mean (SD) population norm utility index score=0.86 (0.12), MID=0.015-0.03						
Davies, 2016[86]	Let's Prevent Diabetes Lifestyle trial, UK, usual care group	447/433	Median (IQR) 0.90 (0.82, 0.95) baseline 0.91 (0.84, 0.96) 36 months	0.10 0.09	NA	(0.14)* (0.14)*

Disutilities in parenthesis represent findings where the disutility of making an intensive lifestyle intervention is lower than that of not making a lifestyle change or lower than the population norm disutility; ^SD that was calculated using other information in the publication(s); *represents a disutility that meets suggested criteria for a MCID compared with the group making intensive lifestyle changes

Abbreviations: DPP=Diabetes Prevention Program; DPPOS=Diabetes Prevention Program Outcomes Study; EQ-5D=EuroQol 5 dimensions; HRQOL=health-related quality of life; IGT=impaired glucose tolerance; IQR=interquartile ratio; MID=minimally important difference; NA=not applicable; NR=not reported; QWB-SA=quality of well-being self-administered; SD=standard deviation; SF-6D=Short Form Health Survey; T2DM=type 2 diabetes mellitus; UK=United Kingdom; U.S.=United States.

Appendix B4 Table 5. Disutilities of Prediabetes vs. Diabetes

Study Author, Year	Disutility of Having Prediabetes	Study Author, Year	Disutility of Having Screen-Detected or Uncomplicated Early Diabetes
Taking Metformin			
QWB-SA: MID=0.03			
DPP/DPPOS, 2012[96]	Range: 0.31-0.32 Mean (SD): 0.32 (0.004)^ 0.31 (year 1, n=1,062) 0.32 (year 2, n=944) 0.32 (year 3, n=837) 0.32 (year 4, n=736) 0.32 (year 5, n=663) 0.32 (year 6, n=619) 0.31 (year 7, n=576) 0.32 (year 8, n=536) 0.32 (year 9, n=500) 0.32 (year 10, n=466)	DPP/DPPOS, 2012[96]	Range: 0.28-0.33 Mean (SD): 0.32 (0.02)^ 0.28* (year 1, n=11) 0.32 (year 2, n=98) 0.31 (year 3, n=175) 0.32 (year 4, n=247) 0.33 (year 5, n=278) 0.33 (year 6, n=287) 0.33 (year 7, n=314) 0.33 (year 8 n=341) 0.34 (year 9, n=363) 0.33 (year 10, n=377)
Making Intensive Lifestyle Changes			
EQ-5D-3L: MID=0.04-0.08			
Maindal, 2014[98] ADDITION-Denmark	0.17 (n=108)	Maindal, 2014[98] ADDITION-Denmark Black, 2015[102] ADDITION-Cambridge	0.16 (n=174) 0.15 (n=852)
QWB-SA: MID=0.03			
DPP/DPPOS, 2012[96]	Range: 0.30-0.31 Mean (SD): 0.31 (0.005)^ 0.30 (year 1, n=1,069) 0.30 (year 2, n=988) 0.30 (year 3, n=917) 0.30 (year 4, n=827) 0.31 (year 5, n=747) 0.31 (year 6, n=674) 0.31 (year 7, n=620) 0.31 (year 8, n=585) 0.31 (year 9, n=553) 0.31 (year 10, n=511)	DPP/DPPOS, 2012[96]	Range: 0.32-0.34 Mean (SD): 0.33 (0.01)^ 0.33* (year 1, n=10) 0.36* (year 2, n=51) 0.33* (year 3, n=103) 0.35* (year 4, n=151) 0.34* (year 5, n=186) 0.32 (year 6, n=227) 0.32 (year 7, n=263) 0.33 (year 8, n=288) 0.32 (year 9, n=302) 0.32 (year 10, n=322)

^SD that was calculated using other information in the publication(s); *represents a disutility that meets suggested criteria for a MCID compared with the prediabetes group.

Abbreviations: DPP=Diabetes Prevention Program; DPPOS=Diabetes Prevention Program Outcomes Study; EQ-5D=EuroQol 5 dimensions; MID=minimally important difference; QWB-SA=quality of well-being self-administered.

Appendix B4 Table 6. Distribution of HRQOL Among Those With Screen-Detected or Early Uncomplicated T2DM and Those With Prediabetes

Study Author, Year	Study Description	Sample Size	HQOL Score (SD) for Participants with Diabetes or Prediabetes	QoL Score of Participants Who Do Not Have Diabetes or Prediabetes
Screen-detected T2DM				
SF-36 PCS Score: Population norm mean (SD)=50 (10), MCID=3-5 points				
Simmons, 2016[76]	ADDITION-Europe trial, routine care group at 5 years F/U	Denmark: 428 Cambridge: 310 Leicester: 84 Netherlands: 144	46.7 (9.6) 44.6 (11.3) 43.4 (10.5) 47.0 (10.5)	NA
SF-36 PCS Score: Population norm mean (SD)=50 (10), MCID=3-5 points				
Simmons, 2016[76]	ADDITION-Europe Trial, Routine Care Group at 5 years F/U	Denmark: 428 Cambridge: 310 Leicester: 84 Netherlands: 144	54.9 (8.5) 54.6 (8.4) 52.2 (9.8) 53.7 (7.4)	NA
EQ-5D VAS Scores: Population norm for the VAS score mean (SD)=80 (20) for the U.S. and UK, 84 (26) for Denmark, and 82 (20) for the Netherlands, MCID=7-8 points				
Simmons, 2016[76]	ADDITION-Europe Trial, Routine Care Group at 5 years F/U	Denmark: 462 Cambridge: 316 Leicester: 88 Netherlands: 144	76.4 (18.5) 78.4 (16.4) 74.8 (18.4) 75.3 (15.6)	NA
Early T2DM (Precomplications)				
SF-36 or SF-12 PCS Score: Population norm mean (SD)=50 (10), MCID=3-5 points				
Hunger, 2014[111]	Longitudinal study, Germany, baseline results	T2DM: 80 No DM: 453	45.3 (NR)	45.3 (NR)
Seppala, 2013[110]	Cross-sectional study, Finland	T2DM grp: 91 No DM: 973	44.3 (9.6)	46.7 (9.5)
Kempf, 2012[109]	Baseline results from a 12-week intervention study, Germany	405	65.2 (NR)	NA
SF-36 or SF-12 PCS Score: Population norm mean (SD)=50 (10), MCID=3-5 points				
Hunger, 2014[111]	Longitudinal study, Germany, baseline results	T2DM: 80 No DM: 453	52.5 (NR)	52.1 (NR)
Seppala, 2013[110]	Cross-sectional study, Finland	T2DM grp: 91 No DM: 973	52.0 (9.3)	53.5 (9.1)
Kempf, 2012[109]	Baseline results from a 12-week intervention study, Germany	405	68.0 (NR)	NA
Prediabetes				
SF-36 or SF-12 PCS Scores: Population norm Mean (SD)=50 (10), MCID=3-5 points				
Hunger, 2014[111]	Longitudinal study, Germany, baseline results	Prediabetes: 442 No diabetes: 453	46.0 (NR)	45.3 (NR)
Seppala, 2013[110]	Cross-sectional study, Finland	IFG: 154 IGT: 165 No DM: 973	45.4 (9.8) 46.2 (9.5)	46.7 (9.5)
Ibrahim, 2014[114]	Cross-sectional, Malaysia, Total group	Total group: 268 Normal weight group: 19 Overweight group: 58 Obese group: 191	81.0 (13.2) 88.0 (9.8) 86.8 (11.1) 78.6 (13.3)	NA
Marrero, 2014[99]	Baseline results from the DPP/DPPOS U.S. study, total group	3,210	50.3 (7.1)	NA

Appendix B4 Table 6. Distribution of HRQOL Among Those With Screen-Detected or Early Uncomplicated T2DM and Those With Prediabetes

Study Author, Year	Study Description	Sample Size	HQOL Score (SD) for Participants with Diabetes or Prediabetes	QoL Score of Participants Who Do Not Have Diabetes or Prediabetes
DiBonaventura, 2015[103]	Cross-sectional study, U.S.	Normal weight group: 1,441 Overweight group: 7,632 Obese I group: 6,087 Obese II group: 2,421 Obese III group: 2,331	50.2 (NR) 49.5 (NR) 47.7 (NR) 45.2 (NR) 42.5 (NR)	52.8 (NR)^ 51.9 (NR)^ 51.1 (NR)^ 49.9 (NR)^ 47.9 (NR)^
le Roux, 2017[115]	SCALE Obesity and Prediabetes trial. Placebo group	749	46.6 (9.0) baseline 49.2 (7.6) 3 years	NA
Rabijewski, 2018[116]	Cross-sectional study, Poland, Men only	Prediabetes: 176 No DM: 184	79.0 (13.5)	81.0 (13.9)*
SF-36 or SF-12 MCS Scores: Population norm mean (SD)=50 (10), MCID=3-5 points				
Hunger, 2014[111]	Longitudinal study, Germany, baseline results	Prediabetes:442 No diabetes: 453	52.9 (NR)	52.1 (NR)
Seppala, 2013[110]	Cross-sectional study, Finland	IFG: 154 IGT: 165 No DM: 973	54.6 (7.6) 53.9 (8.2)	53.5 (9.1)
Ibrahim, 2014[114]	Cross-sectional, Malaysia, Total group	Total group: 268 Normal weight group: 19 Overweight group: 58 Obese group: 191	83.9 (11.5) 85.2 (13.1) 85.6 (9.6) 83.1 (11.9)	NA
Marrero. 2014[99]	DPP/DPPOS U.S. study, total group	3210	54.0 (7.5)	NA
DiBonaventura, 2015[103]	Cross-sectional study, U.S.	Normal weight group: 1441 Overweight group: 7,632 Obese I group: 6,087 Obese II group: 2,421 Obese III group: 2,331	51.4 (NR) 51.6 (NR) 51.1 (NR) 50.8 (NR) 49.7 (NR)	48.3 (NR)^ 47.8 (NR)^ 46.6 (NR)^ 46.0 (NR)^ 45.8 (NR)^
le Roux, 2017[115]	SCALE Obesity and Prediabetes trial. Placebo group	749	54.0 (8.0) baseline 52.6 (9.2) 3 years	NA
Rabijewski, 2018[116]	Cross-sectional study, Poland	Prediabetes: 176 No DM: 184	80.0 (14.2)	83 (14.3)*
RAND-12 PHC Score: Population norm mean (SD)=50 (10), MCID=3-5 points				
Taylor, 2010[113]	Cross-sectional study, Canada	232	46.6 (9.9)	NA
RAND-12 MHC Score: Population norm mean (SD)=50 (10), MCID=3-5 points				
Taylor, 2010[113]	Cross-sectional study, Canada	232	45.2 (9.7)	NA
WHO-5 Well-Being Index: Population norm mean (SD)=70 (NR), MCID=10 points				
Kulzer, 2009[112]	Prevention of Diabetes Self-Management Program (PREDIAS) trial, control group	91	14.3 (4.9) baseline 14.3 (5.1) 1 year	NA

*Significant difference between the diabetes/prediabetes group and the group with no diabetes; ^Differences between the diabetes/prediabetes group and the "no diabetes" group were not provided;

Abbreviations: DPP=Diabetes Prevention Program; DPPOS=Diabetes Prevention Program Outcomes Study; EQ-5D=EuroQol 5 dimensions; HRQOL=health-related quality of life; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; MHC=mental health composite score; MCID=minimally clinically important difference; NA=not applicable; NR=not reported; PHC=physical health composite score; SD=standard deviation; T2DM=type 2 diabetes mellitus; UK=United Kingdom; U.S.=United States.

Appendix B4 Table 7. ICG Study and Sample Characteristics

Author, Year	Location/Study Name	Baseline Year(s)	Sample Size and Description*	Mean Age (SD)	Years of Followup	Glucose Measure Used in Multivariate Analyses	Mean Glucose (SD)	Distribution of Glucose Measure by Quintile
Stamler et al, 1979[170]	Chicago Heart Association Study	1972-1973	7,841 men employed in various industries in Chicago ages 40-59	48.7 (5.6)	5	One-hour plasma glucose	146.5 mg/dL (46.9)	Quintile 1: 40-108 mg/dL Quintile 2: 109-126 Quintile 3: 127-149 Quintile 4: 150-178 Quintile 5: 179-564
Stamler et al, 1979[128]	Chicago Peoples Gas Company Employees	1962	891 white male employees of Peoples Gas Company ages 45-64	NA	13	Casual plasma glucose determination	NA	Quintile 1: 70-88 mg/dL Quintile 2: 89-96 Quintile 3: 97-104 Quintile 4: 105-118 Quintile 5: 119-265
Stamler et al, 1979[128]	Chicago Peoples Gas Company Employees	1965	865 white male employees of Peoples Gas Company ages 40-64	52.9 (6.7)	10	Plasma glucose 1 hour after 50-g oral load	141.4 mg/dL (40.6)	Quintile 1: 58-107 mg/dL Quintile 2: 108-125 Quintile 3: 126-145 Quintile 4: 146-173 Quintile 5: 174-435
Stamler et al, 1979[128]	Chicago Western Electric Employees	1960	1,694 white male employees of Western Electric Company employees, ages 42-58	49.9 (4.5)	15	Two-hour post-load serum glucose after 100-g load	101.1 mg/dL (33.0)	Quintile 1: 42-77 mg/dL Quintile 2: 78-89 Quintile 3: 90-102 Quintile 4: 103-119 Quintile 5: 120-420
Stenhouse et al, 1979[171]	Busselton Population Study	1966	649 men ages 40-59 from Busselton, Australia	49.0 (5.7)	11	One-hour post-load plasma glucose	100.7 mg/dL (31.9)	Quintile 1: 42-75 mg/dL Quintile 2: 76-88 Quintile 3: 89-100 Quintile 4: 101-122 Quintile 5: 123-415

Appendix B4 Table 7. ICG Study and Sample Characteristics

Author, Year	Location/Study Name	Baseline Year(s)	Sample Size and Description*	Mean Age (SD)	Years of Followup	Glucose Measure Used in Multivariate Analyses	Mean Glucose (SD)	Distribution of Glucose Measure by Quintile
Reunanen et al, 1979[172]	Finnish Social Insurance Institution's Coronary Heart Disease Study	1966-1972	3,351 men ages 40-59, samples from nine municipalities and three factories	48.5 (5.8)	4	One-hour post-load plasma glucose	161.1 m/dL (52.8)	Deciles provided for participants examined before and after 12 pm (presented as: Decile X: before 12 pm/after 12 pm) Decile 1: 52-9 6 mg/dL/52-115 mg/dL Decile 2: 97-107/116-135 Decile 3: 108-119/136-149 Decile 4: 120-130/150-162 Decile 5: 131-142/163-178 Decile 6: 143-156/179-192 Decile 7: 157-173/193-207 Decile 8: 174-193/208-228 Decile 9: 194-221/229-250 Decile 10: 222-506/251-473
Pyorala et al, 1979[129]	Helsinki Policemen Study	1966-1967	867 Helsinki policemen ages 40-59	47.4 (4.9)	10	One-hour post load blood glucose	119.6 mg/dL (37.9)	Quintile 1: 30-62 mg/dL Quintile 2: 63-73 Quintile 3: 74-84 Quintile 4: 85-99 Quintile 5: 100-334
Ducimetiere et al, 1979[130]	Paris Prospective Study	1967-1972	6,589 men working in the Paris Civil Services ages 42-53	47.1 (1.9)	5	Two-hour post load glucose (75-g glucose load)	103.3 mg/dL (35.3)	Quintile 1: 30-77 mg/dL Quintile 2: 78-90 Quintile 3: 91-105 Quintile 4: 106-125 Quintile 5: 126-540
Da Silva et al, 1979[173]	Basle Longitudinal Study, Switzerland	1965-1968	1,499 men ages 40-59 in Basel, Switzerland	48.8 (5.6)	5	Two-hour post load blood glucose	107.0 mg/dL (25.1)	Quintile 1: 26-90 mg/dL Quintile 2: 91-100 Quintile 3: 101-109 Quintile 4: 110-121 Quintile 5: 122-320
Fuller et al, 1979[174] †	Whitehall Study, London	1969	18,403 men working as London civil servants ages 40-64	50 (NA)	5	Two-hour post load blood glucose (50-g glucose load)	75.4 mg/dL (16.2)	Quintile 1: 27-65 Quintile 2: 66-71 Quintile 3: 72-76 Quintile 4: 77-93 Quintile 5: 83-504

Appendix B4 Table 7. ICG Study and Sample Characteristics

Author, Year	Location/Study Name	Baseline Year(s)	Sample Size and Description*	Mean Age (SD)	Years of Followup	Glucose Measure Used in Multivariate Analyses	Mean Glucose (SD)	Distribution of Glucose Measure by Quintile
Schroll & Hagerup, 1979[175]	Glostrup Population Studies, age 50 cohort	1964	375 50-year old males from Glostrup, Denmark	50	10	Fasting blood glucose	86.0 mg/dL (11.5)	Quintile 1: 50-76 mg/dL Quintile 2: 77-83 Quintile 3: 84-89 Quintile 4: 90-95 Quintile 5: 96-225
Hawthorne & Gilmour, 1979[176]	Renfrew, Scotland	1972	1,134 males from Renfrew, Scotland, ages 45-64 Separate analyses with anti-hypertensive included/excluded	54.2 (5.5)	6	"Casual blood glucose"‡	96.2 mg/dL (26.7)	Quintile 1: 27-80 mg/dL Quintile 2: 81-88 Quintile 3: 89-96 Quintile 4: 97-107 Quintile 5: 108-518

* This column contains the sample size for which the demographics of the sample were provided; sample size in actual regression models may differ from this and each other.
† Baseline year, average age, and average glucose were not in the Fuller[126] publication, so these were taken from the ICG introduction paper.
‡ Authors describe this measure as follows: "Blood samples were collected afternoons and evenings. A 10ml casual sample of venous blood was taken without venous stasis and plasma total cholesterol was measured by an autoanalyzer technique. Glucose was determined (using whole blood) by the measurement of oxygen consumption."

Abbreviations: ICG=International Collaborative Group; NA=not available; SD=standard deviation.

Appendix B4 Table 8. Associations Between Glucose Measure and All-Cause, Cardiovascular Disease-Related, and CHD-Related Mortality From ICG Studies

Author, Year Study Name	Glucose/Diabetes Measure	All-Cause Deaths/Sample Size	All-Cause Mortality Estimate	Cardiovascular Disease-Related Deaths/Sample Size	Cardiovascular Disease-Related Mortality Estimate (error estimate)	CHD-Related Deaths/Sample Size	CHD-Related Mortality Estimate	Covariates Adjusted for in Models
Stamler, 1979 Chicago Heart Association Study[170]	One-hour post-load plasma glucose	169/6,595	0.00409* (SE 0.00175)	80/6,506	0.00115 (SE 0.00253)	67/6,493	0.00085 (SE 0.00277)	Age, SBP, BMI, cholesterol, number of cigarettes, ex-smoker
Stamler, 1979 Peoples Gas Company 1965 cohort[128]	One-hour post-load plasma glucose	116/840	0.00958** (SE 0.00261)	53/777	0.01295** (SE 0.00378)	40/764	0.01395*** (SE 0.00432)	Age, SBP, BMI, BMI^2, cholesterol, number of cigarettes
Stamler, 1979 Peoples Gas Company 1962 cohort[128]	Casual plasma glucose	190/891	-0.00514 (SE 0.00362)	103/804	-0.01007* (SE 0.00480)	70/771	-0.00921 (SE 0.00566)	Age, SBP, relative weight, cholesterol, number of cigarettes, pulse
Stamler, 1979 Western Electric Co[128]	Two-hour post-load serum glucose	271/1,694	-0.00187 (SE 0.00207)	166/1,589	-0.00217 (SE 0.00261)	136/1,595	-0.00272 (SE 0.00287)	Age, SBP, BMI, cholesterol, number of cigarettes
Stenhouse, 1979 Busselton Population Study[171]	One-hour post-load plasma glucose	56/638	0.0001 (t 0.35)	21/603	-0.0003 (t -1.06)	18/600	-0.0002 (t -0.78)	Age, SBP, relative weight, cholesterol, cigarette smoking
Reunanen, 1979 Finnish Coronary Heart Disease Study[172]	One-hour post-load plasma glucose	121/3,267	0.002 (SE 0.002)	64/3,212	-0.001 (SE 0.003)	38/3,186	-0.007 (SE 0.003)	Age, SBP, BMI, cholesterol, smoking status

Appendix B4 Table 8. Associations Between Glucose Measure and All-Cause, Cardiovascular Disease-Related, and CHD-Related Mortality From ICG Studies

Author, Year Study Name	Glucose/Diabetes Measure	All-Cause Deaths/Sample Size	All-Cause Mortality Estimate	Cardiovascular Disease-Related Deaths/Sample Size	Cardiovascular Disease-Related Mortality Estimate (error estimate)	CHD-Related Deaths/Sample Size	CHD-Related Mortality Estimate	Covariates Adjusted for in Models
Pyorala, 1979 Helsinki policemen[129]	One-Hour post-load blood glucose	70/845	0.002 (SE 0.003)	42/817	0.002 (SE 0.004)	31/806	0.004 (SE 0.004)	Age, SBP, BMI, plasma cholesterol, smoking status
Ducimetiere, 1979 Paris Prospective Study[130]	Two-hour post-load plasma glucose	142/6,484	0.006** (SE 0.002)	41/6,373	0.003 (SE 0.003)	35/6,377	0.002 (SE 0.004)	Age, SBP, BMI, cholesterol, cigarette use
Da Silva, 1979 Basle Longitudinal Study[173]	Two-hour post-load plasma glucose	34/1,491	0.01184 (SE 0.00709)	12/1,469	0.01004 (SE 0.01191)	7/1,464	0.00383 (SE 0.01569)	Age, SBP, BMI, β-lipoproteins, number of cigarettes
Fuller, 1979 Whitehall Study- ages 40-59[174]	Two-hour post-load plasma glucose	414/14,756	-0.001 (t -0.45)	206/14,756	0.002 (t 0.60)	166/14,756	0.003 (t 1.01)	Age, SBP, weight/height^2, cholesterol, smoking status
Fuller, 1979 Whitehall Study- ages 40-64[174]	Two-hour post-load plasma glucose	559/16,873	0.0003 (t 0.12)	275/16,873	0.003 (t 1.10)	221/16,873	0.004 (t 1.48)	Age, SBP, weight/height^2, cholesterol, smoking status
Hawthorne, 1979 Renfrew, Scotland Those taking antihypertensive medications excluded[176]	"Casual blood glucose"	60/1,128	0.007 (SE 0.005)	29/1,097	0.014 (SE 0.007)	22/1,090	-0.009 (SE 0.009)	Age, SBP, relative weight, cholesterol, cigarettes/day, ex-smoker

Appendix B4 Table 8. Associations Between Glucose Measure and All-Cause, Cardiovascular Disease-Related, and CHD-Related Mortality From ICG Studies

Author, Year Study Name	Glucose/Diabetes Measure	All-Cause Deaths/Sample Size	All-Cause Mortality Estimate	Cardiovascular Disease-Related Deaths/Sample Size	Cardiovascular Disease-Related Mortality Estimate (error estimate)	CHD-Related Deaths/Sample Size	CHD-Related Mortality Estimate	Covariates Adjusted for in Models
Hawthorne, 1979 Renfrew, Scotland Those taking antihypertensive medications included[176]	"Casual blood glucose"	100/1,326	0.008 (SE 0.004)	54/1,280	0.011* (SE 0.005)	39/1,265	-0.000 (SE 0.007)	Age, SBP, relative weight, cholesterol, cigarettes/day, ex-smoker
Schroll, 1979 Glostrup Population Studies – age 50 cohort[175]	Fasting blood glucose	43/375	-0.0038 (SD 0.0152)					Glucose, SBP, BMI, cholesterol, smoking status (1-14/day, 15-24/day, 25+/day, ex-smokers)

* p<0.05, ** p<0.001, *** p<0.01

Note: The mortality estimates represent the association between the continuous measure of glucose used in the study and the risk of mortality during the followup period, adjusting for confounders listed in the "Covariates Adjusted for in Model" column. A positive estimate suggests greater levels of the measure of glucose is associated with increased risk of mortality in the study followup period.

Abbreviations: BMI=body mass index; CHD=coronary heart disease; ICG=International Collaborative Group; SBP=systolic blood pressure; SD=standard deviation; SE=standard error.

Appendix B4 Table 9. Trials of Lifestyle Interventions Included in KQ 7

Author, Year, Study Name	Source of Participants	Number of Participants	Intervention	Uptake	Adherence
Morey, 2012, Enhanced Fitness[120]	Screening medical records	180	Counseling intervention with exercise prescriptions	None	Proportion of participants who performed 150 minutes of endurance exercise increased over time from 16% to 42%.
Lindahl, 2009[137]	Recruited from an ongoing community intervention for cardiovascular and diabetes	100	1-month residential program with activity and diet goals followed by additional learning and telephone contact	None	For the 83 ITT sample, 25.0% exercised ≥1 times a week at the start of intervention. At one-, three, five-years, 66.3%, 46.6%, and 42.9% exercised ≥1 times a week, respectively.
Yates, 2009, PREPARE[138]	Recruited from ongoing population-based diabetes screening programs	33 PREPARE & Pedometer; 31 PREPARE	Single-session group session. One group was given a pedometer and one group was not.	None	Change in steps/day compared to baseline (95% CI). No pedometer: 3 months 475 steps (-112 to 1,064); 6 months 154 steps (-582 to 889); 12 months 421 steps (-224 to 1,067); With pedometer: 3 months 1605 steps (712 to 2498), 6 months 1,083 (517 to 1649), 12 months 708 steps (72 to 1344)
Ackermann, 2015, RAPID[139]	Electronic medical records	257	DPP-based intervention at YMCA	161/257 (62.6%) attended at least one session	40% (103/257) completed ≥9 sessions
Sakane, 2015, J-DOIT1[140]	Internet advertising and direct contact invited community healthcare divisions and worksites	1240	Telephone counseling sessions at different frequencies promoting exercise and diet goals	None	The mean number of responses to the calls during the 1-year period was 2.8±0.6 (range 1–3) in centre A, 5.2 ±1.9 (range 1–6) in centre B, and 8.2±3.5 (range 1–13) in centre C. The rates of good adherence were 91.4%, 82.7%, and 81.1% for each centre, respectively.
Davies, 2016, Let's Prevent Diabetes[86]	Recruited from community practices	447	Group-based ILI	346/447 attended the first session	248 participants, 55%, of the intervention participants attended the core session and at least one refresher session. 130 participants, 29%, attended all sessions.

Appendix B4 Table 9. Trials of Lifestyle Interventions Included in KQ 7

Author, Year, Study Name	Source of Participants	Number of Participants	Intervention	Uptake	Adherence
Bhopal, 2014[36]	Direct referral from healthcare professionals, written invitations to potential recruits from general practices, community recruitment	85	Families in the intervention group had 15 visits from a dietitian over 3 years	None	84/85 were present for year 3 followup with dietician; Attendance ranged from 72/85 to 84/85 over the 15 home visits
Saito, 2011, Zensharen[87]	Nationwide recruitment of hospitals and clinics	311	Individualized instruction on diet and exercise	None	92.4% attended at least 9 scheduled visits
Van Name, 2016[141]	Electronic patient registry	61	DPP-based intervention	None	4 participants (7%) attended 0–2 classes, 42 participants (68%) attended at least 14 classes
O'Brien, 2017, PREVENT-DM[142]	Community health fairs at Latino-serving community health centers	33	DPP-based intervention	30/33 attended at least one session	23/33 (69.6%) attended at least 9 sessions
Hellgren, 2014[143]	FINDRISC questionnaire sent to individuals and those with a risk score ≥15 were invited	19 (adherence data for only 15 who remained at 1 year)	Group sessions focused on physical activity	None	53% attended 8/8; 80% attended 7/8
Katula, 2013, HELP-PD[144]	Mass mailings to local zip codes	151	DPP-based intervention	None	Participants attended 58.6% of intervention sessions, made up 18.7%, and missed 22.8%
Juul, 2016[145]	Referrals from general practices	63	Group sessions focused on diet and physical activity	None	Attendance rates of the sessions were 95%, 88%, 87%, 73%, 67%, and 51%
Knowler, 2002, DPP[80]	Mass media, mail, and telephone contacts; recruitment through employment, social groups, and healthcare systems	1,079	Individual and group lessons promoting 7% weight loss and at least 150 minutes of exercise weekly	None	74% and 58% of participants met 150 minutes of physical activity goal at 24 weeks and 2.8 years, respectively

Abbreviations: CI=confidence intervals; DPP=Diabetes Prevention Program; ILI=intensive lifestyle intervention; ITT=intent-to-treat.

Appendix B4 Table 10. Trials of Metformin Included in KQ 7

Author, Year, Study Name	Source of Participants	Number of Participants	Intervention	Uptake	Adherence
O'Brien, 2017, PREVENT-DM[142]	Community health fairs at Latino-serving community health centers	29	Metformin 850 mg twice daily	26/29 took at least 1 dose of medication	11/29 took at least 80% of dispensed doses
Knowler, 2002, DPP[80]	Mass media, mail, and telephone contacts; recruitment through employment, social groups, and healthcare systems	1,079	Metformin 850 mg twice daily	89.2% of metformin group, 91.1% of placebo group took at least some of their pills over time during the original DPP	During DPP, adherence in the original metformin group measured by pill count and defined as ≥80% of pills taken was ~70% during DPP and ~49% over the entire DPPOS

Abbreviations: DPP=Diabetes Prevention Program; DPPOS=Diabetes Prevention Outcome Study.

Appendix B4 Table 11. Studies Not in the Draft Evidence Review That Describe Uptake or Adherence

Author, Year, Study Name	Source of Participants	Number of Participants	Intervention	Uptake	Adherence
Moin, 2019, PRIDE[148]	Electronic medical record search for prediabetic patients, referrals	351	Pharmacist-delivered shared decision making aide offering metformin, DPP, or both	None	83 of the 260 who chose DPP (with or without metformin) completed ≥ 9 DPP sessions
Zigmont, 2018[149]	Company intranet and worksite advertisements	2,158	DPP-based ILI delivered at worksite	5% (117 participants) enrolled	None
Davy, 2017, Resist Diabetes[150]	Newspaper, workplace, and church advertisements	170	Supervised resistance training sessions	None	159/170 (93.5%) went to at least 17/24 sessions for prospective cohort phase (initiation phase); 91% went to 22 of 24 sessions for first 3 months (initiation phase). Self-reported adherence (at least 2 sessions a week) among those present at 9 months was 72% and 78% for low-supervision and high-supervision groups, respectively. At month 15, adherence was 53% in both groups.
Sepah, 2014, Prevent[151]	Online advertisements	220	Online version of DPP	None	187/220 completed ≥4 core lessons. 144/220 completed ≥4 core lessons and ≥1 post-core lesson. 68.4% of 187 core participants completed all 16 core lessons. 187 core participants completed an average of 13.8 core lessons and an average of 3.2 post-core lessons
Wardian, 2018, GLB[152]	Self-referral or primary care physician referral	704	DPP-based ILI	None	704/704 attended the baseline meeting, 492/704 attended week 5 meeting, 385/704 attended week 9 meeting, 364/704 attending week 12 meeting
Vojta, 2013, YMCA DPP[153]	Referrals and community/ employer-based testing events with onsite counseling	2,369	DPP-based ILI delivered at YMCA	None	1,723/2,369 completed ≥9/16 core sessions. 2,104/2,369 completed ≥4 core sessions

Abbreviations: DPP=Diabetes Prevention Program; ILI=intensive lifestyle intervention.

Appendix B4 Table 12. Association Between Glucose Levels or Glycemic Levels and Risk for Target Organ Damage

Author, Year	Glucose or Glycemia Categories	Retinopathy	Nephropathy	Neuropathy	CVD Events	Other	Unadjusted or Adjusted (Variables Used)
Colagiuri, 2002[161]	Low FPG (<140 mg/d L[<7.8 mmol/L]) Intermediate FPG (<180 mg/dL [<7.8 mmol/L to <10.0 mmol/L]) High FPG (>180 mg/dL [>10.0 mmol/L]) (Reference)	Progression of retinopathy OR (95% CI) 0.64 (0.46 to 0.88) 0.76 (0.58 to 0.99) p<0.00001			Stroke OR (95% CI) 0.77 (0.53 to 1.31) 0.74 (0.54 to 1.02) p=0.11 Myocardial infarction OR (95% CI) 0.64 (0.50 to 0.81) 0.96 (0.81 to 1.15) p=0.0014 Microvascular disease OR (95 % CI) 0.39 (0.28 to 0.55) 0.39 (0.30 to 0.52) p<0.00001	All-cause mortality OR (95% CI) 0.68 (0.55 to 0.84) 0.80 (0.68 to 0.94) p=0.0019 Peripheral vascular disease OR (95% CI) 0.30 (0.11 to 0.82) 0.29 (0.13 to 0.67) p=0.00067	Unadjusted
DeBoer, 2018[158]	Glucose Baseline 1-year effect size				Incident CVD* 1.14 (1.01-1.29) 1.07 (1.00-1.14)		Unadjusted
Fuller, 1980[122]	2-h blood-sugar (after 50 g oral glucose load) concentrations Normo-glycemic <96 mg/dL IGT 96-199 mg/dL IGT 110-199 mg/dL New diabetics >200 mg/dL Known insulin dependent Known noninsulin dependent					Death rates per 1,000 59.4 94.5 94.3 175.3 104.2 127.5	Adjusted for age

Appendix B4 Table 12. Association Between Glucose Levels or Glycemic Levels and Risk for Target Organ Damage

Author, Year	Glucose or Glycemia Categories	Retinopathy	Nephropathy	Neuropathy	CVD Events	Other	Unadjusted or Adjusted (Variables Used)
Kalogeropoulos, 2009[66]	Fasting glucose, per SD				Heart failure risk HR (95% CI) 1.19 (1.04 to 1.35)		Adjusted for BMI, age, history of coronary artery disease and smoking, SBP and heart rate, left ventricular hypertrophy on electrocardiogram, creatinine, and albumin levels
Kalogeropoulos, 2009[66]	Hemoglobin A1c, per SD				Heart failure risk HR (95% CI) 1.01 (0.83 to 1.23)		Adjusted for BMI, age, history of coronary artery disease and smoking, SBP and heart rate, left ventricular hypertrophy on electrocardiogram, creatinine, and albumin levels
Kalogeropoulos, 2009[66]	2-h glucose, per SD				Heart failure risk HR (95% CI) 0.88 (0.74 to 1.06)		Adjusted for BMI, age, history of coronary artery disease and smoking, SBP and heart rate, left ventricular hypertrophy on electrocardiogram, creatinine, and albumin levels
Metcalf, 2017[159]	Fasting glucose <5.1 mmol/L (91.98 mg/dL) (Reference) 5.1-5.4 (91.98-97.30 mg/dL) 5.5 -5.9 (99.10-106.31 mg/dL) 6.0 -6.7 (108.11-120.72 mg/dL) >6.9 mmol/L (124.32 mg/dL)	Retinopathy HR (95% CI) 1.33 (0.82 to 2.17) 2.48 (1.66 to 3.83) 3.47 (2.38 to 5.27) 3.33 (2.26 to 5.10)	Renal complications HR (95% CI) 1.12 (0.70 to 1.80) 1.52 (1.01 to 2.33) 2.11 (1.45 to 3.16) 2.64 (1.81 to 3.98)	Neuropathy HR (95% CI) 1.11 (0.37 to 3.46) 1.52 (0.61 to 4.30) 3.00 (1.35 to 7.97) 3.98 (1.78 to 10.62)	CVD events† HR (95% CI) 1.02 (0.88 to 1.18) 0.91 (0.79 to 1.05) 1.10 (0.96 to 1.26) 1.07 (0.96 to 1.22)	Circulatory complications HR (95% CI) 0.65 (0.19 to 2.04) 0.95 (0.37 to 2.58) 1.59 (0.71 to 4.02) 2.40 (1.09 to 6.06)	Adjusted for age, sex, ethnicity, smoking history, 2-h glucose, and HbA1c

Appendix B4 Table 12. Association Between Glucose Levels or Glycemic Levels and Risk for Target Organ Damage

Author, Year	Glucose or Glycemia Categories	Retinopathy	Nephropathy	Neuropathy	CVD Events	Other	Unadjusted or Adjusted (Variables Used)
Metcalf, 2017[159]	2-h glucose <5.4 mmol/L (97.30mg/dL) (Reference) 5.4-6.8 (97.30-122.52 mg/dL) 6.9-8.9(124.32-160.36 mg/dL) 9.0-12.1 (162.16-218.02 mg/dL) >12.2 mmol/L (219.82 mg/dL)	Retinopathy HR (95% CI) 2.29 (1.22 to 4.60) 4.58 (2.61 to 8.83) 10.52 (6.15 to 19.95) 13.41 (7.78 to 25.56)	Renal complications HR (95% CI) 1.30 (0.74 to 2.34) 3.07 (1.92 to 5.15) 6.07 (3.91 to 9.98) 6.92 (4.37 to 11.54)	Neuropathy HR (95% CI) 1.22 (0.69 to 2.19) 2.79 (1.72 to 4.63) 5.28 (3.40 to 8.67) 6.01 (3.81 to 10.01)	CVD events HR (95% CI) 1.23 (1.06 to 1.43) 1.29 (1.12 to 1.49) 1.37 (1.19 to 1.58) 1.23 (1.04 to 1.46)	Circulatory complications HR (95% CI) 1.05 (0.32 to 3.65) 1.06 (0.36 to 3.60) 3.29 (1.38 to 9.78) 3.95 (1.60 to 11.70)	Adjusted for age, sex, ethnicity, smoking history, fasting glucose, and HbA1c
Metcalf, 2017[159]	HbA1c <40 mmol/mol (720.72 mg/dL) (Reference) 40 to 42 mmol/mol (720.72-756.76 mg/dL) 43 to 44 mmol/mol (774.77-792.79 mg/dL) 45 to 50 mmol/mol (810.81-900.90 mg/dL) >51 mmol/mol (918.92 mg/dL)	Retinopathy HR (95% CI) 2.06 (1.43 to 3.04) 1.47 (0.98 to 2.22) 2.81 (2.01 to 4.02) 3.99 (2.85 to 5.73)	Renal complications HR (95% CI) 1.67 (1.11 to 2.54) 1.50 (0.97 to 2.23) 2.54 (1.77 to 3.74) 3.51 (2.44 to 5.20)	Neuropathy HR (95% CI) 1.67 (0.70 to 4.22) 1.75 (0.72 to 4.47) 3.57 (1.65 to 7.83) 3.96 (1.91 to 9.62)	CVD events* HR (95% CI) 1.03 (0.90 to 1.18) 1.04 (0.90 to 1.19) 1.17 (1.03 to 1.33) 1.04 (0.89 to 1.22)	Circulatory complications HR (95% CI) 1.43 (0.55 to 3.96) 1.54 (0.57 to 4.31) 2.78 (1.26 to 6.99) 4.29 (1.96 to 10.84)	Adjusted for age, sex, ethnicity, smoking history, fasting glucose, and 2-h glucose
Metcalf, 2017[159]	Fasting glucose <5.1 mmol/L (91.98 mg/dL) (Reference) 5.1-5.4 (91.98-97.30 mg/dL) 5.5-5.9 (99.10-106.31 mg/dL) 6.0-6.7 (108.11-120.72 mg/dL) >6.9 mmol/L (124.32 mg/dL)				CHD events 1.07 (0.86 to 1.32) 0.92 (0.75 to 1.13) 1.15 (0.94 to 1.40) 1.16 (0.96 to 1.42)		Adjusted for age, sex, ethnicity, and smoking history

Appendix B4 Table 12. Association Between Glucose Levels or Glycemic Levels and Risk for Target Organ Damage

Author, Year	Glucose or Glycemia Categories	Retinopathy	Nephropathy	Neuropathy	CVD Events	Other	Unadjusted or Adjusted (Variables Used)
Metcalf, 2017[159]	2-h glucose <5.4 mmol/L (97.30 mg/dL) (Reference) 5.4-6.8 (97.30-122.52 mg/dL) 6.9-8.9 (124.32-160.36 mg/dL) 9.0-12.1 (162.16-218.02 mg/dL) >12.2 mmol/L (219.82 mg/dL)				CHD HR (95% CI) 1.17 (0.96 to 1.45) 1.15 (0.94 to 1.41) 1.14 (0.93 to 1.40) 1.13 (0.89 to 1.42) Ischemic Stroke HR (95% CI) 1.40 (1.01 to 1.98) 1.82 (1.34 to 2.51) 1.48 (1.08 to 2.05) 1.47 (1.03 to 2.11)		Adjusted for age, sex, ethnicity, smoking history, fasting glucose, and HbA1c
Metcalf, 2017[159]	HbA1c <40 mmol/mol(720.72mg/dL) (Reference) 40 to 42 mmol/mol (720.72-756.76 mg/dL) 43 to 44 mmol/mol (774.77-792.79 mg/dL) 45 to 50 mmol/mol (810.81-900.90 mg/dL) >51 mmol/mol (918.92 mg/dL)				CHD HR (95% CI) 1.27 (1.05 to 1.55) 1.12 (0.90 to 1.38) 1.41 (1.17 to 1.70) 1.27 (1.01 to 1.61)		Adjusted for age, sex, ethnicity, smoking history, fasting glucose, and 2-glucose

Appendix B4 Table 12. Association Between Glucose Levels or Glycemic Levels and Risk for Target Organ Damage

Author, Year	Glucose or Glycemia Categories	Retinopathy	Nephropathy	Neuropathy	CVD Events	Other	Unadjusted or Adjusted (Variables Used)
Nichols, 2008[160] ‡	Normoglycemia Isolated IFG Isolated IGT IFG/IGT	Retinopathy (Prevalence) 0.2 0.2 0.4 0.3 Macular Edema (Prevalence) 0.3 0.3 0.3 0.5	GFR<60 mL/min (Prevalence) 12.3 13.7 17.5 16.8	Peripheral neuropathy (Prevalence) 6.7 6.9 7 7.5	Cardiovascular disease (Prevalence)* 17.5 21.5 23.2 22.8 Congestive heart failure (Prevalence) 5.2 6.7 8.6 10.5 Stroke (Prevalence) 7.6 8.1 10.1 8.8 Any macrovascular complication‖ (Prevalence) 25.8 30.6 33.9 34.1	Any complication (Prevalence) 36.1 40.9 45.5 46.3 Peripheral vascular disease (Prevalence) 4.1 5 4.9 4.8 Any microvascular complication§ (Prevalence) 18.2 19.8 23.0 23.2 Any microvascular or macrovascular complication* (Prevalence) 7.9 9.5 11.5 11.0	Adjusted for age and sex
Robinson, 2016[89]	HbA1c, (per 10 mmol/mol) HbA1c, (per 10%)					Lower limb amputations 1.27 (1.24-1.31), p<0.001 1.30 (1.26-1.35), p<0.001	Adjusted for gender, diabetes history, age at onset, smoking status, height, systolic BP, and TC/HDL ratio.

Appendix B4 Table 12. Association Between Glucose Levels or Glycemic Levels and Risk for Target Organ Damage

Author, Year	Glucose or Glycemia Categories	Retinopathy	Nephropathy	Neuropathy	CVD Events	Other	Unadjusted or Adjusted (Variables Used)
Selvin, 2010[85]	Fasting glucose category <100 mg/dL (Reference) 100 to <126 mg/dL >126 mg/dL				Coronary heart disease HR (95% CI) 1.01 (0.88 to 1.14) 1.00 (0.77 to 1.30) p=0.97 Ischemic Stroke HR (95% CI) 0.93 (0.73 to 1.18) 1.30 (0.85 to 1.98) p=0.63	All-cause mortality HR (95% CI) 1.06 (.94 to 1.19) 1.16 (.91 to 1.47) p=0.20	Adjusted for age, sex, race (black or white), LDL, HDL, log-transformed triglyceride level, BMI, waist to hip ratio, hypertension, family history of diabetes, education, alcohol use, physical-activity index score, and smoking status
Vistisen, 2018[162]	Normal glycaemia FPG <5.6 mmol/L (100.90 mg/dL) and HbA1c <5.7% (Reference) Prediabetes FPG 5.6-6.9 mmol/L (100.90-124.32mg/dL) or HbA1c 5.7-6.4%				Cardiovascular disease (fatal and nonfatal), RR (95% CI) 1.07 (0.90 to 1.26)	CVD or mortality RR (95% CI) 1.12 (0.97 to 1.28)	Adjusted for age, sex, ethnicity, previous CVD, smoking, total cholesterol, HDL cholesterol, systolic blood pressure, and antihypertensive treatment
Vistisen, 2018[162]	H1bA1c <5.7% (Reference) H1bA1c 5.7-6.4% H1bA1c 5.7-5.9% H1bA1c 6.0-6.4%				Cardiovascular disease (fatal and nonfatal) RR (95% CI) 1.12 (0.92 to 1.37) 1.15 (0.91 to 1.44) 1.00 (0.72 to 1.36)	CVD or mortality RR (95% CI) 1.17 (1.00 to 1.38) 1.18 (0.98 to 1.42) 1.13 (0.87 to 1.46)	Adjusted for age, sex, ethnicity, previous CVD, smoking, total cholesterol, HDL cholesterol, systolic blood pressure, and antihypertensive treatment

Appendix B4 Table 12. Association Between Glucose Levels or Glycemic Levels and Risk for Target Organ Damage

Author, Year	Glucose or Glycemia Categories	Retinopathy	Nephropathy	Neuropathy	CVD Events	Other	Unadjusted or Adjusted (Variables Used)
Vistisen, 2018[162]	FPG<5.6 mmol/L (Reference) FPG 5.6-6.9 mmol/L(100.90-124.32 mg/dL) FPG 5.6-6.0 mmol/L(100.90-108.11 mg/dL) FPG 6.1-6.9 mmol/L(109.91-124.32 mg/dL)				Cardiovascular disease (fatal and nonfatal) RR (95% CI) 0.89 (0.74 to 1.08) 0.89 (0.72 to 1.10) 0.90 (0.68 to 1.21)	CVD or mortality RR (95% CI) 0.93 (0.80 to 1.08) 0.91 (0.76 to 1.08) 0.98 (0.77 to 1.24)	Adjusted for age, sex, ethnicity, previous CVD, smoking, total cholesterol, HDL cholesterol, systolic blood pressure, and antihypertensive treatment
Vistisen, 2018[162]	2-h glucose <7.8 mmol/L (140.54) (Reference) 2-h glucose 7.8-11.0 mmol/L(140.54-198.20 mg/dL)				Cardiovascular disease (fatal and nonfatal), rate per 1000 PY (95% CI) 0.88 (0.69 to 1.13)	CVD or mortality RR (95% CI) 1.00 (0.82 to 1.22)	Adjusted for age, sex, ethnicity, previous CVD, smoking, total cholesterol, HDL cholesterol, systolic blood pressure, and antihypertensive treatment

* Included heart attack (myocardial infarction, coronary occlusion, or coronary thrombosis), stroke, transient attacks or mini-stroke, carotid endarterectomy, or other procedure to open blood vessels in the neck)

† Included stroke, coronary heart disease, and other vascular causes and cardiac procedures

‡ Normoglycemia was significantly different from the other three groups ($p<0.001$)

§ Included retinopathy, macular edema, and peripheral neuropathy

‖ Included cardiovascular disease, stroke, peripheral vascular disease, and congestive heart failure

Abbreviations: BMI=body mass index; BP=blood pressure; CHD=chronic heart disease; CI=confidence interval; CVD=cardiovascular disease; FPG=fasting plasma glucose; GFR=glomerular filtration rate; HDL=high-density lipoproteins; HR=hazard ratio; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; LDL=low-density lipoproteins; OR=odds ratio; PY=person-years; RR=relative risk; SBP=systolic blood pressure; SD=standard deviation; TC=total cholesterol.

Appendix B5. Measures of Utility, Health Status, and Quality of Life Used in Studies Addressing Supplemental Questions 5 and 6

Several instruments have been developed to measure utilities, health status, and QoL. The instruments described here were used in studies found to answer SQ5 and SQ6. They include the EuroQol EQ-5D (EQ-5D), The 36 and 12 item Short Form Survey (SF-36 and SF-12), six-dimensional health state short form (SF-6D), the health-related quality of life 15-D (HRQOL 15-D), the Self-Administered Quality of Well-Being Index (QWB-SA), the RAND-12, and the 5-item World Health Organization well-being index (WHO-5).

The EQ-5D includes both a questionnaire that profiles a respondent's health state and a visual analog scale (VAS) that allows a respondent to rate their own overall current health.[177] The EQ VAS is a 0-100 scale that records the respondent's overall current health (on the day it is administered), with higher scores corresponding to higher HRQOL. The EQ-5D index value uses a set of descriptive questions to generate a health state profile that can be assigned a summary index score, also called a health utility score that represents respondents preferences about whether a health state is good or bad. The EQ-5D VAS and index values therefore differ in that the VAS represents the respondents perspective on their own health while the index/utility value represents a societal perspective on a health state. For the purposes of our work, the EQ-5D utility score provides information to answer SQ5 regarding the distribution of disutilities of having diabetes (screen-detected or early diabetes without complications) or prediabetes, and the EQ-5D VAS score provides information to answer SQ6 regarding the distribution of health impacts of having diabetes (without complications) and prediabetes. It's important to note that previously reported EQ-5D utility ranges for the general population vary from country to country. For example, in Canada, scores can range from -0.148 to 0.949;[178] in the United Kingdom, scores can range from -0.285 to 0.950;[179] and in the United States, scores can range from -0.573 to 1.[180] Zero represents a health state considered to be equal to death and a negative score represents health states considered to be worse than death. Conversely, high scores (e.g., a score of 1) represent a health state that reflects perfect health. Finally, there are two versions of the EQ-5D, the EQ-5D-5L and its predecessor (still commonly used), the EQ-5D-3L. Both comprise of 5 health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) but responses to the EQ-5D-3L instrument are based on three levels (no problems, some problems, extreme problems) whereas responses to the EQ-5D-5L instrument are based on 5 levels (no problems, slight problems, moderate problems, severe problems, extreme problems/unable to).

The HRQOL 15-D is another generic, preference-based, standardized and self-administered measure of HRQOL consisting of 15 questions which can be presented as a 15-dimensional profile or as a single index/utility score. As with the other index scores, the 15D index score is obtained by weighting the 15 dimensions with population-based preference weights based on an application of the multi-attribute utility theory.[181] The index scores range from 0 to 1, where 0 represents a state of being dead and 1 represents perfect health.

The QWB-SA is a preference-weighted measure combining three scales of functioning with a measure of symptoms and problems to produce a health state utility score that ranges from 0 (for death) to 1.0 (for asymptomatic full function).[182]

The SF-36 consists of 36 questions that create a profile of scores across 8 health dimensions. The shorter SF-12 includes 12 of the 36 SF-36 questions. In addition to generating scores across each of the 8 dimensions, 2 composite summary scores for mental and physical functioning can be calculated for both the SF-12 and the SF-36—the Physical Component Score (PCS) and the Mental Component Score (MCS). Scores range from 0 (worst health state) to 100 (best health state).[183, 184] The SF-12 and SF-36 PCS and MCS summary scores (and total score where provided) were used to answer SQ6 describing the

distribution of health impacts of having diabetes (without complications) and prediabetes. Similar to the EQ-5D Index value, SF-6D score is a preference-based single utility score estimated using the PCS and MCS summary scores from either the SF-12 or SF-36.[185] Index scores on the SF-6D range from 0.29-1.0.[186] This preference-based utility score was used to help answer SQ5 on the distribution of disutilities associated with uncomplicated diabetes and prediabetes.

The RAND-12 also measures health impact and was used in studies addressing SQ6. It employs the same 12 questions as the SF-12 but is scored differently. The SF-12 and SF-36 summary scores are based on principle component factor analysis with orthogonal factor rotations whereas the RAND-12 employs item response theory (IRT)-based scaling methods and an oblique scoring algorithm.[187]

Another QOL measure relevant to SQ6 is the WHO-5 which measures subjective well-being on a 0 to 5 rating scale for each of 5 questions. The total score across the 5 questions ranges from 0 to 25 and the score is most often multiplied by 4 to align with other QOL measures. Mean population scores from the WHO-5 were not readily available.

Appendix B5 Table 1 provides population norms for the instruments used to measure health utilities (SQ5) and includes suggested thresholds for the minimal clinically important difference (MCID) for each measure. **Appendix B5 Table 2** provides population norms and suggested MIDs for each included QOL measure (SQ6).

Appendix B5 Table 1. Minimal Clinically Important Difference Values and Population Norms for Preference-Based Health Utility Measures Used in Studies Included for SQ5

Measure	MID for Health Utility Values	Population Norms for Health Utility Values* Mean (SD)
QWB-SA	0.03[188]	0.64 (0.50**) U.S.[189]
EQ-5D (U.S.)	0.04-0.08[190]	0.86 (0.50**) U.S.[189] 0.86 (0.23) U.K.[191] 0.87 (NR) Denmark[192] 0.89 (NR) Netherlands[192]
SF-6D	0.03[190]-0.04[193]	0.79 (0.50**) U.S.[189]
15-D*	0.015[194]-0.03[195]	0.86 (0.12) Finland[196]

* 15-D norms could not be found for the U.S. or U.K. populations; population norms are based on a Finnish population (n=2,729) with mean age 66.5.
** SD calculated using other data reported (sample size, mean for ages 45-74, and standard error)

Appendix B5 Table 2. Minimal Clinically Important Difference Values and Population Norms for Quality of Life Measures Used in Studies Included for SQ6

Measure	MID	Mean (SD) Population Norms for QOL Scores*
SF-36	3-5 points for the MCS and PCS[193]	50 (10) (MCS PCS)[197]
SF-12	3-5 points for the MCS and PCS[193]	50 (10) (MCS PCS)[197]
EQ-VAS	7-8 points[198, 199]	US 80.0 (20) (SE 0.1, n=38,678)[200] Denmark 83.7 (26) (SE 0.2, n=16,861) Netherlands 82.0 (19.5) (SE 0.4, n=2,367) UK 82.8 (23) (SE 0.4, n=3395)
RAND-12	3-5 points for the MCS and PCS[193, 201]	50 (10) (MCS PCS)[197, 202]
WHO-5	10 points[203]	54-70 (NR)[203]

Appendix References

X1: Non-English

X2: Ineligible Population

X3: Ineligible Screening

X4: Ineligible Treatment

X5: Ineligible Comparison

X6: Ineligible Outcome

X7: Ineligible Setting

X8: Ineligible Study Design

X9: Ineligible Country

X10: Abstract Only

X11: Poor Quality

X12: Redundant Outcomes

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Appendix D Table 1. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the reported adherence to the intervention?	Did the study have cross-overs or contamination raising concern for bias?	What was the overall attrition? Enter values for both loss to f/u (missing data) and non-completers	What was the differential attrition?	Did the study have high differential attrition (>10% but think about how it might bias) or overall high attrition (depends on duration and outcome; generally 20%) raising concern for bias?
Wu, 2015[204]	Yes	Yes	Yes	NR	No	4%	2%	No
Block, 2015[205] Alive-PD	Yes	Unclear	No	NR	No	11% (3 m) 14% (6 m)	5% (6 m)	No
Bulatova, 2017[206]	Unclear	Unclear	No	NR	No	42%	7%	Yes
Alfawaz, 2018[207]	Yes	Yes	Yes	NR	No	26%	13-27% across arms	Yes
Kumar, 2014[208]	Yes	Unclear	Yes	Unclear (n=7/242 excluded during run-in for "severe noncompliance"; n=2 excluded during study period for poor compliance)	No	1%	0%	No
Hesselink, 2015[209]	Yes	Unclear	No	During year 1, 48% of intervention group received fewer than the 5 recommended visits in study protocol	66% of control group received more than the single visit prescribed for IFG by U.K. guidelines	Sites: 15% Individuals: 19% (12 m) 22% (24 m)	Sites: 13% Individuals: 11% (12 m) 6% (24 m)	Yes
Echouffo-Tcheugui, 2015[210]	Yes	Yes	Unclear	Not reported	Unclear	59%	9.8%	Unclear
Maindal, 2014[98]	Yes	Yes	Unclear	38% received the intervention (attended >3 meetings)	Unclear	58% (141/242) based on heart score for diabetic group	Not reported	Yes

Appendix D Table 1. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the reported adherence to the intervention?	Did the study have cross-overs or contamination raising concern for bias?	What was the overall attrition? Enter values for both loss to f/u (missing data) and non-completers	What was the differential attrition?	Did the study have high differential attrition (>10% but think about how it might bias) or overall high attrition (depends on duration and outcome; generally 20%) raising concern for bias?
Kulzer, 2009[112] Prevention of Diabetes Self-Management Program (PREDIAS)	Yes	Yes	Yes	NR	Unclear	17/182 participants=9.3% dropout	Attrition not reported for control and intervention groups separately (only provide overall dropout rate)	No
Moore, 2011[211]	Unclear	No	Unclear	NR	Unclear	Attrition: 11% (33/307) overall for non-completers overall but varied significantly across measured variables (e.g., 35% for BP, from 0-23% for primary variables-NR)	4% [(25/208)-(8/99)]	Unclear
Morey, 2012[120] The Enhancing Fitness in Older Overweight Veterans with Impaired Glucose Tolerance (Enhanced Fitness) Trial	Unclear	Yes	No	NR	NR	13.2%	3.7%	No
Oldroyd, 2001[212]	Yes	Yes	No	24/39 attended all 6 f/u appointments (62%)	NR	Noncompleters (at 6-months f/u) 14% (67/78)	8% [(7/39)-4/39)]	No

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Yates, 2009[138] The Prediabetes Risk Education and Physical Activity Recommendation and Encouragement (PREPARE)	Yes	Yes	Yes	NR	NR	Noncompleters: 15% (83/98) Missing data: 11% (87/98)	Non-completers (control vs. combined intervention) 13% Missing data (control vs. combined intervention) 6%	Yes
Sakane, 2015[140] The Japan Diabetes Outcome Intervention Trial-1 (J-DOIT1)	Yes	No	Unclear	Proportion with good adherence (>80%) was 91.4%, 82.7%, and 81.1% in centers A, B, and C, respectively	No	Confirm that we need one number here Overall attrition: (217+288)/2,607= 19.3%	3.4% (20.9-17.5)	No
Wang, 2017[213]	Unclear	Unclear	Yes	NR	NR	No attrition	No attrition	No
Duijzer, 2017[214]	Unclear	Yes	Unclear	NR	NR	Attrition at 12 months: 13% (41/316) Attrition at 18 months: 24% (76/316)	At 12 months: 5% [(16/155)-(25/161)] At 18 months: 0% [(37/155)-(39/161)]	No problems with diff attrition at 12 months or 18 months; however, high overall attrition at 18 months.

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Hu, 2017[215]	Yes	Yes	Yes	At 12 months, dietary 80.2%, physical activity 50.8% Attended education curriculum=85.7% SMBG=56.7% Lifestyle behavior changes=ranged from 27-83% across behaviors	NR	Total dropout was 32/434 at 6 months (7.4%) 57/434 at 12 months (13.1%)	At 12 months: 1.9%	No
Cezaretto, 2017[216]	Unclear	Unclear	Yes	Although compliance was defined as 70%, attendance to the interdisciplinary group sessions, compliance (AKA adherence) not reported	NR	25% overall (22+24=46) (47/183) taking into account those who either dropped out or died). (22+1+4+24+3)/183=29.5% taking into account those who dropped out, diet, or had onset of T2DM.	Intervention group=27/97=27.8% Control group=27/59=45.8%	Yes
O'Brien, 2017[142] The *Promotora* Effectiveness Versus Metformin Trial (PREVENT-DM)	Yes	Yes	Yes	ILI group: 70% attended 9/24 sessions Met group: 66% adherence	NR	Total attrition (7/92=7.6%)	2%	No

Appendix D Table 1. Quality Assessment of Controlled Trials (All KQs)

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Van Name, 2016[141]	Unclear	Unclear	No	68% attended (42 subjects) attended at least 14 classes in the ILI group, 7% (4 subjects) attended 0-2 classes	NR	6% (8/130)	0%	No
Ackermann, 2015[139] Reaching Out to Prevent Increases in Diabetes (RAPID)	Yes	Yes	Yes	62.6% of the YDPP group went to at least 1 lesson. 40.0% went to 9 or more intervention lessons	Suggest unclear	Missing wt data:15.5% at 12 months	3.3	No
Juul, 2016[145]	Yes	Yes	Unclear	Attendance rates for the 6 sessions for the intervention group was 95%, 88%, 87%, 73%, 67%, 51%, respectively	Unclear	15% noncompleters for clinical measurements	5% [(11/63)-(8/64)]	No
Yeh, 2016[217]	NR	NR	Unclear	89.2% for core intervention session. 55.8% at 6 monthly post-core sessions	NR	3.3%	6.67%	No
Kaku, 2015[218]	Unclear	Unclear	Yes	NR	NR	3.3%	Suggest NR	No
Dawes, 2015[219]	Unclear (cluster randomized)	Unclear	No	NR	Unclear	5% (of those who responded to the recruitment letter); 33% of participants recruited agreed to participate	1.5%	No

Appendix D Table 1. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the reported adherence to the intervention?	Did the study have cross-overs or contamination raising concern for bias?	What was the overall attrition? Enter values for both loss to f/u (missing data) and non-completers	What was the differential attrition?	Did the study have high differential attrition (>10% but think about how it might bias) or overall high attrition (depends on duration and outcome; generally 20%) raising concern for bias?
Hellgren, 2014[143]	Unclear	Unclear	Yes	NR	Unclear	13%	0-21% (across 3 groups)	Unclear
Davies, 2016[86] Gray, 2016[118] Let's Prevent Diabetes	Unclear	Unclear	No	23% of participants in intervention group did not attend initial education session	Unclear	24%	3%	Unclear
Bhopal, 2014[36] Welsh, 2016[220] The Prevention of Diabetes and Obesity in South Asians (PODOSA) study	Yes	Yes	No	Varied by year and group; nearly all of individual group participants and family members attended scheduled visits (>94%)	Unclear	Individuals: 2% Families: 1%	Individuals: 2% Families: 1%	No
Mann, 2016[221]	Yes (PCPs randomized)	Unclear	Unclear for PCPs; participants mostly similar	NR	Unclear	9%	11%	Yes
Weber, 2016[222] Gokulakrishnan, 2017[223] Diabetes Community Lifestyle Improvement Program (D-CLIP)	Yes	Yes	Yes	Intervention group attended an average of 12 classes (out of 16); 22% attended all 15, and 70% attended 12 or more	Unclear	5%	0%	No

Appendix D Table 1. Quality Assessment of Controlled Trials (All KQs)

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le Roux, 2017[115] SCALE Obesity and Prediabetes Trial	Yes	Yes	Yes	NR	No	3% (analyzed sample at 3 years) 50% (completed treatment at 3 years)	0.5% (analyzed sample at 3 years) 8% (completed treatment at 3 years, higher in liraglutide arm)	Unclear
Kosaka, 2005[224]	Unclear	Unclear	Yes	NR	No	See comments; 8.5% loss to followup over years 1-4	See comments; 2.1% loss to followup over years 1-4	Unclear
Pan, 1997[225] Li, 2008[226] Li, 2014[227] Gong, 2019[228] China Da Qing Diabetes Prevention Outcomes Study (CDQDPOS)	Unclear; cluster randomization	Unclear	Unclear	NR	Unclear	8% at 6 years 6% at 20, 23, and 30 years	NR at 6 years 5% at 20, 23, and 30 years	No
Dyson, 1997[229]	Unclear	Unclear	Unclear	NR	No	11%	7%	Unclear

Appendix D Table 1. Quality Assessment of Controlled Trials (All KQs)

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Eborall, 2007[230] Paddison, 2011[231] ADDITION-Cambridge	Yes	Yes	Yes	Screening group: 32% invited did not attend	Unclear	Response rates Control (not invited to screen): Initial: 54% 3-6 months: 43% 12-15 months: 37% Screening attenders: Initial: 74%* 3-6 months: 66% 12-15 months: 67% Screening nonattenders: Initial: N/A 3-6 months: 50% 12-15 months: 43%	Varies by group and comparison. Higher among screening group attenders than control group and screening nonattenders at all time points.	Yes
Tuomilehto, 2001[232] Uusitupa, 2009[233] Finnish Diabetes Prevention Study (FDPS)	Yes	Yes	Yes	NR	Yes	3%	0%	No

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First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the reported adherence to the intervention?	Did the study have cross-overs or contamination raising concern for bias?	What was the overall attrition? Enter values for both loss to f/u (missing data) and non-completers	What was the differential attrition?	Did the study have high differential attrition (>10% but think about how it might bias) or overall high attrition (depends on duration and outcome; generally 20%) raising concern for bias?
Ramachandran, 2006[234] Indian Diabetes Prevention Programme	Unclear	Unclear	No (see comments)	At study end:† Lifestyle alone: 82% diet, 59% activity Lifestyle plus metformin: 82% diet, 63% activity, 91% metformin 91% Metformin alone: 95% metformin	Unclear	5%	0-4% across groups	No
Chiasson, 2002[235] Chiasson, 2003[236] STOP-NIDDM	Yes	Yes	Yes	29% in acarbose arm and 19% in placebo arm discontinued early; higher % in acarbose arm discontinued due to GI adverse events than placebo arm (19% vs. 5%)	No	4% (loss to followup); 24% discontinued early but were included in analysis	0% (loss to followup); 12% more in acarbose group discontinued early	Unclear

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Diabetes Prevention Program Research Group, 2002[80] Diabetes Prevention Program Research Group, 2005[119] Diabetes Prevention Program Research Group, 2012[97] DPP	Yes	Yes	Yes	Lifestyle intervention: 74% met goal of 150 min of physical activity per week, 58% at most recent visit at trial closure % who took ≥80% of prescribed medication: Placebo: 77% Metformin: 72%	No	0% (all participants included in analyses); at close of study, 7.5% had not attended a scheduled visit within the previous 5 m	0%	No
Diabetes Prevention Program Research Group, 2012[237] Diabetes Prevention Program Research Group, 2009[146] Diabetes Prevention Program Research Group, 2015[79] Apolzan, 2019[238] Diabetes Prevention Program Research Group, 2019[81] DPPOS	Yes	Yes	No (for characteristics at DPPOS enrollment); Yes, for original DPP arms	12% of DPP participants did not continue into DPPOS (censored from adherence outcomes after DPP) Average metformin adherence: (adherent defined as taking ≥80% of prescribed medication): DPP: 72% DPPOS: 49%	Yes; after DPP, all groups were offered a 15-session lifestyle intervention. % of randomized groups attending at least some sessions during open-label extension: Placebo: 57% Metformin: 58% Lifestyle: 40%	12% of DPP participants chose not to continue into DPPOS; an additional 15% did not have microvascular outcome data	0% (similar number in each group participated in DPPOS and had microvascular outcomes)	Unclear

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Aroda, 2016[239]	Yes	Yes	No; analysis limited to DPP participants with B12 measure at DPPOS year 1 or year 9. Higher % in placebo group with diabetes, anemia, and using acid-suppression medication at DPPOS year 1	Average metformin adherence: (adherent defined as taking ≥80% of prescribed medication): DPP: 72% DPPOS: 49%	Yes, at DPPOS year 9, 11.4% of metformin group and 10.1% of placebo group used acid suppression medication; no information about use of B12 or other supplements	Of those randomized, 21% not included at DPPOS year 1 and 30% at DPPOS year 9	0% (similar number in each group met inclusion criteria)	Yes

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Aroda, 2015[240]	Yes	Yes	No, analysis limited to parous women with ≥ live birth; characteristics by treatment arm NR. Women with GDM history were younger than those with no GDM (mean 43 vs. 51 years). Potential misclassification of GDM status due to recall bias, lack of verification, differences in screening practices over time	Unclear	Unclear; women reporting GDM were younger than those with no past GDM. Potential contamination due to differences in GDM screening and treatment among older vs. younger women	13% of DPP participants chose not to continue in DPPOS Men and non-parous women were excluded from GDM subgroup analysis (45%)	3% (difference in DPPOS participation among parous by GDM status)	Yes

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Griffin, 2011[241] Simmons, 2012[242] Van den Donk, 2013[243] Simmons, 2016[76] Griffin, 2019[244] ADDITION-Europe	Yes	NA (cluster randomized	No; slightly lower % in the routine care vs. intensive therapy group reported using antihypertensives (43.7 vs. 46.7), cholesterol lowering medications (15.4 vs. 17), and aspirin (12.6 vs. 15.5); characteristics of practices randomized not provided	NR	Unclear; screening programs and intervention delivery varied by study center. Authors note that trial was undertaken at the same time as other improvements in diabetes care delivery and changes in T2DM treatment guidelines	CVD outcomes: Practices: 7% Participants: 0% For QoL, 27% had missing data (all but 4% were included in multiple imputation analysis)	CVD outcomes: Practices: 7% (11% routine care vs. 4% intensive treatment sites) Participants: 0% For QoL, 4%	No for CVD outcomes; unclear for QoL

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Charles, 2011[245] ADDITION-Denmark	Yes	NA (cluster randomized)	No; slightly fewer participants in the routine care group were on antihypertensives (76% vs. 80%), lipid lowering drugs (75% vs. 81%) and antiglycemics (52 vs. 63%) drugs than the intensive treatment arm. More patients were identified in intensive treatment practices than control practices via screening (number of practices randomized were equal)	NR	Unclear; screening programs and intervention delivery varied by study center	Practices: 5% Participants: 24% (29% for neuropathy outcome)	Practices: 3% Participants: 3%	Yes

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Van den Donk, 2010[95] Janssen, 2009[117] ADDITION-Netherlands	Yes	NA (cluster randomized)	Yes (participants mostly similar); higher % of treatment practices in urban centers than routine care (30% vs. 52%)	NR	Unclear; Dutch guidelines for T2DM updated during study period, authors note that some routine care providers may have offered more intensive treatment of CVD risk factors	12 months: Practices: 0% Participants: 1.4% 3 and 4.5 years (QoL): Varies by measure, up to 28% to 40% did not respond	12 months: Practices: 0% Participants: 1% 3 and 4.5 years (QoL): Authors report no differential missing data	No (12 months); Yes (QoL at 3.5-4 years)
UKPDS, 1998[1] UKPDS	Yes	Yes	Yes	Unclear	Unclear	2-3% (varies by outcome and comparison)	0%	No
Pan, 2003[246]	Unclear	Unclear	No	Medication compliance (for N analyzed): Acarbose: 98% Placebo: 96%	No	4%	2%	No
Park, 2008[247] ADDITION-Cambridge (pilot study)	Yes	Unclear	Yes	82% of intervention group attended screening	No	31%	5%	No
Simmons, 2012[248] ADDITION-Cambridge	Yes	Yes	Yes	78% of intervention group attended screening	No	Unclear	Unclear	Unclear

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Simmons, 2011[249] Rahman, 2012[250] Ely	Unclear	Unclear	No; differences in gender; age and deprivation; adjusted for in analysis	Phase I: 68% of intervention group attended screening Phase II: 45% of intervention group attended screening	No	Unclear	Unclear	Unclear
Davies, 2008[93] Khunti, 2012[94] DESMOND	Yes	Yes	No; not HbA1c, sex, or use of oral hypoglycemic agents	NR	No	4 months: 1.4% 8 months: 4.25 12 months: 6.1%	4 months: 1.18% 8 months: 1.2% 12 months: 1.9%	No
DeFronzo, 2011[251] Espinoza, 2016[252] Actos Now for Prevention of Diabetes Trial (ACT NOW)	Unclear; likely yes (block randomization based on a "randomization code")	Unclear	Yes	Adherence to the study regimen by pill count was greater than 80% in both groups	No	27.6%	7.1%	No
DREAM Trial Investigators, 2006[253] DREAM Trial Investigators, 2006[254] DREAM Trial Investigators, 2008[255] Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial	Yes	Yes	Yes	At least 80% adherence; G1: 75.1%, G2: 71.1%	No	1.9%	.49%	No

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Kawamori, 2009[256]	Yes	Yes	Yes	Compliance with treatment was similarly high in the two treatment; those who did not take their medication were excluded groups	No	15%	2.12%	No
Katula, 2013[144] Pedley, 2018[257] Healthy Living Partnership (HELP PD)	Unclear	Unclear	Yes	Sessions attendance of Intervention group Phase 1: 72.2% (15.5% makeup by phone) Phase 2: 40.4 (22.9% makeup by phone) Across 24 months: 58.6%(18.7% by phone)	No	6 months: 6.97% 12 months: 9.30% 18 months: 14.62% 24 months: 13.29%	6 months: 8.57% 12 months: 2.6% 18 months: 5.21% 24 months: 5.22%	No
Lindahl, 2009[137]	Yes	Yes	Yes	Unclear, reported that adherence was low	No	13.4%	7.4%	No
Lindblad, 2011[258] The Nepi ANtidiabetes StudY (NANSY)	Unclear	Unclear	Yes	Unclear	No	25.9%	Unclear	Unclear

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Lu, 2011[259]	Unclear	Unclear	Yes	Unclear, broken down by each component, significant differences between groups except for agents for dyslipidemia	No	11.9%	5%	No
The NAVIGATOR Study Group, 2010[260] The NAVIGATOR Study Group, 2010[261] Currie, 2017[262] Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Trial	Yes	Yes	Yes	Those taking medication 6 months: 92 vs. 94.2; 1 year: 79.8% vs. 80.8; 3 years: 74.7 vs. 75.9; 5 years 69.9 vs. 71.0	No	19.7%	0.17%	No
Nijpels, 2008[263] DAISI	Yes	Yes	No; not HbA1c	95% compliance (6 reported noncompliance)	No	44.07%	12.07%	No
Penn, 2009[264]	Yes	Yes	Yes	Unclear	No	Year 1:18.62% Year 2: 23.53% Year 3: 28.43% Year 4: 32.35%	Year 1: 5.88% Year 2: 3.92% Year 3: 7.84% Year 4: 5.88%	No
Ramachandran, 2009[265] IDPP-2	Yes	No, sequential	Yes	>80% adherence; G1: 61.3 vs. G2: 60.2	No	9.83%	3.72%	No

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Saito, 2011[87] ZPLS	Yes	Yes	Yes	Unclear	No	12.3%	3.54%	No
Sakane, 2011[266]	Unclear	Unclear	Yes	Unclear, only reported nurses training attendance	No	28.04%	2.78%	No
Zinman, 2010[267] CAnadian Normoglycemia Outcomes Evaluation trial (CANOE)	Yes	Yes	Yes	At least 80%, G1: 78%, G2: 81%	No	13.05%	3.06%	No
Aekplakorn, 2019[268]	Yes	NR	No, differences between groups for weight/BMI	NR	NR	146 (16.7%) of control group; 111 (10.8%) of the intervention group; Overall attrition was 13.5%.	5.9%	No

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Barengo, 2019[269]	Yes	NR	No, there were differences in the percentage of subjects in each of the 3 BMI categories and percentage with a previous increased glucose in blood; for the study participants who were included in the analysis, the percentages of individuals with normoglycemia, isolated IFG, isolated IGT, and IFG and IGT were different	100% of the nutrition and physical activity groups attended at least one group and one individual session	NR	Half of the study participants were lost to followup of at least 18 months; 122/246 (50%) of control group, 136/261 in the nutritional intervention group (52%), and 132/265 in the physical activity intervention group (50%) remained for the data analysis process	<3%	Yes. Overall attrition was 49.5%
Moungngern, 2018[270]	Yes	Unclear	Yes	NR	No	Attrition for completers: 11.2%	3.7%	No

Appendix D Table 1. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the reported adherence to the intervention?	Did the study have cross-overs or contamination raising concern for bias?	What was the overall attrition? Enter values for both loss to f/u (missing data) and non-completers	What was the differential attrition?	Did the study have high differential attrition (>10% but think about how it might bias) or overall high attrition (depends on duration and outcome; generally 20%) raising concern for bias?
Kramer, 2018[271]	Yes	Yes	Yes	75% of all participants attended at least 12 of 16 core sessions with median attendance 14 of 16 initial sessions and 4 of 6 post-core sessions	Unclear	7.5%	1.5%	No
Kulkarni, 2017[272]	Yes	Yes	Unclear	85% +/- 6.5%	No	14.6%	5.3% and 11%	Unclear
Wong, 2013[273] Wong, 2018[274]	Yes	Yes	No, differences between groups for BMI, occupational profile, frequency of eating out, family history of T2DM, and hypertension	NR	No	At 24 months, 32% attrition At 60 months, 45/54 in the intervention group and 41/50 remained; 17% overall attrition	At 24 months. 41/54 in intervention and 29/50 of the control group remained. 24% differential attrition	Yes, high overall and differential attrition at some timepoints but not all

Abbreviations: ACT NOW=Actos Now for Prevention of Diabetes; ADDITION=Anglo-Dutch-Danish Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care; AKA=also known as; BMI=body mass index; CANOE=CAnadian Normoglycemia Outcomes Evaluation trial; CDQDPOS=China Da Qing Diabetes Prevention Outcomes Study; CVD=cardiovascular disease; D-CLIP=Diabetes Community Lifestyle Improvement Program; DAISI=Dutch acarbose intervention study in persons with impaired glucose tolerance; DESMOND=Diabetes education and self management for ongoing and newly diagnosed programme; DM=diabetes mellitus; DPP=Diabetes Prevention Program; DPPOS=Diabetes Prevention Program Outcomes Study; DREAM=Diabetes Reduction Assessment with ramipril and rosiglitazone Medication; FDPS=Finnish Diabetes Prevention Study; GDM=gestational diabetes mellitus; HbA1c/HBA1c=hemoglobin A1c; IDPP-2=Indian Diabetes Prevention Programme-2; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; J-DOIT1=The Japan Diabetes Outcome Intervention Trial-1; KQ=key question; NA=not applicable; NANSY=The Nepi ANtidiabetes StudY; NAVIGATOR=Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; NR=not reported; PCP=primary care physician; PODOSA=The Prevention of Diabetes and Obesity in South Asians; PREDIAS=Prevention of Diabetes Self-Management Program; PREPARE=The Prediabetes Risk Education and Physical Activity Recommendation and Encouragement; PREVENT-DM=The *Promotora* Effectiveness Versus Metformin Trial; QoL=quality of life; RAPID=Reaching Out to Prevent Increases in Diabetes; SCALE=Satiety and Clinical Adiposity–Liraglutide Evidence; STOP-NIDDM=Study TO Prevent Noninsulin-Dependent

Appendix D Table 1. Quality Assessment of Controlled Trials (All KQs)

Diabetes Mellitus; T2DM=type 2 diabetes mellitus; UKPDS=United Kingdom Prospective Diabetes Study; vs.=versus; wt=weight; ZPLS=Zensharen Study for Prevention of Lifestyle Diseases.

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Wu, 2015[204]	Yes	Yes	Yes	Yes	Unclear	Non-completers excluded from analysis	No	Fair	Potential for selection bias; 22% of participants enrolled in placebo run-in excluded (16/73) for unclear reasons. Adherence not reported. Duration of followup on adequate to assess long-term harms.
Block, 2015[205] Alive-PD	Yes	No	Yes	Yes		Imputation (Heckman selection model)	Yes	Fair	More Asian participants (25.2 vs. 16.5) and fewer Hispanic participants (4.3 vs. 8.0) in intervention group than control group. Six months may not be adequate to assess benefit of this behavioral intervention for preventing diabetes.

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Bulatova, 2017[206]	Yes	No	Unclear	Unclear	Yes	Excluded from analysis	No	Poor	Fewer males, diabetics (vs. prediabetics) and patients with metabolic syndrome in control vs. intervention group. Authors note lack of adherence as a limitation, but do not provide rates of adherence. High overall attrition (42%); analysis includes completers only.
Alfawaz, 2018[207]	Yes	No	Unclear	Unclear	Yes	Excluded those lost to followup at 6 m and 12 m; LOCF for those with some missing data (<5% of total data points on a variable)	No	Poor	Unclear masking of provides/outcome assessors. No description of compliance. High overall and differential attrition (greater in arm assigned metformin than lifestyle intervention). Excluded participants from analysis who did not complete 6- or 12-month followup.
Kumar, 2014[208]	Yes	Yes	Unclear	Unclear	Yes	LOCF	No	Fair	

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Hesselink, 2015[209]	Yes	No	No	No	Yes	Excluded from analysis		Poor	Cluster-randomized trial; methods for recruiting participants differed across sites (opportunistic screening/referral, vs. using pre-specified criteria). Participants in intervention group were younger (62 vs. 65 years) and more likely to report being motivated to change their lifestyle (46% vs. 30%) than control group. No description of practice-level characteristics. More practices and participants in control group were lost to followup than intervention group. Potential contamination (more visits for IFG in control group than planned).
Echouffo-Tcheugui, 2015[210]	No	No	No	Unclear	Yes	NA	Yes	Fair	

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Maindal, 2014[98]	No	No	No	Yes	Yes	Not reported	Unclear	Poor	High risk of selection bias and underpowered for differences for subgroup of interest.
Kulzer, 2009[112] Prevention of Diabetes Self-Management Program (PREDIAS)	Unclear	No	Unclear	Yes	Yes	Last value moved forward	Yes	Fair	
Moore, 2011[211]	Yes	No	No	Unclear	Yes	Missing data was excluded	No	Poor	Very high rates of diff attrition and/or overall attrition for all eligible outcomes: BMI, weight, HDL, LDL, BP
Morey, 2012[120] The Enhancing Fitness in Older Overweight Veterans with Impaired Glucose Tolerance (Enhanced Fitness) Trial	Yes	No	Unclear	Yes	Yes	Mixed models	Yes	Fair	
Oldroyd, 2001[212]	Yes	No	No	NR	Yes	None	No	Fair	
Yates, 2009[138]	Yes	No	No	NR	Yes	LOCF and NOCB	No	Fair	
Sakane, 2015[140] The Japan Diabetes Outcome Intervention Trial-1 (J-DOIT1)	No	No	No	No	Yes	LOCF	Yes	Fair	

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Wang, 2017[213]	Yes	NR	Unclear	Unclear	Yes	NA	NR	Poor	High risk of selection bias, poor reporting, underpowered
Duijzer, 2017[214]	Yes	No	No	NR	Yes	Per protocol analysis, missing data were excluded	No	Fair	
Hu, 2017[215]	Yes	No	No	NR	Yes	Missing data were excluded	Yes	Fair	
Cezaretto, 2017[216]	Yes	Unclear	Unclear	Unclear	Yes	Used generalized linear mixed models considering an unstructured covariance matrix, which takes into account missing data	No	Poor	High rate of overall attrition and high rate of differential attribution
O'Brien, 2017[142]	Yes	No	No	Unclear	Yes	Modified intention to treat (excluded those who were in baseline groups who became pregnant)	Yes	Fair	
Van Name, 2016[141]	Yes	No	No	NR	Yes	Per protocol analysis, missing data not included	No	Fair	

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Ackermann, 2015[139] Reaching Out to Prevent Increases in Diabetes (RAPID)	Yes for wt as primary outcome No for A1c and lipids	Yes	Yes	Yes	Yes	Multiple imputation	Yes	Good	
Juul, 2016[145]	Yes	No	No	No	Yes	No imputation, intention to treat	Yes	Fair	
Yeh, 2016[217]	Yes	No	No	NR	Yes	None	No	Poor	Pilot study, very small, poor reporting. High risk of selection bias and perhaps contamination due to lack of blinding, per protocol analyses
Kaku, 2015[218]	Yes	Yes	NR	Yes	Yes	Excluded missing data	Yes	NA	

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Dawes, 2015[219]	Yes	No	No	Unclear	Yes	None (excluded)	No	Poor	Cluster-randomized study with N=6 practice sites randomized. Characteristics of sites not provided; Intervention group included a higher % of males (57% vs. 42%) and Asian participants (46% vs. 4%). Despite cluster design, study was analyzed at individual participant level and analyses were not adjusted for ICC.
Hellgren, 2014[143]	Yes	No	Unclear	Unclear	Yes	None (excluded)	No	Fair	Unclear reporting of randomization; 13% attrition (differential attrition varied 0-21% across groups). Participants lost to followup were excluded from analysis.

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Davies, 2016[86] Gray, 2016[118] Let's Prevent Diabetes	Yes	No	No	Unclear	Yes	LOCF	Yes (modified ITT)	Fair	Cluster-randomized trial. At baseline, intervention group had higher rates of smoking and more lived in socially deprived locations than usual-care group; weight, BMI, and weight circumference were significantly higher in standard-care group than intervention group.
Bhopal, 2014[36] Welsh, 2016[220] The Prevention of Diabetes and Obesity in South Asians (PODOSA) study	Yes	No	No	Unclear	Yes	Excluded those who died or were lost to followup (LOCF for missing data at followup visits)	Modified ITT	Fair	Characteristics of individuals in intervention and control groups mostly similar except for more physical activity in intervention group, and less cholesterol medication in intervention group than control. Low attrition, analysis included nearly all randomized except for 1-2 participants in each group who died or were lost to followup.

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Mann, 2016[221]	Yes	No	No	Unclear	Unclear	None (excluded)	No	Poor	Randomized at provider level; 20 providers (from 2 practices) randomized. Characteristics of providers/practices NR. Intervention is an EMR-based tool to facilitate goal setting. Risk of contamination (providers at same practice randomized to intervention and control). Results analyzed at individual level. Differential attrition (11%, higher in intervention group).
Weber, 2016[222] Gokulakrishnan, 2017[223] Diabetes Community Lifestyle Improvement Program (D-CLIP)	Yes	No	No	Unclear	Unclear	Excluded those who moved or were lost to followup	No	Fair	Excluded participants who moved or were lost to followup; however, attrition was low (and no differential attrition).
le Roux, 2017[115] SCALE Obesity and Prediabetes Trial	Yes	Yes	Yes	Unclear	Yes	LOCF for post-baseline measurements	No	Fair	High rate of attrition/withdrawal at 3 years (50% overall), although analysis accounted for missing data.

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Kosaka, 2005[224]	Yes	No	No	Unclear	Yes	Unclear	No	Fair	Risk of selection bias; selection method for eligible participants from larger cohort not described. N randomized NR; after 1 year of observation, 5.6% in control and 4.7% in intervention group initially randomized dropped out, and 8.5% of those who continued did not attend the final outcome assessment. Handling of missing data unclear.

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Pan, 1997[225] Li, 2008[226] Li, 2014[227] Gong, 2019[228] China Da Qing Diabetes Prevention Outcomes Study (CDQDPOS)	Yes; unclear for 10-year CVD (some cases based on ECG results only, not patient history or symptoms)	No	No	Unclear for 6, 23, and 30-year followup; adjudicators for mortality and CVD outcomes at 20-year blinded to intervention status	Yes	None (excluded)	No	Fair	Cluster randomization at clinic level); characteristics of clinics NR. Unclear whether individuals recruited before or after clinics randomized. At 23 and 30 years followup, an imbalance in smoking status (50% control vs. 38% intervention) was reported and adjusted for in a post hoc analysis. Not reported in previous papers. Unclear validity of CVD outcomes at 10 years and later (some cases based on ECG results alone).

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Dyson, 1997[229]	Yes	No	No	Unclear	Yes	None (excluded)	No	Poor	Table of baseline characteristics not provided; groups were similar in a range of metabolic measures at baseline, aside from triglyceride levels (slightly higher among intervention group vs. control group). Overall attrition 11% (7% differential attrition); analyses did not address missing data.
Eborall, 2007[230] Paddison, 2011[231] ADDITION-Cambridge	Yes	No	No	Unclear	Yes	None (excluded)	No	Fair	Nonrandomized substudy of ADDITION trial. Baseline characteristics similar, but no baseline measures of psychological distress/ anxiety reported. Low response rate among screening group nonattenders; reasons for nonresponse in this group may be associated with outcome (worry about diabetes, distress associated with screening).

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Tuomilehto, 2001[232] Uusitupa, 2009[233] Finnish Diabetes Prevention Study (FDPS)	Yes	No	No	Yes	Yes	None (excluded)	No	Fair	No ITT analysis; however, attrition was low. Control group reported improved diet/exercise habits (varied by goal, 40% decreased sugar intake, 15 increased exercise) raising concern for contamination.
Ramachandran, 2006[234] Indian Diabetes Prevention Programme	Yes	No	No	Unclear	Yes	None (excluded)	No	Fair	Groups mostly similar at baseline except for higher % w/family history of diabetes in control group (59%) than metformin (41%) and LSM+MET group (47%). No ITT analysis; however, overall attrition was low (5%).
Chiasson, 2002[235] Chiasson, 2003[236] STOP-NIDDM	Yes	Yes	Yes	Yes	Yes	Excluded; authors report inclusion of 3% of patients without followup measure did not affect results (provide p-value only)	No	Fair	High rate of early discontinuation (24% overall), more participants in acarbose group withdrew early due to GI adverse effects than control group. Nearly all participants included in 3-year analysis

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Diabetes Prevention Program Research Group, 2002[80] Diabetes Prevention Program Research Group, 2005[119] Diabetes Prevention Program Research Group, 2012[97] DPP	Yes	No for lifestyle vs. medication (participants masked to placebo vs. metformin)	Yes for metformin and placebo groups	Yes	Yes	LOCF	Yes	Good	
Diabetes Prevention Program Research Group, 2012[237] Diabetes Prevention Program Research Group, 2009[146] Diabetes Prevention Program Research Group, 2015[79] Apolzan, 2019[238] Diabetes Prevention Program Research Group, 2019[81] DPPOS	Yes	For study period only, not open-label extension	For study period only, not open-label extension	Unclear	Yes	LOCF (for DPP and those who chose to participate in DPPOS)	No (12% did not participate in open-label phase)	Fair	Analyses combine outcomes from DPP and DPPOS; 12% chose not to participate in DPPOS (plus missing data because of loss to followup in DPPOS). Characteristics differed between those who enrolled vs. not (e.g., higher in those who had developed DM, lower in women with history of GDM). Both groups offered DPP lifestyle intervention prior to DPPOS.

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Aroda, 2016[239]	No; B12 not measured at DPP baseline. After DPPOS year 1, anemia was only assessed in metformin group participants who were actively taking drug	For study period only, not open-label extension	For study period only, not open label extension	Unclear	Unclear	Excluded	No	Poor	Only DPP participants enrolled in DPPOS and had B12 measured during DPPOS were analyzed (missing 20-30% of those randomized); risk of measurement bias (no baseline B12 from DPP, and only those using metformin after DPPOS year 1 had B12 measure). Risk of contamination from use of acid medications; no assessment of whether participants used B12 oral supplements
Aroda, 2015[240]	Yes	For study period only, not open-label extension	For study period only, not open-label extension	Unclear	Yes	LOCF (but limited to those who chose to participate in DPPOS and met post hoc subgroup analysis criteria)	No	Poor	Risk of selection bias; women w/GDM were younger than those with no GDM (by mean 8.5 years), and characteristics by treatment arm not described for analyzed sample. Potential for misclassification of GDM status due to no verification of diagnosis, and potential recall bias.

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Griffin, 2011[241] Simmons, 2012[242] Van den Donk, 2013[243] Simmons, 2016[76] Griffin, 2019[244] ADDITION-Europe	Yes	No	No	Yes	Unclear; 5 years likely not sufficient for some CVD outcomes	Varies by outcome; LOCF for most; others (QoL) excluded from analysis	Yes (modified ITT)	Fair	Risk of selection bias (fewer participants in routine care arm were taking antihypertensives, cholesterol medication, and aspirin at baseline. Risk of contamination due to other QI efforts and changes in guidelines for T2DM care. Five-year followup may not be sufficient for CVD outcomes.

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Charles, 2011[245] ADDITION-Denmark	Unclear; variation outcome measures and procedures varied across sites	No	No	Yes	Unclear; 6 years may not be sufficient for PAD and neuropathy outcomes	Excluded from analysis	No	Fair	Risk of selection bias; more patients with diabetes found in practices randomized to intensive treatment than control (training of staff may have affected participant selection). At baseline, fewer participants in routine-care arm were on medications that may affect outcomes (e.g., antihypertensives). Analysis is limited to participants who had had assessments for PAD and neuropathy (20% overall attrition). Testing for neuropathy differed across centers.

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Van den Donk, 2010[95] Janssen, 2009[117] ADDITION-Netherlands	Yes	No	No	Yes	Yes for most outcomes; unclear for QoL at 1 yr	LOCF for 1 yr outcomes; participants with missing QoL measures at 3.5-4 yrs excluded	Yes (12 months); no for QoL at 3.5-4 yrs	Fair	Risk of selection bias; baseline practice characteristics differed, but participant characteristics were similar, and analyses adjusted for clustering. Potential contamination due to change in national guidelines for T2DM. High attrition at 3.5-4 years for QoL (28-50% missing data) and no ITT.
UKPDS, 1998[1] UKPDS	Yes	No	No	Yes	Yes	LOCF	Yes	Good	
Pan, 2003[246]	Yes	Yes	Yes	Unclear	Unclear (conversion to type 2 DM); yes for others	Unclear	Yes (modified ITT)	Fair	Intervention group was younger than control group (53.4 vs. 55.6, p=0.034), other characteristics similar. Difference in age unlikely to be clinically important. Duration (4 months) may not be sufficient to assess conversion to type 2 DM.

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Park, 2008[247] ADDITION-Cambridge (pilot study)	Yes	Unclear	Unclear	Unclear	Yes	Completers only analysis	No	Fair	Completers analysis; masking and concealment unclear
Simmons, 2012[248] ADDITION-Cambridge	Yes	No	No	Unclear	Yes	Unclear	Yes	Good	
Simmons, 2011[249] Rahman, 2012[250] Ely	Yes	No	No	Unclear	Yes	Imputation	Yes	Fair	
Davies, 2008[93] Khunti, 2012[94] DESMOND	Yes	Yes	No	No	Yes	Unclear	Yes	Fair	
DeFronzo, 2011[251] Espinoza, 2016[252] Actos Now for Prevention of Diabetes Trial (ACT NOW)	Yes	Unclear	Unclear; likely yes	Unclear; likely yes	Yes	NA	No	Fair	Primary and secondary analyses were performed without data imputation since no statistically significance bias was found based on missing data; overall attrition high

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
DREAM Trial Investigators, 2006[253] DREAM Trial Investigators, 2006[254] DREAM Trial Investigators, 2008[255] Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Good	
Kawamori, 2009[256]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Good	
Katula, 2013[144] Pedley, 2018[257] Healthy Living Partnership (HELP PD)	Yes	No	No	Yes	Yes	Unclear	Yes	Fair	
Lindahl, 2009[137]	Yes	No	No	Unclear	Yes	Imputation	Yes	Fair	
Lindblad, 2011[258] The Nepi ANtidiabetes StudY (NANSY)	Yes	Yes	Unclear	Unclear	Yes	Unclear, used ITT but noted when data were missing	Yes	Fair	
Lu, 2011[259]	Yes	No	No	Unclear	Yes	Unclear	Unclear	Fair	

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
The NAVIGATOR Study Group, 2010[260] The NAVIGATOR Study Group, 2010[261] Currie, 2017[262] Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Trial	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Good	
Nijpels, 2008[263] DAISI	Yes	Unclear	Yes	Yes	Yes	ITT and per-protocol, removed for per-protocol analysis	Yes	Fair	
Penn, 2009[264]	Yes	No	No	Yes				Fair	
Ramachandran, 2009[265] IDPP-2	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Fair	
Sakane, 2011[266]	Yes	No	No	No	Yes	Unclear, used ITT	Yes	Fair	
Saito, 2011[87] ZPLS	Yes	No	No	No	Yes	Unclear, noted when it was missing	Yes	Fair	
Zinman, 2010[267] CAnadian Normoglycemia Outcomes Evaluation trial (CANOE)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Good	

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Aekplakorn, 2019[268]	Yes	No	NR	NR	Yes	ITT for diabetes incidence; NR for all other outcomes	ITT for diabetes incidence; NR for all other outcomes	Fair	
Barengo, 2019[269]	Yes	No	No	Yes	Yes	Per-protocol	No	Poor	High risk of bias due to very high overall attrition
Moungngern, 2018[270]	Yes	No	No	Unclear	Yes	Excluded from analysis	No	Fair	
Kramer, 2018[271]	Yes	No	No	Yes	Yes	Excluded	No	Poor	In addition to no ITT analysis, participants could choose whether to receive the intervention face-to-face or by DVD and it is unclear what effect this may have had on contamination and outcomes.
Kulkarni, 2017[272]	Yes	No	No	Unclear	Yes	Excluded	Yes	Fair	

Appendix D Table 2. Quality Assessment of Controlled Trials (All KQs)

First Author, Year Trial Name	Were outcome measurements equal, valid and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did they use an ITT analysis? (i.e., Analyze People in the Groups They Were Randomized to)	Quality Rating (for Benefits)	Comments
Wong, 2013[273] Wong, 2018[274]	Yes, they were valid and reliable; they were equal across groups, but not over time (ascertainment methods changed over time: electronic medical records were retrieved to obtain the diagnosis of event, anthropometric and blood measurements for those who had clinical reading and detailed events recorded within 1-year of assessment. For those recorded at the time beyond 1 year of assessment, the research team arranged health examinations to obtain anthropometric and blood measurements)	No	Unclear	No	Yes	Last value carried forward	Yes. Also had a per-protocol analysis	Fair	

Abbreviations: A1c=glycated hemoglobin; ADDITION=Anglo-Dutch-Danish Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care; BMI=body mass index; BP=blood pressure; CANOE=CAnadian Normoglycemia Outcomes Evaluation trial; CDQDPOS=China Da Qing Diabetes Prevention Outcomes Study; CVD=cardiovascular disease; D-CLIP=Diabetes Community Lifestyle Improvement Program; DAISI=Dutch acarbose intervention study in persons with impaired glucose tolerance; DESMOND=Diabetes education and self management for ongoing and newly diagnosed programme; DM=diabetes mellitus; DPP=Diabetes Prevention Program; DPPOS=Diabetes Prevention Program; DREAM=Diabetes Reduction Assessment with ramipril and rosiglitazone Medication; ECG=electrocardiogram; EMR=electronic medical record; FDPS=Finnish Diabetes Prevention Study; GDM=gestational diabetes mellitus; HDL=high-density lipoproteins; hx=history; IDPP-2=Indian Diabetes Prevention Programme-2; ITT=intention-to-treat; KQ=key question; LDL=low-density lipoproteins; LOCF=last observation carried forward; LSM=lifestyle modification; MET=metformin; NA=not applicable; NANSY=The Nepi ANtidiabetes StudY; NAVIGATOR=Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; NOCB=next observation carried backward; NR=not reported; PAD=peripheral arterial disease; PODOSA=The Prevention of Diabetes and Obesity in South Asians; QoL=quality of life; RAPID=Reaching Out to Prevent Increases in Diabetes; SCALE=Satiety and Clinical Adiposity–Liraglutide Evidence; STOP-NIDDM=Study TO Prevent Noninsulin-Dependent Diabetes Mellitus; T2DM=type 2 diabetes mellitus; ZPLS=Zensharen Study for Prevention of Lifestyle Diseases.

Appendix D Table 3. Quality Assessment of Controlled Trials: Additional Questions for Studies Reporting Harms (KQs 2 and 6 Only)

First Author, Year Trial Name	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid, and reliable?	Was duration of followup adequate for harms assessment?	Quality Rating (for Harms)	Comments
Wu, 2015[204]	Unclear	No	Unclear	Unclear	Poor	Duration of followup may not be adequate to assess long-term harms. No description of whether harms were prespecified or how they were ascertained.
Block, 2015[205] Alive-PD	Unclear	Unclear	Unclear	Unclear	Poor	No description of whether harms were prespecified/defined or how they were ascertained; authors report harms do not differ by group but do not provide data on harms.
Kumar, 2014[208]	Yes	Yes	Yes	Unclear	Fair	Some harms (hypoglycemia) appear to have been prespecified. Not clear whether others were prespecified or how they were defined
Wang, 2017[213]	No	Yes	Yes	No	Poor	Study too small to adequately compare harms across the groups
Ackermann, 2015[139] Reaching Out to Prevent Increases in Diabetes (RAPID)	No	Yes	Yes	Yes	Fair	
Kaku, 2015[218]	Yes	Yes	Yes	No	Fair	
Weber, 2016[222] Gokulakrishnan, 2017[223] Diabetes Community Lifestyle Improvement Program (D-CLIP)	Unclear	No	Yes	Yes	Fair	Unclear whether harms prespecified or clearly defined. Authors describe planned ascertainment during followup visits.

Appendix D Table 3. Quality Assessment of Controlled Trials: Additional Questions for Studies Reporting Harms (KQs 2 and 6 Only)

First Author, Year Trial Name	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid, and reliable?	Was duration of followup adequate for harms assessment?	Quality Rating (for Harms)	Comments
le Roux, 2017[115] SCALE Obesity and Prediabetes Trial	Yes	Yes	Unclear	Yes	Fair	High rate of attrition/withdrawal at 3 years (50% overall), although analysis accounted for missing data.
Eborall, 2007[230] Paddison, 2011[231] ADDITION-Cambridge	Yes	Yes	Yes	Yes	Fair	Nonrandomized substudy of ADDITION trial. Baseline characteristics were similar, but no baseline measures of psychological distress/ anxiety were reported. Low response rate among screening group nonattenders; reasons for nonresponse in this group may be associated with outcome (worry about diabetes, distress associated with screening)
Ramachandran, 2006[234] Indian Diabetes Prevention Programme	Unclear	No	Unclear	Yes	Fair	Harms (and ascertainment technique) not described in detail. Study notes that a safety committee monitored the adverse events.
Chiasson, 2002[235] Chiasson, 2003[236] STOP-NIDDM	Unclear	No	Unclear	Yes	Fair	No description of whether harms were prespecified or how they were ascertained. Safety committee member conducted interim analysis at 1 year to ascertain adverse effects.

Appendix D Table 3. Quality Assessment of Controlled Trials: Additional Questions for Studies Reporting Harms (KQs 2 and 6 Only)

First Author, Year Trial Name	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid, and reliable?	Was duration of followup adequate for harms assessment?	Quality Rating (for Harms)	Comments
Pan, 2003[246]	Unclear	Yes	Yes	Unclear	Fair	Length of followup (4 months) may not be sufficient to detect all important adverse events.
Diabetes Prevention Program Research Group, 2002[80] Diabetes Prevention Program Research Group, 2005[119] Diabetes Prevention Program Research Group, 2012[97] DPP	Yes	Unclear	Unclear	Yes	Fair	Protocol describes question for eliciting side effects but does not clearly state whether harms were prespecified.
Diabetes Prevention Program Research Group, 2012[237] Diabetes Prevention Program Research Group, 2009[146] Diabetes Prevention Program Research Group, 2015[79] Apolzan, 2019[238] Diabetes Prevention Program Research Group, 2019[81] DPPOS	Yes	Yes	No	Yes	Fair	Analysis combines data from RCT and 7- to 8-year open-label phase; 12% chose not to participate in open-label extension. Unclear whether reasons for not participating are related to adverse effects.
Aroda, 2016[239]	No	Yes	No	Unclear	Poor	Post hoc assessment of B12 deficiency from participants in DPP who continued in DPPOS and had a B12 measure. No baseline B12 at enrollment; outcome was not prespecified and measured equally across groups.

Appendix D Table 3. Quality Assessment of Controlled Trials: Additional Questions for Studies Reporting Harms (KQs 2 and 6 Only)

First Author, Year Trial Name	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid, and reliable?	Was duration of followup adequate for harms assessment?	Quality Rating (for Harms)	Comments
Van den Donk, 2010[95] Janssen, 2009[117] ADDITION-Netherlands	Unclear	Yes	Yes	Yes	Good	
Park, 2008[247] ADDITION-Cambridge (pilot study)	Yes	Yes	Yes	Yes	Fair	
Davies, 2008[93] Khunti, 2012[94] DESMOND	Unclear	Unclear	Unclear	Unclear	Poor	No description of whether harms were prespecified/defined or how they were ascertained; only provides those who withdrew not specific to those who withdrew due to adverse events.
DeFronzo, 2011[251] Espinoza, 2016[252] Actos Now for Prevention of Diabetes Trial (ACT NOW)	Yes	Yes	Yes	Unclear	Fair	
DREAM Trial Investigators, 2006[253] DREAM Trial Investigators, 2006[254] DREAM Trial Investigators, 2008[255] Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial	Unclear	Unclear	Unclear	Unclear	Good	
Lu, 2011[259]	Unclear	Unclear	Unclear	Unclear	Poor	

Appendix D Table 3. Quality Assessment of Controlled Trials: Additional Questions for Studies Reporting Harms (KQs 2 and 6 Only)

First Author, Year Trial Name	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid, and reliable?	Was duration of followup adequate for harms assessment?	Quality Rating (for Harms)	Comments
The NAVIGATOR Study Group, 2010[260] The NAVIGATOR Study Group, 2010[261] Currie, 2017[262] Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Trial	Yes	Yes	Yes	Unclear	Good	
Nijpels, 2008[263] DAISI	Yes	Yes	Yes	Unclear	Fair	
Ramachandran, 2009[265] IDPP-2	Unclear	Unclear	Unclear	Unclear	Fair	
Saito, 2011[87] ZPLS	Unclear	Unclear	Unclear	Unclear	Poor	No description of whether harms were prespecified/defined or how they were ascertained; authors report harms do not differ by group but do not provide data on harms.
Zinman, 2010[267] CAnadian Normoglycemia Outcomes Evaluation trial (CANOE)	Yes	Yes	Yes	Unclear	Fair	

Abbreviations: ACT NOW=Actos Now for Prevention of Diabetes; ADDITION=Anglo-Dutch-Danish Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care; CANOE=CAnadian Normoglycemia Outcomes Evaluation trial; D-CLIP=Diabetes Community Lifestyle Improvement Program; DESMOND=Diabetes education and self management for ongoing and newly diagnosed programme; DPP=Diabetes Prevention Program; DPPOS=Diabetes Prevention Program; DREAM=Diabetes Reduction Assessment with ramipril and rosiglitazone Medication; IDPP-2=Indian Diabetes Prevention Programme-2; KQ=key question; NAVIGATOR=Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; RAPID=Reaching Out to Prevent Increases in Diabetes; RCT=randomized, controlled trial; SCALE=Satiety and Clinical Adiposity–Liraglutide Evidence; STOP-NIDDM=Study TO Prevent Noninsulin-Dependent Diabetes Mellitus.

Appendix D Table 4. Quality Assessment of Cohort Studies (KQs 2, 6, 8)

First Author, Year	Were eligibility criteria clearly described?	Were groups similar at baseline?	What was the reported adherence to the intervention?	Did the study have cross-overs or contamination raising concern for bias?	What was the overall attrition? Enter values for both loss to f/u and non-completers	What was the differential attrition?	Did the study have high differential attrition (>10% but think about how it might bias) or overall high attrition (depends on duration and outcome; generally 20%) raising concern for bias?
Lai, 2015[275]	Yes	No	NR	Unclear	NR	NR	Unclear

Abbreviations: KQ=key question; NR=not reported.

Appendix D Table 5. Quality Assessment of Cohort Studies (KQs 2, 6, 8)

First Author, Year	Was assessment of the drug or other intervention exposure (dose and duration) valid and reliable?	Were outcome measurements equal, valid and reliable?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did the analysis adjust for potential confounders? (or are confounders addressed via restriction, matching, or stratification)	Quality Rating	Comments
Lai, 2015[275]	Yes	Yes	No	No	Unclear	Yes	Poor	Age imbalance at baseline. Drug users younger with higher diabetes complications severity index. They adjust for confounders, which results in no significant relationship between drug use and pancreatitis. Lack of detail of loss to followup suggests that it was unmeasured. 2008 to 2011 may be insufficient followup to pancreatitis.

For RCTs and cohorts, definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair: Studies are graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is used for RCTs.

Poor: Studies are graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Additional Detailed Results for Interventions for Screen-Detected Type 2 Diabetes (KQ 4)

The China Da Qing Diabetes Prevention Outcomes Study (CDQDPOS) evaluated a lifestyle intervention with 30 years of followup in China, among people with prediabetes without requiring additional risk factors for diabetes or mortality.[225-228] Here we present additional outcomes from that study not included in the main report. The Da Qing results indicate that an absolute decrease in diabetes incidence of about 24 percent over 6 years (43.6% vs. 67.7%) for participants participating in a lifestyle intervention vs. control[225-227] resulted in a 7 percent reduction in stroke at 30 years (39% vs. 46%; HR, 0.70 [95% CI, 0.59 to 0.96]) and a nonsignificant trend toward reduced coronary heart disease (15% vs. 19%; HR, 0.73 [95% CI, 0.51 to 1.04]) and heart failure (10% vs. 12%; HR, 0.71 [95% CI, 0.48 to 1.04]).[228] At 30 years, there was also a reduction in a composite of microvascular outcomes (19% vs. 24%; HR, 0.65 [95% CI, 0.45 to 0.95]) and retinopathy (14% vs. 19%; HR, 0.60 [95% CI, 0.38 to 0.95]).[228] There was no significant difference between intervention and control groups in nephropathy (4% vs. 5%; HR, 0.68 [95% CI, 0.36 to 1.28]) or neuropathy (3% vs. 5%; HR, 0.57 [95% CI, 0.24 to 1.36]) at the 30-year follow up.[228] The HRs presented here are adjusted for age only.

One study reported on QoL outcomes specific to the ADDITION-Netherlands cohort at 1-[117] and 3-year followups (see **Appendix E Table 1**).[95] Another study reported 5-year QoL outcomes for all three ADDITION-Europe countries (the United Kingdom [2 sites], Denmark and the Netherlands) and conducted a pooled-estimate across the four study sites (see **Appendix E Table 2**).[243] QoL outcomes evaluated included self-reported health status assessed using the 36-item Short Form Health Survey (SF-36), which includes both a physical and mental component score, and the EuroQol 5 dimensions (EQ-5D) questionnaire, which covers five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and includes a Visual Analog Scale (EQ-VAS). General well-being was assessed with the Well-Being Questionnaire (W-BQ12), which measures multiple aspects of well-being, and the Audit of Diabetes-Dependent QoL (ADDQoL) questionnaire was used to assess the impact of diabetes on QoL. Of the 2861 participants alive at followup, 2217 participants completed QoL questionnaires.

At the 5-year followup, pooled analysis across four sites (U.K. Cambridge, U.K. Leicester, Denmark, and the Netherlands) found no statistically significant difference in any QoL measure among patients with screen-detected type 2 diabetes receiving intensive multifactorial treatment and those receiving routine care (**Appendix E Table 2**).[243] This finding of no difference between groups was mirrored in the individual results from each of the four sites with the exception of the U.K. Leicester site, which reported significant differences favoring the intensive treatment group for the SF-36 physical component score (mean difference between groups, -3.78 [95% CI, -7.30 to -0.26]), the EQ-VAS (mean difference between groups, -8.37 [95% CI, -15.15 to -1.59]), and the ADDQoL (mean difference between groups, -1.23 [95% CL, -2.25 to -0.21]) (**Appendix E Table 2**).[243] Similarly, among patients in the ADDITION-Netherlands study, SF-36 QoL measures assessed at the 1- and 3-year followups, and EQ5D QoL measures assessed at the 3-year followup were not significantly different between those receiving intensive multifactorial treatment and those receiving routine care (**Appendix E Table 1**).[95, 117]

None of the included publications reported on symptomatic chronic kidney disease, end-stage renal disease, requirement for dialysis, or need for transplantation. The addition-Europe study reported on nephropathy, defined as the presence of either microalbuminuria or macroalbuminuria, at 5 years.[76] Microalbuminuria (defined as urinary-albumin-creatinine ratio [ACR] ≥ 2.5 mg/mmol for men and ≥ 3.5 mg/mmol for women), macroalbuminuria (defined as ACR ≥25 mg/mmol) and estimated glomerular filtration rate (eGFR) were used to assess for nephropathy. Of 2861 people still alive at 5 years, 87.1% (n=2493) had data for urinary ACR, and 94.7 percent (n=2710) had data for eGFR (**Appendix E Table 3**). Pooled analysis from across the four ADDITION-Europe sites (U.K. Cambridge, U.K. Leicester, Denmark, and the Netherlands) found that at 5-years followup, there was no difference in the presence of any albuminuria among patients with screen-detected type 2 diabetes receiving intensive multifactorial treatment and those receiving routine care (22.7% vs. 24.4%, respectively, OR, 0.88 [95% CI, 0.72 to 1.07].[76] The pooled estimate for the presence of macroalbuminuria also found no difference between groups (4.0% vs. 3.4%, OR, 1.15 [95% CI, 0.76 to 1.74]), and there was no difference in mean eGFR (4.31 ml/minute versus 6.44 ml/min, mean difference, -1.39 ml/minute [95% CI, -2.97 to 0.19) (**Appendix E Table 3**).[76] Prespecified subgroup analysis found no significant interactions based on sex or age.

None of the included publications reported on vision changes, symptoms of retinopathy, or blindness. The addition-Europe study reported on any retinopathy as a secondary outcome at 5-years followup.[76] Retinopathy was assessed using gradable digital images that were categorized as "any retinopathy compared with no retinopathy" and "severe or proliferative retinopathy compared with no, mild or moderate retinopathy using the Early Treatment Diabetic Retinopathy Study (ETDRS) semiquantitative scale. Of 2861 people still alive at 5 years, retinal photographs were retrieved for 76.5 percent (n=2190) (**Appendix E Table 3**). Pooled analysis from across the four ADDITION-Europe sites (U.K. Cambridge, U.K. Leicester, Denmark, and the Netherlands) found that at 5-years followup, there was no statistically significant difference in the presence of any retinopathy among patients with screen-detected type 2 diabetes receiving intensive multifactorial treatment and those receiving routine care (10.1% vs. 12.1%, respectively, OR, 0.84 [95% CI, 0.64 to 1.10] (**Appendix E Table 3**).[76] Prespecified subgroup analysis found no significant interactions based on sex or age.

The ADDITION-Europe study reported on any neuropathy as a secondary outcome at 5-years followup,[76] and ADDITION-Denmark reported on a variety of peripheral neuropathy measures at 6-years followup.[245] Peripheral neuropathy was assessed using the self-administered Michigan Neuropathy Screening Instrument (MNSI) (which defined patients as having peripheral neuropathy if they had a score of ≥7); the Brief Pain Inventory Short form (which defined patients as having painful diabetic neuropathy if they indicated having pain in both legs and /or both arms); light touch sensory testing (which defined peripheral neuropathy as the inability to feel one or more test sites); and the Vibration Detection Threshold (VDT) (which defined peripheral neuropathy as values ≥95th percentile)[76, 245] Of 2861 people in the ADDITION-Europe study still alive at 5 years, peripheral neuropathy data were available for 80.8 percent (n=2312). Of 1533 people enrolled in the ADDITION-Denmark study, 6-year peripheral neuropathy data were available on 1161 (**Appendix E Table 3**).[245]

Pooled analysis from across the four ADDITION-Europe sites (U.K. Cambridge, U.K. Leicester, Denmark, and the Netherlands) (n=2312) found that at 5-years followup, there was no

statistically significant difference in the presence of any neuropathy among patients with screen-detected type 2 diabetes receiving intensive multifactorial treatment and those receiving routine care (4.86% vs. 5.91%, respectively, OR, 0.95 [95% CI, 0.68 to 1.34] (**Appendix E Table 3**).[76] Similarly, across multiple measures at 6-years followup in the ADDITION-Denmark study, there was no significant difference in the prevalence of peripheral neuropathy among those receiving intensive multifactorial treatment and those receiving routine care (data shown in figure only).[245]

Additional Detailed Results for KQ 8

The Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial recruited people with prediabetes across several countries, with a median of 3 years followup.[253-255] The DREAM results found an absolute decrease in diabetes incidence of about 14 percent over 3 years (10.6% vs. 25.0% after rosiglitazone vs. control)[254] and no significant difference in all-cause mortality (1.1% vs. 1.3%) or cardiovascular events (composite of cardiovascular death, cardiac resuscitation, MI, stroke, revascularization procedure, new angina with documented ischemia or heart failure) over the same time period (2.9% vs. 2.1%).[255]

The STOP NIDDM trial recruited people with prediabetes and BMI between 25 and 40 across several countries, who were randomized to acarbose or placebo with mean 3.3 years of followup for diabetes and cardiovascular events (coronary heart disease, cardiovascular death, congestive heart failure, cerebrovascular event, or peripheral vascular disease).[235, 236] The STOP NIDDM results found that an absolute decrease in diabetes incidence of about 9 percent over 3.3 years with acarbose (32.4% vs. 41.5% for acarbose vs. control)[235] and 2.5 percent fewer major cardiovascular events (2.2% vs. 4.7%).[236]

The SCALE trial recruited people across 27 countries with prediabetes and BMI>30, or prediabetes and BMI>27 with hypertension and/or dyslipidaemia.[115] Participants were randomized to liraglutide or placebo with 3.3 years of followup to diabetes and a composite of cardiovascular events (acute coronary syndrome, cerebrovascular, heart failure, stent thrombosis, revascularization procedure, hospitalizations for cardiac arrhythmia). The SCALE reported an absolute decrease in diabetes incidence of about 4 percent over 3 years (1.7% vs. 6.1% of participants after a liraglutide vs. control) and did not find a statistically significant reduction in cardiovascular events over the same time period.[115]

The Actos Now For Prevention of Diabetes Trial (ACT NOW) trial recruited people with IGT and BMI>25 (>22 in Asian Americans) and at least one other risk factor for diabetes in the United States.[251, 252] Participants were randomized to Pioglitazone or placebo, with 2.2 years followup to diabetes and a cardiovascular composite (atypical chest pain, cardiac arrhythmia, carotid endarterectomy, coronary artery bypass/revascularization, coronary artery disease without revascularization, new or worsening angina, new or worsening CHF, nonfatal MI, peripheral vascular disease with claudication or revascularization, TIA, malignant hypertension). The ACT NOW results found an absolute decrease in diabetes incidence of about 12 percent over 2 years (5.0% vs. 16.7% of participants after pioglitazone vs. control)[251, 252] and no difference in cardiovascular events over the same time period.[251]

Appendix E. Additional Results

The Let's Prevent Diabetes study recruited people with screen detected prediabetes in the United Kingdom for a lifestyle intervention with 3-year followup to all outcomes.[86, 118] Incidence of diabetes was similar in the intervention and control groups (14.3% vs. 15.5%) as was quality of life (measured using a 15 dimensional score 0.91 vs. 0.91).[86, 118]

Appendix E Table 1. Quality of Life Outcomes at 1- and 3-Year Followups Among Individuals With Screen-Detected Type 2 Diabetes (KQ 4)

First Author, Year Trial Name Country	QoL Outcomes at 1-Year Followup	QoL Outcomes at 3-Year Followup
van den Donk, 2010[95] Janssen, 2009[117] ADDITION-Netherlands Netherlands	G1: N=255 G2: N=243 **Short form-36 Mean (SD)** **Physical functioning** G1 baseline: 77.4 (21.9) G1 1-year: 80.1 (21.2) G2 baseline: 78.3 (22.0) G2 1-year:78.1 (23.2) p=0.22 **Role physical** G1 baseline: 82.8 (31.4) G1 1-year: 80.3 (35.0) G2 baseline: 84.9 (30.0) G2 1-year: 81.1 (33.5) p=0.93 **Bodily pain** G1 baseline: 80.8 (22.1) G1 1-year: 79.2 (22.7) G2 baseline: 84.7 (20.7) G2 1-year: 82.2 (22.4) p=0.97 **General health** G1 baseline: 59.1 (11.5) G1 1-year: 63.3 (18.4) G2 baseline: 59.7 (12.0) G2 1-year: 64.4 (18.1) p=0.63 **Vitality:** G1 baseline: 49.3 (14.4) G1 1-year: 64.8 (20.4) G2 baseline: 52.2 (13.2) G2 1-year: 67.1 (18.4) p=0.81 **Social functioning** G1 baseline: 87.9 (20.0) G1 1-year: 83.0 (22.0) G2 baseline: 89.0 (17.2) G2 1-year: 85.7 (19.2) p=0.37 **Role emotional** G1 baseline: 88.2 (28.6) G1 1-year: 86.2 (30.9) G2 baseline: 85.4 (32.4) G2 1-year: 89.9 (26.0) p=0.25	G1: N=145-163 G1: N=160-178 **Short form 36 Mean (SEM)** **Physical functioning** G1 baseline: 77.6 (1.7) G1 3 years: 77.3 (1.8) Change: -0.3 (-3.4, 2.8) G2 baseline: 78.4 (1.8) G2 3 years:79.1 (1.7) Change: 0.7 (-2.5, 3.8) Difference: -1.2 (-6.1, 3.7) **Role physical** G1 baseline: 83.8 (2.3) G1 3 years: 76.6 (2.7) G1 Change: -7.3 (-12.4, -2.1) G2 baseline: 85.4 (2.4) G2 3 years: 83.4 (2.4) G2 Change: -2.0 (-7.0, 3.0) Difference: -5.3 (-12.5, 1.9) **Bodily pain** G1 baseline: 80.5 (1.7) G1 3 years: 78.0 (1.8) G1 Change: -2.5 (-5.7, 0.7) G2 baseline: 84.7 (1.7) G2 3 years: 81.1 (1.6) G2 Change: -3.6 (-6.8, -0.4) Difference: 1.1 (-3.4, 5.6) **General health** G1 baseline: 59.5 (0.9) G1 3 years: 64.2 (1.5) G1 Change: 4.7 (2.3, 7.2) G2 baseline: 59.6 (1.0) G2 3 years: 65.8 (1.5) G2 Change: 6.2 (3.7, 8.7) Difference: -1.5 (-5.0, 2.0) **Vitality:** G1 baseline: 49.2 (1.1) G1 3 years: 65.6 (1.6) G1 Change: 16.4 (13.0, 19.7) G2 baseline: 51.4 (1.1) G2 3 years: 67.7 (1.6) G2 Change: 16.3 (13.4, 19.2) Difference: 0.03 (-4.6, 4.7)

Appendix E Table 1. Quality of Life Outcomes at 1- and 3-Year Followups Among Individuals With Screen-Detected Type 2 Diabetes (KQ 4)

First Author, Year Trial Name Country	QoL Outcomes at 1-Year Followup	QoL Outcomes at 3-Year Followup
van den Donk, 2010[95] Janssen, 2009[117] ADDITION-Netherlands Netherlands (continued)		**Social functioning** G1 baseline: 89.3 (1.4) G1 3 years: 83.2 (1.7) G1 Change: -6.1 (-9.4, -2.8) G2 baseline: 90.0 (1.3) G2 3 years: 86.2 (1.6) G2 Change: -3.8 (-6.8, -0.9) Difference: -2.3 (-7.0, 2.3) **Role emotional** G1 baseline: G1 baseline: 89.3 (2.1) G1 3 years: 84.8 (2.4) G2 Change: -4.6 (-10.3, 1.1) 87.9 (2.4) G2 3 years: 87.0 (2.4) G2 Change: -0.8 (-5.6,3.9) Difference: -3.7 (-11.2,3.7) **Mental health** G1 baseline: 68.1 (1.0) G1 3 years: 75.9 (1.4) Change: 7.8 (5.1;10.5) G2 baseline: 71.1 (0.9) G2 3 years: 79.7 (1.2) Change: 8.6 (6.1,11.1) Difference: -0.8 (-4.5,2.8) **EQ5D** G1 baseline: 0.81 (0.02) G1 3 years: 0.81 (0.02) G1 change: 0.0002 (-0.03,0.03) G2 baseline: 0.81 (0.02) G2 3 years: 0.81 (0.02) G2 change: 0.001 (-0.03,0.03) Difference: -0.002 (-0.04,0.04)

Abbreviations: ADDITION=Anglo-Dutch-Danish Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care; G=Group; SD=standard deviation; SEM=Standard Error of the Mean.

Appendix E Table 2. Quality of Life Outcomes at 5-Year Followup Among Individuals With Screen-Detected Type 2 Diabetes (KQ 4)

First Author, Year Trial Name Country	Denmark	U.K., Cambridge	U.K. Leicester	Netherlands 5-Year Followup	Pooled Across Countries Mean Difference (95% CI)
van den Donk, 2013[243] Simmons, 2016[76] ADDITION-Europe Denmark, U.K., Netherlands	**At 5-year followup** SF-36 (n=1093) PCS mean score (SD) G1: 46.7 (10.0) G2: 46.7 (9.6) Mean difference (95% CI) -0.32 (-1.36, 0.72) MCS mean score (SD) G1: 55.3 (9.1) G2: 54.9 (8.5) Mean difference (95% CI) -0.63 (-1.70, 0.44) EuroQol EQ-5D (n=1158) mean score (SD) G1: 0.85 (0.21) G2: 0.84 (0.22) Mean difference (95% CI) -0.02 (-0.04, 0.00) EQ-VAS (n=1153) mean score (SD) G1: 76.9 (16.9) G2: 76.4 (18.5) Mean difference (95% CI) -1.05 (-3.00, 0.90)	**At 5-year followup** SF-36 (n=660) PCS mean score (SD) G1: 43.9 (11.6) G2: 44.6 (11.3) Mean difference (95% CI) 0.83 (-0.96, 2.61) MCS mean score (SD) G1: 53.4 (9.0) G2: 54.6 (8.4) Mean difference (95% CI) 1.14 (-0.14, 2.41) EuroQol EQ-5D (n=663) mean score (SD) G1: 0.81 (0.23) G2: 0.83 (0.22) Mean difference (95% CI) 0.02 (-0.01, 0.05) EQ-VAS (n=671) mean score (SD) G1: 76.1 (18.0) G2: 78.4 (16.4) Mean difference (95% CI) 2.72 (-0.09, 5.52)	**At 5-year followup** SF-36 (n=143) PCS mean score (SD) G1: 44.3 (11.4) G2: 43.4 (10.5) Mean difference (95% CI) -3.78 (-7.30, -0.26) MCS mean score (SD) G1: 50.9 (10.1) G2: 52.2 (9.8) Mean difference (95% CI) -1.51 (-5.33, 2.31) EuroQol EQ-5D (n=145) mean score (SD) G1: 0.75 (0.31) G2: 0.79 (0.23) Mean difference (95% CI) -0.02 (-0.09, 0.06) EQ-VAS (n=148) mean score (SD) G1: 78.3 (16.3) G2: 74.8 (18.4) Mean difference (95% CI) -8.37 (-15.15, -1.59)	**At 5-year followup** SF-36 (n=321) PCS mean score (SD) G1: 46.8 (10.4) G2: 47.0 (10.5) Mean difference (95% CI) 0.42 (-1.63, 2.46) MCS mean score (SD) G1: 54.3 (8.2) G2: 53.7 (7.4) Mean difference (95% CI) -0.64 (-2.53, 1.26) EuroQol EQ-5D (n=320) mean score (SD) G1: 0.86 (0.18) G2: 0.82 (0.26) Mean difference (95% CI) -0.03 (-0.07, 0.01) EQ-VAS (n=319) mean score (SD) G1: 76.5 (13.7) G2: 75.3 (15.6) Mean difference (95% CI) -1.87 (-4.92, 1.18)	**At 5-year followup** SF-36 PCS Pooled estimate -0.21 (-1.48, 1.05) I^2=44% SF-36 MCS Pooled estimate -0.01 (-1.21, 0.99) I^2=50% EQ-5D Pooled estimate -0.01 (-0.03, 0.02) I^2=49% EQ-VAS Pooled estimate -1.17 (-4.20, 1.87) I^2=73% W-BQ-general Pooled estimate -0.32 (-1.31, 0.66) I^2=66%

Appendix E Table 2. Quality of Life Outcomes at 5-Year Followup Among Individuals With Screen-Detected Type 2 Diabetes (KQ 4)

First Author, Year Trial Name Country	Denmark	U.K., Cambridge	U.K. Leicester	Netherlands 5-Year Followup	Pooled Across Countries Mean Difference (95% CI)
van den Donk, 2013[243] Simmons, 2016[76] ADDITION-Europe Denmark, U.K., Netherlands (continued)	W-BQ12 General (n-1127) mean score (SD) G1: 28.5 (5.9) G2: 28.1 (6.3) Mean difference (95% CI) -0.60 (-1.28, 0.08) Negative (n=1147) mean score (SD) G1: 1.1 (2.0) G2: 1.1 (1.8) Mean difference (95% CI) 0.10 (-0.12, 0.32) Positive (n=1148) mean score (SD) G1: 9.4 (2.5) G2: 9.2 (2.8) Mean difference (95% CI) -0.31 (-0.63, 0.01) Energy (n=1144) mean score (SD) G1: 8.1 (2.7) G2: 8.0 (2.8) Mean difference (95% CI) -0.21 (-0.52, 0.10) ADDQoL (n=900) G1: -0.73 (1.15) G2: -0.69 (1.07) Mean difference (95% CI) 0.02 (-0.13, 0.17)	W-BQ12 General (n=656) mean score (SD) G1: 25.5 (6.5) G2: 26.4 (5.9) Mean difference (95% CI) 0.81 (-0.10, 1.71) Negative (665) mean score (SD) G1: 1.7 (2.4) G2: 1.4 (2.1) Mean difference (95% CI) -0.28 (-0.61, 0.06) Positive (n=667) mean score (SD) G1: 8.2 (2.8) G2: 8.4 (2.7) Mean difference (95% CI) 0.35 (-0.28, 0.57) Energy (n=667) mean score (SD) G1: 7.0 (2.7) G2: 7.3 (2.6) Mean difference (95% CI) 0.35 (-0.01, 0.72) ADDQoL (n=586) G1: -0.84 (1.29) G2: -0.87 (1.30) Mean difference (95% CI) -0.07 (-0.28, 0.13)	W-BQ12 General (n=136) mean score (SD) G1: 25.3 (6.7) G2: 25.0 (6.3) Mean difference (95% CI) -2.21 (-4.64, 0.22) Negative (n=145) mean score (SD) G1: 1.9 (2.5) G2: 2.1 (2.5) Mean difference (95% CI) 0.78 (-0.33, 1.89) Positive (n=144) mean score (SD) G1: 8.2 (2.6) G2: 8.0 (2.9) Mean difference (95% CI) -0.99 (-2.06, 0.09) Energy (n=140) mean score (SD) G1: 7.1 (2.7) G2: 7.1 (2.3) Mean difference (95% CI) -0.48 (-1.37, 0.41) ADDQoL (n=126) G1: -1.20 (1.78) G2: -2.39 (2.52) Mean difference (95% CI) -1.23 (-2.25, -0.21)	W-BQ12 General (n=312) mean score (SD) G1: 27.6 (6.3) G2: 27.4 (5.7) Mean difference (95% CI) -0.45 (-1.82, 1.18) Negative (n=318) mean score (SD) G1: 1.1 (1.9) G2: 1.1 (1.8) Mean difference (95% CI) 0.06 (-0.37, 0.48) Positive (n=321) mean score (SD) G1: 8.0 (3.1) G2: 8.1 (2.6) Mean difference (95% CI) -0.13 (-0.80, 0.54) Energy (n=316) mean score (SD) G1: 8.5 (2.6) G2: 8.5 (2.3) Mean difference (95% CI) -0.08 (-0.61, 0.45) ADDQoL (n=304) G1: -0.55 (0.86) G2: -0.55 (0.92) Mean difference (95% CI) 0.02 (-0.18, 0.22)	W-BQ-negative Pooled estimate 0.01 (-0.25, 0.27) I^2=45% W-BQ-positive Pooled estimate -0.19 (-0.53, 0.15) I^2=41% W-BQ-energy Pooled estimate -0.04 (-0.38, 0.31) I^2=54% ADDQoL Pooled estimate -0.04 (-0.20, 0.13) I^2=50%

Abbreviations: ADDITION=Anglo-Dutch-Danish Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care; ADDQoL=Anglo-Dutch-Danish Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care quality of life; CI=confidence interval; EQ-5D=EuroQol 5 Dimensions; EQ-VAS=EuroQol Visual Analogue Scale; G=Group; MCS=mental component scale; PCS=physical component scale; SD=standard deviation; SF-36=36-item Short Form Health Survey; U.K.=United Kingdom; W-BQ=12-Item short form of the Well-Being Questionnaire.

Appendix E Table 3. Results of Outcomes for Chronic Kidney Disease, Retinopathy, and Neuropathy Among Individuals With Screen-Detected Type 2 Diabetes (KQ 4)

First Author, Year Trial Name Country	Chronic Kidney Disease G1 N (%) G2 N (%) HR (95% CI)	Visual Impairment G1 N (%) G2 N (%) HR (95% CI)	Neuropathy G1 N (%) G2 N (%) HR (95% CI)
Simmons, 2016[76] ADDITION-Europe Denmark, U.K., the Netherlands	At 5-year followup Any albuminuria (yes/no) # patients (%) G1: 316/1392 (22.7) G2: 269/1101 (24.4) OR, (95% CI) 0.88 (0.72, 1.07) Macroalbuminuria # patients (%) G1: 56/1392 (4.0) G2: 37/1101 (3.4) OR, (95% CI) 1.15 (0.76,1.74) Estimated Glomerular Filtration Rate (eGFR) (n=2710) Mean (SD) G1: 4.31 (0.49) ml/min G2: 6.44 (0.9) ml/min Mean difference (95% CI) -1.39 (-2.97, 0.19) ml/min No interaction based on age or sex	At 5-year followup Any retinopathy (yes/no) # patients (%) G1: 125/1232 (10.1) G2: 116/958 (12.1) OR, (95% CI) 0.84 (0.64, 1.10) No interaction based on age or sex	At 5-year followup Any neuropathy (yes/no) G1: 63/1296 (4.86) G2: 60/1016 (5.91) OR, (95% CI) 0.95 (0.68, 1.34)
Charles, 2011[245] ADDITION-Denmark Denmark	NR	NR	At 6-years followup (n=1161) Light touch sensation, 1/8 Prevalence (SD) G1 (n=387): 17.8% (14.1, 22.0) G2 (n=231): 20.3% (15.3, 26.1) Vibration detection threshold, >95th percentile Prevalence (SD) G1 (n=235): 22.6% (17.2, 28.1) G2 (n=136): 25.7% (18.3, 33.2) Light touch + VDT Prevalence (SD) G1 (n=229): 30.1% (24.1, 36.1) G2 (n=135) 34.8% (26.7, 43.0) MNSI Questionnaire, cut ≥7 Prevalence (SD) G1 (n=656): 8.7% (6.5, 10.9) G2 (n=430): 9.3% (6.5, 12.1) Pain Prevalence (SD) G1 (n=581): 4.6% (2.9, 6.4) G2 (n=400): 4.5% (2.5, 6.5) For all outcomes: OR point estimate favored G1 but was nonsignificant (data was presented visually, data NR)

Abbreviations: ADDITION=Anglo-Dutch-Danish Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care; CI=confidence interval; eGFR=Estimated Glomerular Filtration Rate; MNSI=Michigan Neuropathy Screening Instrument; NR=not reported; OR=odds ratio; SD=standard deviation; VDT=Vibration Detection Threshold.

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Studies Evaluating Lifestyle Interventions (including those that also evaluated medications)												
Ackermann, 2015[139] Reaching Out to Prevent Increases in Diabetes (RAPID)	RCT; 9 urban primary care clinics in Indianapolis, Indiana	Low-income adults with IFG, IGT, or elevated HbA1c, BMI ≥24 kg/m^{2,} and no diagnosis of DM	G1: Group-based YMCA DPP (YDPP) intervention (n=257) G2: Usual care plus brief counseling & information on community resources (n=252)	1	G1: 50.8 (12.2) G2: 51.2 (12.0)	G1: 187 (72.8) G2: 173 (68.7)	G1: 166 (65) G2: 165 (65)	G1 6.1 (0.3) G2 6.0 (0.3)	NR	G1: 37.1 (8.7) G2: 36.5 (8.3)	Overall: 132.2 (14.6) NR NR G1: 133.5 (15.2) G2: 130.9 (13.8) NR	Good
Aekplakorn, 2019[268]	RCT; primary care units in 8 provinces. Thailand	30-65 years of age without a history of diabetes but with impaired glucose tolerance testing	G1: lifestyle program with 17 sessions (34 PCUs, 1,030 total) G2: Usual care with one-time education program (34 PCUs, 873 total)	2	G1: 50.9 (6.3) G2: 50.8 (6.5)	G1: 809 (78.5 %) G2: 708 (81.1%)	NR	NR	G1: 97.1 (12.5) G2: 97.9 (12.3)	G1: 26.7 G2: 27.3	NR	Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Bhopal, 2014[36] Welsh, 2016[220] The Prevention of Diabetes and Obesity in South Asians (PODOSA) study	RCT; 2 National Health Service regions in Scotland	Indian or Pakistani adults aged 35+ y with IGT or IFG, no diagnosis of DM (other than gestational DM), and waist 90+ cm (men) or 80+ cm (women)	G1: Lifestyle intervention with family support and visits to dietician (n=85) G2: Standardized advice with family support (n=86)	3	G1: 52.8 (10.2) G2: 52.2 (10.3)	G1: 46 (44) G2: 47 (45)	G1: 85 (100) G2: 86 (100)	NR	G1: 104.4 (10.8) G2: 104.4 (10.8)	G1: 30.6(5.0) G2: 30.5 (4.6)	G1: 136.9 (21.8) G2: 137.0 (19.7) G1: 82.7 (12.5) G2: 83.5 (10.7) Current tobacco use G1:6 (7) G2: 5 (6)	Fair
Block, 2015[205] Alive-PD	RCT; Ambulatory care health care delivery system in CA, U.S.	Adults aged 30-69 y with IFG or HbA1c in prediabetes range, and BMI of 27+ kg/m^2 (non-Asians) or 25+ kg/m^2 (Asians)	G1: Alive-PD behavioral intervention for diabetes prevention delivered via the Web, Internet, mobile phone, and automated phone calls (n=163) G2: Usual care (n=176)	0.5	G1: 54.9 (9.1) G2: 55.0 (8.8)	G1: 54 (30.7) G2: 52 (31.9)	G1: 56 (31.8) G2:54 (33.1)	Overall 5.6 (0.3) G1: 5.6 (0.3) G2: 5.6 (0.3)	Overall 109.9 (8.4) G1: 110.1 (8.6) G2: 109.6 (8.3)	G1: 31.2 (4.3) G2: 31.1 (4.5)	G1: 130.4 (14.5) G2: 130.5 (15.0) G1: 82.6 (8.7) G2: 82.0 (8.1) NR	Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Davies, 2016[86] Gray, 2016[118] Let's Prevent Diabetes	Cluster RCT; 44 general practices in Leicestershire, U.K.	Adults aged 40-75 (White European) or 25-75 (South Asian) y with screen-detected prediabetes (IFG and/or IGT)	G1: Let's Prevent Diabetes lifestyle intervention (n=447) G2: Usual care (all received booklet with DM information) (n=433)	3	G1: 63.9 (7.6) G2: 63.9 (7.9)	G1:36.9 (NR) G2:35.8 (NR)	G1: 70 (16.2) G2: 70 (15.7)	G1: 6.1 (0.4) G2: 6.1 (0.4)	G1: 102.6 (12.6) G2: 100.8 (12.6)	G1:32.0 (5.2) G2:33.1 (5.8)	G1: 147.9 (20.7) G2:147.7 (17.7) G1:86.6 (11.0) G2:86. 2(10.6) G1:38 (8.5) G2:22 (5.1)	Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Diabetes Prevention Program Research Group, 2002[80] Diabetes Prevention Program Research Group, 2005[119] Diabetes Prevention Program Research Group, 2012[97] DPP Diabetes Prevention Program Research Group, 2012[237] Diabetes Prevention Program Research Group, 2009[146]	RCT (DPP) and open-label extension (DPPOS); 27 clinical centers throughout the U.S. Following double-blind phase, all participants were invited to participate in an open-labeled extension (DPPOS)	Adults aged 25+ y with IFG and IGT, no diagnosis of DM, and BMI 24+ kg/m^2 (non-Asians) or 22+ kg/m^2 (Asians)	G1: Intensive lifestyle intervention* (n =1079; 910 enrolled in DPPOS) G2: Standard lifestyle recommendations plus metformin at a dose of 850 mg twice daily (n=1073; 924 enrolled in DPPOS) G3: Standard lifestyle recommendation plus placebo twice daily (n =1082; 932 enrolled in DPPOS)	DPP: 2.8 DPPOS: 10-15†	G1: 50.6 (11.3) G2: 50.9 (10.3) G3: 50.3 (10.4)	G1: 734 (68.0) G2: 710 (66.2) G3: 747 (69.0)	G1: 499 (46.2) G2:471 (43.9) G3: 496 (45.8)	G1: 5.91 (0.51) G2:5.91 (0.50) G3: 5.91 (0.50)	G1: 106.3 (8.1) G2: 106.5 (8.5) G3: 106.7 (8.4)	G1:33.9 (6.8) G2:33.9 (6.6) G3:34.2 (6.7)	NR	DPP: Good DPPOS: Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Diabetes Prevention Program Research Group, 2015[79] Apolzan, 2019[238] Diabetes Prevention Program Research Group, 2019[81] DPPOS												
Hellgren, 2014[143]	RCT; Sweden	Adults aged 35–75 y with IGT and a FINDRISC questionnaire risk score >11.	G1: Intensive intervention (focused only on physical activity) (n=19) G2: Basic intervention (n=18) G3: Usual care, with written and verbal information on IGT (n=15)	1	G1: 66 (9) G2: 63 (10) G3: 68 (5)	24 (53.3)	NR	G1: 5.8 (NR) G2: 5.8 (NR) G3: 6.0 (NR)	G1: 106.2 (9.0) G2: 108.0 (10.8) G3: 106.2 (10.8)	G1: 30 (4) G2: 29 (4) G3: 30 (6)	G1: 148 (19) G2: 82 (10) G3: NR G1: 144 (21) G2: 153 (17) G3: 145 (18) G1: 83 (9) G2: 83 (12) G3: 78 (7)	Fair
Hu, 2017[215]	RCT; Rural areas in Hunan Province, China	Adults aged 60 y with prediabetes‡	G1: Synthetic intervention (n=214) G2: Standard health advice (n=220)	1	G1: 69.2 (6.8) G2: 69.5 (6.3)	G1: 121 (56.5) G2: 133 (60.5)	NR	G1:5.7 (0.9) G2: 5.8 (1.1)	G1: 111.0 (10.9) G2: 109.8 (8.8)	G1: 23.5 (3.2) G2: 23.9 (3.7)	NR	Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Katula, 2013[144] Pedley, 2018[257] Healthy Living Partnership (HELP PD)	RCT; community-based sites in North Carolina, U.S.	Volunteers with IFG and BMI 25-39 kg/m^2 (eligibility criteria targeted representative sample in the community)	G1: Lifestyle weight loss intervention adapted from DDPLI with exercise and reduction in caloric intake (n=151) G2: Enhanced usual care with nutrition counseling (n=150)	2	G1: 57.3 (10.1) G2: 58.5 (9)	G1: 87 (57.6) G2: 86 (57.3)	G1: 40 (26.5) G2: 39 (26.0)	NR	G1: 105.4 (12.5) G2: 105.7 (10.0)	G1: 32.8 (3.9) G2: 32.6 (4.1)	NR	Fair
Kosaka, 2005[224]	RCT; Hospital medical center in Japan	Males with IGT and no previous history of diabetes	G1: Lifestyle intervention (n=356) G2: Usual care (n=102)	4	NR	0 (0)	NR	NR	NR	G1: 24.0 (2.3) G2: 23.8 (2.1)	G1: 123 (18) G2: 124 (17) G1: 78 (13) G2: 79 (11) NR	Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Kulkarni, 2018[272]	RCT; outpatient medicine or endocrine clinic in one hospital system, India	18 years or older, screened positive prediabetes, free of CVD	G1: intensive lifestyle – standard lifestyle with use of a healthcare facilitator with weekly reminders and monthly phone calls (35) G2: intensive lifestyle and metformin – 500 BID (35) G3: advice on standard lifestyle modifications (standard care) (33)	6 months	G1: 45.3 (10.9) G2: 49.4 (9.2) G3: 49 (9.8)	G1: 25 (71.4%) G2: 21 (60%) G3: 23 (69.7%)	NR	G1: 6.13 G2: 6.1 G3: 6.05	G1: 109.4 G2: 108.9 G3: 109.3	G1: 29.3 G2: 28.1 G3: 28.5	G1: 123 (13) G2: 124 (10) G3: 124 (10) NR NR	Fair
Kulzer, 2009[112] Prevention of Diabetes Self-Management Program (PREDIAS)	RCT: Germany	Adults aged 20-70 y with IGT or IFG, or Diabetes Risk Score >10, or advisement of PCP, and BMI ≥26 kg/m^2	G1: PREDIAS group lifestyle intervention based on the Diabetes Prevention Program (n=91) G2: Control (received the PREDIAS written information and patient materials (n=91)	1	56.3 (10.1)	78 (43)	NR	G1: 5.7 (0.5) G2: 5.7 (0.6)	G1: 105.7 (12.4 G2: 105.5 (12.4)	G1: 31 (4.7) G2: 32 (5.7)	G1: 141.8 (18.6) G2: 139.1 (15.9) G1: 88.5 (10.5) G2: 87.3 (9.7) NR	Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Lindahl, 2009[137]	RCT; Sweden	Adults recruited from community intervention program on CVD and diabetes, with IGT and BMI >27 kg/m^2	G1: Intensive lifestyle with one-month residential stay (n=151 randomized, but only n=100 directly invited; 50 assigned as substitutes) G2: Usual care (n=150 randomized, but only n=100 directly invited; 50 assigned as substitutes)	5	G1: 52.2 (9) G2: 53.5 (8.4)	G1: 58 (69.9) G2: 52 (61.2)	NR	NR	G1: 105.1 (23.8) G2: 111.4 (22.7)	G1: 31.2 (3.1) G2: 30.2 (3.4)	G1: 140.7 (19.3) G2: 141.3 (18.8) G1: 84.2 (10.0) G2: 85.7 (9.8) Daily smoker G1: 6 (7.2) G2: 7 (8.2) Ex-smoker G1: 29 (34.9) G2: 22 (25.9)	Fair
Morey, 2012[120] The Enhancing Fitness in Older Overweight Veterans with Impaired Glucose Tolerance (Enhanced Fitness) Trial	Controlled clinical trial; VA Medical Center, Durham, NC, U.S.	Adults aged 60+ y with IFG, no diagnosis of DM, and BMI 25- 45 kg/m^2	G1: Counseling intervention focused on physical activity (n=180) G2: Usual care control (n=122)	1	G1: 67.1 (6.3) G2: 67.7 (6.2)	G1: 7 (3.9) G2: 3 (2.5)	G1: 51 (28.3) G2: 39 (32.0)	G1: 5.9 (0.4) G2: 5.9 (0.4)	G1: 110.5 (6.95) G2: 110.6 (7.10)	G1: 31.35 (3.75) G2: 30.97 (3.45)	NR NR NR	Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Moungngern, 2018[270]	RCT; outpatient department, Thailand	18 years of age or older, 11-20% increased risk of developing T2DM in next 12 years, A1c 5.7-6.4 or FPG 100-125 or HDL <35 or triglycerides >250 of history of GDM or delivery of infant >4 kg	G1: lifestyle program (nurse-managed health promotion program), group activities at 1, 2, 8 weeks (n=61) G2: routine self care (n=64)	6 months	G1: 55.9 (9.3) G2: 53.6 (9.8)	G1: 47 (77%) G2: 46 (71.9%)	NR	G1: 6 G2: 6	G1: 98 G2: 99	G1: 27.8 G2: 27.9	NR	Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
O'Brien, 2017[142] The *Promotora* Effectiveness Versus Metformin Trial (PREVENT-DM)	RCT; Health center in Philadelphia, PA, U.S.	Latinas aged ≥20 y with impaired fasting glucose and/or elevated HbA1c	G1: Intensive group-based adaptation of the DPP lifestyle intervention delivered by *promotoras (*community healthcare workers (n=33) G2: Metformin 850 mg twice daily (n=29) G3: Standard care plus written educational materials on diabetes prevention (n=30)	1	G1: 45.5 (12.3) G2: 45.8 (11.7) G3: 44.0 (13.6)	92 (100)	92 (100)	G1: 5.9 (0.2) G2: 6.0 (0.2) G3: 5.9 (0.3)	G1: 97.5 (7.5) G2: 94.6 (10.1) G3: 96.0 (10.7)	G1: 34.4 (7.9) G2: 33.2 (5.5) G3: 32.2 (5.7)	G1: 118.4 (13.9) G2: 122.2 (19.8) G3: 118.3 (17.6) G1: 74.5 (9.8) G2: 75.9 (10.2) G3: 73.3 (9.0) NR	Fair
Oldroyd, 2001[212]	RCT; Hospital clinical research facility Newcastle upon Tyne, U.K.	Adults aged 24– 75 y with IGT	G1: Behavioral intervention (n=39) G2: Control (n=39)	0.5	G1: 58.2 (NR) G2: 57.5 (NR)	G1: 19 (54) G2: 10 (32)	NR	G1: 5.8 (0.7) G2: 5.9 (0.5)	G1: 108.0 (16.2) G2: 111.6 (16.2)	G1: 30.4 (5.6) G2: 29.9 (4.9)	G1: 137.2 (19.9) G2: 132.8 (16.4) G1: 77.0 (12.6) G2: 75.5 (9.8) NR	Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Pan, 1997[225] Li, 2008[226] Li, 2014[227] Gong, 2019[228] China Da Qing Diabetes Prevention Outcomes Study (CDQDPOS)	Cluster RCT; Health care clinics in Da Qing, China	Adults aged >25 y with IGT	G1: Combined 6-year lifestyle (diet, exercise, or diet + exercise) intervention: (n=438) G2: Control (n=138)	30-year followup	G1: 44.7 (SE 0.4) G2: 46.6 (SE 0.8)	G1: 205 (47) G2: 59 (43)	NR	NR	G1: 100.8 (SE 14.4) G2: 99.4 (SE 14.4)	G1: 25.6 (4.0) G2: 26.2 (3.8)	G1: 131.9 (24.3) G2: 133.4 (26.0) G1: 87.0 (14.1) G2: 87.8 (15.4) G1: 169 (39) G2: 69 (50)	Fair
Penn, 2009[264]	RCT; Hospital clinical research facility Newcastle upon Tyne, U.K.	Adults ages 40+ y with IGT, no previous diagnosis of DM, and BMI >25 kg/m^2	G1: Individual behavioral intervention (n=51) G2: Usual care and standard health promotion advice (n=51)	Mean 3.1	G1: 56.8 (40-72) G2: 57.4 (38-74)	G1: 30 (58.8) G2: 31 (60.8)	NR	NR	G1: 102.6 (10.8) G2: 104.4 (9.0)	G1: 34.1 (5.5) G2: 33.5 (4.6)	NR	Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Ramachandran, 2006[234] Indian Diabetes Prevention Programme	RCT; India	Adults aged 35-55 y with IGT and no previous diagnosis of DM	G1: Lifestyle Intervention (n=133) G2: Metformin (n=133) G3: Lifestyle Intervention + Metformin (n=129) G4: Standard health care advice (n=136)	3	G1: 46.1 (5.7) G2: 45.9 (5.9) G3: 46.3 (5.7) G4: 45.2 (5.7)	G1: 29 (21.8) G2:26 (19.5) G3: 24 (18.6) G4: 32 (23.5)	NR	G1: 6.1 (0.5) G2: 6.2 (0.6) G3: 6.2 (0.6) G4: 6.2 (0.5)	G1: 97.2 (12.6) G2: 97.2 (14.4) G3: 97.2 (14.4) G4: 99.0 (14.4)	G1: 25.7 (3.3) G2: 25.6 (3.7) G3: 25.6 (3.3) G4: 26.3 (3.7)	G1:121.5 (14.4) G2: 120.7 (15.9) G3: 122.4 (14.3) G4: 124.1 (16.0) G1: 74.4 (8.1) G2: 74.4 (9.2) G3: 74.9 (8.1) G4: 76.2 (8.6) G1: 29 (21.8) G2: 23 (17.3) G3: 27 (20.9) G4: 36 (26.5)	Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Saito, 2011[87] ZPLS	RCT; 38 hospitals and clinics in Japan	Japanese adults aged 30-60 y with IFG, no DM diagnosis, and BMI ≥24 kg/m^2	G1: Frequent intervention (received individual instructions and followup support for lifestyle modification 9 times over 36 months) (n=311) G2: Control group (received individual instructions and followup support for lifestyle modification 4 times over 12 months). (n=330)	3	G1: 50 (44-54) G2: 48 (41-54) Median and IQR	G1: 87 (28) G2: 96 (29)	NR	G1: 5.4 (0.4) G2: 5.4 (0.4)	G1: 108 (8) G2: 107 (8)	G1: 26.9 (2.6) G2: 27.1 (2.6)	G1: 130 (16) G2: 131 (16) G1: 81 (11) G2: 81 (12) G1: 78 (25) G2: 92 (28)	Fair
Sakane, 2011[266]	RCT; 32 community health care institutions and company clinics across Japan	Adults aged 30-60 with IGT who had not yet begun lifestyle modifications on their own	G1: Repeated sessions of group and individual lifestyle modification intervention (n=152) G2: one group session at baseline on healthy lifestyle and prevention of DM (n=152)	3	G1: 51 (7) G2: 51 (6)	NR	NR	NR	G1: 106.2 (9.0) G2: 109.8 (9.0)	G1: 24.8 (3.6) G2: 24.5 (3.2)	NR	Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Sakane, 2015[140] The Japan Diabetes Outcome Intervention Trial-1 (J-DOIT1)	Cluster RCT; 17 community and company healthcare divisions across Japan	Adults aged 25-60 y with IFG but no diagnosis of diabetes	G1: 1-year telephone-delivered lifestyle support intervention (n=1,240) G2: Control (n=1,367)	Median 4.2	G1: 48.9 (7.8) G2: 48.9 (7.5)	G1: 217 (17.5) G2: 217 (15.9)	NR	NR	Median: 106.2	G1: 24.4 (3.2) G2: 24.3 (3.1)	NR NR NR	Fair
Tuomilehto, 2001[232] Uusitupa, 2009[233] Finnish Diabetes Prevention Study (FDPS)	RCT; Finland	Adults aged 40-65 y with IGT, no diagnosis of diabetes, and BMI > 25 kg/m^2	Original Study: G1: physical activity, weight reduction and dietary counseling intervention (n=265) G2: General diet & exercise (n=257) 10-y followup study: G1: same as above (n=257) G2: Same as above (n=248)	Original study: mean 3.2 10-y followup study: mean 10.6 y	Original study G1: 55 (7) G2: 55 (7) 10-y followup study G1: 55.4 (7.3) G2: 55.0 (6.9)	Original study G1: 174 (65.7) G2: 176 (68.5) 10-year followup study G1: 169 (65.8) G2: 170 (68.5)	NR	NR	Original study G1: 109 (14) G2: 110 (13) 10-year followup study G1: 109.8 (14.4) G2: 111.6 (12.6)	Original study G1: 31.3 (4.6) G2: 31.0 (4.5) 10-y followup study G1: 31.4 (4.6) G2: 31.2 (4.5)	Original study G1: 140 (18) G2: 136 (17) G1: 86 (9) G2: 86 (10) NR 10-y followup study: G1: 139.6 (17.7) G2: 136.2 (17.4) G1: 85.7 (9.4) G2: 85.6 (10.0) G1: 18 (7.0) G2: 18 (7.3)	Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Van Name, 2016[141]	RCT; Community Health Center in New Haven, CT, U.S.	Women aged 18 and 65 y with at least one DM risk factor and prediabetes	G1: Intensive Lifestyle Intervention (modified DPP) (n=65) G2: Usual care (n=65)	1	G1: 43.8 (10.8) G2: 43.0 (9.7)	122 (100)	127 (98)	G1: 5.8 (0.36) G2: 6.0 (0.33)	G1: 102.6 (9.5) G2: 101.5 (11.1)	G1: 35.4 (8.5) G2: 35.2 (7.3)	G1: 119.1 (19.0) G2: 123.0 (16.7) G1: 77.3 (11.3) G2: 79.8 (11.0) NR	Fair
Wong, 2013[273] Wong, 2018[274]	RCT; Community Health Project Hong Kong	Chinese professional drivers who were identified as pre-diabetics within last 3 months, had a mobile phone, no h/o DM	G1: Short message service (SMS) intervention (54) G0: Control (usual care) (50)	5	G1: 54.1 (6.1) G2: 55.2 (6.5)	G1: 5 (9.3%) G2: 2 (4%)	NR	NR	G1: 105.5 (7.6) G2: 106.2 (8.8)	G1: 25.55 (2.94) G2: 26.25 (2.95)	G1: 136.54 (15.88) G2: 133.9 (16.45) G1: 80.32 (10.67) G2: 80.86 (11.04) G1: 9 (17%) G2: 4 (8%)	Fair

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Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Yates, 2009[138] The Prediabetes Risk Education and Physical Activity Recommendation and Encouragement (PREPARE)	RCT; Leicester, U.K.	Individuals with BMI ≥25 kg/m^2 (or ≥23 kg/m^2 if South Asian) and IGT, detected in ongoing population-based diabetes screening programs	G3: Physical activity intervention without pedometer use (n=29) G2: Physical activity intervention with pedometer use (n=29) G1: Control (usual care) (n=29)	1	G1: 66 (8) G2: 64 (7) G3: 65 (10)	G1: 9 (31) G2: 9 (31) G3: 12 (41)	G1: 4 (14) G2: 9 (31) G3: 9 (31)	NR	G1: 100.8 (9.0) G2: 100.8 (10.8) G3: 102.6 (9.0)	G1: 28.7 (4.8) G2: 29.5 (4.9) G3: 29.8 (4.4)	G1: 139 (15) G2: 144 (17) G3: 141 (15) G1: 79 (10) G2: 82 (8) G3: 81 (10) G1: 1 (3) G2: 2 (7) G3: 5 (17)	Fair
Studies Evaluating Pharmacological Interventions (not including those that also evaluated lifestyle interventions from above)												
Chiasson, 2002[235] Chiasson, 2003[236] STOP-NIDDM	RCT; Hospitals in 9 countries	Individuals aged 40-70 y with IGT, and BMI 25- 40 kg/m^2	G1: Acarbose 100 mg 3x a day (n=714) G2: Placebo (n=715)	Mean 3.3 (1.2)	G1: 54.3 (7.9) G2: 54.6 (7.9)	G1: 353 (52) G2: 342 (50)	G1: 18 (3) G2: 16 (2)	NR	G1: 112.2 (8.9) G2: 112.5 (9.6)	G1: 31.0 (4.3) G2: 30.9 (4.2)	G1: 131.4 (16.3) G2: 130.9 (16.2) G1: 82.8 (9.4) G2: 82.0 (9.3) G1: 79 (12) G2: 99 (14)	Fair

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Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
DeFronzo, 2011[251] Espinoza, 2016[252] Actos Now for Prevention of Diabetes Trial (ACT NOW)	RCT; 8 centers in the U.S.	Patients aged 18+ y with IGT, BMI ≥25 kg/m^2 (>22 kg/m^2 for Asian Americans), and at least one other risk factor for diabetes	G1: Pioglitazone 30 mg/day for one month, increased to 45 mg/day (n=303) G2: Placebo (n=299)	Median: 2.4 Mean: 2.2	52.3 (11.8)	349 (58) OR 252 (41.9)	G1: 69 (22.8) G2: 55 (18.3)	G1: 5.5 (0.4) G2: 5.5 (0.4)	G1: 105 (0.4) G2: 105 (0.4) Mg/dL	G1: 33.0 (0.4) G2: 34.5 (0.4)	G1: 127 (0.9) G2: 128 (0.9) G1: 74 (0.6) G2: 74 (0.6) NR	Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
DREAM Trial Investigators, 2006[253] DREAM Trial Investigators, 2006[254] DREAM Trial Investigators, 2008[255] Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial	Multiple countries	Adults aged >30 years with IFG and/or IGT	G1: Ramapril 15 mg/day (n=2623) G2: Placebo (n=2646) G3: Rosiglitazone 0.8mg/day (n=2635) G4: Placebo (n=2634) Patients randomized twice, to ramapril or placebo and rosiglitazone or placebo due to 2x2 factorial design	Median: 3 (Range: 2.5-4.7)	G1:54.7 (10.9) G2:54.7 (10.9) G3:54.6 (10.9) G4:54.8 (10.9)	G1: 1567 (59.7) G2: 1553 (58.7) G3: 1536 (58.3) G4: 1584 (60.1)	NR	NR	G1 median (IQR): 106.3 (97.3-113.5) G2 median (IQR): 106.5 (97.3-115.3) G3: 104.4 (12.6) G4: 104.4 (12.6)	G1:30.9 (5.6) G2:30.9 (5.7) G3:30.8 (5.6) G4:31.0 (5.6)	G1: 136.1 (18.6) G2: 136.0 (18.1) G3: 135.9 (17.9) G4: 136.3 (18.8) G1: 83.4 (10.8) G2: 83.4 (10.8) G3: 83.3 (10.6) G4: 83.5 (10.9) Current or previous tobacco use G1: 1,158 (44.1) G2: 1,192 (45.0) G3: 1,157 (43.9) G4: 1,193 (45.3)	Good

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Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Kaku, 2015[218]	RCT; Multicenter, Japan	Japanese patients aged ≥20 y with suspected IGT	G1: Sitagliptin 25g once daily (n=82) G2: Sitagliptin 50g once daily (n=77) G3: Placebo (n=83)	0.15 (8 weeks)	G1: 63.1(9.5) G2: 61.9 (9.3) G3: 61.9 (10.6)	G1: 38 (46.3) G2: 32 (41.6) G3: 35 (42.2)	NR	G1: 6.01 (0.25) G2: 6.02 (0.28) G3: 5.98 (0.27)	G1: 105.5 (9.2) G2: 106.6 (10.1) G3: 105.7 (8.8)	G1: 26 (3) G2: 25 (4) G3: 25 (3)	NR NR NR	Fair
Kawamori, 2009[256]	RCT; Multicenter, Japan	Adults aged 30-79 y with IGT	G1: Voglibose 0.2 mg 3x/daily (n=897) G2: Placebo (n=883)	48.1 weeks (SD 36.3 weeks) G1 45.0 weeks (34.7) G2 51.3 weeks (37.6)	G1: 55.7 (9.1) G2: 55.7 (9.2)	G1: 356 (39.7) G2: 351 (39.8)	NR	NR	G1: 104.4 (0.55) G2: 105.3 (10.1)	G1: 25.76 (3.70) G2: 25.89 (3.82)	NR	Good
le Roux, 2017[115] SCALE Obesity and Prediabetes Trial	RCT; 191 clinical research sites in 27 countries in Europe, North America, South America, Asia, Africa, and Australia	Adults aged 18+ y with prediabetes, no diagnosis of DM, and BMI ≥30 kg/m^2 (≥27 kg/m^2 with dyslipidaemia and/or hypertension)	G1: Liraglutide (starting at 0.6 mg daily; weekly 0.6 mg increases to 3.0 mg with standardized lifestyle counseling (n=1505) G2: Placebo with standardized lifestyle counseling (n=749)	3.3 (172 weeks)	G1: 47.5 (11.7) G2: 47.3 (11.8)	G1: 1141 (76) G2: 573 (77)	G1: 249 (17) G2: 121 (16)	G1: 5.8 (0.3) G2: 5.7 (0.3)	G1: 99.0 (10.8) G2: 99.0 (9.0)	G1: 38.8 (6.4) G2: 39.0 (6.3)	G1: 124.7 (12.9) G2: 125.0 (12.8) G1: 79.4 (8.4) G2: 79.8 (8.3) NR	Fair

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Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Lindblad, 2011[258] The Nepi ANtidiabetes StudY (NANSY)	RCT; Primary care, Sweden	Adults aged 40-70 y with IFG	G1: glimepiride 1 mg/daily (n=136) G2: placebo (n=138)	Mean 3.7	G1: 60.4 (6.8) G2: 59.6 (6.7)	G1: 48 (35.3) G2: 63 (45.7)	NR	G1: 4.89 (0.54) G2: 4.87 (0.46)	NR	G1: 29.9 (4.6) G2: 29.6 (4.2)	G1: 144 (18) G2: 141 (18) G1: 82 (9.1) G2: 82 (9.2) G1: NR (18.0) G2: NR (21.3)	Fair
Lu, 2011[259]	RCT; Beijing, China	Adults aged 40-80 y with screen-detected impaired glucose regulation, no diagnosis of DM, and BMI ≥19 kg/m^2	G1: Patients with I-IGT: acarbose (50 mg three times daily) + lifestyle intervention; patients with I-IFG or IFG/IGT: metformin (0.25 g 3x daily) + lifestyle intervention (n=106) G2: Annual diabetes education (n=104)	2	G1: 62.44 (9.16) G2: 64.72 (7.93)	G1: 45 (47.4) G2: 41 (47.7)	NR	G1: 5.91 (0.34) G2: 5.98 (0.43)	G1: 106.0 (7.7) G2: 107.3 (9.2)	G1: 27.07 (3.30) G2: 26.92 (3.65)	G1: 129.65 (16.86) G2: 130.06 (19.54) G1: 78.95 (9.49) G2: 78.83 (10.79) NR	Fair
Pan, 2003[246]	RCT; Five centers in the mainland of China	35-70 years old with BMI =19-34. Screen-detected IGT (WHO criteria)	G1: Acarbose (n=125) G2: Placebo (n=127)	16 weeks	G1: 53.4 (8.63) G2: 55.6 (8.31)	G1: NR (60.8) G2: NR (59.1)	NR	G1: 6.51 (0.72) G2: 6.61 (0.62)	NR	G1: 25.6 (2.99) G2: 25.8 (3.22)	G1:125.4 (14.1) G2: 126.8 (14.9) G1: 78 (7.8) G2: 78.1 (8.4) NR	Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
The NAVIGATOR Study Group, 2010[260] The NAVIGATOR Study Group, 2010[261] Currie, 2017[262] Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Trial	RCT; 806 clinical centers in 40 countries	Adults with elevated FPG, IGT, and ≥1 CV risk factors (if aged 55+ y) or known CVD (if aged 50+)	G1: Nateglinide 60 mg/3 times daily (n=4,645) G2: Placebo (n=4,661) G3: Valsartan 160 mg/once daily (n=4,631) G4: Placebo (n=4,675) Patients randomized twice, to nateglinide or placebo and valsartan or placebo due to 2x2 factorial design All patients also required to participate in lifestyle intervention program	Median: 5 y for incidence of diabetes	G1: 63.7 (6.8) G2: 63.8 (6.9) G3: 63.7 (6.8) G4: 63.8 (6.8)	G1: 2,368 (51.0) G2: 2,343 (50.3) G3: 2,314 (50.0) G4: 2,397 (51.3)	G1 791 (17.0) G2 781 (16.8) G3 782 (16.9) G4 790 (16.9)	G1: 5.8 (0.45) G2: 5.8 (0.48) G3: 5.79 (0.47) G4 5.82 (0.46)	G1: 109.8 (8.1) G2: 109.8 (8.3) G3: 109.8 (8.1) G4: 109.8 (8.1)	G1: 30.5 (5.4) G2: 30.5 (5.4) G3: 30.4 (5.5) G4: 30.6 (5.3)	G1: 139.8 (17.5) G2: 139.5 (17.4) G3: 139.4 (17.8) G4: 139.9 (17.1) G1: 82.6 (10.3) G2: 82.5 (10.2) G3: 82.5 (10.4) G4: 82.6 (10.1) G1: 519 (11.2) G2: 506 (10.9) G3: 518 (11.2) G4: 507 (10.8)	Good
Nijpels, 2008[263] DAISI	RCT; subjects invited from population register in Hoorn, the Netherlands	Adults aged 45-70 y with IGT, and HbA1c ≤7.0%	G1: Acarbose 50 mg 3x daily (n=60) G2: Placebo (n=58)	3	G1: 58.5 (7.9) G2: 56.5 (7.0)	G1: 30 (50.8) G2: 29 (50.0)	NR	G1: 5.9 (0.5) G2: 5.6 (0.6)	G1: 118.8 (9.0) G2: 117.0 (10.8)	G1: 28.4 (3.9) G2: 29.5 (3.8)	NR NR G1: 15 (24.6) G2: 14 (23.3)	Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Ramachandran, 2009[265] IDPP-2	RCT; Community-based, India	Asian Indian adults aged 35 to 55 y with IGT	G1: Pioglitazone, 30 mg daily plus lifestyle modification (n=204) G2: Placebo plus lifestyle modification (n=203)	3	G1: 45.1 (6.1) G2: 45.5 (6.3)	G1: 26 (12.7) G2: 28 (13.8)	NR	G1: 5.8 (0.4) G2: 5.8 (0.4)	G1: 100.8 (12.6) G2: 102.6 (10.8)	G1: 26.0 (3.5) G2: 26.2 (3.3)	G1: 117.7 (10.8) G2: 117.9 (11.1) G1: 75.4 (10.9) G2: 75.6 (11.5) G1: 37 (18.1) G2: 47 (23.2)	Fair
Weber, 2016[222] Gokulakrishnan, 2017[223] Diabetes Community Lifestyle Improvement Program (D-CLIP)	RCT; Community-based recruitment in Chennai, India	Adults aged 20-65 y with prediabetes and BMI 23 to <27.5 kg/m2 (overweight) or ≥ 27.5 (obese) and/or waist circumference ≥90cm (men) or ≥80cm (women)	G1: Stepwise intervention of adapted DPP lifestyle classes plus metformin 500 mg twice daily at 4 months if at high risk of developing diabetes (n=283) G2: Standard of care (n=295)	3 Mean 2.54 (range 4-48 months)	44.4 (9.3) G1: 44.8 (9.0) G2: 44.0 (9.5)	212 (36.8) G1: 102 (36.0) G2: 110 (37.5)	NR	6.0 (0.5) G1: 6.0 (0.5) G2: 6.0 (0.5)	Overall 102.6 (9.0) G1: 102.6 (9.0) G2: 102.6 (9.0)	27.9 (3.7) G1: 27.9 (3.7) G2: 27.8 (3.7)	NR	Fair

Appendix E Table 4. Characteristics of Studies that Evaluated Interventions for People With Prediabetes (KQs 4, 6, 7, 9)

Author, Year Trial Name	Design; Setting	Participants	Groups (No. Participants)	Followup, y	Age, Mean (SD or IQR), y	No. (%) F	No. (%) Non-white	HbA1C Mean (%)(SD)	FPG, Mean (SD) mg/dL	BMI, Mean, kg/m2	Mean BP Systolic (mm Hg) (SD) Mean BP Diastolic (mm Hg) (SD) No. (%) Smokers	Quality
Zinman, 2010[267] CAnadian Normoglycemia Outcomes Evaluation trial (CANOE)	RCT; Clinics in Ontario, Canada	Residents of Ontario Canada aged 18-75 y with >1 diabetes risk factor with screen-detected IGT	G1: rosiglitazone 2 mg and metformin 500 twice daily and lifestyle intervention (n=103) G2: placebo and lifestyle intervention (n=104)	3.9 (3.0-4.6 y) Median (IQR)	G1: 50.0 (44.0-61.0) G2: 55.0 (46.0-61.0) Median (IQR)	G1: 67 (65.0) G2: 71 (68.3)	G1: 26 (25.3) G2: 27 (26)	NR	G1: 97.2 (90.0-104.4) G2: 97.2 (90.0-106.2) Median (IQR)	G1: 31.3 (27.1-35.7) G2: 32.0 (28.3-36.8) Median (IQR)	G1: 130.0 (115.5-139.0) G2: 127.5 (118.0-140.8) G1: 80.0 (74.5-87.5) G2: 81.8 (75.3-87.5) Median (IQR) G1: 6 (5.8) G2: 10 (9.6)	Good

* Following the DPP double-blinded phase, participants were unmasked to their treatment assignments and placebo was stopped. All participants, including the origional intensive lifesstyle group were offered a group-administered version of the 16-session lifestyle curriclum. Those previously assigned to metformin continued to receive metforming 850 mg twice daily, unmasked, as appropriate (unless there were safety concerns or they developed diabetes and required management by their own physician).

† Followup varies by outcome, although most open-label DPPOS analyses were conducted 10-15 years from randomization (or 7-12 years after participants were unblinded).

‡ Three groups: (1) IFG group: fasting plasma glucose of 6.1–7.0 mmol/L (110–126 mg/dL) and a 2-h post-glucose load of <7.8 mmol/L (140 mg/dL); (2) IGT group: fasting plasma glucose of 6.1 mmol/L (110 mg/dL) and a 2-h post-glucose load of 7.8–11.1 mmol/L (140–200 mg/dL); (3) IFG+IGT group.

Abbreviations: ACT NOW=Actos Now for Prevention of Diabetes; BMI=body mass index; BP=blood pressure; CA=California; CDQDPOS=China Da Qing Diabetes Prevention Outcomes Study' CV=cardiovascular; CVD=cardiovascular disease; D-CLIP=Diabetes Community Lifestyle Improvement Program; DAISI=Dutch acarbose intervention study in persons with impaired glucose tolerance; DM=diabetes mellitus; DPP=Diabetes Prevention Program; DDPLI=Diabetes Prevention Program lifestyle intervention; DPPOS=Diabetes Prevention Program Outcomes Study; DREAM=Diabetes Reduction Assessment with ramipril and rosiglitazone Medication; FDPS=Finnish Diabetes Prevention Study; FINDRISC=Finnish Diabetes Risk Score; FPG=fasting plasma glucose; G=Group; GDM=gestational diabetes mellitus; HbA1c/HBA1c=hemoglobin A1c; HDL=high density lipoprotein; h/o=history of; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; IQR=interquartile ratio; J-DOIT1=The Japan Diabetes Outcome Intervention Trial-1; NANSY=The Nepi ANtidiabetes StudY; NAVIGATOR=Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; NR=not reported; PCP=primary care physician; PODOSA=The Prevention of Diabetes and Obesity in South Asians; PREDIAS=Prevention of Diabetes Self-Management Program; PREPARE=The Prediabetes Risk Education and Physical Activity Recommendation and Encouragement; PREVENT-DM=The *Promotora* Effectiveness Versus Metformin Trial; RAPID=Reaching Out to Prevent Increases in Diabetes; RCT-randomized, controlled trial; SCALE=Satiety and Clinical Adiposity–Liraglutide Evidence; SD=standard deviation; STOP-NIDDM=Study TO Prevent Noninsulin-Dependent Diabetes Mellitus; T2DM=type 2 diabetes mellitus; U.K.=United Kingdom; U.S.=United States; y=year; YDPP=YMCA diabetes prevention program; ZPLS=Zensharen Study for Prevention of Lifestyle Diseases.

Appendix E Table 5. Mortality Results From Trials Evaluating Interventions for People With Prediabetes (KQ 4)

Source First Author, Year Trial Name	G1 (N) G2 (N)	Followup (y)	Mortality G N (%), or G1% vs. G2%; HR (95% CI)
Diabetes Prevention Program Research Group, 2002[80] Diabetes Prevention Program Research Group, 2005[119] Diabetes Prevention Program Research Group, 2012[97] DPP	G1: Intensive lifestyle intervention (n =1079) G2: Standard lifestyle recommendations plus metformin at a dose of 850 mg twice daily (n=1073) G3: Standard lifestyle recommendation plus placebo twice daily (n =1082)	3.2	All-cause deaths (N/100 person years of followup) G1: 0.10 G2: 0.20 G3: 0.16 No significant difference between groups CVD Related Deaths G1:2 G2:1 G3:4
Hellgren, 2014[143]	G1: Intensive physical activity intervention (n=19) G2: Basic intervention (n=18) G3: Usual care (written and verbal information on IGT (n=15)	1	One person died from causes not related to the study (group in which the person was assigned is unclear)
Juul, 2016[145]	G1: Brief theory-based health promotion intervention (n=63) G2: Control (n=64)	1	No deaths during the study period
Morey, 2012[120] The Enhancing Fitness in Older Overweight Veterans with Impaired Glucose Tolerance (Enhanced Fitness) Trial	G1: Counseling intervention focused on physical activity (n=180) G2: Usual care control (n=122)	1	GI: 2 (1.1) G2:1 (0.8)

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Source First Author, Year Trial Name	G1 (N) G2 (N)	Followup (y)	Mortality G N (%), or G1% vs. G2%; HR (95% CI)
Pan, 1997[225] Li, 2008[226] Li, 2014[227] Gong, 2019[228] China Da Qing Diabetes Prevention Outcomes Study (CDQDPOS)	G1: Combined 6-year lifestyle (diet, exercise, or diet + exercise) intervention: (n=438) G2: Control (n=138)	20, 23, 30	20-year followup: All-cause mortality: 25% vs. 29%; HR, 0.96 (0.65 to 1.41) CVD mortality: 12% vs. 17%: HR, 0.83 (0.48 to 1.40) 23-year followup: All-cause mortality: 28% vs.38%; HR, 0.71 (0.51 to 0.99) Women: 15% vs. 29%; HR, 0.46 (0.24 to 0.87) Men: 40% vs. 46%; HR, 0.97 (0.65 to 1.46) CVD mortality: 12% vs. 20%; HR, 0.59 (0.36 to 0.96) Women: 6% vs. 17%; HR, 0.28 (0.11 to 0.71) Men: 17% vs. 22%: HR, 0.91 (0.50 to 1.65) **30-year followup:** All-cause mortality: 46% vs. 56%; HR, 0.74 (0.61 to 0.89) Women: 24% vs. 41%; HR, 0.59 (0.38 to 0.91) Men: 58% vs. 66%; HR, 0.85 (0.66 to 1.09) CVD mortality: 22% vs. 30%; HR, 0.67 (0.48 to 0.94) Women: 13% vs. 20%; HR, 0.61 (0.36 to 1.02) Men: 27% vs. 35%; HR, 0.73 (0.47 to 1.12)
Ramachandran, 2006[234] Indian Diabetes Prevention Programme	G1: Lifestyle Intervention (n=133) G2: Metformin (n=133) G3: Lifestyle Intervention + Metformin (n=129) G4: Control (n=136)	3	G1: 1 (0.8) G2: 0 (0) G3: 1 (0.8) G4: 1 (0.7)
Saito, 2011[87] ZPLS	G1: Frequent lifestyle modification (9 sessions over 3y) (n=311) G2: Control (4 lifestyle modification sessions over 1yr) (n=330)	3	G1: 1 (0.3) G2: 0 (0)
Tuomilehto, 2001[232] Uusitupa, 2009[233] Finnish Diabetes Prevention Study (FDPS)	G1: physical activity, weight reduction and dietary counseling intervention (n=257) G2: General diet & exercise (n=248)	10.6	G1: 6 (2.2 per 1000 person years) G2: 10 (3.8 per 1000 person years) HR, 0.57 (0.21-1.58)

Appendix E Table 5. Mortality Results From Trials Evaluating Interventions for People With Prediabetes (KQ 4)

Source First Author, Year Trial Name	G1 (N) G2 (N)	Followup (y)	Mortality G N (%), or G1% vs. G2%; HR (95% CI)
DREAM Trial Investigators, 2006[253] DREAM Trial Investigators, 2006[254] DREAM Trial Investigators, 2008[255] Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial	G1: Ramapril 15 mg/day (n=2623) G2: Placebo (n=2646) G3: Rosiglitazone 0.8mg/day (n=2635) G4: Placebo (n=2634) Patients randomized twice, to ramapril or placebo and rosiglitazone or placebo (2x2 factorial design)	3	All-cause mortality: G1 vs. G2 1.2% (31/2623) vs. 1.2% (32/2646) HR, 0.98 (0.60 to 1.61) G3 vs. G4 1.1% (30/2635) vs. 1.3% (33/2634) HR, 0.91 (0.56 to 1.49) CVD mortality: G1 vs. G2 0.5% (12/2623) vs. 0.4% (10/2646) HR, 1.21 (0.52 to 2.80) G3 vs. G4 0.5% (12/2635) vs. 0.4% (10/2634) HR, 1.20 (CI 0.52 to 2.77)
Kawamori, 2009[256]	G1: Voglibose 0.2 mg 3x/daily (n=897) G2: Placebo (n=883)	0.9	G1: 6 (0.7) G2: 0 (0)
le Roux, 2017[115] SCALE Obesity and Prediabetes Trial	G1: Liraglutide (starting at 0.6 mg daily; weekly 0.6 mg increases to 3.0 mg with standardized lifestyle counseling (n=1505) G2: Placebo with standardized lifestyle counseling (n=749)	3.3	All-cause mortality: G1: 2 (0.1) G2: 2 (0.3) CVD mortality: G1: 1 (0.1) G2: 0 (0)
Lindblad, 2011[258] The Nepi ANtidiabetes StudY (NANSY)	G1: glimepiride 1 mg/daily (n=136) G2: placebo (n=138)	3.7	All-cause mortality: G1: 5 (3.7) G2: 2 (1.4) CVD mortality: G1: 1 (0.7) G2: 2 (1.4)

Appendix E Table 5. Mortality Results From Trials Evaluating Interventions for People With Prediabetes (KQ 4)

Source First Author, Year Trial Name	G1 (N) G2 (N)	Followup (y)	Mortality G N (%), or G1% vs. G2%; HR (95% CI)
The NAVIGATOR Study Group, 2010[260] The NAVIGATOR Study Group, 2010[261] Currie, 2017[262] Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Trial*	G1: Nateglinide 60 mg/3 times daily (n=4645) G2: Placebo (n=4661) G3: Valsartan 160 mg/once daily (n=4631) G4: Placebo (n=4675)	6	All-cause mortality G1 vs. G2: 6.7% (310/4645) vs. 6.7% (312/4661) HR, 1.00 (0.85 to 1.17) G3 vs. G4: 6.4% (295/4631) vs. 7.0% (327/4675) HR, 0.90 (0.77 to 1.05) CVD mortality G1 vs. G2: 2.7% (126/4645) vs. 2.5% (118/4661) HR, 1.07 (0.83 to 1.38) G3 vs. G4: 2.8% (128/4631) vs. 2.5% (116/4675) HR, 1.09 (0.85 to 1.40) Renal mortality G3 vs. G4: 0.1% (4/4631) vs. 0.1% (4/4675) HR, 1.00 (0.25 to 3.98)
Nijpels, 2018[263] DAISI	G1: Acarbose 50 mg 3x daily (n=60) G2: Placebo (n=58)	3	G1: 1 (1.7) G2: 3 (5.2)
Ramachandran, 2009[265] IDPP-2	G1: Pioglitazone 30 mg daily plus lifestyle modification (n=204; 181 analyzed) G2: Placebo plus lifestyle (n=203;186 analyzed)	3	G1: 2 (1.1) G2: 1 (0.5)
Weber, 2016[222] Gokulakrishnan, 2017[223] Diabetes Community Lifestyle Improvement Program (D-CLIP)	G1: Stepwise intervention of adapted DPP lifestyle classes plus metformin 500 mg twice daily at 4 months if at high risk of developing diabetes (n=283) G2: Standard of care (n=295)	3	No deaths during the study period

* The NAVIGATOR Trial randomized participants twice, to nateglinide or placebo and valsartan or placebo using a 2x2 factorial design. All participants were also offered a lifestyle intervention program.

Abbreviations: CDQDPOS=China Da Qing Diabetes Prevention Outcomes Study; CI=confidence interval; CVD=cardiovascular disease; D-CLIP=Diabetes Community Lifestyle Improvement Program; DAISI=Dutch acarbose intervention study in persons with impaired glucose tolerance; DPP=Diabetes Prevention Program; DREAM=Diabetes Reduction Assessment with ramipril and rosiglitazone Medication; FDPS=Finnish Diabetes Prevention Study; G=Group; HR=hazard ratio; IDPP-2=Indian Diabetes Prevention Programme-2; IGT=impaired glucose tolerance; NANSY=The Nepi ANtidiabetes StudY; NAVIGATOR=Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; SCALE=Satiety and Clinical Adiposity–Liraglutide Evidence; ZPLS=Zensharen Study for Prevention of Lifestyle Diseases.

Appendix E Table 6. Cardiovascular Disease Events in Trials Evaluating Interventions for People With Prediabetes (KQ 4)

Source First Author, Year Trial Name	G1 (N) G2 (N)	Followup, Years	CVD Events G: N (%), or G1 vs. G2; HR (95% CI)
Ackermann, 2015[139] Reaching Out to Prevent Increases in Diabetes (RAPID)	G1: Group-based YMCA DPP intervention (n=257) G2: Usual care plus brief counseling and information on community resources (n=252)	1	Self-reported cardiovascular events* G1: 1 (0.5) G2: 2 (0.9) p=0.99
Diabetes Prevention Program Research Group, 2002[80] Diabetes Prevention Program Research Group, 2005[119] Diabetes Prevention Program Research Group, 2012[97] DPP	G1: Intensive lifestyle intervention (n=1,079) G2: Standard lifestyle recommendations plus metformin at a dose of 850 mg twice daily (n=1,073) G3: Standard lifestyle recommendation plus placebo twice daily (n=1,082)	3.2	Composite nonfatal CVD events G1: 24 (2.2%); 9.7 events per 1,000 patient-years G2: 16 (1.5%); 5.2 events per 1,000 patient-years G3: 18 (1.7%); 7.3 events per 1,000 patient-years No significant differences between placebo and either of the two groups
Morey, 2012[120] The Enhancing Fitness in Older Overweight Veterans with Impaired Glucose Tolerance (Enhanced Fitness) Trial	G1: Counseling intervention focused on physical activity (n=180) G2: Usual care control (n=122)	1	One person had a transient ischemic attack that resulted in a hospitalization, and one person was diagnosed with myocardial infarction. Unclear whether events were in intervention or usual care group.†
Oldroyd, 2001[212]	G1: Behavioral intervention group (n=39 randomized; 35 analyzed) G2: Control group (n=39 randomized; 32 analyzed)	0.5	Incident severe ischemic heart disease G1: 1 (2.86) G2: 0 (0)

Appendix E Table 6. Cardiovascular Disease Events in Trials Evaluating Interventions for People With Prediabetes (KQ 4)

Source First Author, Year Trial Name	G1 (N) G2 (N)	Followup, Years	CVD Events G: N (%), or G1 vs. G2; HR (95% CI)
Pan, 1997[225] Li, 2008[226] Li, 2014[227] Gong, 2019[228] China Da Qing Diabetes Prevention Outcomes Study (CDQDPOS)	G1: Combined 6-year lifestyle (diet, exercise, or diet+exercise) intervention: (n=438) G2: Control (n=138)	20, 30	20-year followup Incidence of any first CVD event‡ 41% vs. 44%; HR 0.98 (0.71 to 1.37) 30-year followup Incidence of CVD event 195 (44.5) vs, 80 (58); HR 0.74 (0.59 to 0.92) Women: 73 vs. 29; HR 0.69 (0.51 to 0.92) Men: 122 vs. 51; HR 0.80 (0.60 to 1.06) Stroke 156 (35.6) vs, 62 (44.9); HR 0.75 (0.59 to 0.96) Women: 55 (26.8) vs. 22 (37.3); HR 0.68 (0.48 to 0.96) Men: 101 (43.3) vs. 40 (50.6); HR 0.83 (0.61 to 1.11) Coronary heart disease 61 (13.9) vs, 26 (18.8); HR 0.73 (0.51 to 1.04) Women: 22 (10.7) vs. 7 (11.9); HR 0.92 (0.39 to 2.13) Men: 39 (16.7) vs. 19(24.1); HR 0.68 (0.43 to 1.10) Heart Failure 39 (8.9) vs. 16 (11.6); HR 0.71 (0.48 to 1.04) Women: 14 (6.8) vs. 6 (10.2); HR 0.60 (0.29 to 1.25) Men: 25 (10.7) vs. 10 (12.6); HR 0.81 (0.41 to 1.60)
Penn, 2009[264]	G1: Individual behavioral intervention (n=51) G2: Usual care and standard health promotion advice (n=51)	3.1	Cerebral infarction G1: 1 (0.8) G2: 0 (0.0)
Ramachandran, 2006[234] Indian Diabetes Prevention Programme	G1: Lifestyle intervention (n=133) G2: Metformin (n=133) G3: Lifestyle intervention+metformin (n=129) G4: Standard health care advice (n=136)	3	CVD events (not defined): G1: 4 G2: 0 G3: 5 G4: 2
Sakane, 2015[140] The Japan Diabetes Outcome Intervention Trial-1 (J-DOIT1)	G1: 1-year telephone-delivered lifestyle support intervention (n=1,240) G2: Control (n=1,367)	5.5	Ischemic heart disease: G1: 1 (0.08) G2: 2 (0.15) Stroke: G1: 3 (0.24) G2: 2 (0.15)

Appendix E Table 6. Cardiovascular Disease Events in Trials Evaluating Interventions for People With Prediabetes (KQ 4)

Source First Author, Year Trial Name	G1 (N) G2 (N)	Followup, Years	CVD Events G: N (%), or G1 vs. G2; HR (95% CI)
Tuomilehto, 2001[232] Uusitupa, 2009[233] Finnish Diabetes Prevention Study (FDPS)	G1: lifestyle intervention with ≥5% weight loss goal, individualized dietary and exercise information (n=257) G2: general information about diet and exercise (n=248)	10.6	Incident fatal and nonfatal CVD events based on hospitalization registry ICD codes (acute coronary events, coronary heart disease, stroke and hypertensive disease): G1: 22.9 per 1,000 person-years (57 events) G2: 22.0 per 1,000 person-years (54 events) HR 1.04 (0.72 to1.51)
Chiasson, 2002[235] Chiasson, 2003[236] STOP-NIDDM	G1: Acarbose (n=682) G2: Placebo (n=686)	3.3	Major CVD event (coronary heart disease, cardiovascular death, congestive heart failure, cerebrovascular event, and peripheral vascular disease): 2.2% (15/682) vs. 4.7% (32/686) HR 0.51 (0.28 to 0.95)
DeFronzo, 2011[251] Espinoza, 2016[252] Actos Now for Prevention of Diabetes Trial (ACT NOW)	G1: Pioglitazone 30 mg/day for one month, increased to 45 mg/day (n=303) G2: Placebo (n=299)	2.4	CVD system events 9% (26/303) vs. 8% (23/299) Atypical chest pain 0.33% (1/303) vs. 1.34% (4/299) Cardiac arrhythmia 1.65% (5/303) vs. 0.67% (2/299) Coronary artery bypass/revascularization 0.66% (2/303) vs. 2.01% (6/299) Coronary artery disease without revascularization 0.66% (2/303) vs. 0.33% (1/299) New or worsening angina 1.98% (6/303) vs. 1.34% (4/299) New or worsening CHF 0.33% (1/303) vs. 0.33% (1/299) Nonfatal MI 0.66% (2/303) vs. 0.33% (1/299) Peripheral vascular disease with claudication or revascularization 1.98% (6/303) vs. 0.00% (0/299) TIA 0.33% (1/303) vs. 0.33% (1/299) Malignant hypertension 0.00% (0/303) vs. 0.33% (1/299)

Appendix E Table 6. Cardiovascular Disease Events in Trials Evaluating Interventions for People With Prediabetes (KQ 4)

Source First Author, Year Trial Name	G1 (N) G2 (N)	Followup, Years	CVD Events G: N (%), or G1 vs. G2; HR (95% CI)
DREAM Trial Investigators, 2006[253] DREAM Trial Investigators, 2006[254] DREAM Trial Investigators, 2008[255] Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial	G1: Ramapril 15 mg/day (n=2,623) G2: Placebo (n=2,646) G3: Rosiglitazone 0.8mg/day (n=2,635) G4: Placebo (n=2,634) Patients randomized twice, to Ramipril or placebo and rosiglitazone or placebo due to 2x2 factorial design	3	Cardiovascular composite events incidence[§] G1 vs.G2 2.6% (69/2623) vs. 2.4% (64/2646); HR 1.09 (0.78 to 1.53) G3 vs. G4 2.9% (77/2635) vs. 2.1% (56/2634); HR 1.38 (CI 0.98 to 1.95) MI: G1 vs. G2 0.5% (14/2623) vs. 0.4% (11/2646); HR 1.29 (0.59 to 2.84) G3 vs. G4 0.6% (16/2635) vs. 0.3% (9/2634); HR 1.78 (0.79 to 4.03) Stroke: G1 vs. G2 0.2% (4/2623) vs. 0.3% (8/2646); HR 0.50 (0.15 to 1.66) G3 vs. G4 0.3% (7/2635) vs. 0.2% (5/2634); HR 1.40 (0.44 to 4.40) Congestive heart failure: G1 vs. G2 0.5% (12/2623) vs. 0.2% (4/2646); HR 3.06 (0.99 to 9.48) G3 vs. G4 0.5% (14/2635) vs. 0.1% (2/2634); HR 7.04 (1.60 to 31.0) New angina: G1 vs. G2 0.9% (24/2623) vs. 0.8% (20/2646); HR 1.21 (0.67 to 2.19) G3 vs. G4 0.9% (24/2635) vs. 0.8% (20/2634); HR 1.20 (CI 0.66 to 2.17) Cardiovascular death, MI, stroke: G1 vs. G2 1% (27/2623) vs. 1.1% (29/2646); HR 0.94 (0.56 to 1.59) G3 vs. G4 1.3% (33/2635) vs. 0.9% (23/2634); HR 1.43 (CI 0.84 to 2.44)
le Roux, 2017[115] SCALE Obesity and Prediabetes Trial	G1: Daily liraglutide intervention with standardized lifestyle counseling (n=1,505) G2: Placebo with standardized lifestyle counseling (n=749)	3.3	Nonfatal myocardial infarctions: G1: 3 (0.2%) G2: 1 (0.1%) Nonfatal strokes: G1: 2 (0.1%) G2: 2 (0.3%)

Appendix E Table 6. Cardiovascular Disease Events in Trials Evaluating Interventions for People With Prediabetes (KQ 4)

Source First Author, Year Trial Name	G1 (N) G2 (N)	Followup, Years	CVD Events G: N (%), or G1 vs. G2; HR (95% CI)
The NAVIGATOR Study Group, 2010[260] The NAVIGATOR Study Group, 2010[261] Currie, 2017[262] Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Trial[ll]	G1: Nateglinide 60 mg/3 times daily (n=4,645) G2: Placebo (n=4,661) G3: Valsartan 160 mg/once daily (n=4,631) G4: Placebo (n=4,675)	6	Fatal or nonfatal myocardial infarction G1 vs. G2: 2.9% (135/4645) vs. 3.1% (143/4,661) HR 0.95 (0.75 to 1.20) G3 vs. G4: 3% (138 /4631) vs. 3% (140/4,675) HR 0.97 (0.77 to 1.23) Fatal or nonfatal stroke G1 vs. G2: 2.4% (111/4645) vs. 2.7% (126/4,661) HR 0.89 (0.69 to 1.15) G3 vs. G4: 2.3% (105/4631) vs. 2.8% (132/4,675) HR 0.79 (0.61 to 1.02) Hospitalization for unstable angina G1 vs. G2: 4.8% (222/4645) vs. 5.4% (254/4,661) HR 0.87 (0.73 to 1.05) G3 vs. G4: 5.2% (242/4631) vs. 5.0% (234/4,675) HR 1.02 (0.86 to 1.23) Hospitalization for heart failure G1 vs. G2: 1.8% (85/4645) vs. 2.1% (100/4,661) HR 0.85 (0.64 to 1.14) G3 vs. G4: 2% (91/4631) vs. 2% (94/4,675) HR 0.97 (0.72 to 1.29) Arterial revascularization G1 vs. G2: 7.1% (332/4,645) vs. 6.8% (315/4,661) HR 1.06 (0.91 to 1.24) G3 vs. G4: 6.8% (316/4,631) vs. 7.1% (331/4,675) HR 0.94 (0.80 to 1.10) Hospitalization for a cardiovascular reason G1 vs. G2: 19% (883/4,645) vs. 18.9% (882/4,661) HR 1.00 (0.91 to 1.09) G3 vs. G4: 19.1% (886/4,631) vs. 18.8% (879/4,675) HR 1.00 (0.91 to 1.10)
Ramachandran, 2009[265] IDPP-2	G1: lifestyle modification plus pioglitazone, 30 mg (n=204; 181 analyzed) G2: lifestyle modification plus placebo (n=203; 186 analyzed)	3	Heart disease requiring hospitalization: G1: 2 (1.1%) G2: 1 (0.5%)

Appendix E Table 6. Cardiovascular Disease Events in Trials Evaluating Interventions for People With Prediabetes (KQ 4)

Source First Author, Year Trial Name	G1 (N) G2 (N)	Followup, Years	CVD Events G: N (%), or G1 vs. G2; HR (95% CI)
Zinman, 2010[267] CAnadian Normoglycemia Outcomes Evaluation trial (CANOE)	G1: rosiglitazone 2 mg and metformin 500 BID and lifestyle intervention (n=103) G2: placebo and lifestyle intervention (n=104)	3.9	Myocardial infarction: G1: 1 G2: 0 Heart failure: G1: 1 G2: 0

* No additional details provided, including categories or types of cardiovascular events elicited from participants.
† The events were considered adverse events possibly related to the increae in physical activity (per study authors).
ǂ Defined as first nonfatal or fatal cardiovascular events including myocardial infarction, sudden death, stroke, or amputation; authors also defined myocardial infarction cases on the basis of ECG results obtained during the physical examination on study followup visits.
§ Defined as first occurrence of CVD death, cardiac resuscitation, nonfatal myocardial infarction, stroke, revascularization procedure, new stable or unstable angina with documented ischemia, or heart failure.
ǁ The NAVIGTOR Trial randomized participants twice to nateglinide or placebo and valsartan or placebo using a 2x2 factorial design. All participants were also offered a lifestyle intervention program.

Abbreviations: ACT NOW=Actos Now for Prevention of Diabetes Trial; CANOE=CAnadian Normoglycemia Outcomes Evaluation; CDQDPOS=China Da Qing Diabetes Prevention Outcomes Study; CI=confidence interval; CVD=cardiovascular disease; DPP=Diabetes Prevention Program; ECG=electrocardiogram; FDPS=Finnish Diabetes Prevention Study; G=group; HR=hazard ratio; ICD=International Classification of Diseases; IDPP-2=Indian Diabetes Prevention Programme-2; J-DOIT1=The Japan Diabetes Outcome Intervention Trial-1; KQ=key question; N=number; NAVIGATOR=Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; RAPID=Reaching Out to Prevent Increases in Diabetes.

Appendix E Table 7. Quality of Life, Renal Disease, and Other Health Outcome Results From Trials Evaluating Interventions for People With Prediabetes (KQ 4)

Source First Author, Year Trial Name	Groups (N) Followup	Health Outcome G1 N (%) G2 N (%)
Davies, 2016[86] Gray, 2016[118] Let's Prevent Diabetes	G1: Let's Prevent Diabetes lifestyle intervention (n=447) G2: Usual care (all received booklet with DM information) (n=433) 3 years	Quality of Life Score (15 dimensional), Median (IQR) G1 Baseline: 0.90 (0.82, 0.95) G1 36 months:0.91 (0.84, 0.96) G2 Baseline:0.91 (0.84, 0.96) G2 36 months: 0.89 (0.82, 0.95) Overall Mean Effect* 0.01 (95% CI, 0.001, 0.02)
Diabetes Prevention Program Research Group, 2002[80] Diabetes Prevention Program Research Group, 2005[119] Diabetes Prevention Program Research Group, 2012[97] DPP	G1: Intensive lifestyle intervention (n =1079) G2: Standard lifestyle recommendations plus metformin at a dose of 850 mg twice daily (n=1073) G3: Standard lifestyle recommendation plus placebo twice daily (n =1082) 3.2 years	Difference in Mean Changes from baseline in intervention group compared to placebo group (SD)† Short Form-6D, G1 vs. G2: 0.0084 (0.0041) vs. 0.0019 (0.0041); p<0.05‡ SF-36 Physical component summary (SD), G1 vs. G2: 1.57 (0.30) vs. 0.15 (0.30); p<0.01 SF-36 Mental component summary, G1 vs. G2: -0.29 (0.32) vs. 0.22 (0.32) SF-36 domain scores (SD), G1 vs. G2: Physical function: 3.58 (0.71) vs. 0.13 (0.71); p<0.01 Role Physical : 1.86 (0.99) vs. 1.32 (0.99) Body pain: 1.93 (0.78) vs. 0.50 (0.78); p<0.01 General health: 3.23 (0.66) vs. 0.06 (0.66); p<0.01 Vitality: 2.05 (0.77) vs. 0.09 (0.76); p<0.01 Social functioning: 0.97 (0.66) vs. 0.81 (0.66) Role emotional: 0.20 (0.95) vs. 0.78 (0.95) Mental health: -0.50 (0.57) vs. 0.32 (0.57)
Diabetes Prevention Program Research Group, 2012[237] Diabetes Prevention Program Research Group, 2009[146] Diabetes Prevention Program Research Group, 2015[79] Apolzan, 2019[238] Diabetes Prevention Program Research Group, 2019[81] DPPOS	G1: Standard lifestyle recommendations plus 850 mg metformin twice daily for 3.2 y; then open label metformin for additional 7-8 y and offered original DPP lifestyle intervention (n=924) G2: Standard lifestyle recommendation plus placebo twice daily and offered original DPP lifestyle intervention (n=932) 15 years (double blind phase 3.2 years)	Participants whose most recent HbA1c was ≥ 6.5%: Retinopathy: G1 vs. G3, RR 0.61 (0.37-1.01), p =0.05 Neuropathy: G1 vs. G3, RR 0.38 (0.19-0.75), p =0.01 Nephropathy: Incidence shown in figure only, difference between intervention groups and placebo not statistically significant

Appendix E Table 7. Quality of Life, Renal Disease, and Other Health Outcome Results From Trials Evaluating Interventions for People With Prediabetes (KQ 4)

Source First Author, Year Trial Name	Groups (N) Followup	Health Outcome G1 N (%) G2 N (%)
Kulzer, 2009[112] Prevention of Diabetes Self-Management Program (PREDIAS)	G1: PREDIAS group lifestyle intervention based on the Diabetes Prevention Program (n=91) G2: Control (received the PREDIAS written information and patient materials (n=91) 1 year	World Health Organization-Five Well-Being Index (WHO-5), change from baseline: G1: 1.4 (3.9), p=0.015 G2: 0.0 (4.2), p=0.901 Between group, p=0.101
Morey, 2012[120] The Enhancing Fitness in Older Overweight Veterans with Impaired Glucose Tolerance (Enhanced Fitness) Trial	G1: Counseling intervention focused on physical activity (n=180) G2: Usual care control (n=122) 1 year	SF-36 General Health G1 Baseline: 61.39 (39.40) G1 3 Months: 59.84 (42.59) G1 12 Months: 58.12 (42.29) G2 Baseline: 65.78 (39.52) G2 3 Months: 66.37 (42.75) G2 12 Months: 61.68 (41.82) P =0.92 SF-36 Physical Function G1 Baseline: 62.94 (20.97) G1 3 Months: 63.97 (21.30) G1 12 Months: 62.52 (21.79) G2 Baseline: 66.88 (20.60) G2 3 Months: 67.08 (19.86) G2 12 Months: 66.24 (20.91)P =0.09
le Roux, 2017[115] SCALE Obesity and Prediabetes Trial	G1: Liraglutide (starting at 0.6 mg daily; weekly 0.6 mg increases to 3.0 mg with standardized lifestyle counseling (n=1505) G2: Placebo with standardized lifestyle counseling (n=749) 3.3 year	SF-36 Physical component summary, mean change from baseline score (SD) G1: 3.1 (7.3) G2: 2.6 (7.6) RD, 0.9 (0.2 to 1.6) p=0.0156 SF-36 Mental component summary, mean change from baseline score (SD) G1: -0.5 (8.7) G2: -1.4 (9.2) RD 0.8 (-0.1 to 1.6) p=0.08

Appendix E Table 7. Quality of Life, Renal Disease, and Other Health Outcome Results From Trials Evaluating Interventions for People With Prediabetes (KQ 4)

Source First Author, Year Trial Name	Groups (N) Followup	Health Outcome G1 N (%) G2 N (%)
The NAVIGATOR Study Group, 2010[260] The NAVIGATOR Study Group, 2010[261] Currie, 2017[262] Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Trial	G1: Nateglinide 60 mg/3 times daily (n=4645) G2: Placebo (n=4661) G3: Valsartan 160 mg/once daily (n=4631) G4: Placebo (n=4675) Patients randomized twice, to nateglinide or placebo and valsartan or placebo due to 2x2 factorial design 5 years	NR End-stage renal disease (ESRD) G3: 5 (0.1) G4: 5 (0.1) HR, 0.96 (0.28 to 3.31) Amputations: G1: 1 (<0.1) G2: 6 (0.1) G3: 5 (0.1) G4: 2 (<0.1)
Pan, 1997[225] Li, 2008[226] Li, 2014[227] Gong, 2019[228] China Da Qing Diabetes Prevention Outcomes Study (CDQDPOS)	G1: Combined 6-year lifestyle (diet, exercise, or diet+exercise) intervention: (n=438) G2: Control (n=138) 30 years	Composite Microvascular Disease[§] G1: 76 (17.4) G2: 33 (23.9) HR, 0.65 (0.45 to 0.95) Women: 42 vs. 16; HR, 0.69 (0.37 to 1.32) Men: 34 vs. 17; HR, 0.61 (0.35 to 1.06) Retinopathy[‖] G1: 56 (12.8) G2: 26 (18.8) HR, 0.60 (0.38 to 0.95) Women: 34 (16.6) vs. 13 (22.0); HR, 0.71 (0.34 to 1.48) Men: 22 (9.4) vs. 13 (16.4); HR, 0.50 (0.25 to 1.002) Nephropathy[¶] G1: 16 (3.6) G2: 7 (5.1) HR, 0.68 (0.36 to 1.28) Women: 8 (3.9) vs. 1(1.7); HR, 2.18 (0.28 to 16.72) Men: 8 (3.4) vs. 6 (7.6); HR, 0.43 (0.18 to 1.04) Neuropathy[#] G1: 14 (3.2) G2: 7 (5.1) HR, 0.57 (0.24 to 1.36) Women: 4 (2.0) vs. 3 (5.1); HR, 0.35 (0.08 to 1.63) Men: 10 (4.3) vs. 4 (5.1); HR, 0.79 (0.21 to 2.95)

* Adjusted for baseline value and clusters.

† Scores worsend from baseline in all groups for the SF-6D and SF-36 PCS and MCS; the decline for SF-6D and PCS was lower in the intensive lifestyle group than placebo or metformin groups but did not meet the minimally important difference of 3% (defined by authors).

‡ Difference between grous remains statisically significant when controlling for age, sex, race/ethnicity, baseline weight and physical activity, medical and psychiatric comorbidiy but magnitude is smalle: 0.009 (SD 0.14).

Appendix E Table 7. Quality of Life, Renal Disease, and Other Health Outcome Results From Trials Evaluating Interventions for People With Prediabetes (KQ 4)

[§]Composite microvascular disease defined as an aggregate of retinopathy, nephropathy, or neuropathy.
[l] Retinopathy defined as a history of photocoagulation, blindness from retinal disease, or proliferative retinopathy.
[¶] Nephropathy defined as a history of end stage renal disease, renal dialysis, renal transplantation, death from chronic kidney disease.
[#] Neuropathy defined as a history of lower extremity ulceration, gangrene, or amputation.

Abbreviations: CI=confidence interval; DM=diabetes mellitus; DPP=Diabetes Prevention Program; DPPOS=Diabetes Prevention Program; ESRD=end-stage renal disease; IQR=interquartile ratio; N=Number; NAVIGATOR=Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; PREDIAS=Prevention of Diabetes Self-Management Program; SCALE=Satiety and Clinical Adiposity–Liraglutide Evidence; SD=standard deviation; U.K.=United Kingdom; VDT=Vibration Detection Threshold; WHO=World Health Organization.

Appendix E Table 8. Mortality and Cardiovascular Event Outcomes Among Individuals With Newly Diagnosed Type 2 Diabetes (KQ 5)

First Author, Year Trial Name Country	G1 (N) G2 (N)	Mortality G1 vs. G2; HR (95% CI)	CVD Events G1 vs. G2; HR (95% CI)
Yang, 2013[276] China	G1: 75 G2: 75	NR	Myocardial Infarction 7-year followup (per protocol) G1: 1//75 (1.3%) G2: .1/75 (1.3%) RR, 1.0 (0.06 to 15.7) Transient Ischemic Attack 7-year followup (per protocol) G1: 0//75 (0%) G2: 2/75 (2.7%) RR, 2.0 (0.01 to 4.1)
UKPDS Group 1998[1] UK Prospective Diabetes Study (UKPDS) U.K.	G1: 2729 G2: 619 G3: 615 G4: 911 G5a: 1138 G5b: 896	Median 10.0-year followup G1 vs. G5a All-cause mortality: 18% vs. 19%; RR, 0.94 (0.80 to 1.10) Diabetes-related death: 10% vs. 11%; RR, 0.90 (0.73 to 1.11) Fatal myocardial infarction: 7.6% vs. 7.9%; RR, 0.94 (0,68 to 1.30) Fatal stroke: 1.6% vs.1.3%; RR, 1.17 (0.54 to 2.54) Sudden death: 0.88% vs. 1.6%; RR, 0.54 (0.24 to 1.21) Median 11.1-year followup G2 vs. G5b All-cause mortality: 22% vs. 21%; RR, 1.02 (0.82 to 1.27) Diabetes-related death: 12% vs.13%; RR, 0.92 (0.68 to 1.23) Fatal myocardial infarction: 9.0% vs. 8.9%; RR, 0.99 (0.64 to 1.56) Fatal stroke: 1.5% vs.1.3%; RR, 1.06 (0.34 to 3.30) Sudden death: 0.97% vs. 1.7%; RR, 0.57 (0.16 to 1.97) G3 vs. G5b All-cause mortality: 20% vs. 21%; RR, 0.91 (0.73 to 1.15) Diabetes-related death: 12% vs.13%; RR, 0.92 (0.69 to 1.24) Fatal myocardial infarction: 7.5% vs. 8.9%; RR, 0.82 (0,51 to 1.33) Fatal stroke: 2.6% vs.1.3%; RR, 1.90 (0.71 to 5.09) Sudden death: 1.1% vs. 1.7%; RR, 0.67 (0.21 to 2.16)	Median 10.0-year followup G1 vs. G5a Myocardial infarction: 14% vs. 16%; RR, 0.84 (0.71 to 1.00) Stroke:5.4 % vs. 4.9%; RR, 1.11 (0.81 to 1.51) Median 11.1-year followup G2 vs. G5b Myocardial infarction: 16% vs. 18%; RR, 0.87 (0.68 to 1.12) Stroke: 5.3% vs. 5.2%; RR, 1.01 (0.65 to 1.58) G3 vs. G5b Myocardial infarction: 15% vs. 18%; RR, 0.78 (0.60 to 1.01) Stroke: 7.3% vs.5.2%; RR, 1.38 (0.52 to 2.08) G4 vs. G5b Myocardial infarction: 16% vs. 18%; RR, 0.87 (0.70 to 1.09) Stroke: 4.6% vs. 5.2%; RR, 0.86 (0.57 to 1.31)
UKPDS Group 1998[1] UKPDS U.K. (continued)		G4 vs. G5b All-cause mortality: 20% vs. 21%; RR, 0.93 (0.76 to 1.14) Diabetes-related death: 12% vs.13%; RR, 0.90 (0.69 to 1.18) Fatal myocardial infarction: 8.7% vs. 8.9%; RR, 0.96 (0,63 to 1.43) Fatal stroke: 1.5% vs. 1.3%; RR, 1.13 (0.41 to 3.12) Sudden death: 0.99% vs. 1.7%; RR, 0.58 (0.19 to 1.70)	

Appendix E Table 8. Mortality and Cardiovascular Event Outcomes Among Individuals With Newly Diagnosed Type 2 Diabetes (KQ 5)

First Author, Year Trial Name Country	G1 (N) G2 (N)	Mortality G1 vs. G2; HR (95% CI)	CVD Events G1 vs. G2; HR (95% CI)
UKPDS Group, 1998[277] UKPDS† Metformin for overweight substudy U.K.	G1: 342 G2: 411	10-year followup results (G1 vs. G2) All-cause mortality: 50/342 (14.6) vs. 89/411 (21.7); RR, 0.64 (0.45 to 0.91) Diabetes-related death: 28/342 (8.2) vs. (13.4) 55/411; RR, 0.58 (0.37 to 0.91)	10-year followup results (G1 vs. G2) MI: 39 (11.4) vs. 73 (17.8); RR, 0.61 (0.41 to 0.89) Stroke: 12/342 (3.5) vs. 23/411 (5.6); RR, 0.59 (0.29 to 1.18)
Holman, 2008[278] UKPDS U.K.	G1: 2729 G2: 342 G3: 1138 G4: 411	10-years post-trial monitoring results G1 vs. G3 All-cause mortality: 43% (1162/2729) vs. 47% (537/1138); RR, 0.87, (0.79 to 0.96) Diabetes-related death: 23% (618/2729) vs. 26% (297/1138); RR, 0.83 (0.73 to 0.96) G2 vs. G4 All-cause mortality: 44% (152/342) vs. 53% (217/411); RR, 0.73 (0.59 to 0.89) Diabetes-related death: 24% (81/342) vs. 29% (120/411); RR, 0.70 (0.53 to 0.92)	10-years post-trial monitoring results G1 vs. G3 Myocardial infarction: 25% (678/2729) vs. 28% (319/1138); RR, 0.85 (0.74 to 0.97) Stroke: 9.5% (38/2729) vs. 10.2% (34/1138); RR, 0.91 (0.73 to 1.13) G2 vs. G4 Myocardial infarction: 24% (81/342) vs. 31% (126/411); RR, 0.67 (0.51 to 0.89) Stroke: 9.9% (34/342) vs. 10.2% (42/411); RR, 0.80 (0.50 to 1.27)
Holman, 2008[92] UKPDS Group, 1998[279] Hypertension in diabetes Study embedded in UKPDS	G1: 758 G2: 390 Post-trial monitoring group (n=884)	9-year followup G1 vs. G2 All-cause mortality: 17.7% (134/758) vs. 21.3% (83/390); RR, 0.82 (0.63 to 1.08) Diabetes-related death: 10.8% (82/758) vs. 15.9% (62/390) RR, 0.68 (0.49 to 0.94) Post-trial monitoring 10 years results G1 vs. G2 All-cause mortality: 49% (373/758) vs. 54% (211/390); RR, 0.89 (0.75 to 1.06) Diabetes-related death: 27% (203/758) vs. 31% (122/390) RR, 0.84 (0.67 to 1.05)	9-year followup G1 vs. G2 Myocardial infarction: 14.1% (107/758) vs. 17.7% (69/390) RR, 0.79, (0.59 to 1.07) Stroke: 5.0% (38/758) vs. 8.7% (34/390); RR, 0.56 (0.35 to 0.89) Post-trial monitoring 10 years results G1 vs. G2 Myocardial infarction: 27% (205/758) vs. 29.5% (115/390); RR, 0.90 (0.71 to 1.13) Stroke: 12% (90/758) vs. 15% (58/390); RR, 0.77 (0.55 to 1.07)
Davies, 2008[93] Khunti, 2012[94] DESMOND U.K.	G1: 437 G2: 387	G1 vs. G2 All-cause mortality at 4-month: 0% (0/437) vs. 0.5% (2/387) RR, 0.18 (0.01 to 3.68) All-cause mortality at 8-months: 0.5% (2/437) vs. 1% (4/387) RR, 0.44 (0.08 to 2.40) All-cause mortality at 12-months: 0.5% (2/437) vs. 1.3% (5/387) RR, 0.35 (0.07 to 1.82) All-cause mortality at 3-yr f/u: 3.9% (15/437) vs. 2.5% (11/387) RR, 1.21 (0.56 to 2.60)	NR

Abbreviations: CI=confidence interval; CVD=cardiovascular disease; DESMOND=Diabetes education and self management for ongoing and newly diagnosed programme; G=group; HR=hazard ratio; KQ=key question; NR=not reported; RR=relative risk; U.K.=United Kingdom; UKPDS=United Kingdom Prospective Diabetes Study; vs.=versus.

Appendix E Table 9. Quality of Life Outcomes Among Individuals With Newly Diagnosed Type 2 Diabetes (KQ 5)

Source First Author, year Trial Name Country	Groups N	Quality of Life
Davies, 200893 Khunti, 2012[94] DESMOND U.K.	G1: 437 G2: 387	Quality of life, WHOQOL-BREF Median score (IQR) (G1, n=299; G2, n=237) Overall satisfaction with quality of life: G1 3 years: 4.0 (4, 4) G2 3 years: 4.0 (4, 5) Model summary coefficient (95% CI): -0.04 (-0.17 to 0.08) p-value 0.48 Overall satisfaction with health: G1 3 years: 4.0 (3, 4) G2 3 years: 4.0 (3, 4) Model summary coefficient (95% CI): -0.01 (-0.20 to 0.18) p-value 0.94 Physical quality of life: G1 3 years: 26.0 (22, 29) G2 3 years: 25.5 (22,29) Model summary coefficient (95% CI): -0.15 (-0.84 to 0.55) p-value 0.68 Psychological quality of life: G1 3 years: 23.0 (20 to 25) G2 3 years: 23.0 (20 to 25) Model summary coefficient (95% CI): -0.10 (-0.61 to 0.42) p-value 0.71 Social quality of life: G1 3 years: 11.0 (9, 12) G2 3 years: 11.0 (10,12) Model summary coefficient (95% CI): 0.05 (-0.37 to 0.47) p-value 0.81 Environmental quality of life: G1 3 years: 31.0 (28,34) G2 3 years: 31.0 (28, 34) Model summary coefficient (95% CI): -0.01 (-0.67 to 0.65) p-value 0.98 No differences between groups in the WHOQOL-Brief at 4, 8, and 12-months f/u (data not shown)

Abbreviations: CI=confidence interval; DESMOND=Diabetes education and self management for ongoing and newly diagnosed programme; IQR=interquartile range; N=Number; QoL=quality of life; U.K.=United Kingdom; WHOQOL-BREF=World Health Organization Quality of Life.

Appendix E Table 10. Chronic Kidney Disease, Amputations, and Visual Impairment Outcomes Among Individuals With Newly Diagnosed Type 2 Diabetes (KQ 5)

Source First Author, Year Trial Name Country	Groups N	Chronic Kidney Disease G1 N (%) G2 N (%) HR (95% CI)	Amputations G1 N (%) G2 N (%) HR (95% CI)	Visual Impairment G1 N (%) G2 N (%) HR (95% CI)
UKPDS Group 1998[1] U.K. Prospective Diabetes Study (UKPDS) U.K.	G1: 2729 G2: 619 G3: 615 G4: 911 G5a: 1138 G5b: 896	10-year followup Renal Failure G1 vs. G5a: G1: 16 (0.6) G5a: 9 (0.8) RR, 0.73 (0.25 to 2.14) G2 vs. G5b: G2: 6 (0.2) G5b: 8 (0.9) RR, 1.09 (0.27 to 4.37) G3 vs. G5b: G3: 4 (0.7) G5b: 8 (0.9) RR, 0.72 (0.15 to 3.50) G4 vs. G5b: G4: 5 (0.5) G5b: 8 (0.9) RR, 0.61 (0.14 to 2.64)	10-year followup G1 vs. G5a: G1: 27 (1.0) G5a: 18 (1.6) RR, 0.61 (0.28 to 1.33) G2 vs. G5b: G2: 5 (0.8) G5b: 15 (1.7) RR, 0.47 (0.12 to 1.77) G3 vs. G5b: G3: 5 (0.8) G5b: 15 (1.7) RR, 0.48 (0.13 to 1.80) G4 vs. G5b: G4: 15 (1.6) G5b: 15 (1.7) RR, 0.95 (0.37 to 2.45)	10-year followup Retinal photocoagulation G1 vs. G5a: G1: 207 (7.6) G5a: 117 (10.3) RR, 0.71 (0.53 to 0.96) G2 vs. G5b: G2: 55 (8.9) G5b: 101 (11.3) RR, 0.77 (0.50 to 1.18) G3 vs. G5b: G3: 45 (7.3) G5b: 101 (11.3) RR, 0.63 (0.40 to 1.00) G4 vs. G5b: G4: 72 (7.9) G5b: 101 (11.3) RR, 0.67 (0.45 to 0.99) Vitreous Hemorrhage G1 vs. G5a: G1: 19 G5a: 10 RR, 0.77 (0.28 to 2.11) G2 vs. G5b: G2: 8 (1.3) G5b: 10 (1.1) RR, 1.14 (0.34 to 3.86) G3 vs. G5b: G3: 6 (1.0) G5b: 10 (1.1) RR, 0.73 (0.18 to 2.98) G4 vs. G5b: G4: 5 (0.5) G5b: 10 (1.1) RR, 0.48 (0.12 to 1.96) Blind in one eye G1 vs. G5a: G1: 78 (2.8) G5a: 38 (3.2) RR, 0.84 (0.51 to 1.40) G2 vs. G5b: G2: 21 (3.4) G5b: 36 (4.0) RR, 0.64 (0.41 to 1.70) G3 vs. G5b: G3: 15 (2.4) G5b: 36 (4.0) RR, 0.61 (0.27 to 1.34) G4 vs. G5b: G4: 29 (3.2) G5b: 36 (4.0) RR, 0.75 (0.39 to 1.43)

Appendix E Table 10. Chronic Kidney Disease, Amputations, and Visual Impairment Outcomes Among Individuals With Newly Diagnosed Type 2 Diabetes (KQ 5)

Source First Author, Year Trial Name Country	Groups N	Chronic Kidney Disease G1 N (%) G2 N (%) HR (95% CI)	Amputations G1 N (%) G2 N (%) HR (95% CI)	Visual Impairment G1 N (%) G2 N (%) HR (95% CI)
UKPDS Group 1998[1] U.K. Prospective Diabetes Study (UKPDS)* U.K. (continued)				Cataract extraction G1 vs. G5a: G1: 149 (2.8) G5a: 80 (3.2) RR, 0.76 (0.53 to 1.08) G2 vs. G5b: G2: 33 (5.3) G5b: 70 (7.8) RR, 0.67 (0.39 to 1.15) G3 vs. G5b: G3: 44 (7.2) G5b: 70 (7.8) RR, 0.91 (0.55 to 1.50) G4 vs. G5b: G4: 50 (5.5) G5b: 70 (7.8) RR, 0.68 (0.42 to 1.10)
UKPDS Group, 1998[277] UKPDS* Metformin for overweight substudy U.K.	G1: 342 G2: 411	NR	Median followup 10.7 years G1 vs. G2 6/342 (1.8) vs. 9/411 (2.2); RR, 0.74 (0.19 to 2.89)	Blindness in one eye G1 vs. G2 12/342 (3.5) vs. 13 (3.2); RR, 1.07 (0.38 to 2.99)
Holman, 2008[92] UKPDS Group, 1998[279] Hypertension in diabetes Study embedded in UKPDS	G1: 758 G2: 390 Post-trial monitoring group (n=884)	G1 vs. G2 Renal Failure 9-year followup 1.1% (8/758) vs. 1.8% (7/390) RR, 0.53 (0.15 to 2.21) Urinary albuminuria ≥50 mg/l At 3 years 18.3% (113/618) vs. 23.7% (75/317) RR, 0.77 (0.55 to 1.09) At 6 years 20.3% (110/543) vs. 28.5% (78/274) RR, 0.71 (0.51 to 0.99) At 9 years 28.8% (86/299) vs. 33.1% (55/166) RR, 0.87 (0.60 to 1.26)	9-year followup G1 vs. G2 1.1% (8/758) vs. 2.1% (8/390) RR, 0.51 (0.14 to 1.86)	G1 vs. G2 Progression of retinopathy ≥2 steps At Median 1.5 years 20.2% (93/461) vs. 23.1% (56/243) RR, 0.88 (0.60 to 1.29) At Median 4.5 years 27.5% (113/411) vs. 36.7% (76/207) RR, 0.75 (0.55 to 1.02) At Median 7.5 years 34.0% (102/300) vs. 51.3% (78/152) RR, 0.66 (0.50 to 0.89) Deterioration in vision by ≥3 ETDRS lines Median 1.5 years 5.4% (31/575) vs. 6.8% (20/293)

Appendix E Table 10. Chronic Kidney Disease, Amputations, and Visual Impairment Outcomes Among Individuals With Newly Diagnosed Type 2 Diabetes (KQ 5)

Source First Author, Year Trial Name Country	Groups N	Chronic Kidney Disease G1 N (%) G2 N (%) HR (95% CI)	Amputations G1 N (%) G2 N (%) HR (95% CI)	Visual Impairment G1 N (%) G2 N (%) HR (95% CI)
Holman, 2008[92] UKPDS, 2008[279] Hypertension in diabetes Study embedded in UKPDS† (continued)		Urinary albuminuria ≥300 mg/l At 3 years 3.2% (20/618) vs. 5.7% (18/317) RR, 0.57 (0.25 to 1.29) At 6 years 5.3% (29/543) vs. 8.6% (24/274) RR, 0.61 (0.31 to 1.21) At 9 years 7.0% (21/299) vs. 6.6% (11/166) RR, 1.06 (0.42 to 2.67)		RR, 0.79 (0.39 to 1.62) Median 4.5 years 7.5% (39/523) vs. 8.9% (23/257) RR, 0.83 (0.44 to 1.59) Median 7.5 years 10.2% (34/332) vs. 19.4% (35/180) RR, 0.53 (0.30 to 0.93)

Abbreviations: CI=confidence interval; ETDRS=Early Treatment Diabetic Retinopathy Study; G=group; HR=hazard ratio; KQ=key question; N=Number; NR=not reported; RR=relative risk; U.K.=United Kingdom; UKPDS=United Kingdom Prospective Diabetes Study; vs.=versus.

Appendix E Table 11. Harms Reported in Included Trials of Interventions for People With Screen-Detected or Newly Diagnosed Type 2 Diabetes Reporting Harms (KQ 6)

Author, Year Trial Name Country	Mortality G1 (N) G2 (N) HR (95% CI)	Hypoglycemic Events Requiring Medical Attention G1 N (%) G2 N (%) HR (95% CI)	All Cause Withdrawals G1 N (%) G2 N (%) HR (95% CI)	Other Adverse Events G1 N (%) G2 N (%) HR (95% CI)
Davies, 2008[93] Khunti, 2012[94] DESMOND U.K.	NR	NR	G1 21/437 (4.8) G2 23/387 (5.9) RR, 0.81 (95% CI 0.45 to 1.44)	NR
van den Donk, 2010[95] Janssen, 2009[117] ADDITION-Netherlands	NR	G1 1/255 (0.4) G2 0/243 (0)	G1: 5/255 (2) G2: 2/243 (1) RR, 2.38 (0.47 to 12.16)	
U.K. Prospective Diabetes Study (UKPDS) Group, 1998[1] U.K.	Death from hypoglycemia G1 vs. G5a: G1: 1/2729 (0) G5a: 0/1138 (0) G2 vs. G5b: G2: 0/619 (0) G5b: 0/896 (0) G3 vs. G5b: G3: 0/615 (0) G5b: 0/896 (0) G4 vs. G5b: G4: 1/911 (0) G5b: 0/896 (0)	Major hypoglycemic episodes G1: NR G2: 1.0% (6/619) G3: 1.4% (9/615) G4: 1.8% (16/911) G5a: NR G5b: 0.7% (6/896) G2 vs. G5b RR, 1.45 (0.47 to 4.47) G3 vs. G5b RR, 2.19 (0.78 to 6.11) G4 vs. G5b RR, 2.62 (1.03 to 6.67)	NR	NR
Kumar, 2014[208] India	G1: 0 G2: 0	G1: 0 G2: 0	G1: 0/107 (0) G2: 0/106 (0)	Treatment-related AEs: G1: 6/107 (5.6) G2: 8/106 (7.5) RR, 0.74 (0.27 to 2.07) Serious adverse events: G1: 0 G2: 0

Abbreviations: AE=adverse events; CI=confidence interval; DESMOND=Diabetes education and self management for ongoing and newly diagnosed programme; G=group; HR=hazard ratio; KQ=key question; NR=not reported; RR=relative risk; UKPDS=United Kingdom Prospective Diabetes Study; vs.=versus.

Appendix E Table 12. Harms Reported in Included Trials of Interventions for People With Prediabetes (KQ 6)

Source First Author, year Trial Name	Groups (N participants) Followup, y	Hypoglycemic Events G1 N (%) G2 N (%)	All Cause Withdrawals Due to Adverse Events G1 N (%) G2 N (%)	Gastrointestinal Adverse Events G1 N (%) G2 N (%)	Other Adverse Events G1 N (%) G2 N (%)
Ackermann, 2015[139] Reaching Out to Prevent Increases in Diabetes (RAPID)	G1: Group-based YMCA DPP intervention (n=257) G2: Usual care plus brief counseling & information on community resources (n=252) 1 year	NR	NR	NR	Joint sprains or strains G1: 58 (22.6) G2: 58 (22.9) P = 0.99 Muscle or joint aches G1: 125 (48.6) G2: 127 (50.5) P = 0.7
Bhopal, 2014[36] Welsh, 2016[220] The Prevention of Diabetes and Obesity in South Asians (PODOSA) study	G1: Lifestyle intervention with family support and visits to dietician (n=85) G2: Standardized advice with family support (n=86) 3 years	NR	NR	NR	Total events perceived by participants to be attributable to the intervention: G1: 3 (3.5) G2: 4 (4.7) Moderate events perceived by participants to be attributable to the intervention: G1: 2 (2.3) - arthritis in knee causing pain on walking (n=1), and worries about changing habits (n=2) G2: 0 (0)

Appendix E Table 12. Harms Reported in Included Trials of Interventions for People With Prediabetes (KQ 6)

Source First Author, year Trial Name	Groups (N participants) Followup, y	Hypoglycemic Events G1 N (%) G2 N (%)	All Cause Withdrawals Due to Adverse Events G1 N (%) G2 N (%)	Gastrointestinal Adverse Events G1 N (%) G2 N (%)	Other Adverse Events G1 N (%) G2 N (%)
Diabetes Prevention Program Research Group, 2002[80] Diabetes Prevention Program Research Group, 2005[119] Diabetes Prevention Program Research Group, 2012[97] Diabetes Prevention Program Research Group, 2015[79] DPP	G1: Intensive lifestyle intervention (n=1079; 910 enrolled in DPPOS) G2: Standard lifestyle recommendations plus metformin 850 mg twice daily (n=1073; 924 enrolled in DPPOS) G3: Standard lifestyle recommendation plus placebo twice daily (n=1082; 932 enrolled in DPPOS) DPP: 2.8 y DPPOS: 15y	NR	NR	DPP (2.8 years): GI symptoms (events/ per 100 person-years) G1: 12.9 G2: 77.8 G3: 30.7 G1 vs. G3, p <0.0167 G2 vs. G3, p <0.0167	DPP (2.8 years): No deaths attributed to study intervention Musculoskeletal symptoms (events per 100 person-years) G1: 24.1 G2: 20.0 G3: 21.1 G1 vs. G3, p<0.0167 Hospitalization (% with one or more admissions) G1: 15.6 G2: 15.9 G3: 16.1 DPPOS (DPP + DPPOS, 15 years post-randomization): Risk for sprains or fractures needing medical attention G1: 4.3 events per 100 patient years G2: 4.1 events per 100 patient years G3: 3.7 events per 100 patient years No cases of lactic acidosis were reported in about 40000 patient-years of followup

Appendix E Table 12. Harms Reported in Included Trials of Interventions for People With Prediabetes (KQ 6)

Source First Author, year Trial Name	Groups (N participants) Followup, y	Hypoglycemic Events G1 N (%) G2 N (%)	All Cause Withdrawals Due to Adverse Events G1 N (%) G2 N (%)	Gastrointestinal Adverse Events G1 N (%) G2 N (%)	Other Adverse Events G1 N (%) G2 N (%)
Diabetes Prevention Program Research Group, 2012[237] Diabetes Prevention Program Research Group, 2009[146] Diabetes Prevention Program Research Group, 2015[79] Apolzan, 2019[238] DPPOS	G1: Standard lifestyle recommendations plus 850 mg metformin twice daily for 3.2 y; then open label metformin for additional 7-8 y and offered original DPP lifestyle intervention (n=924) G2: Standard lifestyle recommendation plus placebo twice daily and offered original DPP lifestyle intervention (n=932) Double blind phase: 2 y Open label phase: 9 y	Non serious hypoglycemia events G1: 7 G2: 8 Serious hypoglycemia events G1: 0 G2: 0	NR	% reporting GI symptoms in past year (average during DPP through year 4): G1: 28% G2:16% p = 0.01 Rates of GI symptom reports declined throughout DPPOS and were similar between groups by years 6-9, but remained significantly higher (p<0.10) in G1 vs. G2 over DPP +DPPOS (average per group over 9-years NR) % of participants reporting GI symptoms attributed to study medication over past 3 months (average during DPP through year 4): G1: 9.5% G2: 1.1% p < 0.001	Adverse events during DPP (in metformin vs. placebo groups only): Non-serious anemia G1: 50 G2: 38 Serious anemia G1: 2 G2: 1 Lactic acidosis G1: 0 G2: 0
Juul, 2016[145]	G1: Brief theory-based health promotion intervention (n=63) G2: Control (n=64) 1 year	NR	NR	NR	No adverse events were reported

Appendix E Table 12. Harms Reported in Included Trials of Interventions for People With Prediabetes (KQ 6)

Source First Author, year Trial Name	Groups (N participants) Followup, y	Hypoglycemic Events G1 N (%) G2 N (%)	All Cause Withdrawals Due to Adverse Events G1 N (%) G2 N (%)	Gastrointestinal Adverse Events G1 N (%) G2 N (%)	Other Adverse Events G1 N (%) G2 N (%)
O'Brien, 2017[142] The Promotora Effectiveness Versus Metformin Trial (PREVENT-DM)	G1: Intensive group-based adaptation of the DPP lifestyle intervention delivered by promotoras (community healthcare workers (n=33) G2: Metformin 850 mg twice daily (n=29) G3: Standard care plus written educational materials on diabetes prevention (n=30) 1 year	NR	Withdrawals due to medication side effects G1: 0 (0) G2: 1 (3.4) G3: 0 (0)	GI adverse events: G1: 0 (0) G2: 8 (28) G3: 0 (0)	Any adverse events: G1: 0 (0) G2: 10 (34.4) G3: 0 (0) Adverse events experienced in G2: Gastrointestinal: 8 (27.6) Dizziness/vertigo: 1 (3.4) Headache: 1 (3.4)
Pan, 1997[225] Li, 2008[226] Li, 2014[227] Gong, 2019[228] China Da Qing Diabetes Prevention Outcomes Study (CDQDPOS)	G1: Combined 6-year lifestyle (diet, exercise, or diet + exercise) intervention (n=438) G2: Control (n=138) 6 years (intervention); 23 years post-intervention followup; 30 years post-intervention followup	NR	NR	NR	No adverse events were recorded.

Appendix E Table 12. Harms Reported in Included Trials of Interventions for People With Prediabetes (KQ 6)

Source First Author, year Trial Name	Groups (N participants) Followup, y	Hypoglycemic Events G1 N (%) G2 N (%)	All Cause Withdrawals Due to Adverse Events G1 N (%) G2 N (%)	Gastrointestinal Adverse Events G1 N (%) G2 N (%)	Other Adverse Events G1 N (%) G2 N (%)
Saito, 2011[87] ZPLS	G1: Frequent intervention (received individual instructions and followup support for lifestyle modification 9 times over 36 months) (n=311) G2: Control group (received individual instructions and followup support for lifestyle modification 4 times over 12 months). (n=330) 3 years	NR	NR	NR	Authors report that there were no serious adverse events reported from any study center
Sakane, 2015[140] The Japan Diabetes Outcome Intervention Trial-1 (J-DOIT1)	G1: 1-year telephone-delivered lifestyle support intervention (n=1,240) G2: Control (n=1,367) 4.2 years	NR	NR	NR	All adverse events: G1: 24 (1.9) G2: 25 (1.8) Cancer: G1: 5 (0.4) G2: 8 (0.6) Musculoskeletal problems: G1: 6 G2: 3 Four cases of musculoskeletal problems in the intervention arm and one in the control arm might have been related to study treatment, per authors Other adverse events: G1: 9 (0.7) G2: 9 (0.7)

Appendix E Table 12. Harms Reported in Included Trials of Interventions for People With Prediabetes (KQ 6)

Source First Author, year Trial Name	Groups (N participants) Followup, y	Hypoglycemic Events G1 N (%) G2 N (%)	All Cause Withdrawals Due to Adverse Events G1 N (%) G2 N (%)	Gastrointestinal Adverse Events G1 N (%) G2 N (%)	Other Adverse Events G1 N (%) G2 N (%)
Chiasson, 2002[235] Chiasson, 2003[236] STOP-NIDDM	G1: Acarbose 100 mg 3x a day (n=714) G2: Placebo (n=715) 3.3 years	NR	Medication discontinuation due to adverse events: G1: 136(19) G2: 37 (5)	Any GI adverse events: G1: 597 (83) G2: 426 (60) p<0.001 Flatulence: G1: 486 (68) G2: 196 (27) Diarrhea: G1: 229 (32) G2: 123 (17)	Patients with any adverse events: G1: 698 (98) G2: 675 (95)
DeFronzo, 2011[251] Espinoza, 2016[252] Actos Now for Prevention of Diabetes Trial (ACT NOW)	G1: Pioglitazone 30 mg/day for one month, increased to 45 mg/day (n=303) G2: Placebo (n=299) 2.4 years (median)	NR	Withdrawals due to weight gain: G1: 9 G2: 3	Digestive system G1: 13 (4.29) G2: 12 (4.01)	Patients experiencing any adverse event: G1: 141 (47) G2: 121 (40) p=0.03 Specific adverse events: Bone fractures G1: 8 (2.64) G2: 7 (2.34) Central nervous system G1: 6 (2.0) G2: 5 (1.67) Edema* G1: 39 (12.87) G2: 19 (6.27) p=0.007 Cancer: G1: 3 (1) G2: 8 (3) Endocrine system G1: 1 (0.33) G2: 3 (1.00)

Appendix E Table 12. Harms Reported in Included Trials of Interventions for People With Prediabetes (KQ 6)

Source First Author, year Trial Name	Groups (N participants) Followup, y	Hypoglycemic Events G1 N (%) G2 N (%)	All Cause Withdrawals Due to Adverse Events G1 N (%) G2 N (%)	Gastrointestinal Adverse Events G1 N (%) G2 N (%)	Other Adverse Events G1 N (%) G2 N (%)
DeFronzo, 2011[251] Espinoza, 2016[252] Actos Now for Prevention of Diabetes Trial (ACT NOW) (continued)					Immune system G1: 2 (0.66) G2: 4 (1.34) Musculoskeletal system G1: 12 (3.96) G2: 13 (4.35) Ophthalmologic system G1: 0 (0.00) G2: 1 (0.33) Respiratory system G1: 9 (2.97) G2: 6 (2.01) Reproductive system G1: 4 (1.32) G2: 4 (1.34) Skin G1: 6 (2.0) G2: 3 (1.00) Urogenital system G1: 5 (1.65) G2: 3 (1.00) Weight gain > 1 kg G1: 205 (67.66) G2: 128 (42.81)

Appendix E Table 12. Harms Reported in Included Trials of Interventions for People With Prediabetes (KQ 6)

Source First Author, year Trial Name	Groups (N participants) Followup, y	Hypoglycemic Events G1 N (%) G2 N (%)	All Cause Withdrawals Due to Adverse Events G1 N (%) G2 N (%)	Gastrointestinal Adverse Events G1 N (%) G2 N (%)	Other Adverse Events G1 N (%) G2 N (%)
DREAM Trial Investigators, 2006[253] DREAM Trial Investigators, 2006[254] DREAM Trial Investigators, 2008[255] Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial	G1: Ramipril 15 mg/day (n=2623) G2: Placebo (n=2646) G3: Rosiglitazone 0.8mg/day (n=2635) G4: Placebo (n=2634) Patients randomized twice, to ramipril or placebo and rosiglitazone or placebo due to 2x2 factorial design 3 years	NR	Primary reasons for discontinuation of ramipril and placebo: Participant's decision to stop medication G1: 456 (17.4) G2: 468 (17.7) Cough G1: 254 (9.7) G2: 48 (1.8) Physician's advice G1: 60 (2.3) G2: 66 (2.5) Peripheral edema G1: 26 (1.0) G2: 29 (1.1) Angioedema G1: 3 (0.1) G2: 4 (0.2) Most common reasons for stopping rosiglitazone and placebo: Participant refusal G3: 503 (18.9) G4: 439 (16.7) Edema G3: 127 (4.8) G4: 41 (1.6)	NR	NR

Appendix E Table 12. Harms Reported in Included Trials of Interventions for People With Prediabetes (KQ 6)

Source First Author, year Trial Name	Groups (N participants) Followup, y	Hypoglycemic Events G1 N (%) G2 N (%)	All Cause Withdrawals Due to Adverse Events G1 N (%) G2 N (%)	Gastrointestinal Adverse Events G1 N (%) G2 N (%)	Other Adverse Events G1 N (%) G2 N (%)
DREAM Trial Investigators, 2006[253] DREAM Trial Investigators, 2006[254] DREAM Trial Investigators, 2008[255] Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial (continued)			Physician's advice G3: 50 (1.9) G4: 39 (1.5) Weight gain G3: 50 (1.9) G4: 15 (0.6) Hypoglycemia G3: 1 (0.04) G4: 3 (0.11)		

Appendix E Table 12. Harms Reported in Included Trials of Interventions for People With Prediabetes (KQ 6)

Source First Author, year Trial Name	Groups (N participants) Followup, y	Hypoglycemic Events G1 N (%) G2 N (%)	All Cause Withdrawals Due to Adverse Events G1 N (%) G2 N (%)	Gastrointestinal Adverse Events G1 N (%) G2 N (%)	Other Adverse Events G1 N (%) G2 N (%)
Kaku, 2015[218]	G1: Sitagliptin 25g once daily (n=82) G2: Sitagliptin 50g once daily (n=77) G3: Placebo (n=83) 8 weeks	Hypoglycemia requiring medical attention NR Any Hypoglycemia G1: 7 (8.6) G2: 5 (6.1) G3: 4 (5.1) Symptomatic hypoglycemia G1: 2 (2.5) G2: 0 (0.0) G3: 0 (0.0)	No participants withdrew due to adverse effects of study treatment	GI disorders G1: 5 (6.2) G2: 4 (4.9) G3: 7 (9.0	No deaths occurred during the study Any drug-related adverse event G1: 10 (12.3) G2: 5 (6.1) G3: 7 (9.0) Other AEs classified by system organ classes with incidence ≥4 in one or more treatment groups: Infections and infestations G1: 8 (9.9) G2: 11 (13.4) G3: 12 (15.4) Metabolism and nutrition disorders G1: 7 (8.6) G2: 5 (6.1) G3: 4 (5.1) Respiratory, thoracic and mediastinal disorders G1: 3 (3.7) G2: 5 (6.1) G3: 1 (1.3)
Kawamori, 2009[256]	G1: Voglibose 0.2 mg TID 3x/daily (n=897) G2: Placebo (n=883) 48 weeks	NR	Discontinuations due to any adverse events: G1: 62 (7%) G2: 55 (6%) p=0.57 Discontinuations due to adverse events attributable to intervention: G1: 46 (5%) G2: 24 (3%) p=0.01	NR	NR

Appendix E Table 12. Harms Reported in Included Trials of Interventions for People With Prediabetes (KQ 6)

Source First Author, year Trial Name	Groups (N participants) Followup, y	Hypoglycemic Events G1 N (%) G2 N (%)	All Cause Withdrawals Due to Adverse Events G1 N (%) G2 N (%)	Gastrointestinal Adverse Events G1 N (%) G2 N (%)	Other Adverse Events G1 N (%) G2 N (%)
le Roux, 2017[115] SCALE Obesity and Prediabetes Trial	G1: Liraglutide (starting at 0.6 mg daily; weekly 0.6 mg increases to 3.0 mg with standardized lifestyle counseling (n=1505) G2: Placebo with standardized lifestyle counseling (n=749) 3.3 years	Severe hypoglycemic events requiring third-party assistance G1: 0 (0) G2: 0 (0)	Withdrawals due to adverse events G1: 199 (13) G2: 46 (6)	Nausea: G1: 614 (41) G2: 125 (17) Diarrhea: G1: 379 (41) G2: 107 (14) Pancreatitis G1:10 (0.6) G2: 2 (0.2)	Total number of participants reporting any adverse events: G1: 1421 (95) G2: 668 (89) Total number of participants reporting any serious adverse events: G1: 227 (15) G2: 96 (13) Other specific adverse events: Malignant breast neoplasms in females G1: 7 (0.5) G2: 0 (0) Malignant thyroid neoplasms G1: 1 (0.1) G2: 0 (0)
Lu, 2011[259]	G1: Patients with I-IGT: acarbose (50 mg three times daily) + lifestyle intervention; patients with I-IFG or IFG/IGT: metformin (0.25 g 3x daily) + lifestyle intervention (n=106) G2: Annual diabetes education (n=104) 2 years	NR	Withdrawal due to Adverse Event G1: 1 (0.9) G2: 0 (0)	NR	NR

Appendix E Table 12. Harms Reported in Included Trials of Interventions for People With Prediabetes (KQ 6)

Source First Author, year Trial Name	Groups (N participants) Followup, y	Hypoglycemic Events G1 N (%) G2 N (%)	All Cause Withdrawals Due to Adverse Events G1 N (%) G2 N (%)	Gastrointestinal Adverse Events G1 N (%) G2 N (%)	Other Adverse Events G1 N (%) G2 N (%)
The NAVIGATOR Study Group, 2010[260] The NAVIGATOR Study Group, 2010[261] Currie, 2017[262] Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Trial	G1: Nateglinide 60 mg/3 times daily (n=4645) G2: Placebo (n=4661) G3: Valsartan 160 mg/once daily (n=4631) G4: Placebo (n=4675) Patients randomized twice to nateglinide or placebo and valsartan or placebo due to 2x2 factorial design All patients also required to participate in lifestyle intervention program 5 years	All hypo-glycemia adverse events G1: 911 (20) G2: 527 (11) G3: 731 (15.8) G4: 707 (15.1) Mild (maximum severity) G1: 676 G2: 411 Moderate (maximum severity) G1: 214 G2: 104 Severe (maximum severity) G1: 21 G2: 12	Discontinuation of the study drug due to an adverse event: G1: 520 (11.2) G2: 485 (10.4) G3: 556 (12.0) G4: 531 (11.4)	Diarrhea G1: 593 (13) G2: 586 (13) G3: 612 (13.2) G4: 567 (12.1)	Initiation of dialysis G3: 4 (0.1) G4: 4 (0.1) HR 0.97 (0.24 to 3.88) Serum creatinine >530 µmol/L G3: 1 (0) G4: 1 (0) HR 0.93 (0.06 to 4.9) Doubling of serum creatinine G3: 18 (0.4) G4: 18 (0.4) HR 1.00 (0.52 to 1.92) Hospitalization for renal failure G3: 34 (0.7) G4: 35 (0.7) HR 0.96 (0.6 to 1.54) Renal dysfunction adverse event G3: 118 (2.5) G4: 126 (2.7) HR 0.93 (0.73 to 1.20) Hypotension related G1: 1855 (40) G2: 1789 (38) G3: 1964 (42.4) G4: 1680 (35.9) p<0.001 for G3 vs. G4 Back pain G1: 752 (16) G2: 705 (15) G3: 775 (16.7) G4: 682 (14.6) Nasopharyingitis G1: 807 (17) G2: 798 (17) G3: 808 (17.4) G4: 797 (17.0)

Appendix E Table 12. Harms Reported in Included Trials of Interventions for People With Prediabetes (KQ 6)

Source First Author, year Trial Name	Groups (N participants) Followup, y	Hypoglycemic Events G1 N (%) G2 N (%)	All Cause Withdrawals Due to Adverse Events G1 N (%) G2 N (%)	Gastrointestinal Adverse Events G1 N (%) G2 N (%)	Other Adverse Events G1 N (%) G2 N (%)
The NAVIGATOR Study Group, 2010[260] The NAVIGATOR Study Group, 2010[261] Currie, 2017[262] Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Trial (continued)					Arthralgia G1: 759 (16) G2: 762 (16) G3: 758 (16.4) G4: 763 (16.3) Hypertension G1: 797 (17) G2: 846 (18) G3: 693 (15.0) G4: 950 (20.3) Renal dysfunction G3: 136 (2.9) G4: 146 (3.1) Hyperkalemia G3: 35 (0.8) G4: 35 (0.7) Hypokalemia G3: 45 (1.0) G4: 83 (1.8) Angioedema G3: 89 (1.9) G4: 123 (2.6) Influenza G1: 602 (13) G2: 630 (14) G3: 615 (13.3) G4: 617 (13.2) Pain in extremity G1: 568 (12) G2: 530 (11) G3: 567 (12.2) G4: 531 (11.4)

Appendix E Table 12. Harms Reported in Included Trials of Interventions for People With Prediabetes (KQ 6)

Source First Author, year Trial Name	Groups (N participants) Followup, y	Hypoglycemic Events G1 N (%) G2 N (%)	All Cause Withdrawals Due to Adverse Events G1 N (%) G2 N (%)	Gastrointestinal Adverse Events G1 N (%) G2 N (%)	Other Adverse Events G1 N (%) G2 N (%)
The NAVIGATOR Study Group, 2010[260] The NAVIGATOR Study Group, 2010[261] Currie, 2017[262] Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Trial (continued)					Osteoarthritis G1: 576 (12) G2: 578 (12) G3: 554 (12.0) G4: 600 (12.8) Upper respiratory tract infection G1: 525 (11) G2: 556 (12) G3: 546 (11.8) G4: 535 (11.4) Headache G1: 559 (12) G2: 604 (13) G3: 537 (11.6) G4: 626 (13.4) Cough G1: 478 (10) G2: 450 (10) G3: 462 (10.0) G4: 466 (10.0) Fatigue G1: 462 (10) G2: 432 (9) Peripheral edema G1: 500 (11) G2: 486 (10) G3: 431 (9.3) G4: 555 (11.9) Bronchitis G1: 477 (10) G2: 477 (10) G3: 463 (10.0) G4: 491 (10.5)
Nijpels, 2008[263] DAISI	G1: Acarbose 50 mg 3x daily (n=60) G2: Placebo (n=58) 3 years	NR	Withdrawals due to adverse events: G1: 22 (36.7) G2: 8 (13.8)	NR	NR

Appendix E Table 12. Harms Reported in Included Trials of Interventions for People With Prediabetes (KQ 6)

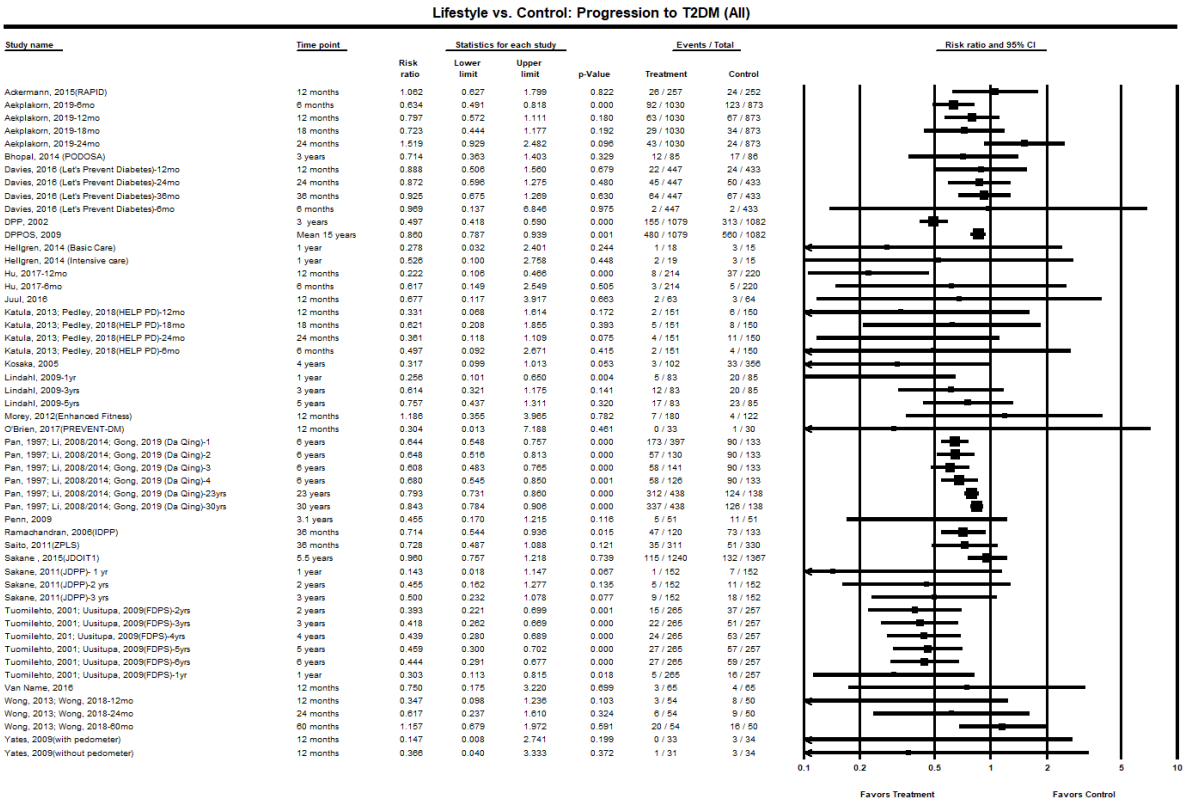
Source First Author, year Trial Name	Groups (N participants) Followup, y	Hypoglycemic Events G1 N (%) G2 N (%)	All Cause Withdrawals Due to Adverse Events G1 N (%) G2 N (%)	Gastrointestinal Adverse Events G1 N (%) G2 N (%)	Other Adverse Events G1 N (%) G2 N (%)
Ramachandran, 2009[265] IDPP-2	G1: Pioglitazone, 30 mg daily plus lifestyle modification (n=204) G2: Placebo plus lifestyle modification (n=203) 3 years	NR	NR	NR	Other major events (not defined), excluding death or CVD: G1: 4 G2: 10 Minor adverse events (hypoglycemic symptoms, joint pain, fracture, fever, renal stone, hypothyroidism, breathlessness, elevated liver enzymes): G1: 28 G2: 22
Pan, 2003[246]	G1: Acarbose 50 mg 3x daily (n=125) G2: Placebo (n=127) 16 weeks	NR	Withdrawn due to adverse events G1: 2 (1.6) G2: 3 (2.4)	Flatulence G1: NR (15.9) G2: NR (6.1) Enlarged abdomen G2: NR (13.5) G1: NR (3.8) Diarrhea G2: NR (9.5) G1: NR (2.3) Hepatitis: G1: 1 (0.8) G2: 0 (0.0)	Drug-related adverse events with a 'possible' or 'probable' relation to the study drug G1: NR (35.7) G2: NR (18.2) Tenosynovitis G1: 0 (0.0) G2 1 (0.8) Glaucoma: G1: 1 (0.8) G2: 0 (0.0) Cerebral infarction G1: 1 (0.8) G2: 0 (0.0)

Appendix E Table 12. Harms Reported in Included Trials of Interventions for People With Prediabetes (KQ 6)

Source First Author, year Trial Name	Groups (N participants) Followup, y	Hypoglycemic Events G1 N (%) G2 N (%)	All Cause Withdrawals Due to Adverse Events G1 N (%) G2 N (%)	Gastrointestinal Adverse Events G1 N (%) G2 N (%)	Other Adverse Events G1 N (%) G2 N (%)
Weber, 2016[222] Gokulakrishnan, 2017[223] Diabetes Community Lifestyle Improvement Program (D-CLIP)	G1: Stepwise intervention of adapted DPP lifestyle classes plus metformin 500 mg twice daily at 4 months if at high risk of developing diabetes (n=283) G2: Standard of care (n=295) 3 years	NR	NR	NR	No severe adverse events (e.g., hospitalization, severe injury or illness) related to participation in the study, no injuries related to the exercise program, and no adverse events from diet changes Some participants reported mild or moderate gastritis related to taking metformin, but none of these cases were severe enough to stop taking the medication One participant developed a rash after taking metformin, which resolved after metformin was discontinued.
Zinman, 2010[267] CAnadian Normoglycemia Outcomes Evaluation trial (CANOE)	G1: rosiglitazone 2 mg and metformin 500 twice daily and lifestyle intervention (n=103) G2: placebo and lifestyle intervention (n=104) 3.9 years	Hypoglycemia (severity NR): G1: 2 (2) G2: 1 (1)	Stopped study medication due to concerns about side-effects from rosiglitazone: G1: 4 (4) G2: 7 (7)	Any GI event (diarrhea, nausea/vomiting, abdominal pain, constipation, flatulence, frequent/soft stools): G1: 37 G2: 19 Diarrhea G1: 16 (16) G2: 6 (6) p=0.025	Any adverse effect potentially related to study or study drug (diarrhea, nausea/vomiting, abdominal pain, constipation, flatulence, frequent/soft stools, swollen ankles, bloating/water retention, allergic reaction, vertigo) G1: 42 (41) G2: 27 (26)

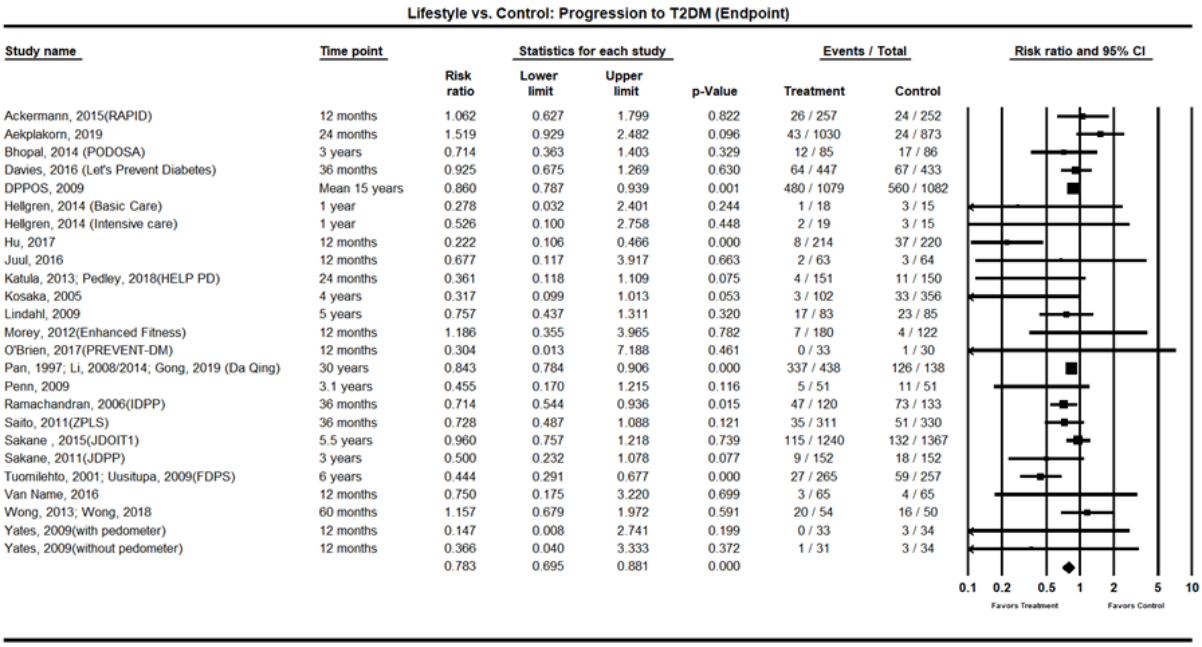
* Edema was defined as an increase above baseline by two or more grades on one or more distinct study visits.

Appendix F Figure 1. Lifestyle vs. Control: Progression to T2DM



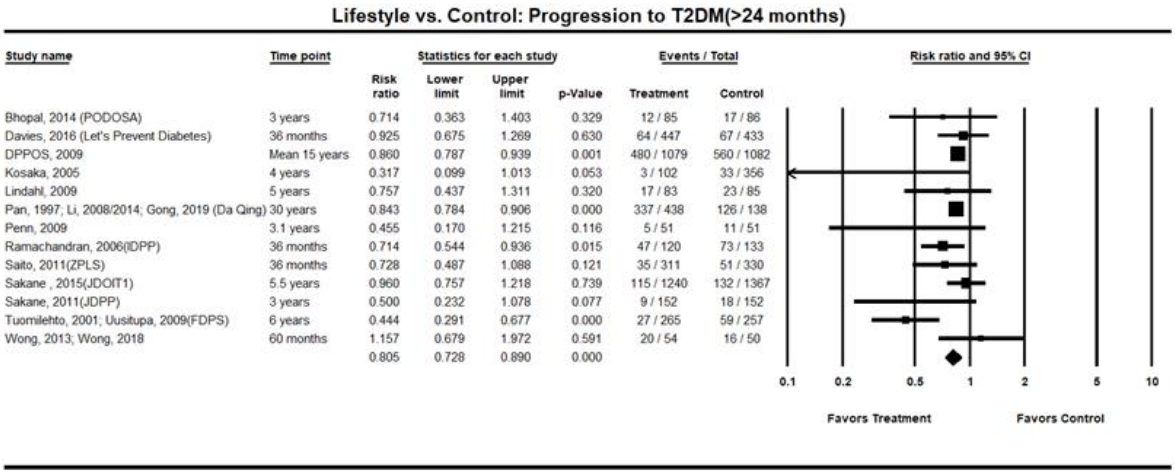
I-squared: N/A; p=N/A

Appendix F Figure 2. Lifestyle vs. Control: Progression to T2DM (Endpoint)



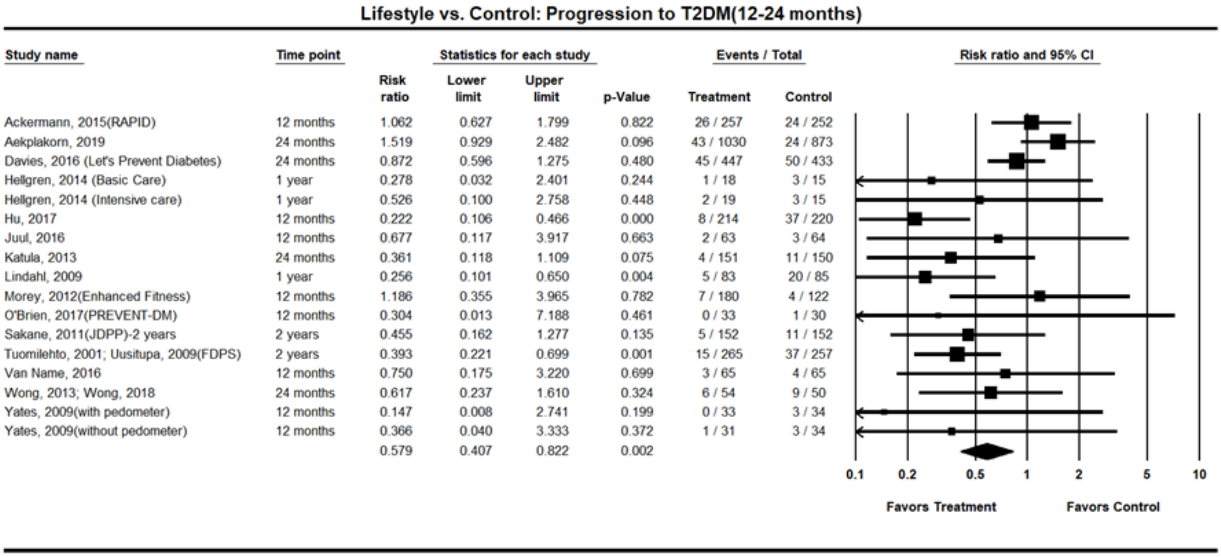
I-squared: 46.76; p=0.006

Appendix F Figure 3. Lifestyle vs. Control: Progression to T2DM (>24 Months)



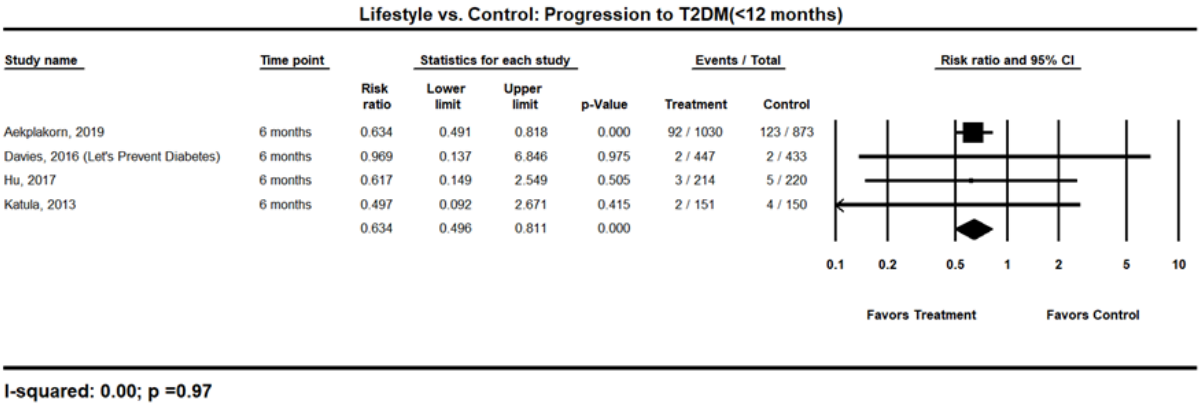
I-squared: 40.56; p =0.064

Appendix F Figure 4. Lifestyle vs. Control: Progression to T2DM (12-24 Months)



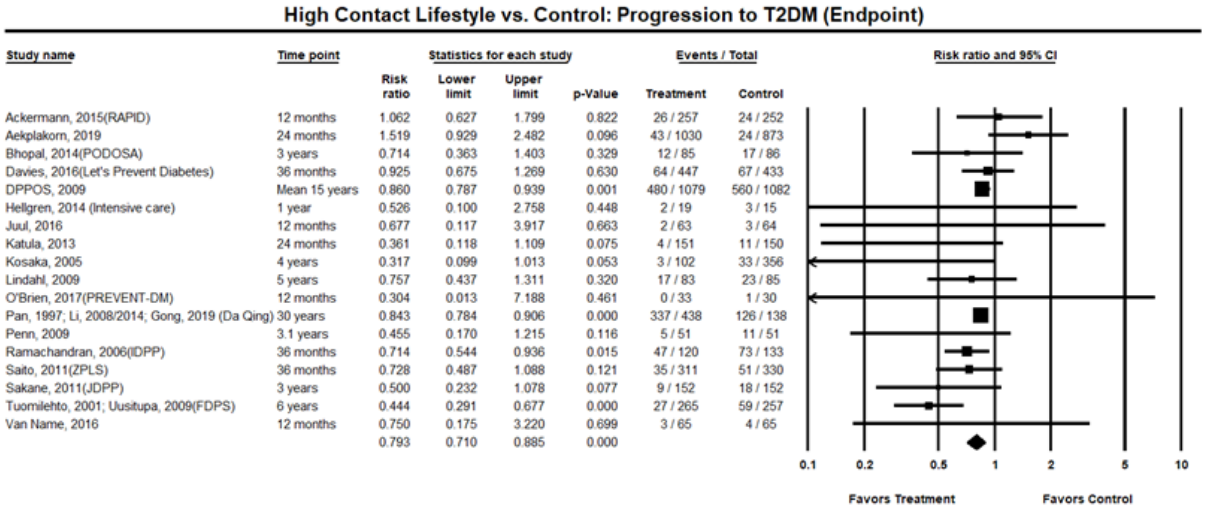
I-squared: 55.70; p =0.003

Appendix F Figure 5. Lifestyle vs. Control: Progression to T2DM (<12 Months)



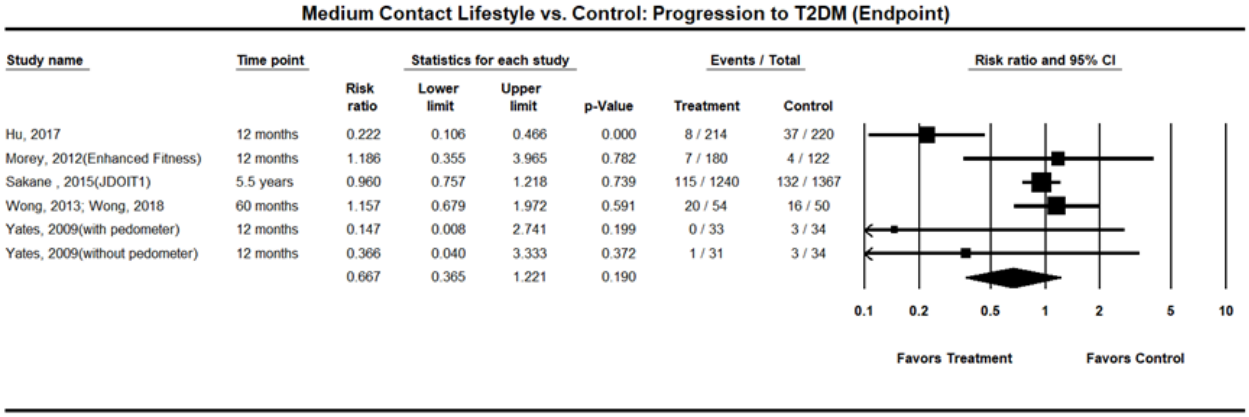
I-squared: 0.00; p =0.97

Appendix F Figure 6. High Contact Lifestyle vs. Control: Progression to T2DM



I-squared: 36.62; p =0.61

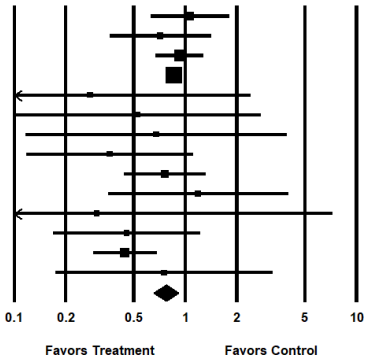
Appendix F Figure 7. Medium Contact Lifestyle vs. Control: Progression to T2DM



I-squared: 70.70; p =0.004

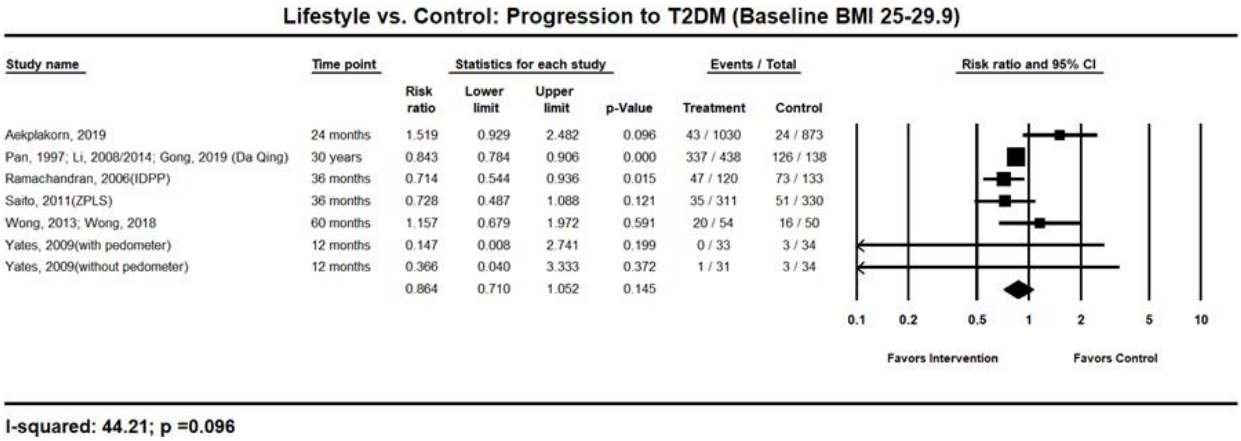
Appendix F Figure 8. Lifestyle vs. Control: Progression to T2DM (Baseline BMI >30)

Study name	Time point	Statistics for each study				Events / Total	
		Risk ratio	Lower limit	Upper limit	p-Value	Treatment	Control
Ackermann, 2015(RAPID)	12 months	1.062	0.627	1.799	0.822	26 / 257	24 / 252
Bhopal, 2014 (PODOSA)	3 years	0.714	0.363	1.403	0.329	12 / 85	17 / 86
Davies, 2016(Let's Prevent Diabetes)-36mo	36 months	0.925	0.675	1.269	0.630	64 / 447	67 / 433
DPPOS, 2009	Mean 15 years	0.860	0.787	0.939	0.001	480 / 1079	560 / 1082
Hellgren, 2014 (Basic Care)	1 year	0.278	0.032	2.401	0.244	1 / 18	3 / 15
Hellgren, 2014 (Intensive care)	1 year	0.526	0.100	2.758	0.448	2 / 19	3 / 15
Juul, 2016	12 months	0.677	0.117	3.917	0.663	2 / 63	3 / 64
Katula, 2013-24mo	24 months	0.361	0.118	1.109	0.075	4 / 151	11 / 150
Lindahl, 2009-5 yrs	5 years	0.757	0.437	1.311	0.320	17 / 83	23 / 85
Morey, 2012(Enhanced Fitness)	12 months	1.186	0.355	3.965	0.782	7 / 180	4 / 122
O'Brien, 2017(PREVENT-DM)	12 months	0.304	0.013	7.188	0.461	0 / 33	1 / 30
Penn, 2009	3.1 years	0.455	0.170	1.215	0.116	5 / 51	11 / 51
Tuomilehto, 2001;Uusitupa, 2009(FDPS)-6yrs	6 years	0.444	0.291	0.677	0.000	27 / 265	59 / 257
Van Name, 2016	12 months	0.750	0.175	3.220	0.699	3 / 65	4 / 65
		0.766	0.648	0.906	0.002		



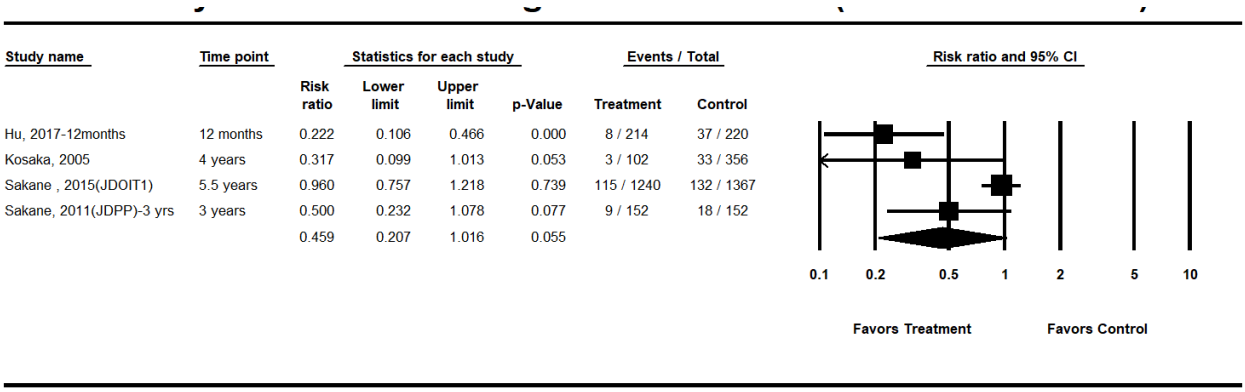
I-squared: 20.13; p=0.235

Appendix F Figure 9. Lifestyle vs. Control: Progression to T2DM (Baseline BMI 25-29.9)



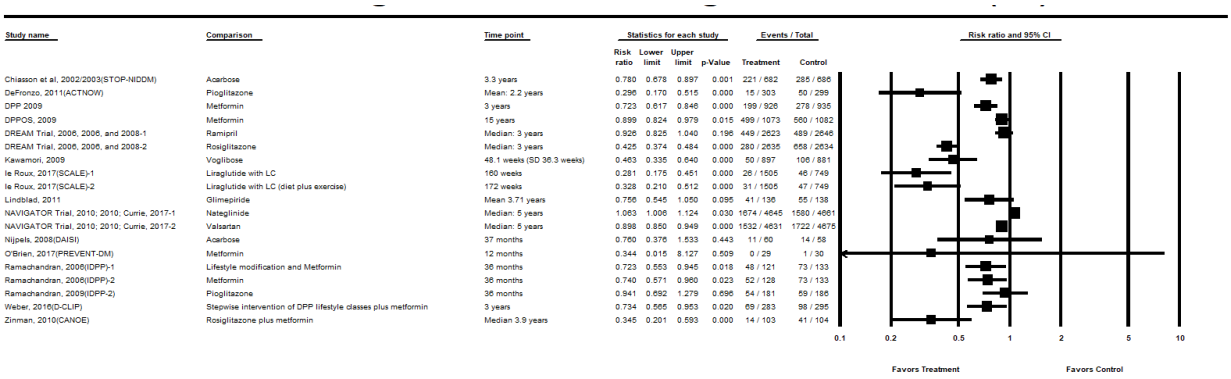
I-squared: 44.21; p =0.096

Appendix F Figure 10. Lifestyle vs. Control: Progression to T2DM (Baseline BMI <25)



I-squared: 82.92; p=0.001

Appendix F Figure 11. Pharmacological vs. Control: Progression to T2DM (All)

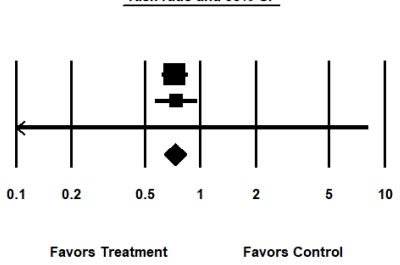


Study name	Comparison	Time point	Risk ratio	Lower limit	Upper limit	p-Value	Treatment	Control
Chiasson et al, 2002/2003(STOP-NIDDM)	Acarbose	3.3 years	0.780	0.678	0.897	0.001	221 / 682	285 / 686
DeFronzo, 2011(ACTNOW)	Pioglitazone	Mean: 2.2 years	0.296	0.179	0.515	0.000	15 / 303	59 / 299
DPP 2009	Metformin	3 years	0.723	0.617	0.846	0.000	199 / 926	278 / 935
DPPOS, 2009	Metformin	15 years	0.899	0.824	0.979	0.015	499 / 1073	560 / 1082
DREAM Trial, 2006, 2006, and 2008-1	Ramipril	Median: 3 years	0.926	0.825	1.040	0.196	449 / 2623	489 / 2646
DREAM Trial, 2006, 2006, and 2008-2	Rosiglitazone	Median: 3 years	0.425	0.374	0.484	0.000	280 / 2635	658 / 2634
Kawamori, 2009	Voglibose	48.1 weeks (SD 36.3 weeks)	0.463	0.335	0.640	0.000	50 / 897	106 / 881
le Roux, 2017(SCALE)-1	Liraglutide with LC	160 weeks	0.281	0.175	0.451	0.000	26 / 1505	46 / 749
le Roux, 2017(SCALE)-2	Liraglutide with LC (diet plus exercise)	172 weeks	0.328	0.210	0.512	0.000	31 / 1505	47 / 749
Lindblad, 2011	Glimepiride	Mean 3.71 years	0.756	0.545	1.050	0.095	41 / 136	55 / 138
NAVIGATOR Trial, 2010; 2010; Currie, 2017-1	Nateglinide	Median: 5 years	1.063	1.006	1.124	0.030	1674 / 4645	1580 / 4661
NAVIGATOR Trial, 2010; 2010; Currie, 2017-2	Valsartan	Median: 5 years	0.898	0.850	0.949	0.000	1532 / 4631	1722 / 4675
Nijpels, 2008(DAISI)	Acarbose	37 months	0.760	0.376	1.533	0.443	11 / 60	14 / 58
O'Brien, 2017(PREVENT-DM)	Metformin	12 months	0.344	0.015	8.127	0.509	0 / 29	1 / 30
Ramachandran, 2006(IDPP)-1	Lifestyle modification and Metformin	36 months	0.723	0.553	0.945	0.018	48 / 121	73 / 133
Ramachandran, 2006(IDPP)-2	Metformin	36 months	0.740	0.571	0.960	0.023	52 / 128	73 / 133
Ramachandran, 2009(IDPP-2)	Pioglitazone	36 months	0.941	0.692	1.279	0.696	54 / 181	59 / 186
Weber, 2016(D-CLIP)	Stepwise intervention of DPP lifestyle classes plus metformin	3 years	0.734	0.566	0.953	0.020	69 / 283	98 / 295
Zinman, 2010(CANOE)	Rosiglitazone plus metformin	Median 3.9 years	0.345	0.201	0.593	0.000	14 / 103	41 / 104

I-squared: N/A; p=N/A

Appendix F Figure 12. Metformin vs. Control: Progression to T2DM (With DPP)

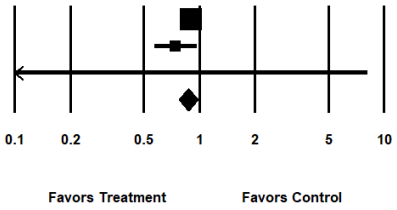
Study name	Comparison	Time point	Statistics for each study				Events / Total	
			Risk ratio	Lower limit	Upper limit	p-Value	Treatment	Control
DPP 2009	Metformin	3 years	0.723	0.617	0.846	0.000	199 / 926	278 / 935
IDPP/Ramachandran, 2006(IDPP)	Metformin	36 months	0.740	0.571	0.960	0.023	52 / 128	73 / 133
O'Brien, 2017(PREVENT-DM)	Metformin	12 months	0.344	0.015	8.127	0.509	0 / 29	1 / 30
			0.726	0.635	0.831	0.000		



I-squared:0.00; p=0.888

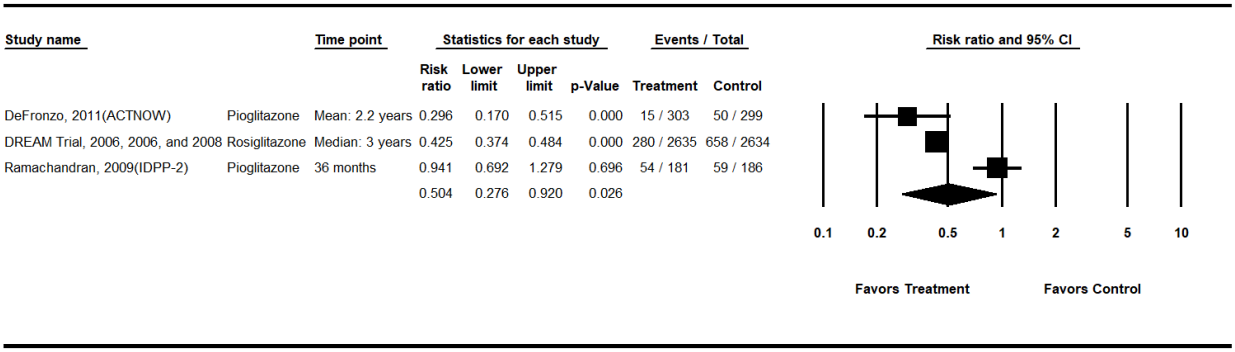
Appendix F Figure 13. Metformin vs. Control: Progression to T2DM (With DPPOS)

Study name	Comparison	Time point	Risk ratio	Lower limit	Upper limit	p-Value	Events / Total: Treatment	Events / Total: Control
DPPOS, 2009	Metformin	15 years	0.899	0.824	0.979	0.015	499 / 1073	560 / 1082
IDPP/Ramachandran, 2006(IDPP)	Metformin	36 months	0.740	0.571	0.960	0.023	52 / 128	73 / 133
O'Brien, 2017(PREVENT-DM)	Metformin	12 months	0.344	0.015	8.127	0.509	0 / 29	1 / 30
			0.866	0.769	0.975	0.018		



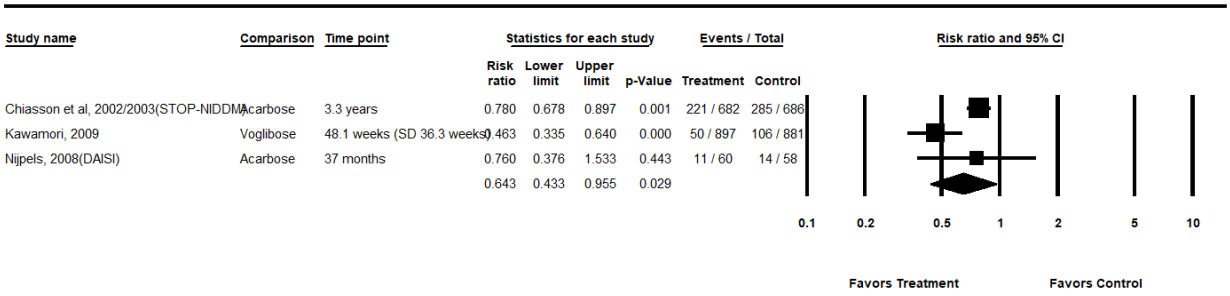
I-squared:11.68; p=0.322

Appendix F Figure 14. Thiazolidinediones vs. Control: Progression to T2DM



I-squared:91.86; p=0.000

Appendix F Figure 15. Alpha Glucosidase Inhibitor vs. Control: Progression to T2DM

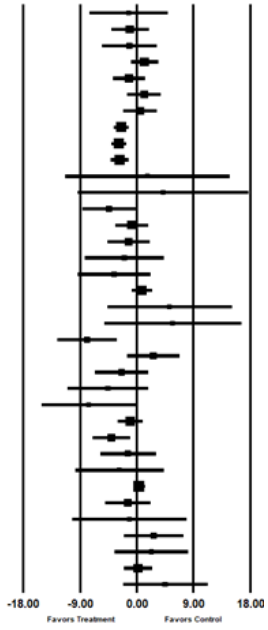


I-squared: 76.27; p=0.015

Appendix F Figure 16. Lifestyle vs. Control: Systolic Blood Pressure (All)

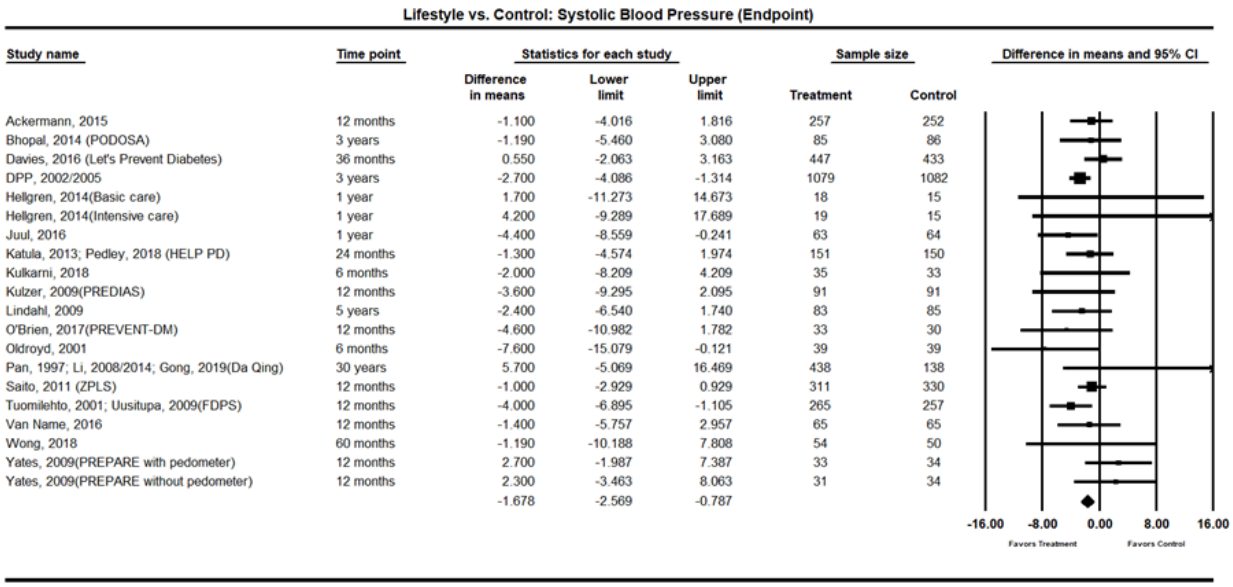
Lifestyle vs. Control: Systolic Blood Pressure (All)

Study name	Time point	Difference in means	Lower limit	Upper limit	p-Value	Sample size: Treatment	Sample size: Control
Ackermann, 2015-instrumental variable	12 months	-1.300	-7.474	4.874	0.680	257	252
Ackermann, 2015-ITT	12 months	-1.100	-4.016	1.816	0.460	257	252
Bhopal, 2014 (PODOSA)	3 years	-1.190	-5.460	3.080	0.585	85	86
Davies, 2016(Let's Prevent Diabetes)-12mo	12 months	1.220	-0.857	3.297	0.250	447	433
Davies, 2016(Let's Prevent Diabetes)-24mo	24 months	-1.260	-3.794	1.274	0.330	447	433
Davies, 2016(Let's Prevent Diabetes)-6mo	6 months	1.170	-1.441	3.781	0.380	447	433
Davies, 2016 (Let's Prevent Diabetes)-36mo	36 months	0.550	-2.063	3.163	0.680	447	433
DPP, 2002/2005-1yr	1 years	-2.500	-3.609	-1.391	0.000	1079	1082
DPP, 2002/2005-2yrs	2 years	-2.880	-3.989	-1.771	0.000	1079	1082
DPP, 2002/2005-3yrs	3 years	-2.700	-4.086	-1.314	0.000	1079	1082
Hellgren, 2014(Basic care)2	1 year	1.700	-11.273	14.673	0.797	18	15
Hellgren, 2014(Intensive care)2	1 year	4.200	-9.289	17.689	0.542	19	15
Juul, 2016	1 year	-4.400	-8.559	-0.241	0.038	63	64
Katula, 2013; Pedley, 2018 (HELP PD)-12mo	12 months	-0.800	-3.318	1.718	0.534	151	150
Katula, 2013; Pedley, 2018 (HELP PD)-24mo	24 months	-1.300	-4.574	1.974	0.436	151	150
Kulkarni, 2018	6 months	-2.000	-8.209	4.209	0.528	35	33
Kulzer, 2009(PREDIAS)	12 months	-3.600	-9.295	2.095	0.215	91	91
Pan, 1997; Li, 2008/2014; Gong, 2019(Da Qing)-6yrs	6 years	0.800	-0.711	2.311	0.300	438	138
Pan, 1997; Li, 2008/2014; Gong, 2019(Da Qing)-20yrs	20 years	5.200	-4.625	15.025	0.300	438	138
Pan, 1997; Li, 2008/2014; Gong, 2019(Da Qing)-30yrs	30 years	5.700	-5.069	16.469	0.300	438	138
Lindahl, 2009-1yr	1 year	-7.900	-12.522	-3.278	0.001	83	85
Lindahl, 2009-3yrs	3 years	2.600	-1.540	6.740	0.218	83	85
Lindahl, 2009-5yrs	5 years	-2.400	-6.540	1.740	0.256	83	85
O'Brien, 2017(PREVENT-DM)	12 months	-4.600	-10.982	1.782	0.158	33	30
Oldroyd, 2001	6 months	-7.600	-15.079	-0.121	0.046	39	39
Saito, 2011 (ZPLS)	12 months	-1.000	-2.929	0.929	0.310	311	330
Tuomilehto, 2001	12 months	-4.000	-6.895	-1.105	0.007	265	257
Van Name, 2016	12 months	-1.400	-5.757	2.957	0.529	65	65
Wong, 2013-6mo	6 months	-2.760	-9.738	4.218	0.438	54	50
Wong, 2013-12mo	12 months	0.340	-0.520	1.200	0.438	54	50
Wong, 2013 -24mo	24 months	-1.420	-5.010	2.170	0.438	54	50
Wong, 2018-60mo	60 months	-1.190	-10.188	7.808	0.795	54	50
Yates, 2009(PREPARE with pedometer)-12mo	12 months	2.700	-1.987	7.387	0.259	33	34
Yates, 2009(PREPARE without pedometer)-12mo	12 months	2.300	-3.463	8.063	0.434	31	34
Yates, 2009-(PREPARE with pedometer)-6mo	6 months	0.200	-1.982	2.382	0.857	33	34
Yates, 2009(PREPARE without pedometer)-6mo	6 months	4.500	-2.157	11.157	0.185	31	34



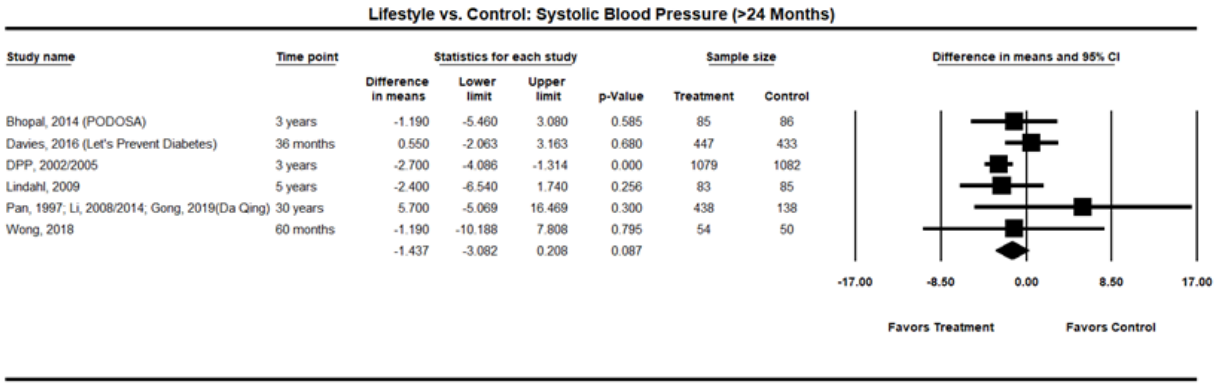
I-squared: N/A; p=N/A

Appendix F Figure 17. Lifestyle vs. Control: Systolic Blood Pressure (Endpoint)



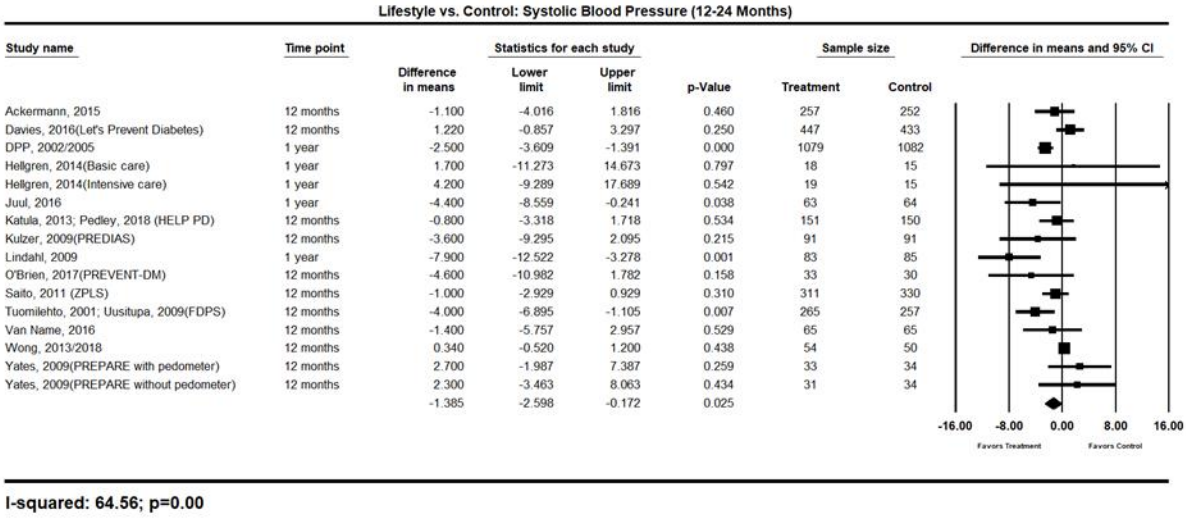
I-squared: 11.43; p=0.31

Appendix F Figure 18. Lifestyle vs. Control: Systolic Blood Pressure (>24 Months)

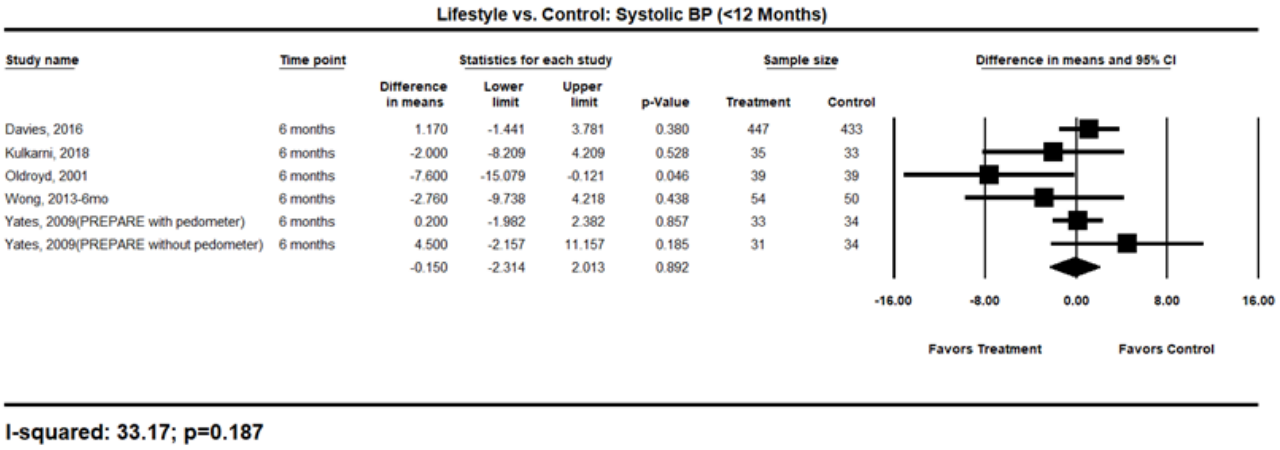


I-squared: 25.97; p=0.240

Appendix F Figure 19. Lifestyle vs. Control: Systolic Blood Pressure (12-24 Months)

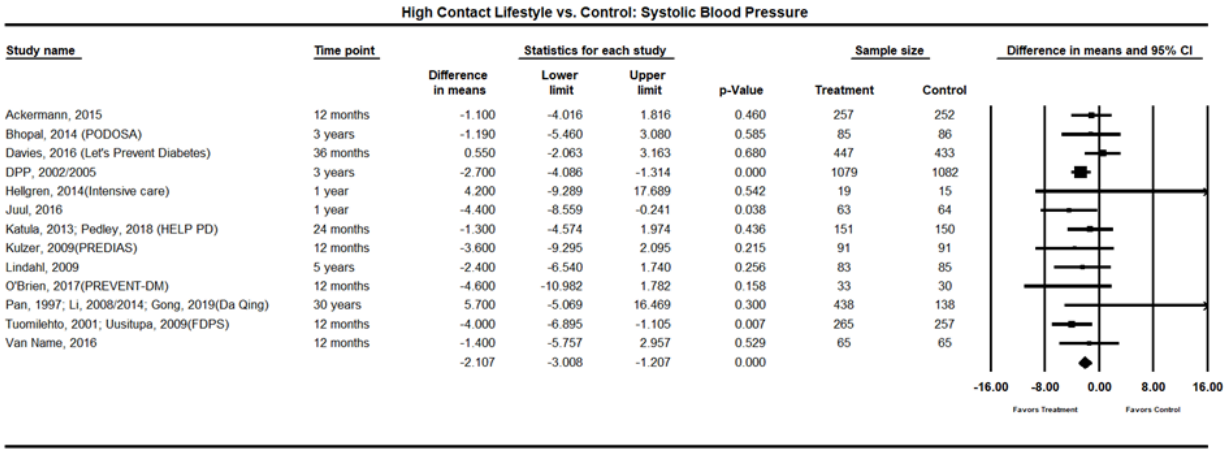


Appendix F Figure 20. Lifestyle vs. Control: Systolic Blood Pressure (<12 Months)



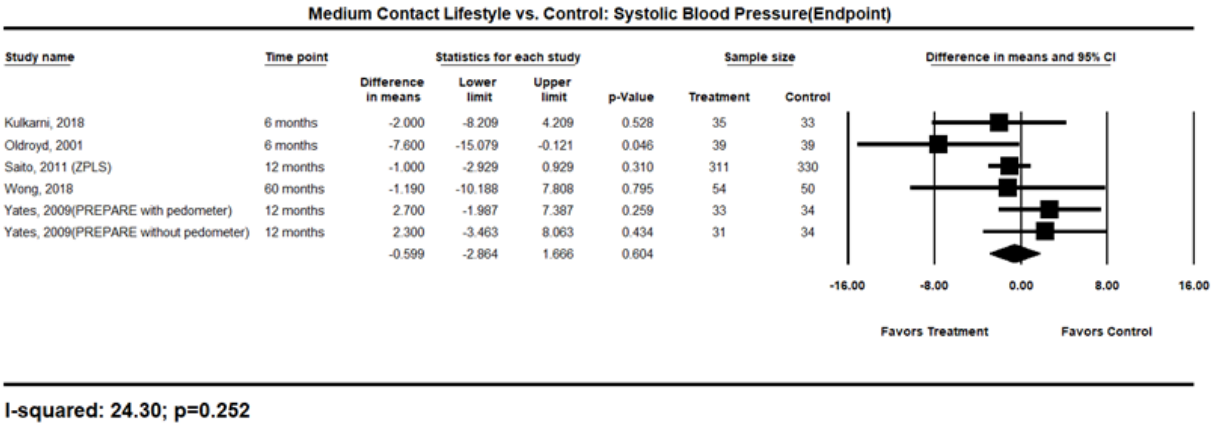
I-squared: 33.17; p=0.187

Appendix F Figure 21. High Contact Lifestyle vs. Control: Systolic Blood Pressure



I-squared: 1.53; p=0.431

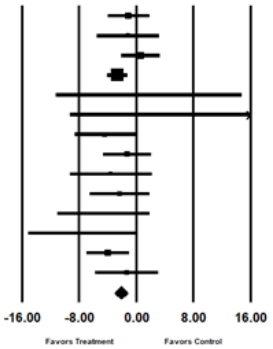
Appendix F Figure 22. Medium Contact Lifestyle vs. Control: Systolic Blood Pressure



Appendix F Figure 23. Lifestyle vs. Control: Systolic Blood Pressure (BMI >30)

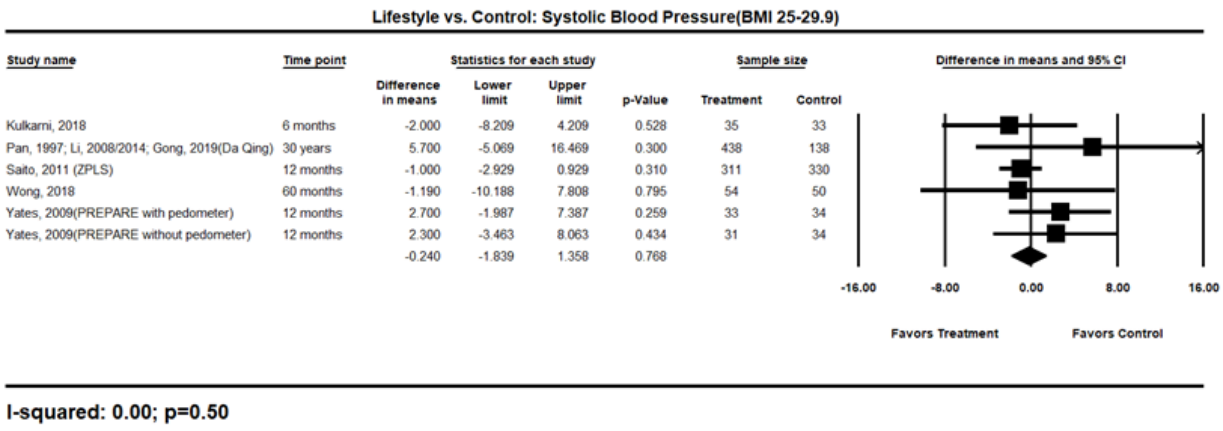
Lifestyle vs. Control: Systolic Blood Pressure (BMI>30)

Study name	Time point	Statistics for each study				Sample size		Difference in means and 95% CI
		Difference in means	Lower limit	Upper limit	p-Value	Treatment	Control	
Ackermann, 2015	12 months	-1.100	-4.016	1.816	0.460	257	252	
Bhopal, 2014 (PODOSA)	3 years	-1.190	-5.460	3.080	0.585	85	86	
Davies, 2016 (Let's Prevent Diabetes)	36 months	0.550	-2.063	3.163	0.680	447	433	
DPP, 2002/2005	3 years	-2.700	-4.086	-1.314	0.000	1079	1082	
Hellgren, 2014(Basic care)	1 year	1.700	-11.273	14.673	0.797	18	15	
Hellgren, 2014(Intensive care)	1 year	4.200	-9.289	17.689	0.542	19	15	
Juul, 2016	1 year	-4.400	-8.559	-0.241	0.038	63	64	
Katula, 2013; Pedley, 2018 (HELP PD)	24 months	-1.300	-4.574	1.974	0.436	151	150	
Kulzer, 2009(PREDIAS)	12 months	-3.600	-9.295	2.095	0.215	91	91	
Lindahl, 2009	5 years	-2.400	-6.540	1.740	0.256	83	85	
O'Brien, 2017(PREVENT-DM)	12 months	-4.600	-10.982	1.782	0.158	33	30	
Oldroyd, 2001	6 months	-7.600	-15.079	-0.121	0.046	39	39	
Tuomilehto, 2001; Uusitupa, 2009(FDPS)	12 months	-4.000	-6.895	-1.105	0.007	265	257	
Van Name, 2016	12 months	-1.400	-5.757	2.957	0.529	65	65	
		-2.231	-3.106	-1.356	0.000			



I-squared: 0.00; p=0.49

Appendix F Figure 24. Lifestyle vs. Control: Systolic Blood Pressure (BMI 25-29.9)

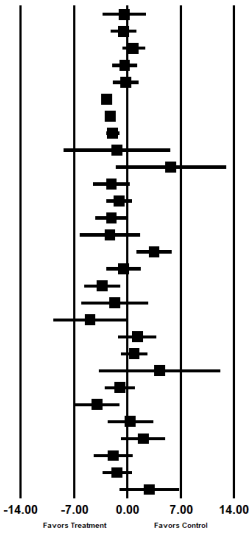


I-squared: 0.00; p=0.50

Appendix F Figure 25. Lifestyle vs. Control: Diastolic Blood Pressure (All)

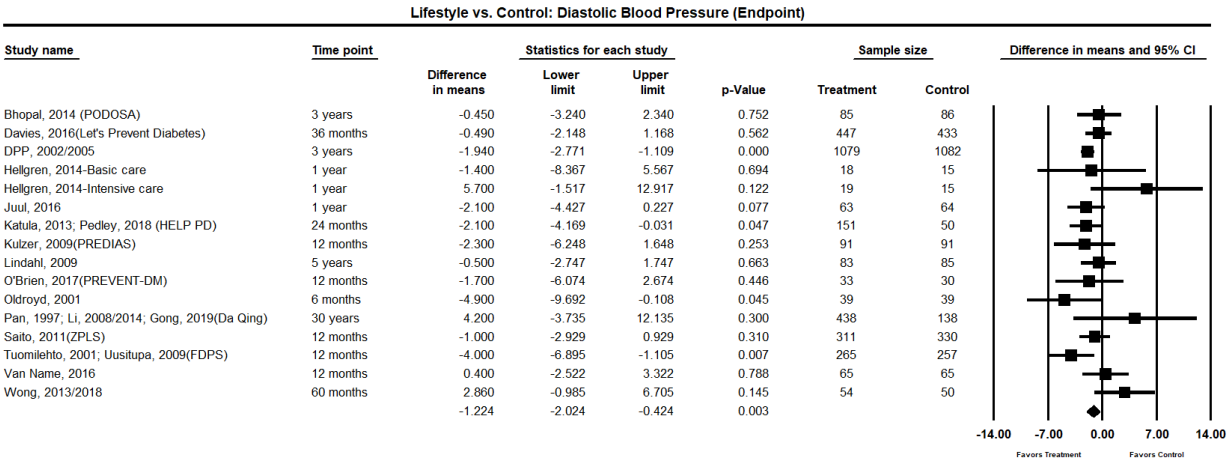
Lifestyle vs. Control: Diastolic Blood Pressure (All)

Study name	Time point	Statistics for each study				Sample size	
		Difference in means	Lower limit	Upper limit	p-Value	Treatment	Control
Bhopal, 2014 (PODOSA)	3 years	-0.450	-3.240	2.340	0.752	85	86
Davies, 2016(Let's Prevent Diabetes) - 36mo	36 months	-0.490	-2.148	1.168	0.562	447	433
Davies, 2016(Let's Prevent Diabetes)-12mo	12 months	0.800	-0.658	2.258	0.282	447	433
Davies, 2016(Let's Prevent Diabetes)-24mo	24 months	-0.370	-1.923	1.183	0.640	447	433
Davies, 2016(Let's Prevent Diabetes)-6mo	6 months	-0.220	-1.898	1.458	0.797	447	433
DPP, 2002/2005-1yr	1 years	-2.710	-3.264	-2.156	0.000	1079	1082
DPP, 2002/2005-2yrs	2 years	-2.260	-2.814	-1.706	0.000	1079	1082
DPP, 2002/2005-3yrs	3 years	-1.940	-2.771	-1.109	0.000	1079	1082
Hellgren, 2014-Basic care 2	1 year	-1.400	-8.367	5.567	0.694	18	15
Hellgren, 2014-Intensive care 2	1 year	5.700	-1.517	12.917	0.122	19	15
Juul, 2016	1 year	-2.100	-4.427	0.227	0.077	63	64
Katula, 2013; Pedley, 2018-12mo (HELP PD)	12 months	-1.100	-2.736	0.536	0.187	151	50
Katula, 2013; Pedley, 2018-24mo (HELP PD)	24 months	-2.100	-4.169	-0.031	0.047	151	50
Kulzer, 2009(PREDIAS)	12 months	-2.300	-6.248	1.648	0.253	91	91
Lindahl, 2009 - 3 yrs	3 years	3.500	1.253	5.747	0.002	83	85
Lindahl, 2009 - 5 yrs	5 years	-0.500	-2.747	1.747	0.663	83	85
Lindahl, 2009-1 yr	1 year	-3.300	-5.633	-0.967	0.006	83	85
O'Brien, 2017(PREVENT-DM)	12 months	-1.700	-6.074	2.674	0.446	33	30
Oldroyd, 2001	6 months	-4.900	-9.692	-0.108	0.045	39	39
Pan, 1997; Li, 2008/2014; Gong, 2019(Da Qing)-6yrs	6 years	1.300	-1.156	3.756	0.300	438	138
Pan, 1997; Li, 2008/2014; Gong, 2019(Da Qing)-20yrs	20 years	0.900	-0.800	2.600	0.300	438	138
Pan, 1997; Li, 2008/2014; Gong, 2019(Da Qing)-30yrs	30 years	4.200	-3.735	12.135	0.300	438	138
Saito, 2011(ZPLS)	12 months	-1.000	-2.929	0.929	0.310	311	330
Tuomilehto, 2001; Uusitupa, 2009 (FDPS)	12 months	-4.000	-6.895	-1.105	0.007	265	257
Van Name, 2016	12 months	0.400	-2.522	3.322	0.788	65	65
Wong, 2013/2018-6mo	6 months	2.070	-0.783	4.923	0.155	54	50
Wong, 2013/2018-12mo	12 months	-1.820	-4.328	0.688	0.155	54	50
Wong, 2013/2018-24mo	24 months	-1.350	-3.210	0.510	0.155	54	50
Wong, 2013/2018-60mo	60 months	2.860	-0.985	6.705	0.145	54	50



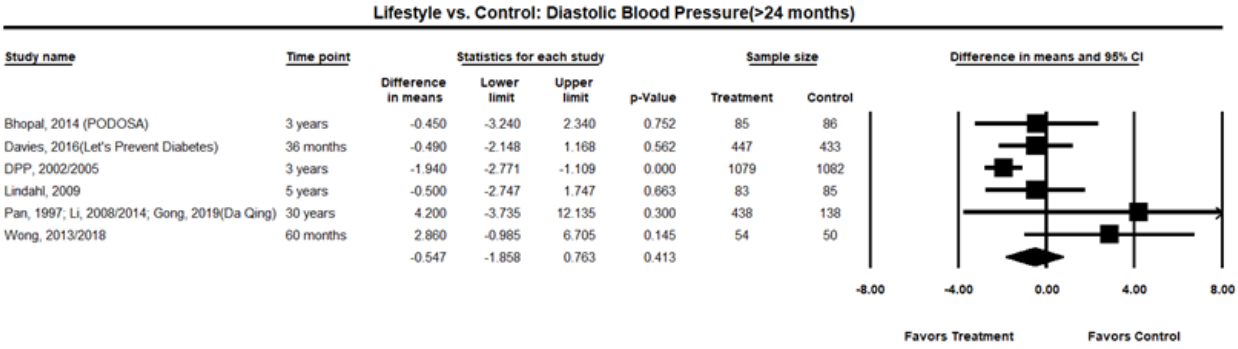
I-squared: N/A; p=N/A

Appendix F Figure 26. Lifestyle vs. Control: Diastolic Blood Pressure (Endpoint)



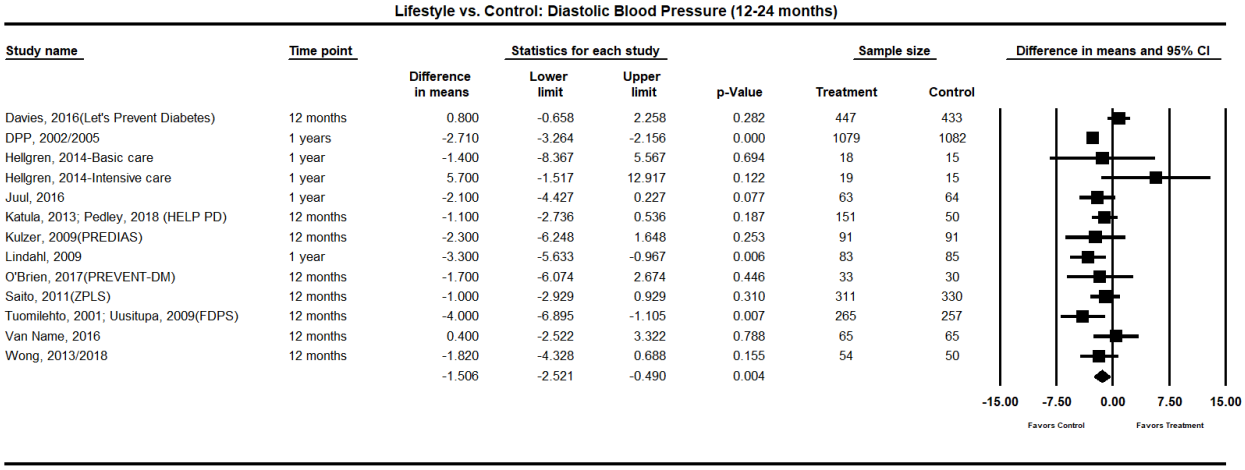
I-squared: 31.62; p=0.110

Appendix F Figure 27. Lifestyle vs. Control: Diastolic Blood Pressure (>24 Months)



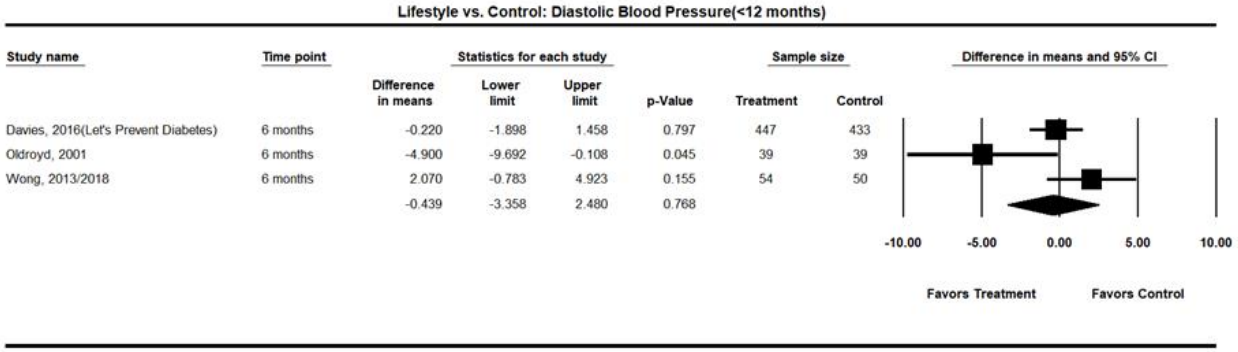
I-squared: 51.82; p=0.065

Appendix F Figure 28. Lifestyle vs. Control: Diastolic Blood Pressure (12-24 Months)



I-squared: 63.22; p=0.001

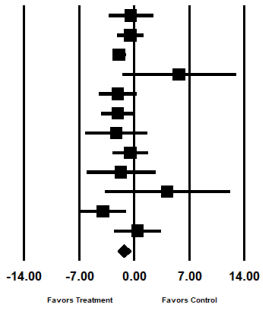
Appendix F Figure 29. Lifestyle vs. Control: Diastolic Blood Pressure (<12 months)



Appendix F Figure 30. High Contact Lifestyle vs. Control: Diastolic Blood Pressure

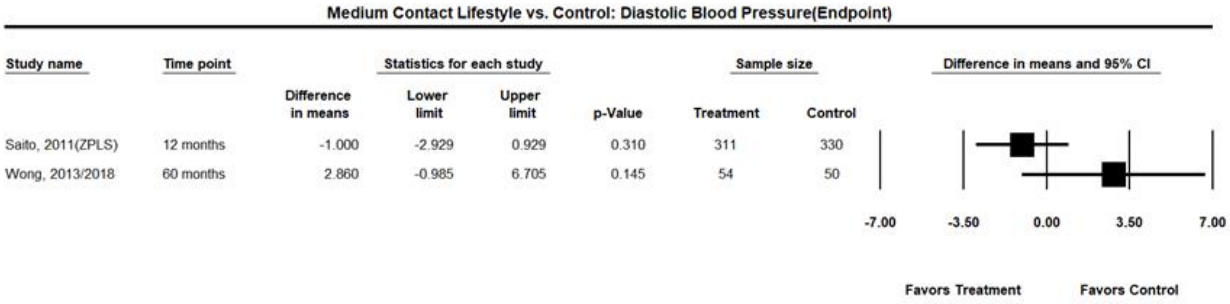
High Contact Lifestyle vs. Control: Diastolic Blood Pressure (Endpoint)

Study name	Time point	Difference in means	Statistics for each study: Lower limit	Upper limit	p-Value	Sample size: Treatment	Control
Bhopal, 2014 (PODOSA)	3 years	-0.450	-3.240	2.340	0.752	85	86
Davies, 2016(Let's Prevent Diabetes)	36 months	-0.490	-2.148	1.168	0.562	447	433
DPP, 2002/2005	3 years	-1.940	-2.771	-1.109	0.000	1079	1082
Hellgren, 2014-Intensive care	1 year	5.700	-1.517	12.917	0.122	19	15
Juul, 2016	1 year	-2.100	-4.427	0.227	0.077	63	64
Katula, 2013; Pedley, 2018 (HELP PD)	24 months	-2.100	-4.169	-0.031	0.047	151	50
Kulzer, 2009(PREDIAS)	12 months	-2.300	-6.248	1.648	0.253	91	91
Lindahl, 2009	5 years	-0.500	-2.747	1.747	0.663	83	85
O'Brien, 2017(PREVENT-DM)	12 months	-1.700	-6.074	2.674	0.446	33	30
Pan, 1997; Li, 2008/2014; Gong, 2019(Da Qing)	30 years	4.200	-3.735	12.135	0.300	438	138
Tuomilehto, 2001; Uusitupa, 2009(FDPS)	12 months	-4.000	-6.895	-1.105	0.007	265	257
Van Name, 2016	12 months	0.400	-2.522	3.322	0.788	65	65
		-1.352	-2.166	-0.537	0.001		



I-squared: 25.84; p=0.190

Appendix F Figure 31. Medium Contact Lifestyle vs. Control: Diastolic Blood Pressure

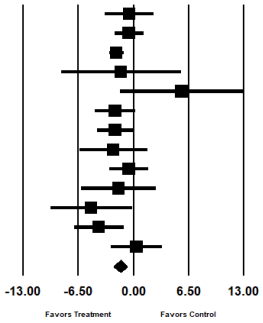


I-squared: N/A; p=N/A

Appendix F Figure 32. Lifestyle vs. Control: Diastolic Blood Pressure (BMI >30)

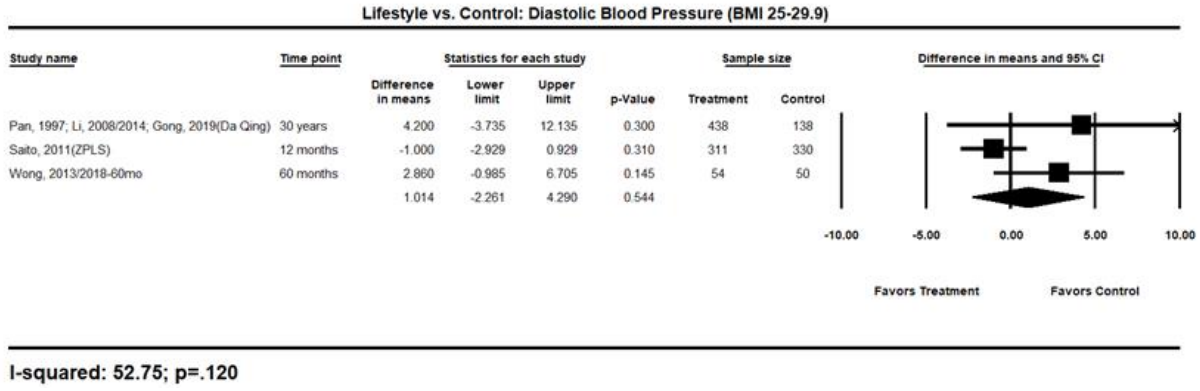
Lifestyle vs. Control: Diastolic Blood Pressure (BMI>30)

Study name	Time point	Statistics for each study				Sample size		Difference in means and 95% CI
		Difference in means	Lower limit	Upper limit	p-Value	Treatment	Control	
Bhopal, 2014 (PODOSA)	3 years	-0.450	-3.240	2.340	0.752	85	86	
Davies, 2016(Let's Prevent Diabetes)	36 months	-0.490	-2.148	1.168	0.562	447	433	
DPP, 2002/2005	3 years	-1.940	-2.771	-1.109	0.000	1079	1082	
Hellgren, 2014-Basic care	1 year	-1.400	-8.367	5.567	0.694	18	15	
Hellgren, 2014-Intensive care	1 year	5.700	-1.517	12.917	0.122	19	15	
Juul, 2016	1 year	-2.100	-4.427	0.227	0.077	63	64	
Katula, 2013; Pedley, 2018-24mo (HELP PD)	24 months	-2.100	-4.169	-0.031	0.047	151	50	
Kulzer, 2009(PREDIAS)	12 months	-2.300	-6.248	1.648	0.253	91	91	
Lindahl, 2009	5 years	-0.500	-2.747	1.747	0.663	83	85	
O'Brien, 2017(PREVENT-DM)	12 months	-1.700	-6.074	2.674	0.446	33	30	
Oldroyd, 2001	6 months	-4.900	-9.692	-0.108	0.045	39	39	
Tuomilehto, 2001; Uusitupa, 2009(FDPS)	12 months	-4.000	-6.895	-1.105	0.007	265	257	
Van Name, 2016	12 months	0.400	-2.522	3.322	0.788	65	65	
		-1.515	-2.265	-0.764	0.000			



I-squared: 18.12; p=0.261

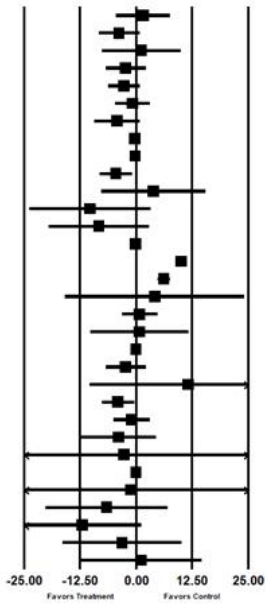
Appendix F Figure 33. Lifestyle vs. Control: Diastolic Blood Pressure (BMI 25-29.9)



Appendix F Figure 34. Lifestyle vs. Control: Total Cholesterol (All)

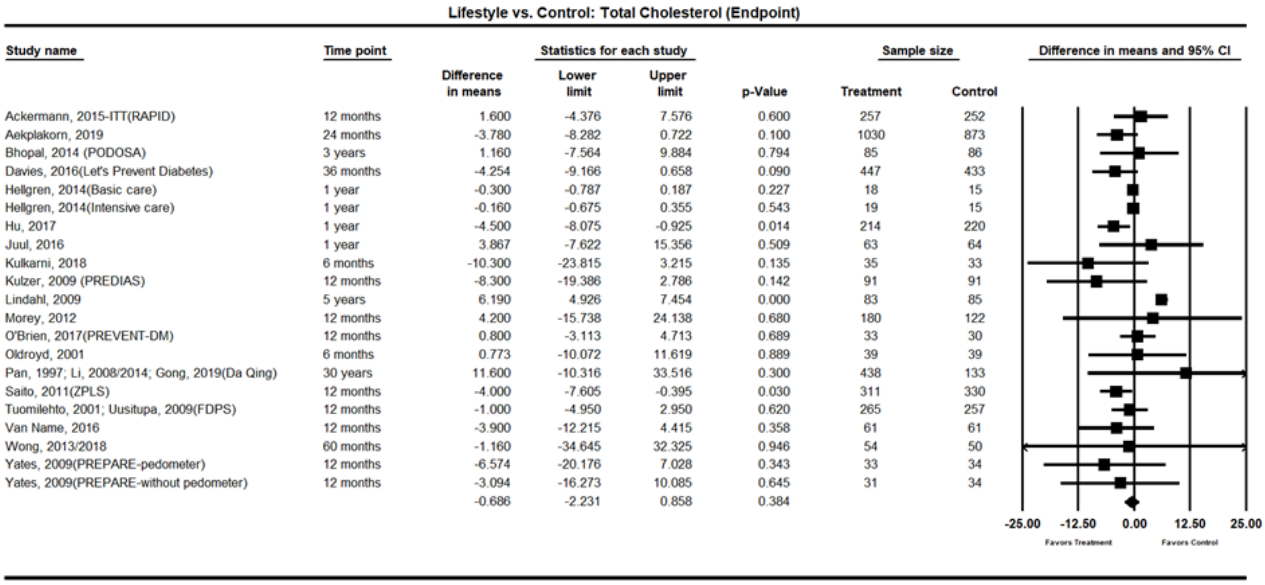
Lifestyle vs. Control: Total Cholesterol (All)

Study name	Time point	Difference in means	Statistics for each study: Lower limit	Upper limit	p-Value	Sample size: Treatment	Control
Ackermann, 2015-ITT(RAPID)	12 months	1.600	-4.376	7.576	0.600	257	252
Aekplakorn, 2019	24 months	-3.780	-8.282	0.722	0.100	1030	873
Bhopal, 2014 (PODOSA)	3 years	1.160	-7.564	9.884	0.794	85	86
Davies, 2016 (Let's Prevent Diabetes) -6 mo	6 months	-2.320	-6.705	2.065	0.300	447	433
Davies, 2016 (Let's Prevent Diabetes)-12mo	12 months	-2.707	-6.208	0.794	0.130	447	433
Davies, 2016 (Let's Prevent Diabetes)-24mo	24 months	-0.773	-4.573	3.026	0.690	447	433
Davies, 2016(Let's Prevent Diabetes)-36mo	36 months	-4.254	-9.166	0.658	0.090	447	433
Hellgren, 2014(Basic care)-2	1 year	-0.300	-0.787	0.187	0.227	18	15
Hellgren, 2014(Intensive care)-2	1 year	-0.160	-0.675	0.355	0.543	19	15
Hu, 2017	1 year	-4.500	-8.075	-0.925	0.014	214	220
Juul, 2016	1 year	3.867	-7.622	15.356	0.509	63	64
Kulkarni, 2018	6 months	-10.300	-23.815	3.215	0.135	35	33
Kulzer, 2009 (PREDIAS)	12 months	-8.300	-19.386	2.786	0.142	91	91
Lindahl, 2009-1yr	1 year	-0.120	-0.289	0.049	0.163	83	85
Lindahl, 2009-3yrs	3 years	10.060	8.796	11.324	0.000	83	85
Lindahl, 2009-5yrs	5 years	6.190	4.926	7.454	0.000	83	85
Morey, 2012	12 months	4.200	-15.738	24.138	0.680	180	122
O'Brien, 2017(PREVENT-DM)	12 months	0.800	-3.113	4.713	0.689	33	30
Oldroyd, 2001	6 months	0.773	-10.072	11.619	0.889	39	39
Pan, 1997; Li, 2008/2014; Gong, 2019(Da Qing)-6yrs	6 years	0.004	-0.004	0.012	0.300	438	138
Pan, 1997; Li, 2008/2014; Gong, 2019(Da Qing)-20yrs	20 years	-2.320	-6.703	2.063	0.300	438	138
Pan, 1997; Li, 2008/2014; Gong, 2019(Da Qing)-30yrs	30 years	11.600	-10.316	33.516	0.300	438	133
Saito, 2011(ZPLS)	12 months	-4.000	-7.605	-0.395	0.030	311	330
Tuomilehto, 2001; Uusitupa, 2009(FDPS)	12 months	-1.000	-4.950	2.950	0.620	265	257
Van Name, 2016	12 months	-3.900	-12.215	4.415	0.358	61	61
Wong, 2013/2018-12mo	12 months	-2.700	-80.639	75.239	0.946	54	50
Wong, 2013/2018-24mo	24 months	0.003	-0.084	0.090	0.946	54	50
Wong, 2013/2018-60mo	60 months	-1.160	-34.645	32.325	0.946	54	50
Yates, 2009(PREPARE-pedometer)-12mo	12 months	-6.574	-20.176	7.028	0.343	33	34
Yates, 2009(PREPARE-pedometer)-6mo	6 months	-11.988	-25.019	1.043	0.071	33	34
Yates, 2009(PREPARE-without pedometer)-12mo	12 months	-3.094	-16.273	10.085	0.645	31	34
Yates, 2009(PREPARE-without pedometer)-6mo	6 months	1.160	-12.158	14.478	0.864	31	34



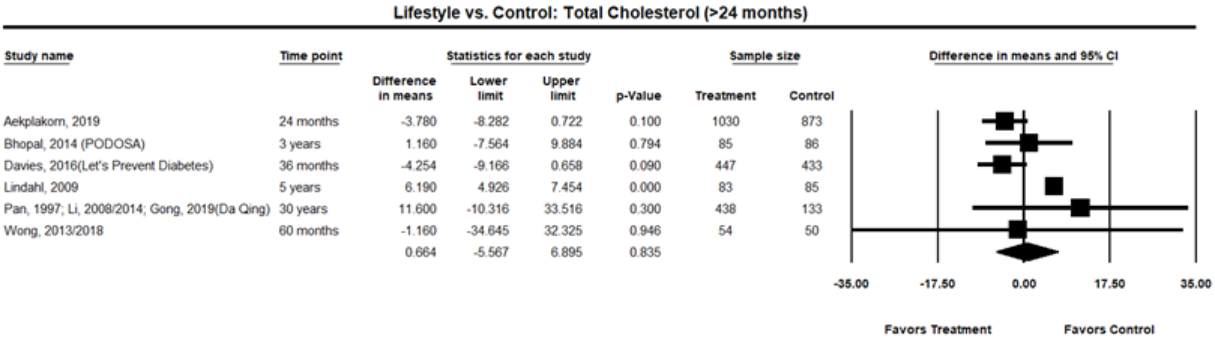
I-squared: N/A; p=N/A

Appendix F Figure 35. Lifestyle vs. Control: Total Cholesterol (Endpoint)



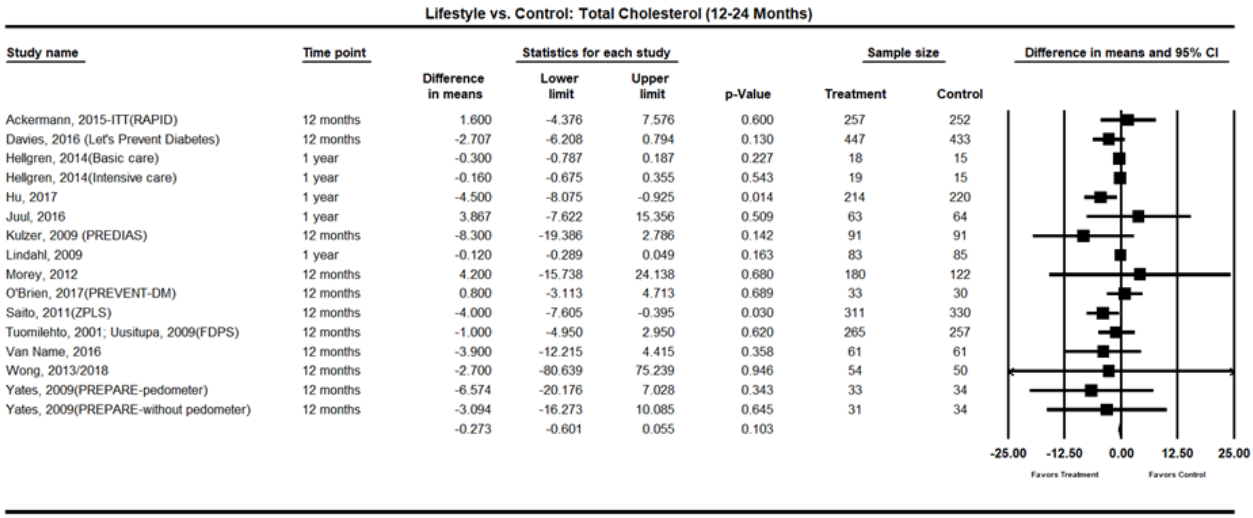
I-squared: 83.17; p=0.00

Appendix F Figure 36. Lifestyle vs. Control: Total Cholesterol (>24 Months)



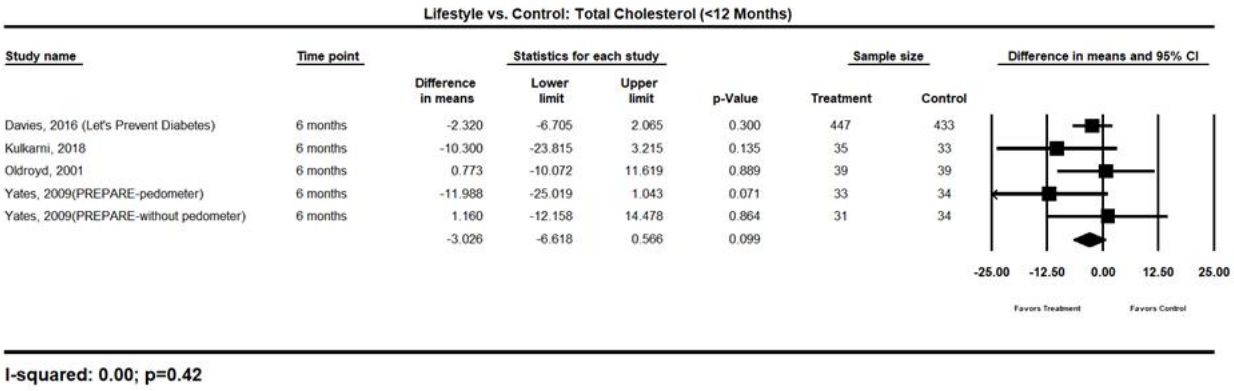
I-squared: 84.76 p=0.00

Appendix F Figure 37. Lifestyle vs. Control: Total Cholesterol (12-24 Months)

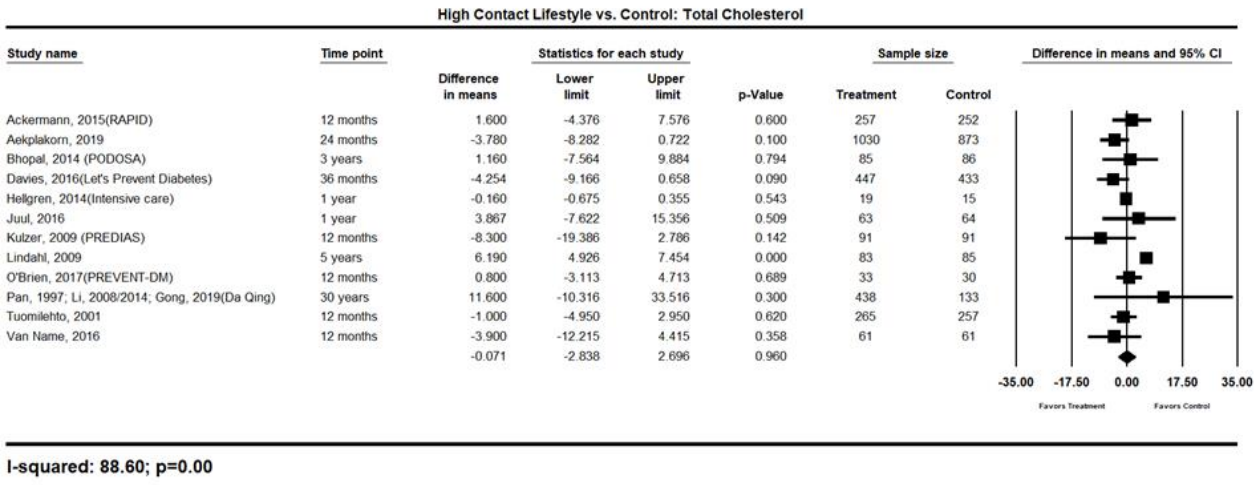


I-squared: 16.11; p=0.269

Appendix F Figure 38. Lifestyle vs. Control: Total Cholesterol (<12 Months)

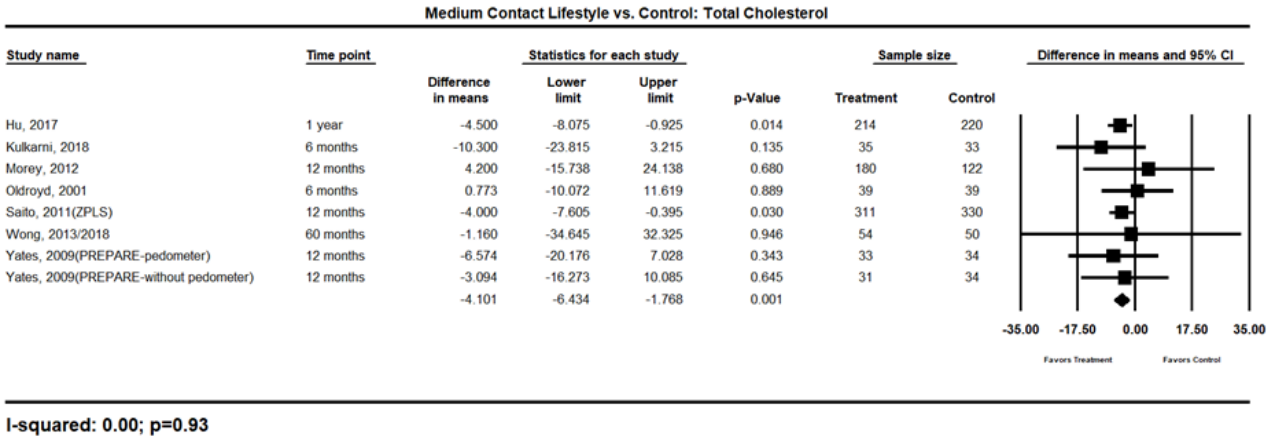


Appendix F Figure 39. High Contact Lifestyle vs. Control: Total Cholesterol



I-squared: 88.60; p=0.00

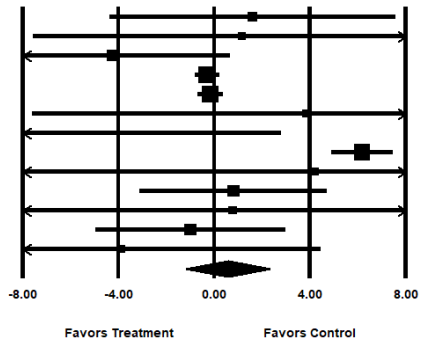
Appendix F Figure 40. Medium Contact Lifestyle vs. Control: Total Cholesterol



I-squared: 0.00; p=0.93

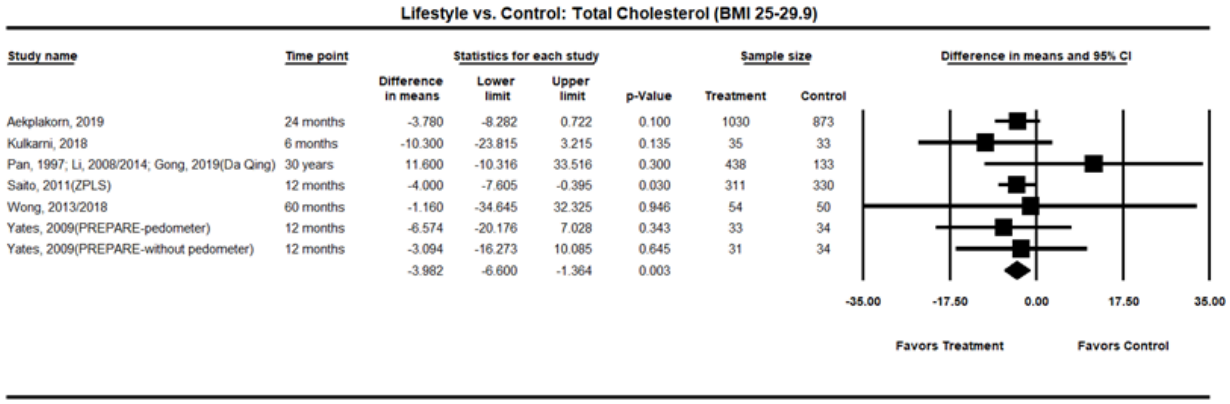
Appendix F Figure 41. Lifestyle vs. Control: Total Cholesterol (BMI >30)

Study name	Time point	Statistics for each study				Sample size	
		Difference in means	Lower limit	Upper limit	p-Value	Treatment	Control
Ackermann, 2015-ITT(RAPID)	12 months	1.600	-4.376	7.576	0.600	257	252
Bhopal, 2014 (PODOSA)	3 years	1.160	-7.564	9.884	0.794	85	86
Davies, 2016(Let's Prevent Diabetes)-36mo	36 months	-4.254	-9.166	0.658	0.090	447	433
Hellgren, 2014(Basic care)-2	1 year	-0.300	-0.787	0.187	0.227	18	15
Hellgren, 2014(Intensive care)-2	1 year	-0.160	-0.675	0.355	0.543	19	15
Juul, 2016	1 year	3.867	-7.602	15.336	0.509	52	56
Kulzer, 2009 (PREDIAS)	12 months	-8.300	-19.386	2.786	0.142	91	91
Lindahl, 2009-5yrs	5 years	6.190	4.926	7.454	0.000	83	85
Morey, 2012	12 months	4.200	-15.738	24.138	0.680	180	122
O'Brien, 2017(PREVENT-DM)	12 months	0.800	-3.113	4.713	0.689	33	30
Oldroyd, 2001	6 months	0.773	-10.042	11.589	0.889	35	32
Tuomilehto, 2001; Uusitupa, 2009(FDPS)	12 months	-1.000	-4.950	2.950	0.620	265	257
Van Name, 2016	12 months	-3.900	-12.215	4.415	0.358	61	61
		0.555	-1.205	2.315	0.536		



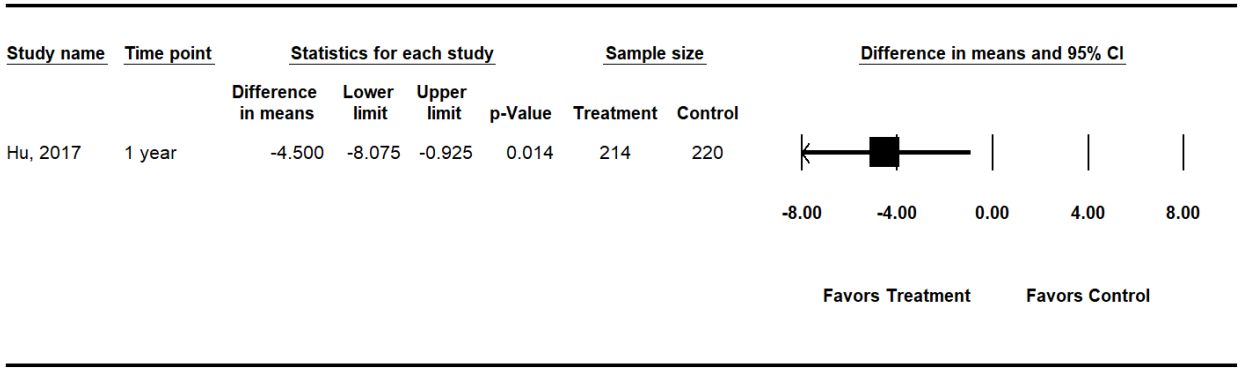
I-squared: 87.97; p=0.00

Appendix F Figure 42. Lifestyle vs. Control: Total Cholesterol (BMI 25-29.9)



I-squared: 0.00; p=0.81

Appendix F Figure 43. Lifestyle vs. Control: Total Cholesterol (BMI <25)

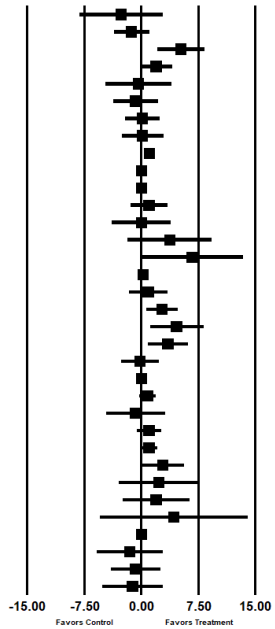


I-squared:N/A; p=N/A

Appendix F Figure 44. Lifestyle vs. Control: High Density Lipoprotein (All)

Lifestyle vs. Control: High Density Lipoprotein (All)

Study name	Time point	Difference in means	Lower limit	Upper limit	p-Value	Sample size: Treatment	Sample size: Control
Ackermann, 2015-instrumental variable	12 months	-2.700	-8.127	2.727	0.330	257	252
Ackermann, 2015-ITT(RAPID)	12 months	-1.300	-3.607	1.007	0.269	257	252
Aekplakorn, 2019	24 months	5.200	2.107	8.293	0.001	1030	873
Bhopal, 2014(PODOSA)	3 years	1.934	-0.114	3.981	0.064	85	86
Davies, 2016 (Let's Prevent Diabetes)-12mo	12 months	-0.387	-4.683	3.909	0.860	447	433
Davies, 2016(Let's Prevent Diabetes) -36mo	36 months	-0.773	-3.663	2.116	0.600	447	433
Davies, 2016(Let's Prevent Diabetes) -6mo	6 months	0.116	-2.147	2.379	0.920	447	433
Davies, 2016(Let's Prevent Diabetes)-24mo	24 months	0.155	-2.527	2.836	0.910	447	433
DPP, 2002/2005	3 years	1.100	0.446	1.754	0.001	1073	1082
Hellgren, 2014-(Basic care)-2	1 year	0.060	-0.062	0.182	0.337	18	15
Hellgren, 2014-(Intensive care)-2	1 year	0.000	-0.003	0.003	0.949	19	15
Hu, 2017	1 year	1.000	-1.402	3.402	0.415	214	220
Juul, 2016	1 year	0.000	-3.830	3.830	1.000	63	64
Katula, 2013; Pedley, 2018-12mo (HELP PD)	12 months	3.700	-1.808	9.208	0.188	151	150
Katula, 2013; Pedley, 2018-24mo (HELP PD)	24 months	6.700	0.086	13.314	0.047	151	150
Kulkarni, 2018	6 months	0.200	-0.138	0.538	0.246	35	33
Kulzer, 2009(PREDIAS)	12 months	0.900	-1.587	3.387	0.478	91	91
Lindahl, 2009-1 yr	1 year	2.700	0.669	4.731	0.009	83	85
Lindahl, 2009-3yr	3 years	4.640	1.150	8.130	0.009	83	85
Lindahl, 2009-5yr	5 years	3.480	0.862	6.098	0.009	83	85
Morey, 2012(Enhanced Fitness)	12 months	-0.200	-2.593	2.193	0.870	180	122
Moungngern, 2018	6 months	0.000	0.000	0.000	0.044	61	64
O'Brien, 2017(PREVENT-DM)	12 months	0.800	-0.230	1.830	0.128	33	30
Oldroyd, 2001	6 months	-0.773	-4.579	3.032	0.690	39	39
Saito, 2011(ZPLS)	12 months	1.000	-0.596	2.596	0.220	311	330
Tuomilehto, 2001; Uusitupa, 2009(FDPS)	12 months	1.000	-0.040	2.040	0.059	265	257
Van Name, 2016	12 months	2.800	0.076	5.524	0.044	65	65
Wong, 2013/2018-12mo	12 months	2.320	-2.936	7.577	0.387	54	50
Wong, 2013/2018-24mo	24 months	1.934	-2.447	6.314	0.387	54	50
Wong, 2013/2018-60mo	60 months	4.254	-5.383	13.891	0.387	54	50
Yates, 2009-(PREPARE with pedometer)-12mo	12 months	0.000	-0.002	0.002	0.927	33	34
Yates, 2009-(PREPARE with pedometer)-6mo	6 months	-1.547	-5.835	2.741	0.479	33	34
Yates, 2009-(PREPARE without pedometer)-12mo	12 months	-0.773	-3.940	2.394	0.632	31	34
Yates, 2009-(PREPARE without pedometer)-6mo	6 months	-1.160	-5.060	2.740	0.560	31	34

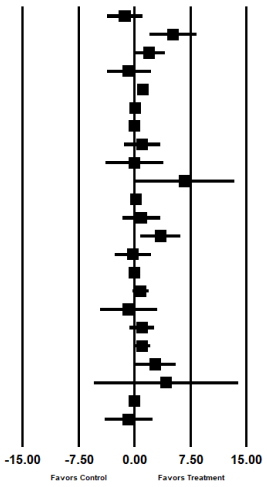


I-squared: N/A; p=N/A

Appendix F Figure 45. Lifestyle vs. Control: High Density Lipoprotein (Endpoint)

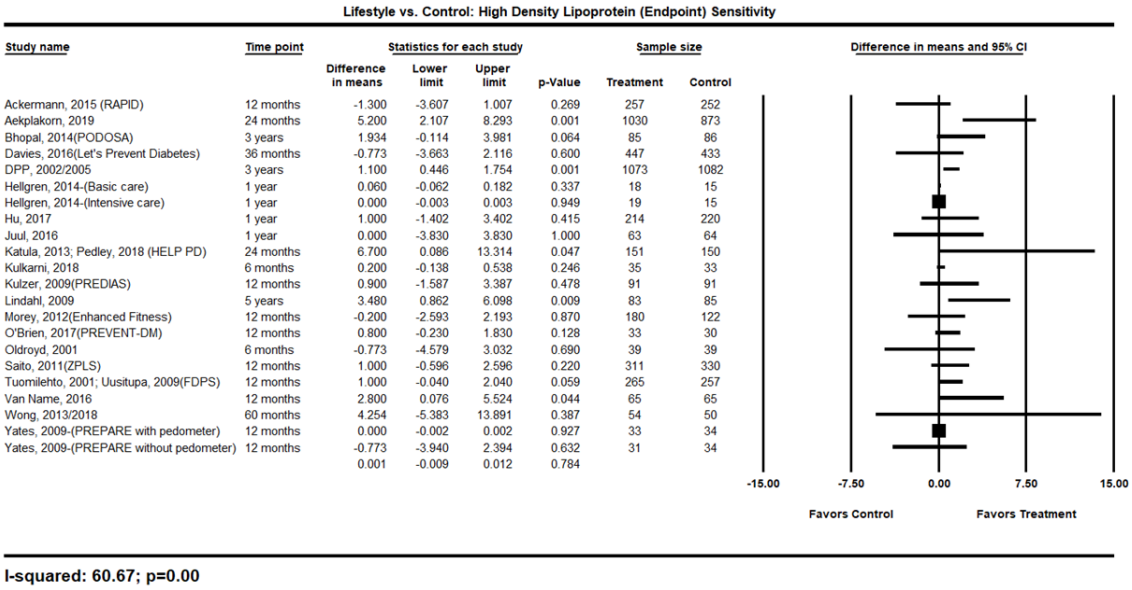
Lifestyle vs. Control: High Density Lipoprotein (Endpoint)

Study name	Time point	Difference in means	Lower limit	Upper limit	p-Value	Sample size: Treatment	Sample size: Control
Ackermann, 2015 (RAPID)	12 months	-1.300	-3.607	1.007	0.269	257	252
Aekplakorn, 2019	24 months	5.200	2.107	8.293	0.001	1030	873
Bhopal, 2014(PODOSA)	3 years	1.934	-0.114	3.981	0.064	85	86
Davies, 2016(Let's Prevent Diabetes)	36 months	-0.773	-3.663	2.116	0.600	447	433
DPP, 2002/2005	3 years	1.100	0.446	1.754	0.001	1073	1082
Hellgren, 2014-(Basic care)	1 year	0.060	-0.062	0.182	0.337	18	15
Hellgren, 2014-(Intensive care)	1 year	0.000	-0.003	0.003	0.949	19	15
Hu, 2017	1 year	1.000	-1.402	3.402	0.415	214	220
Juul, 2016	1 year	0.000	-3.830	3.830	1.000	63	64
Katula, 2013; Pedley, 2018 (HELP PD)	24 months	6.700	0.086	13.314	0.047	151	150
Kulkarni, 2018	6 months	0.200	-0.138	0.538	0.246	35	33
Kulzer, 2009(PREDIAS)	12 months	0.900	-1.587	3.387	0.478	91	91
Lindahl, 2009	5 years	3.480	0.862	6.098	0.009	83	85
Morey, 2012(Enhanced Fitness)	12 months	-0.200	-2.593	2.193	0.870	180	122
Moungngern, 2018	6 months	0.000	0.000	0.000	0.044	61	64
O'Brien, 2017(PREVENT-DM)	12 months	0.800	-0.230	1.830	0.128	33	30
Oldroyd, 2001	6 months	-0.773	-4.579	3.032	0.690	39	39
Saito, 2011(ZPLS)	12 months	1.000	-0.596	2.596	0.220	311	330
Tuomilehto, 2001; Uusitupa, 2009(FDPS)	12 months	1.000	-0.040	2.040	0.059	265	257
Van Name, 2016	12 months	2.800	0.076	5.524	0.044	65	65
Wong, 2013/2018	60 months	4.254	-5.383	13.891	0.387	54	50
Yates, 2009-(PREPARE with pedometer)	12 months	0.000	-0.002	0.002	0.927	33	34
Yates, 2009-(PREPARE without pedometer)	12 months	-0.773	-3.940	2.394	0.632	31	34
		0.000	-0.004	0.004	0.883		



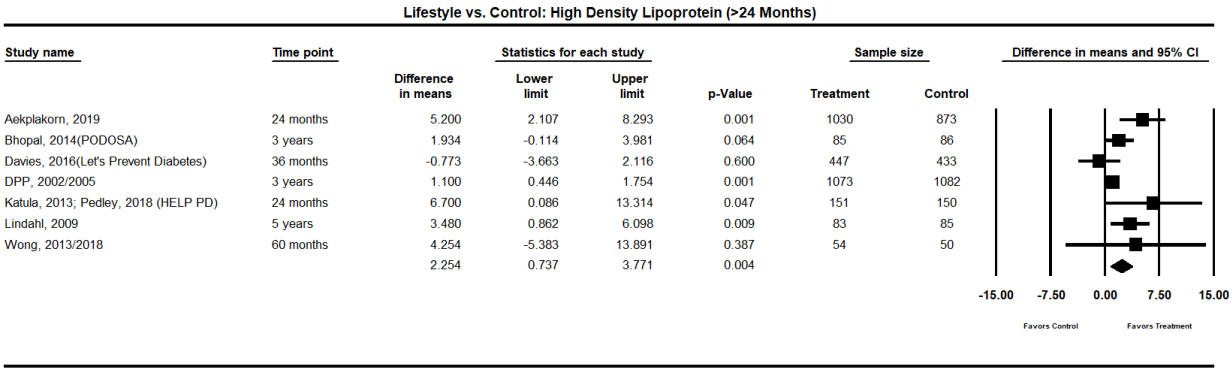
I-squared: 58.80; p=0.00

Appendix F Figure 46. Lifestyle vs. Control: High Density Lipoprotein (Endpoint) Sensitivity Analysis



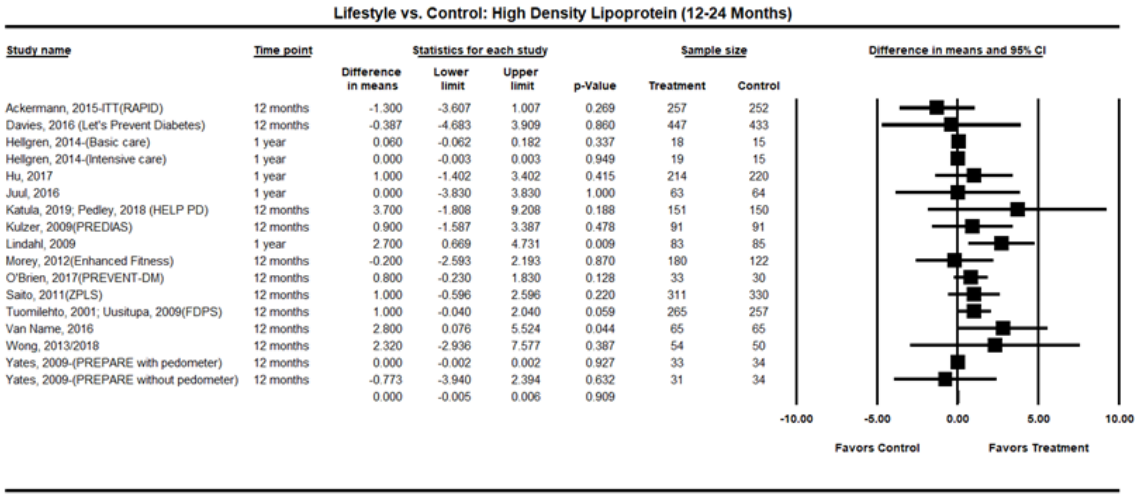
Note: This sensitivity analysis removed one study from Figure 45 (Moungngern, 2018), a study that found no difference between groups, had just 125 participants, and was potentially overweighted in the meta-analysis.

Appendix F Figure 47. Lifestyle vs. Control: High Density Lipoprotein (>24 Months)



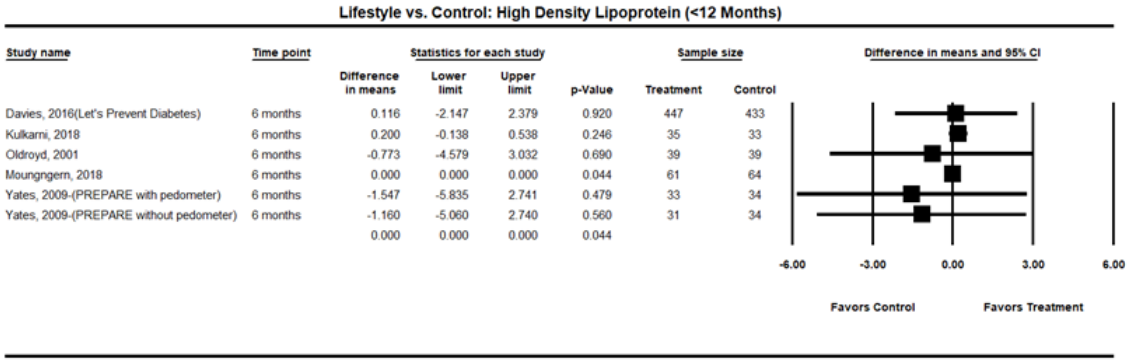
I-squared: 57.96; p=0.27

Appendix F Figure 48. Lifestyle vs. Control: High Density Lipoprotein (12-24 Months)



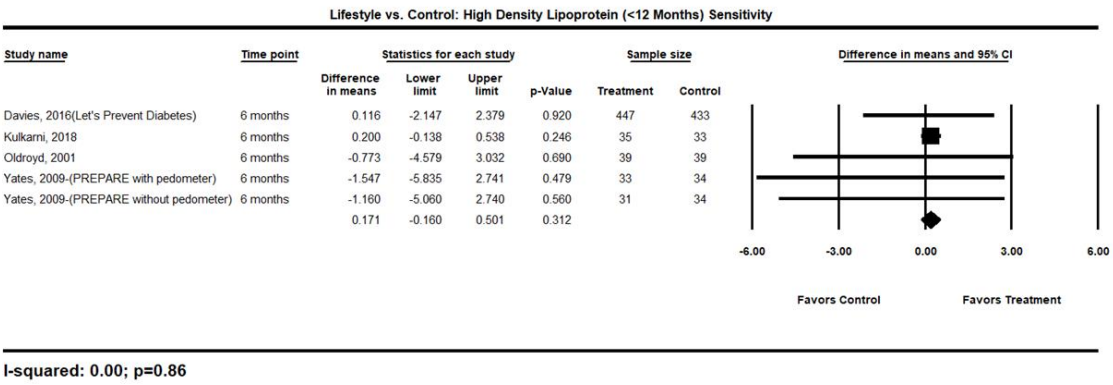
I-squared: 34.16; p=0.083

Appendix F Figure 49. Lifestyle vs. Control: High Density Lipoprotein (<12 Months)



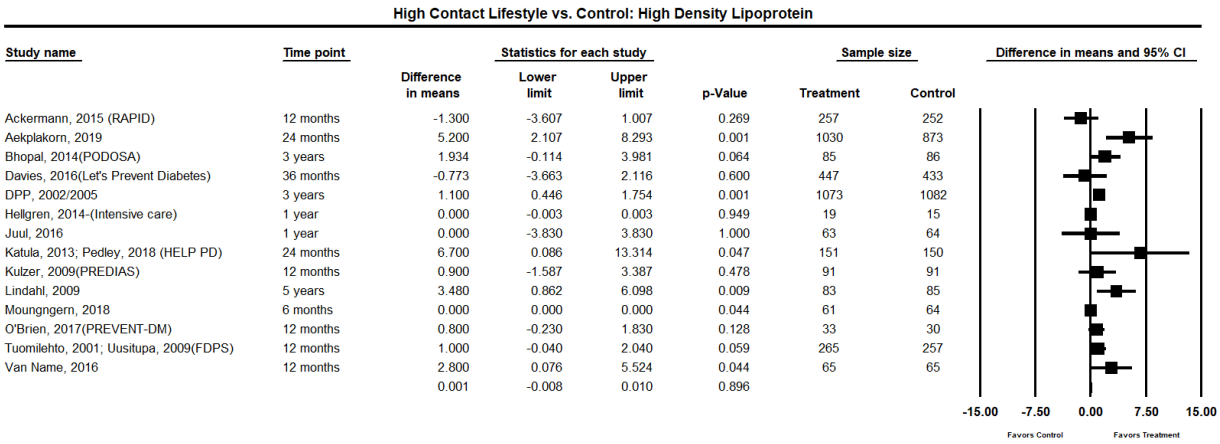
I-squared: 0.00; p=0.80

Appendix F Figure 50. Lifestyle vs. Control: High Density Lipoprotein (<12 Months) Sensitivity Analysis



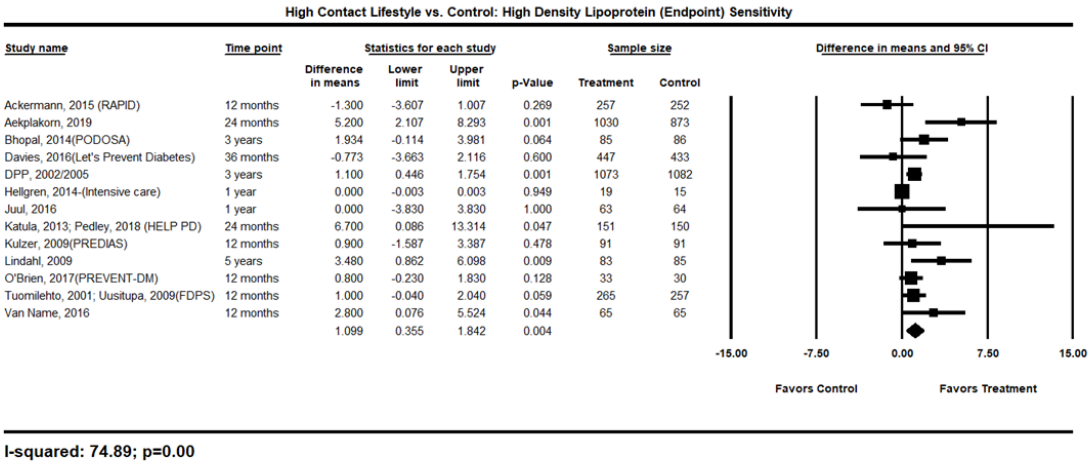
Note: This sensitivity analysis removed one study from Figure 49 (Moungngern, 2018), a study that found no difference between groups, had just 125 participants, and was potentially overweighted in the meta-analysis.

Appendix F Figure 51. High Contact Lifestyle vs. Control: High Density Lipoprotein



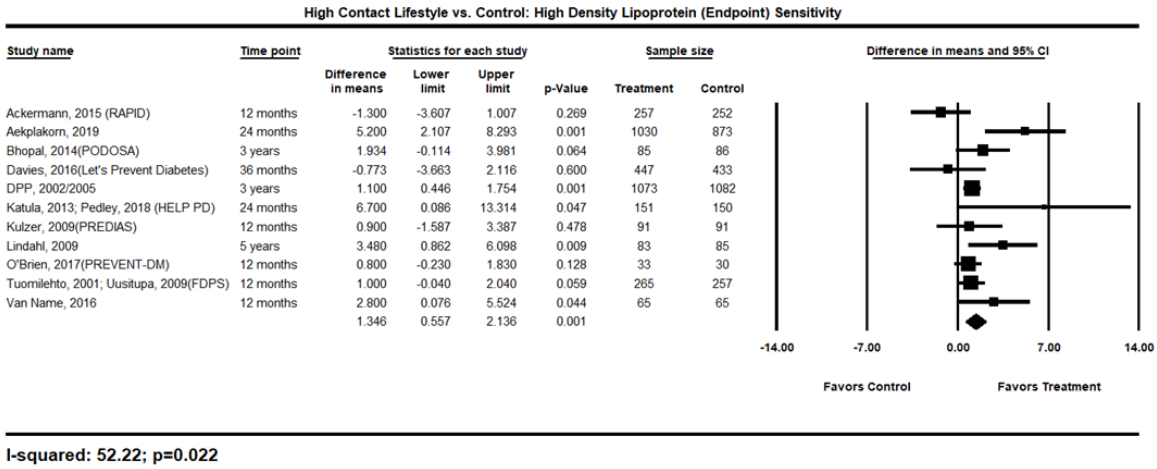
I-squared: 72.80; p=0.000

Appendix F Figure 53. High Contact Lifestyle vs. Control: High Density Lipoprotein Sensitivity Analysis



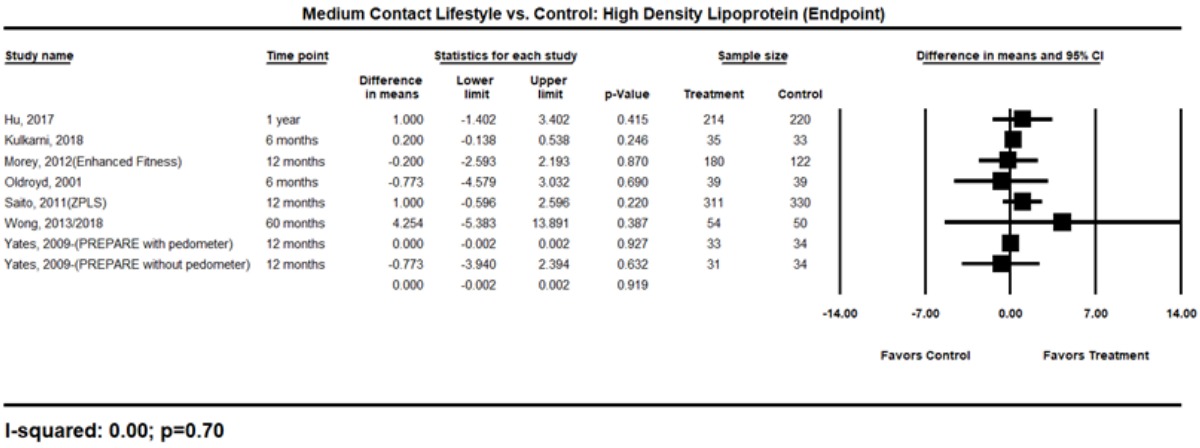
Note: This sensitivity analysis removed one study from Figure 51 (Moungngern, 2018), a study that found no difference between groups, had just 125 participants, and was potentially overweighted in the meta-analysis.

Appendix F Figure 53. High Contact Lifestyle vs. Control: High Density Lipoprotein Sensitivity Analysis



Note: This sensitivity analysis removed three studies from Figure 51 (Hellgren, 2014; Juul, 2016; and Moungngern, 2018) that found no difference between groups and were potentially overweighted in the meta-analysis.

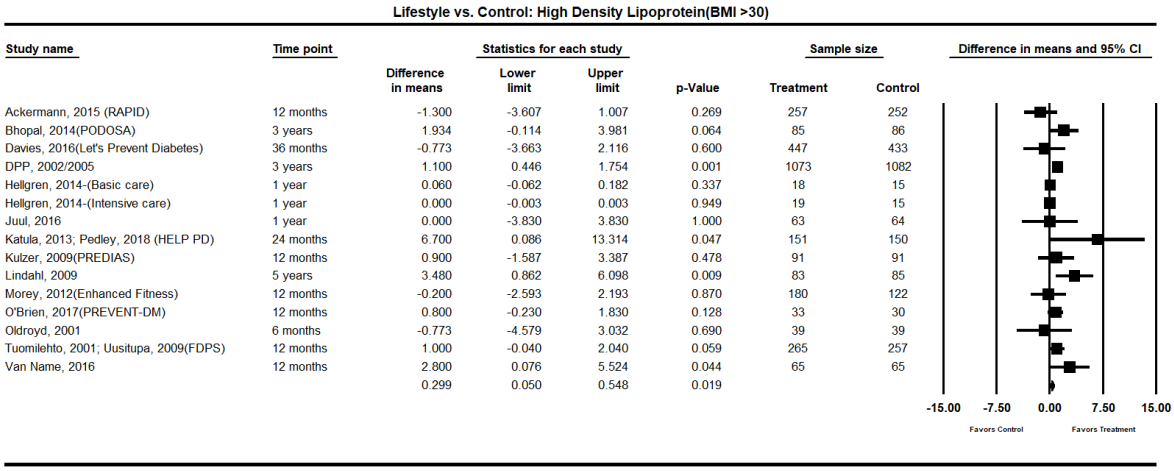
Appendix F Figure 54. Medium Contact Lifestyle vs. Control: High Density Lipoprotein



I-squared: 0.00; p=0.70

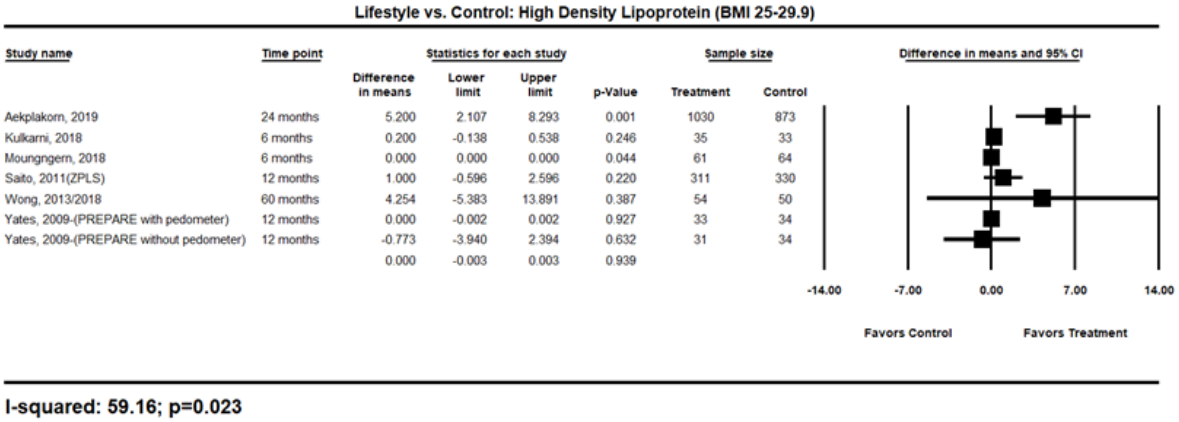
Appendix F Figure 54. Medium Contact Lifestyle vs. Control: High Density Lipoprotein

Appendix F Figure 55. Lifestyle vs. Control: High Density Lipoprotein (BMI >30)



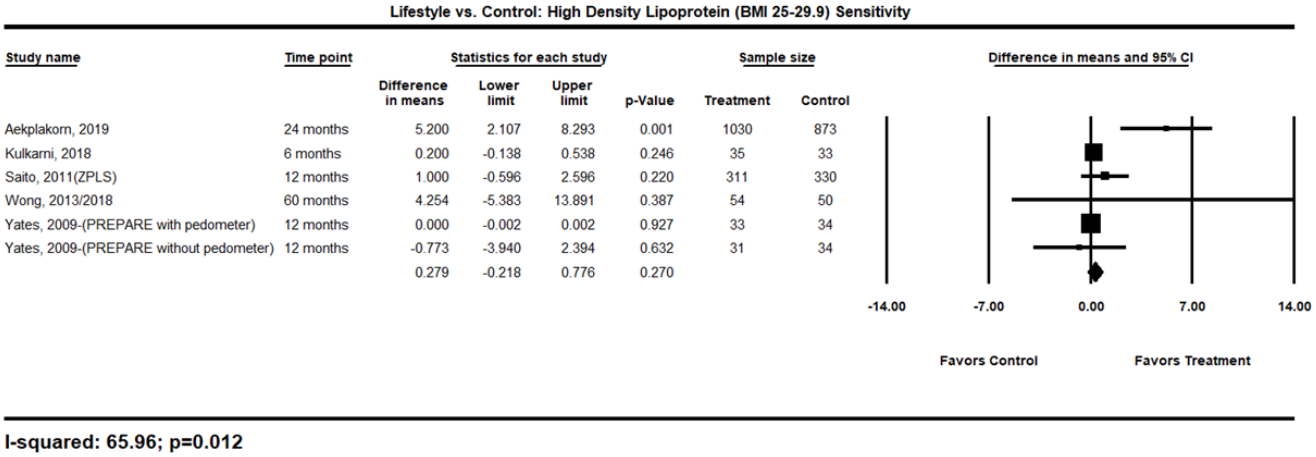
I-squared: 63.20; p=0.001

Appendix F Figure 56. Lifestyle vs. Control: High Density Lipoprotein (BMI 25-29.9)



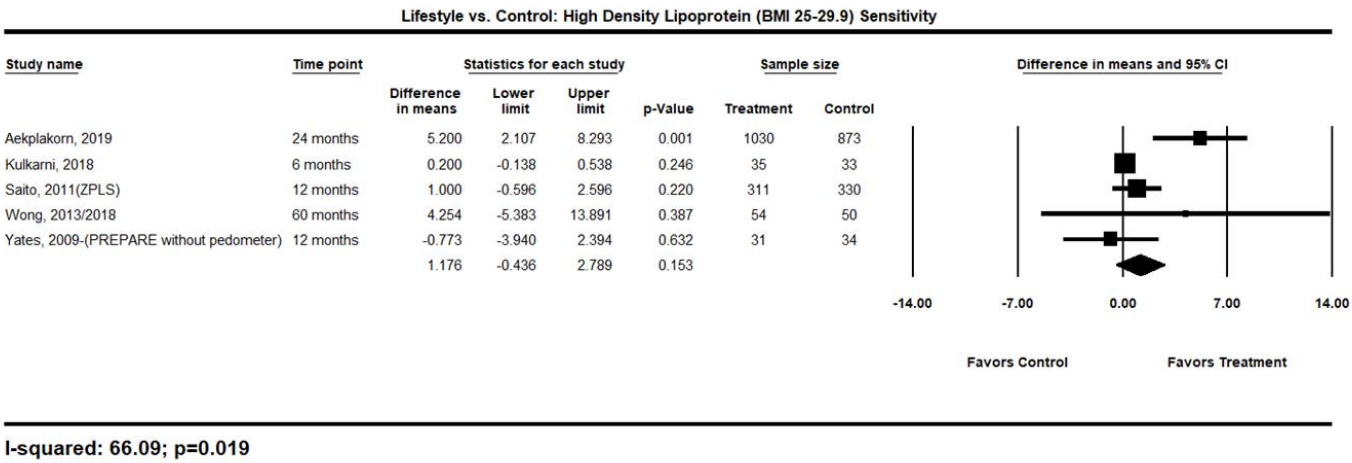
I-squared: 59.16; p=0.023

Appendix F Figure 57. Lifestyle vs. Control: High Density Lipoprotein (BMI 25-29.9) Sensitivity Analysis



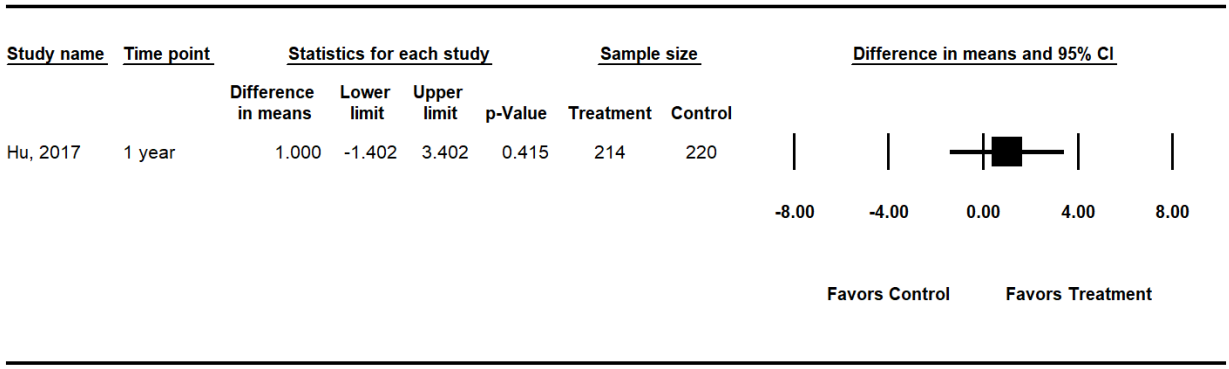
Note: This sensitivity analysis removed one study from Figure 56 (Moungngern, 2018), a study that found no difference between groups, had just 125 participants, and was potentially overweighted in the meta-analysis.

Appendix F Figure 58. Lifestyle vs. Control: High Density Lipoprotein (BMI 25-29.9) Sensitivity Analysis



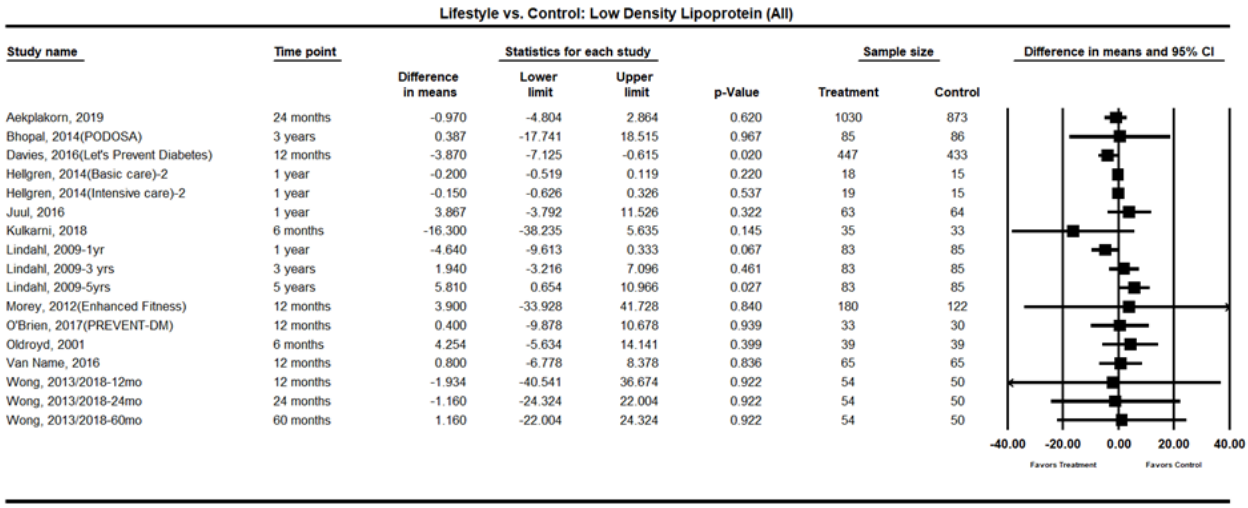
Note: This sensitivity analysis removed two studies from Figure 56 (Moungngern, 2018; Yates, 2009 [PREPARE with pedometer]) that found no difference between groups and were potentially overweighted in the meta-analysis.

Appendix F Figure 59. Lifestyle vs. Control: High Density Lipoprotein (BMI <25)



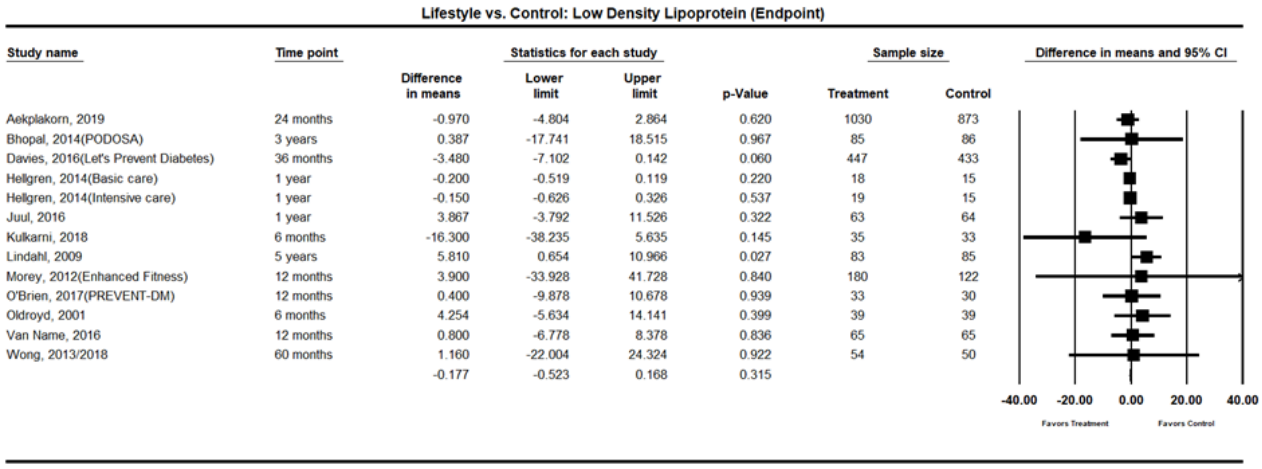
I-squared:N/A; p=N/A

Appendix F Figure 60. Lifestyle vs. Control: Low Density Lipoprotein (All)



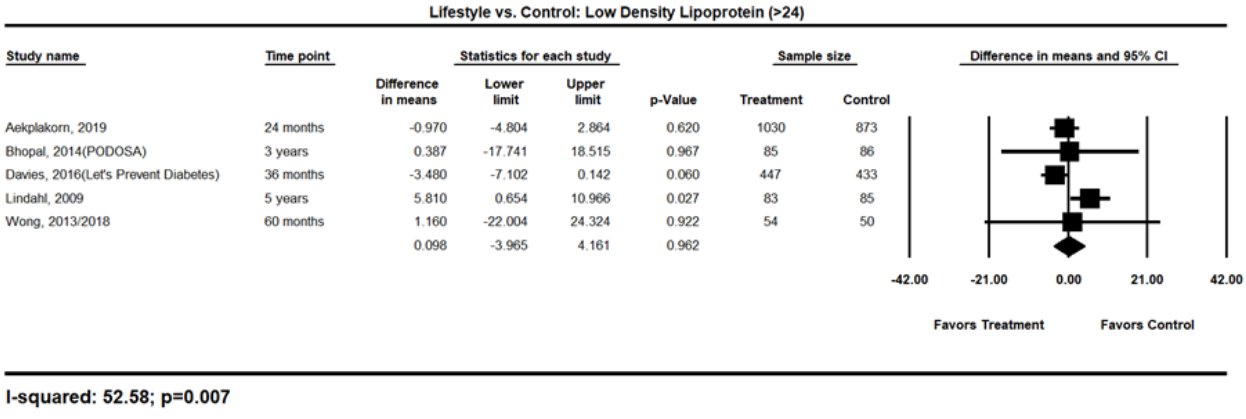
I-squared: N/A; p=N/A

Appendix F Figure 61. Lifestyle vs. Control: Low Density Lipoprotein (Endpoint)



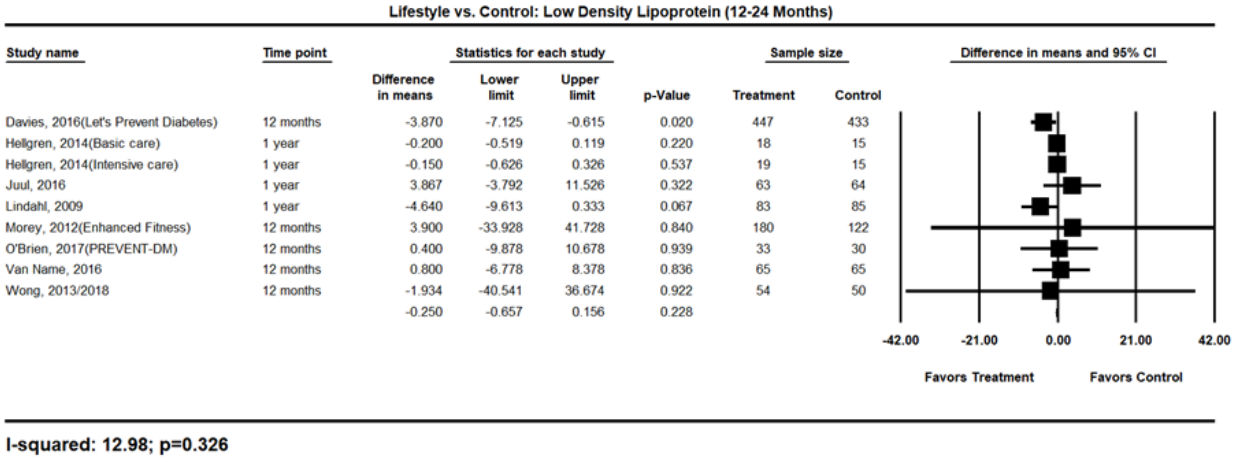
I-squared: 4.94; p=0.397

Appendix F Figure 62. Lifestyle vs. Control: Low Density Lipoprotein (>24 Months)



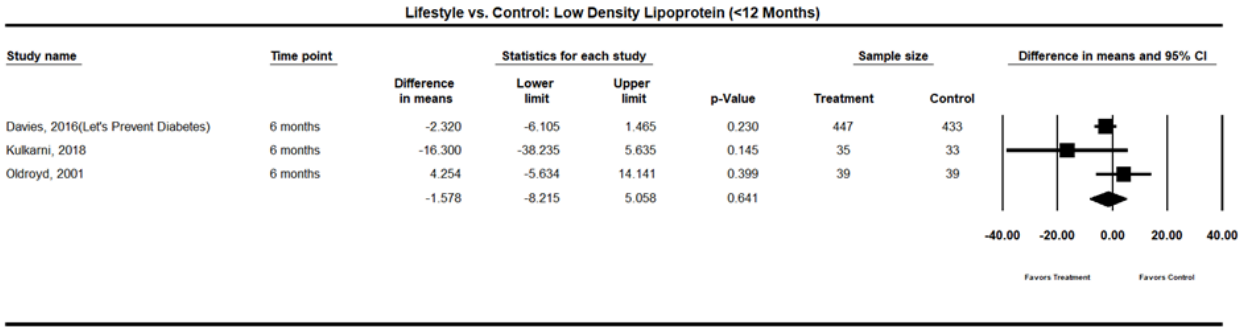
I-squared: 52.58; p=0.007

Appendix F Figure 63. Lifestyle vs. Control: Low Density Lipoprotein (12-24 Months)



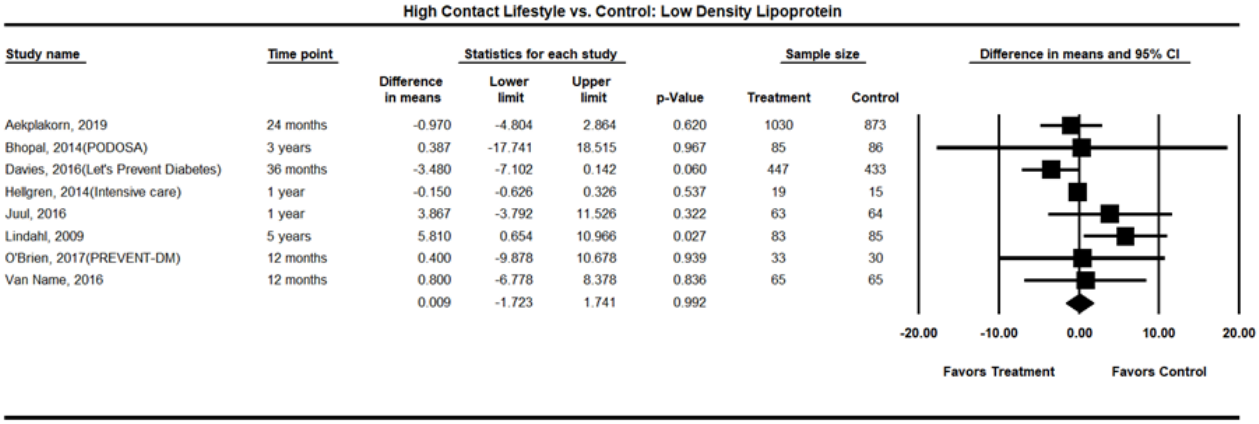
I-squared: 12.98; p=0.326

Appendix F Figure 64. Lifestyle vs. Control: Low Density Lipoprotein (<12 Months)



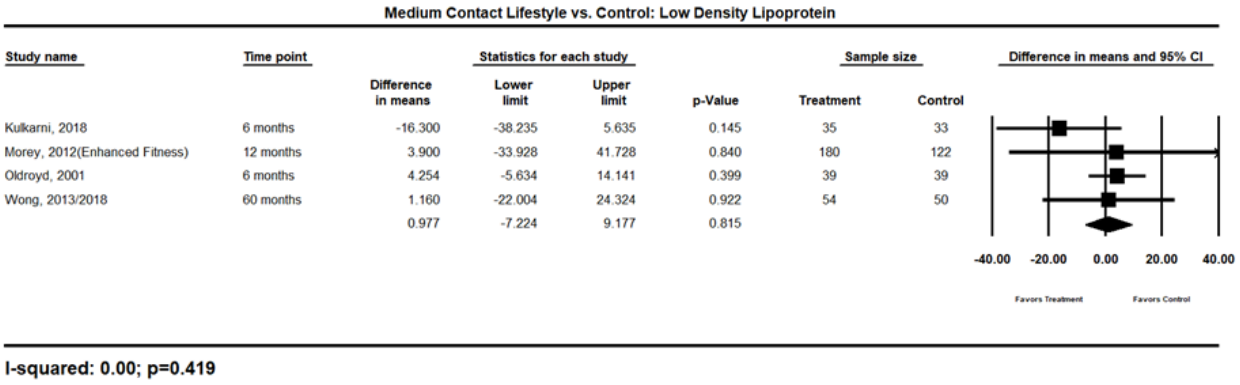
I-squared: 37.31; p=0.203

Appendix F Figure 65. High Contact Lifestyle vs. Control: Low Density Lipoprotein



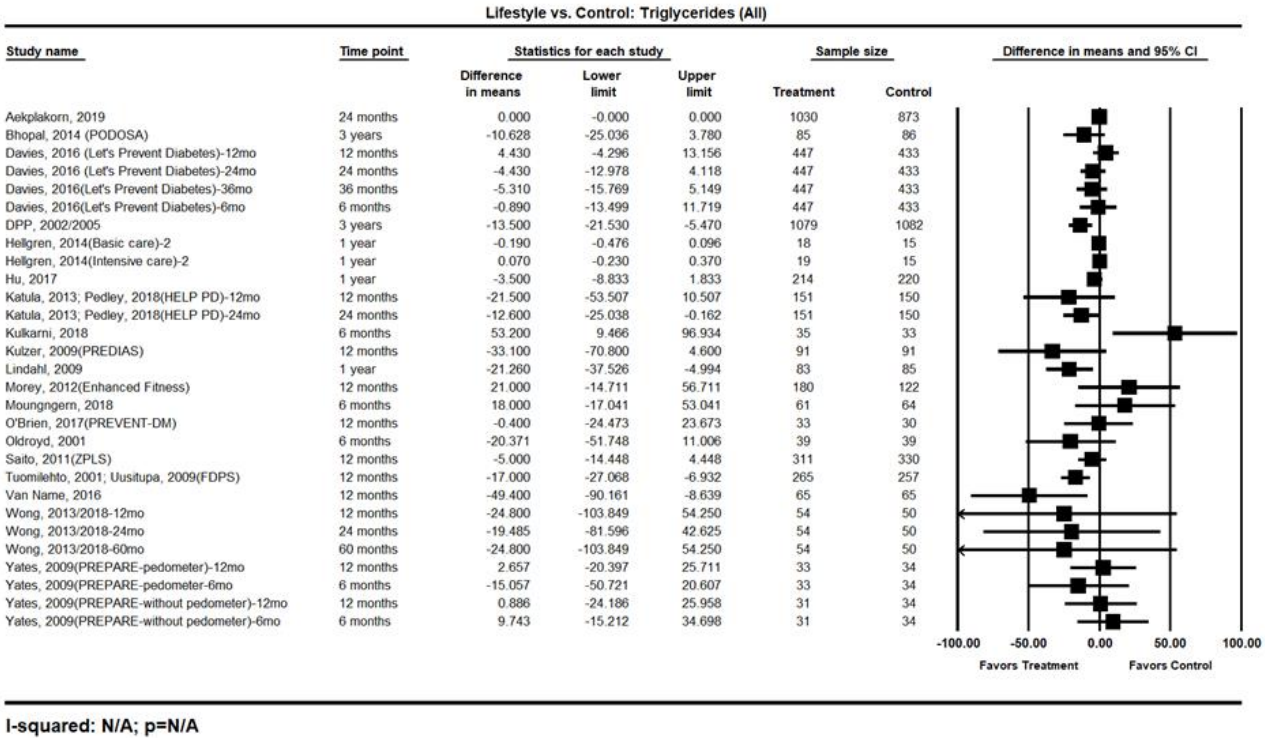
I-squared: 27.74; p=0.207

Appendix F Figure 66. Medium Contact Lifestyle vs. Control: Low Density Lipoprotein



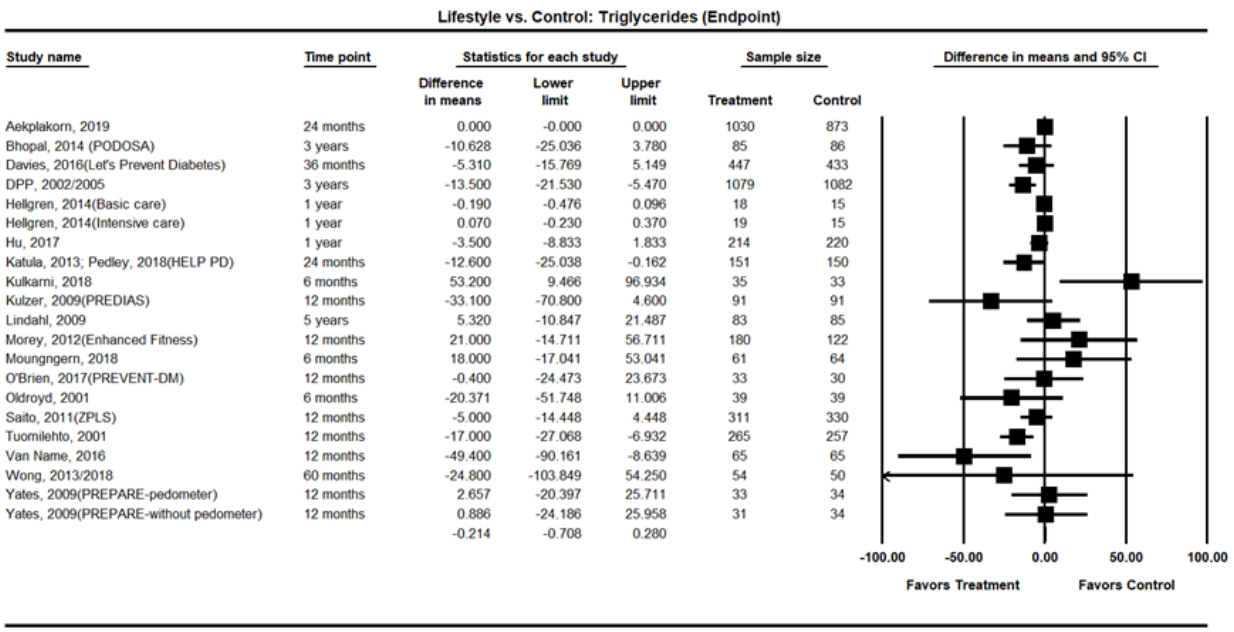
I-squared: 0.00; p=0.419

Appendix F Figure 67. Lifestyle vs. Control: Triglycerides (All)



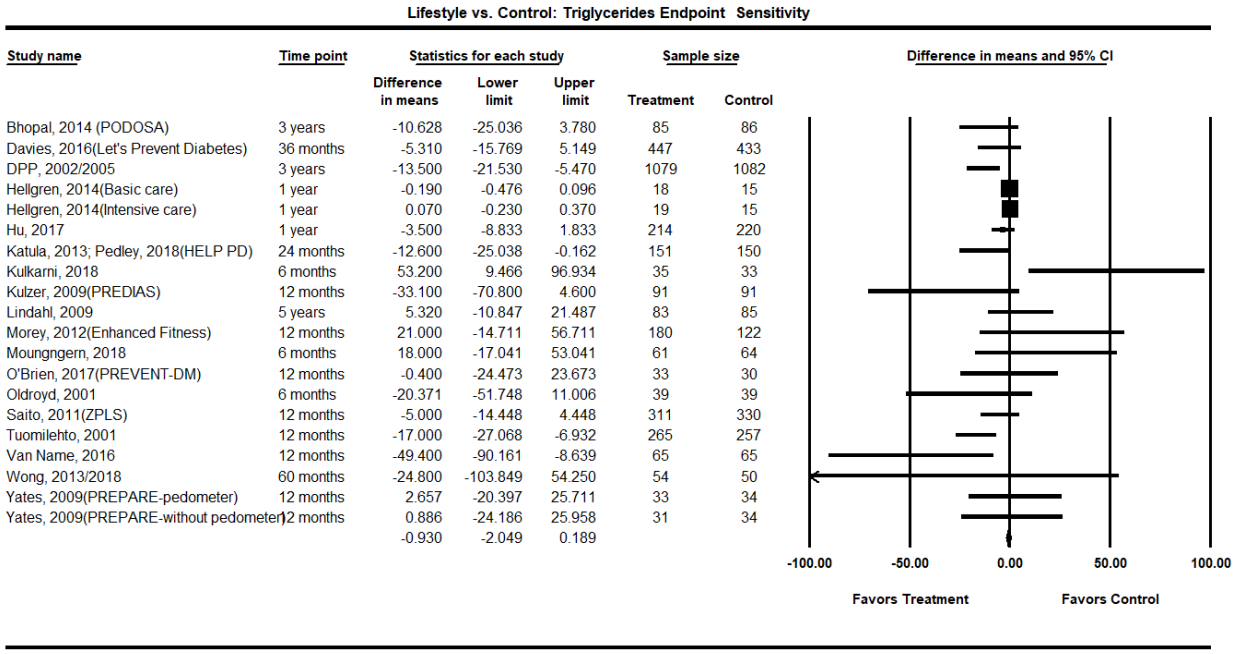
I-squared: N/A; p=N/A

Appendix F Figure 68. Lifestyle vs. Control: Triglycerides (Endpoint)



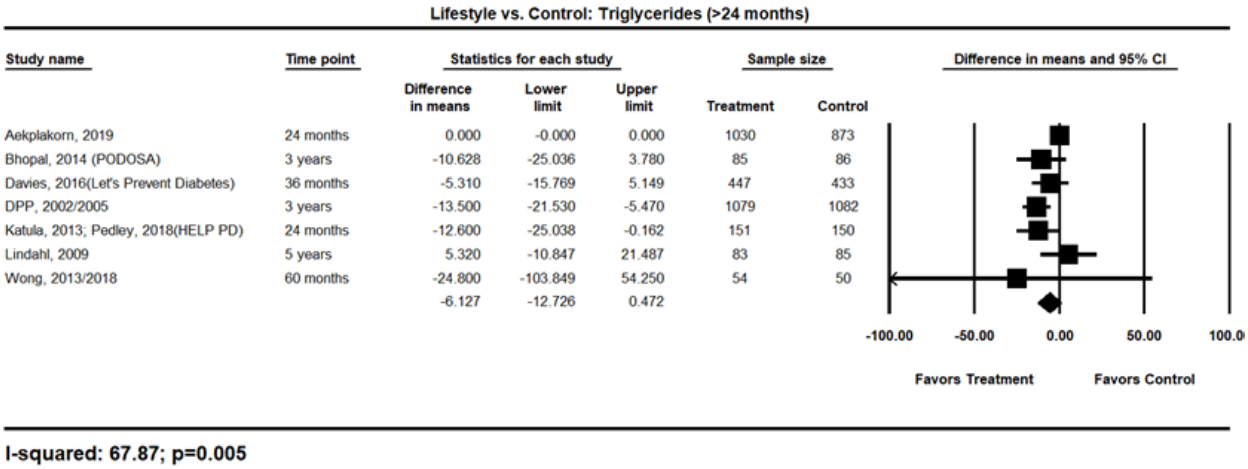
I-squared: 61.95; p=0.00

Appendix F Figure 69. Lifestyle vs. Control: Triglycerides (Endpoint) Sensitivity Analysis



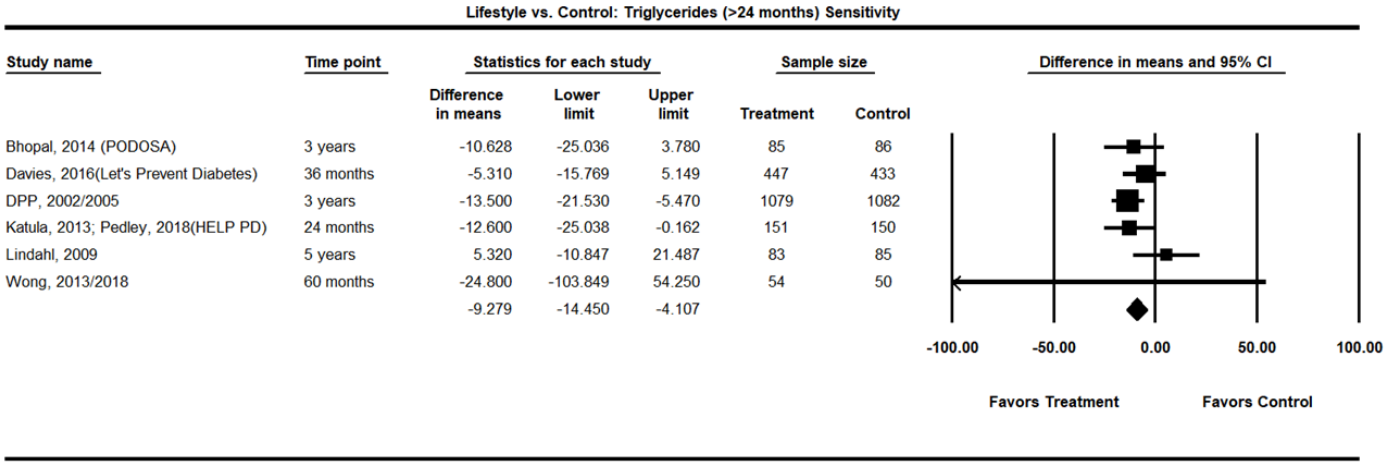
Note: This sensitivity analysis removed one study from Figure 68 (Aekplakorn, 2019), a study that found no difference between groups and was potentially overweighted in the meta-analysis.

Appendix F Figure 70. Lifestyle vs. Control: Triglycerides (>24 Months)



I-squared: 67.87; p=0.005

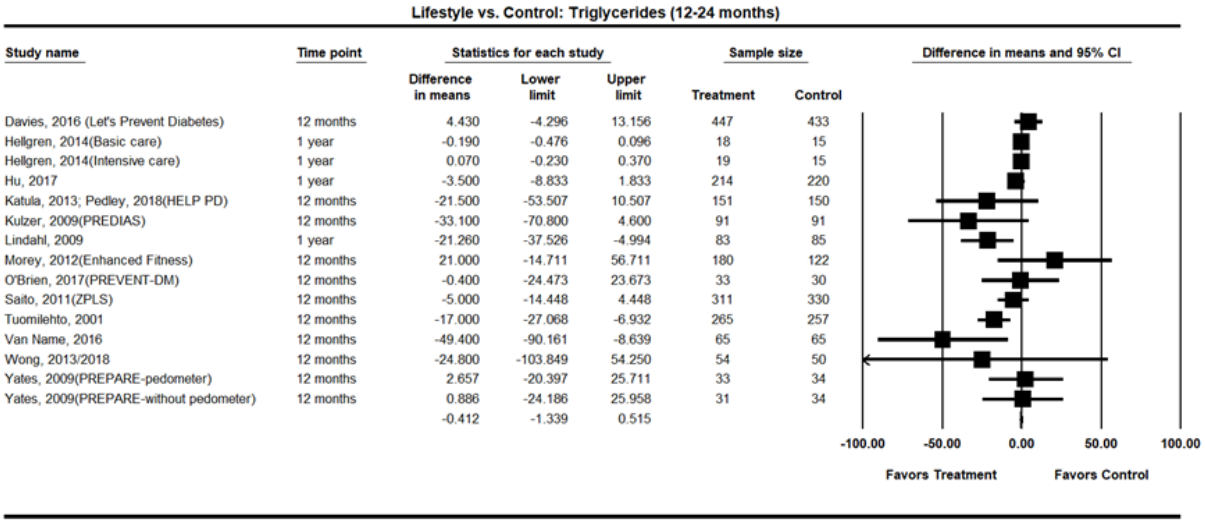
Appendix F Figure 71. Lifestyle vs. Control: Triglycerides (>24 Months) Sensitivity Analysis



I-squared: 3.87; p=0.392

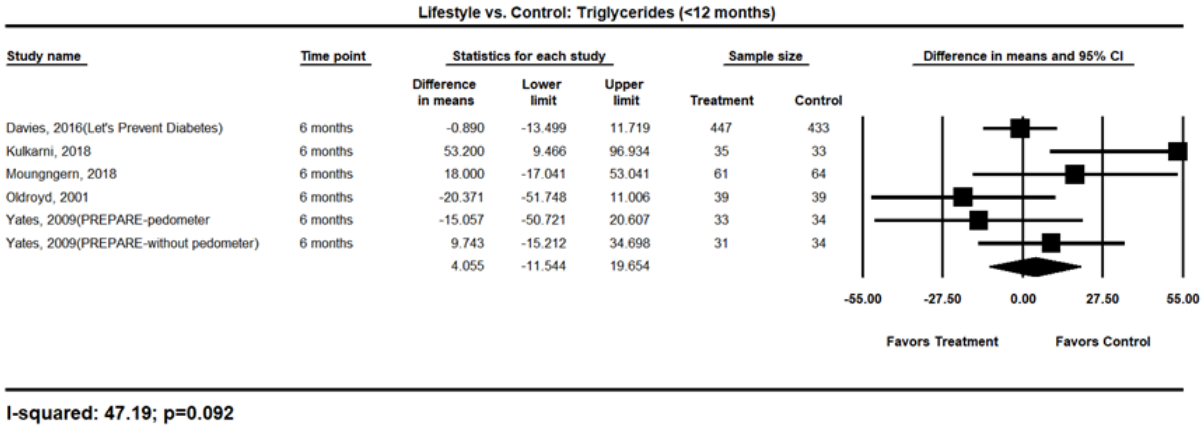
Note: This sensitivity analysis removed one study from Figure 70 (Aekplakorn, 2019), a study that found no difference between groups and was potentially overweighted in the meta-analysis.

Appendix F Figure 72. Lifestyle vs. Control: Triglycerides (12-24 Months)



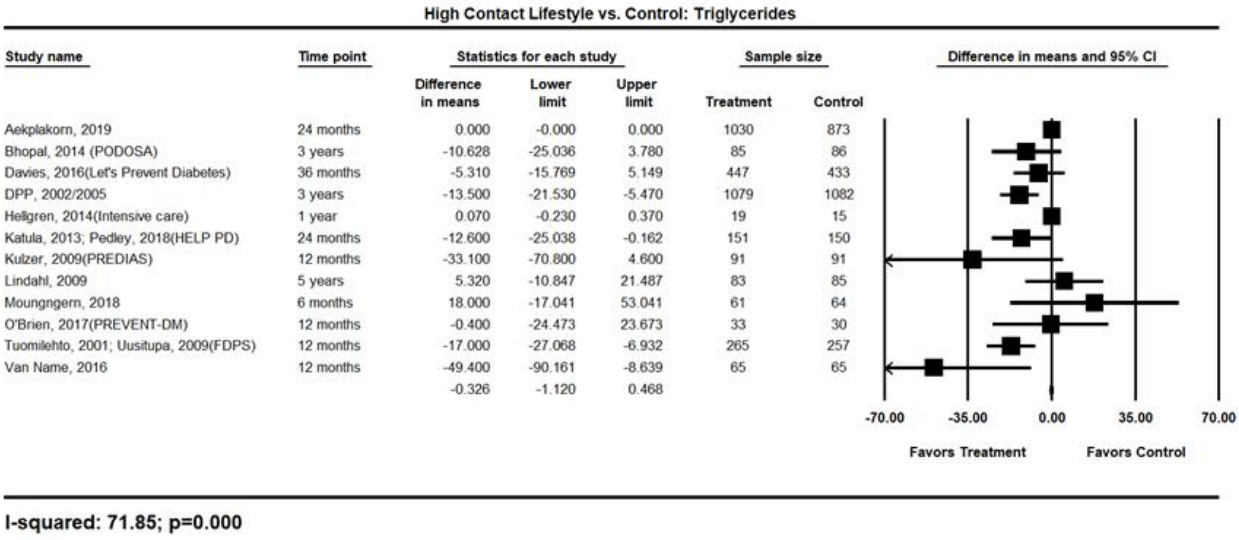
I-squared: 59.54; p=0.002

Appendix F Figure 73. Lifestyle vs. Control: Triglycerides (<12 Months)



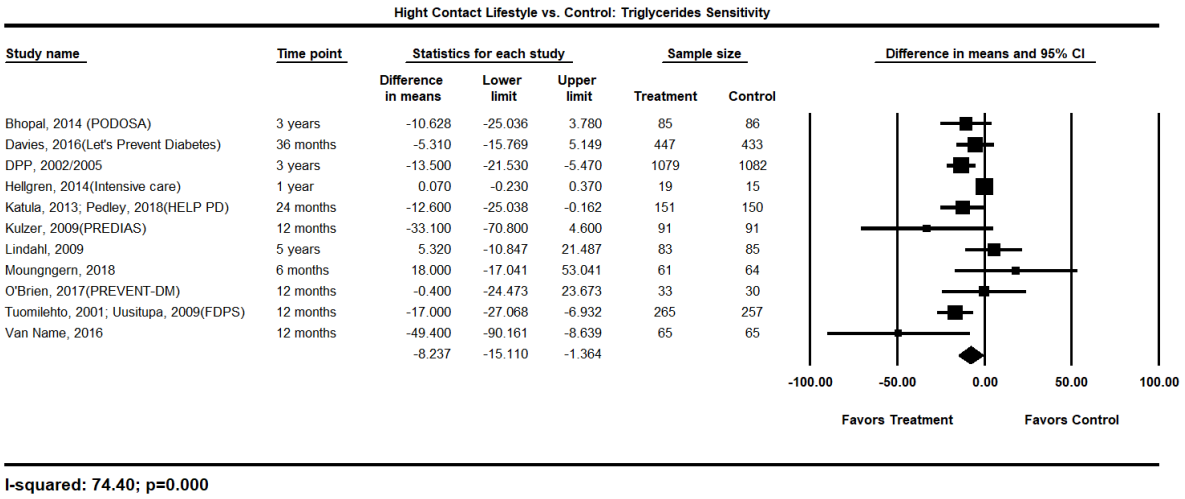
I-squared: 47.19; p=0.092

Appendix F Figure 74. High Contact Lifestyle vs. Control: Triglycerides



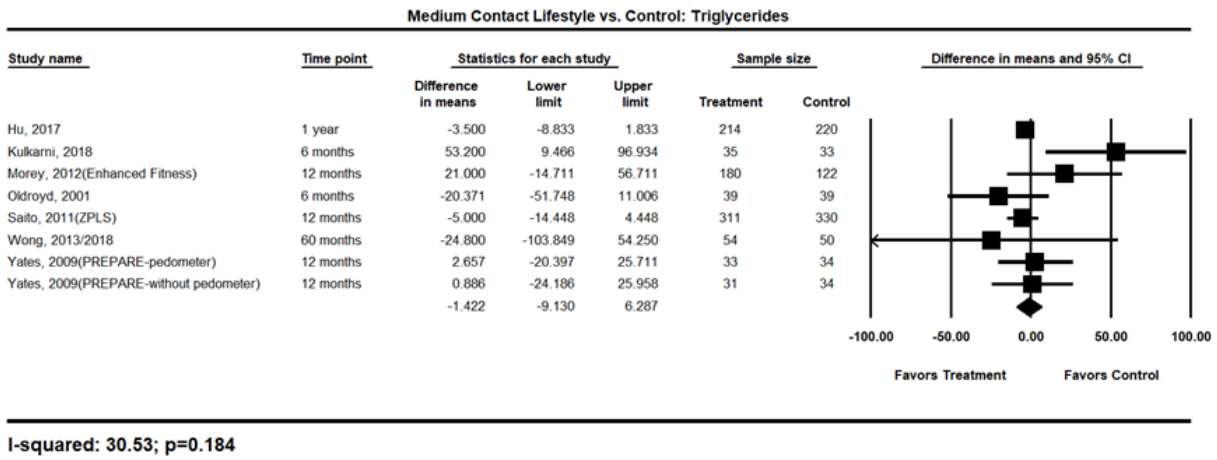
I-squared: 71.85; p=0.000

Appendix F Figure 75. High Contact Lifestyle vs. Control: Triglycerides Sensitivity Analysis



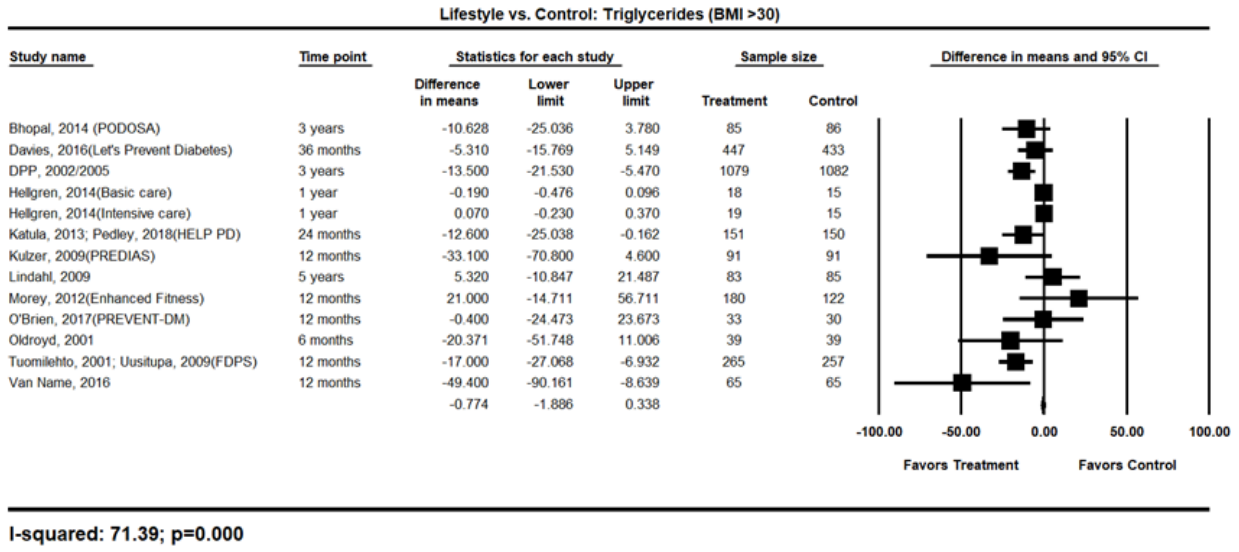
Note: This sensitivity analysis removed one study from Figure 74 (Aekplakorn, 2019), a study that found no difference between groups and was potentially overweighted in the meta-analysis.

Appendix F Figure 76. Medium Contact Lifestyle vs. Control: Triglycerides



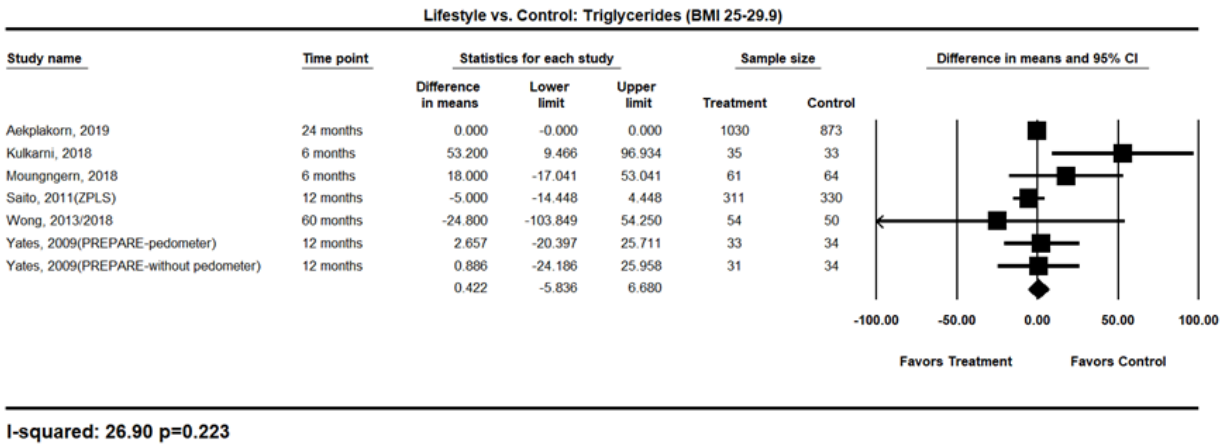
I-squared: 30.53; p=0.184

Appendix F Figure 77. Lifestyle vs. Control: Triglycerides (BMI >30)



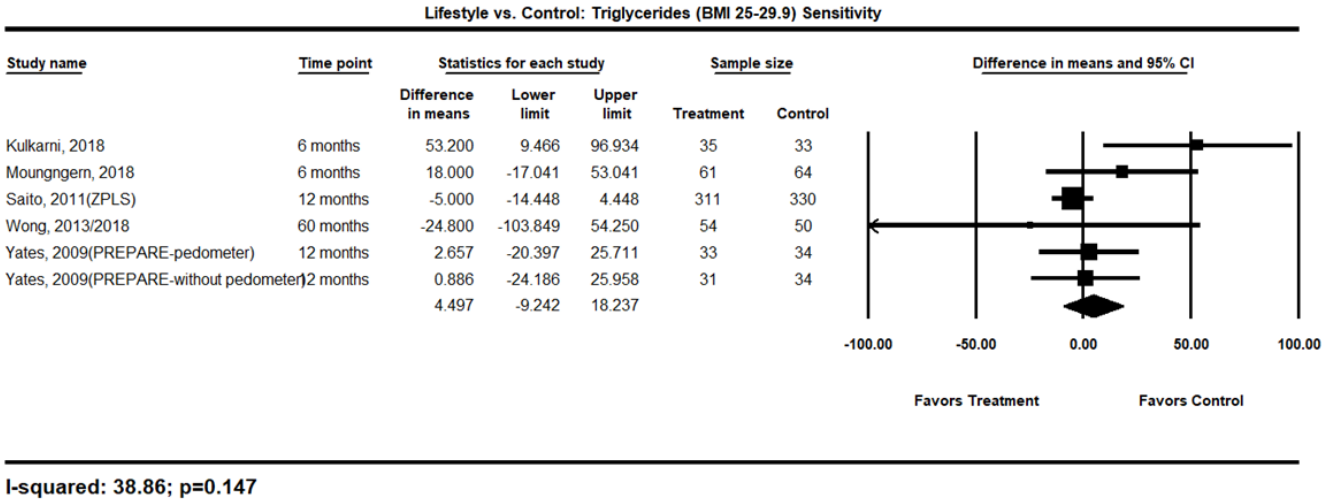
I-squared: 71.39; p=0.000

Appendix F Figure 78. Lifestyle vs. Control: Triglycerides (BMI 25-29.9)



I-squared: 26.90 p=0.223

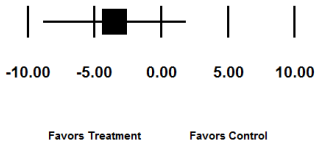
Appendix F Figure 79. Lifestyle vs. Control: Triglycerides (BMI 25-29.9) Sensitivity Analysis



Note: This sensitivity analysis removed one study from Figure 78 (Aekplakorn, 2019), a study that found no difference between groups and was potentially overweighted in the meta-analysis.

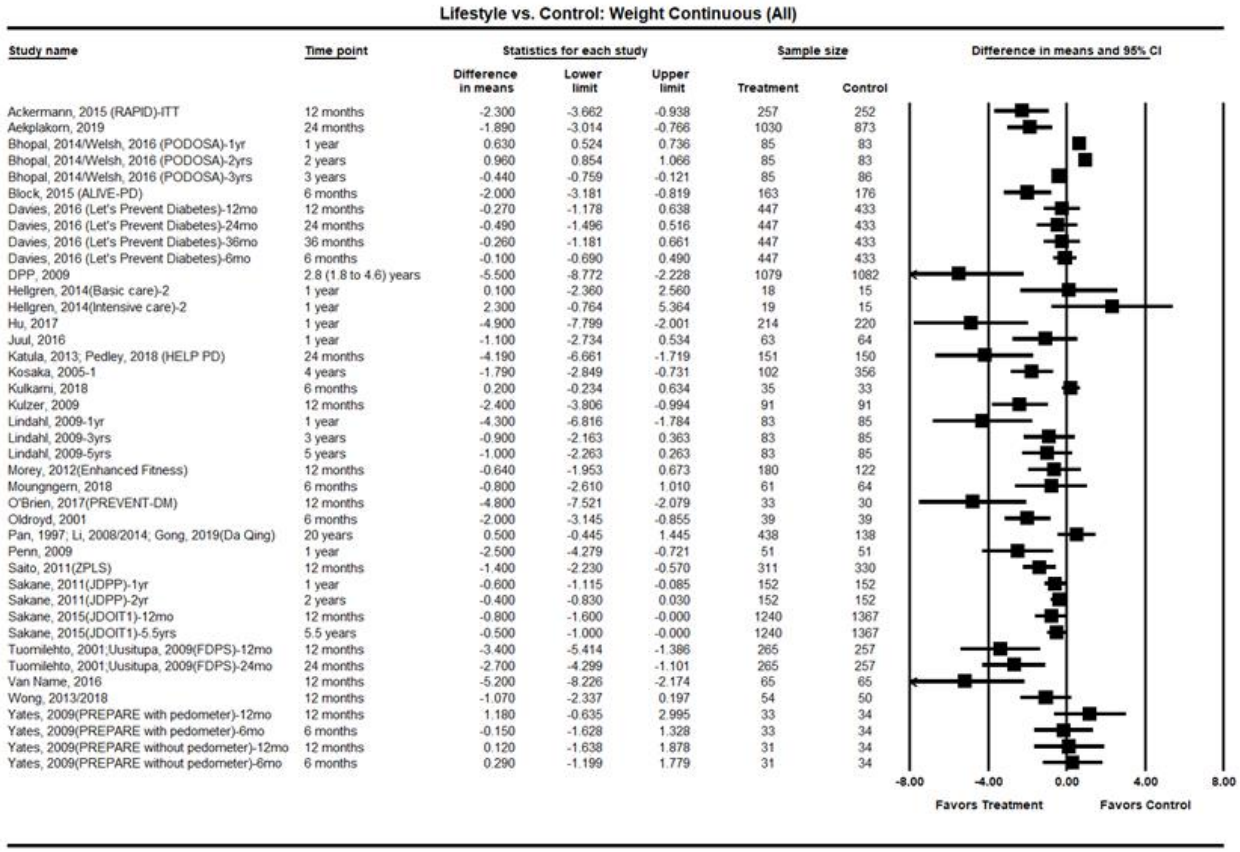
Appendix F Figure 80. Lifestyle vs. Control: Triglycerides (BMI <25)

Study name	Time point	Statistics for each study			Sample size		Difference in means and 95% CI
		Difference in means	Lower limit	Upper limit	Treatment	Control	
Hu, 2017	1 year	-3.500	-8.833	1.833	214	220	

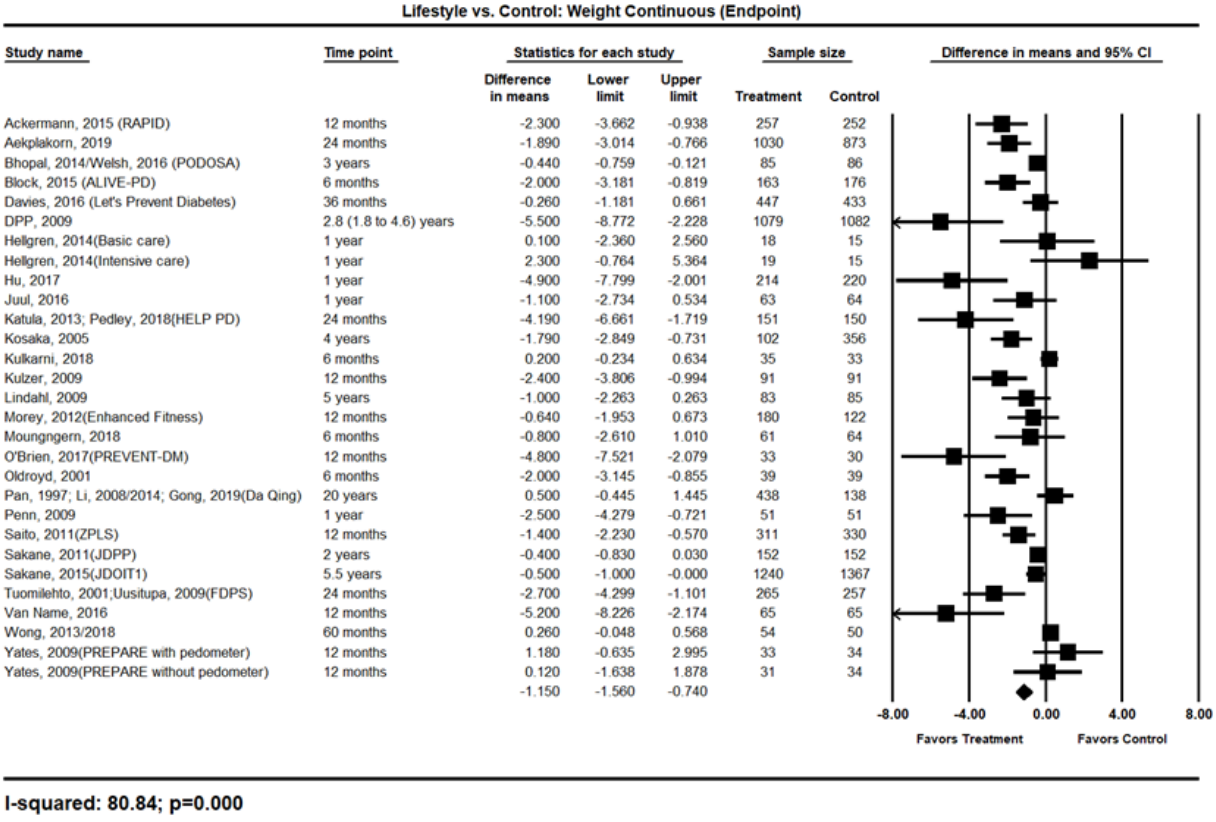


I-squared:N/A; p=N/A

Appendix F Figure 81. Lifestyle vs. Control: Weight Continuous (All)

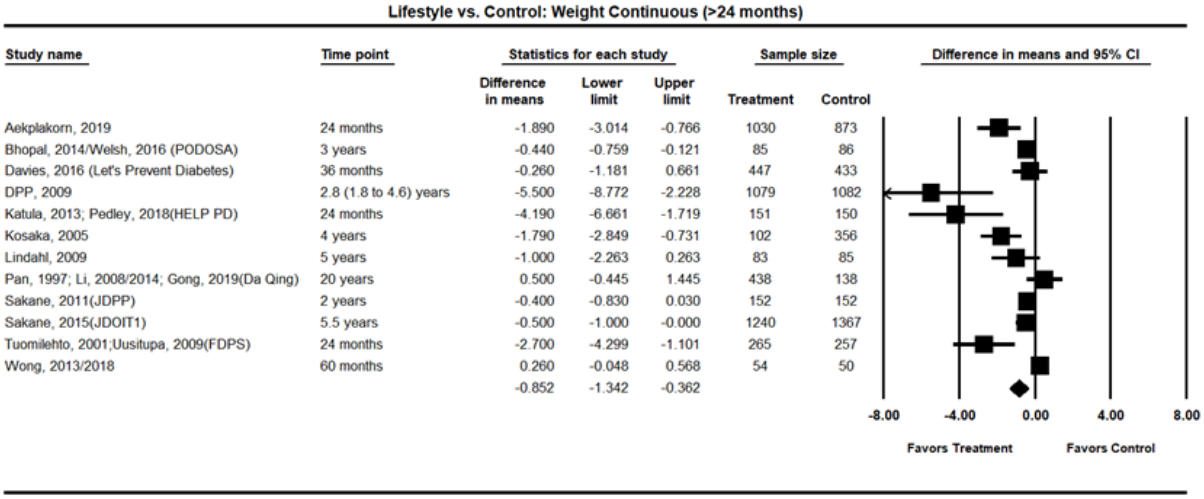


Appendix F Figure 82. Lifestyle vs. Control: Weight Continuous (Endpoint)



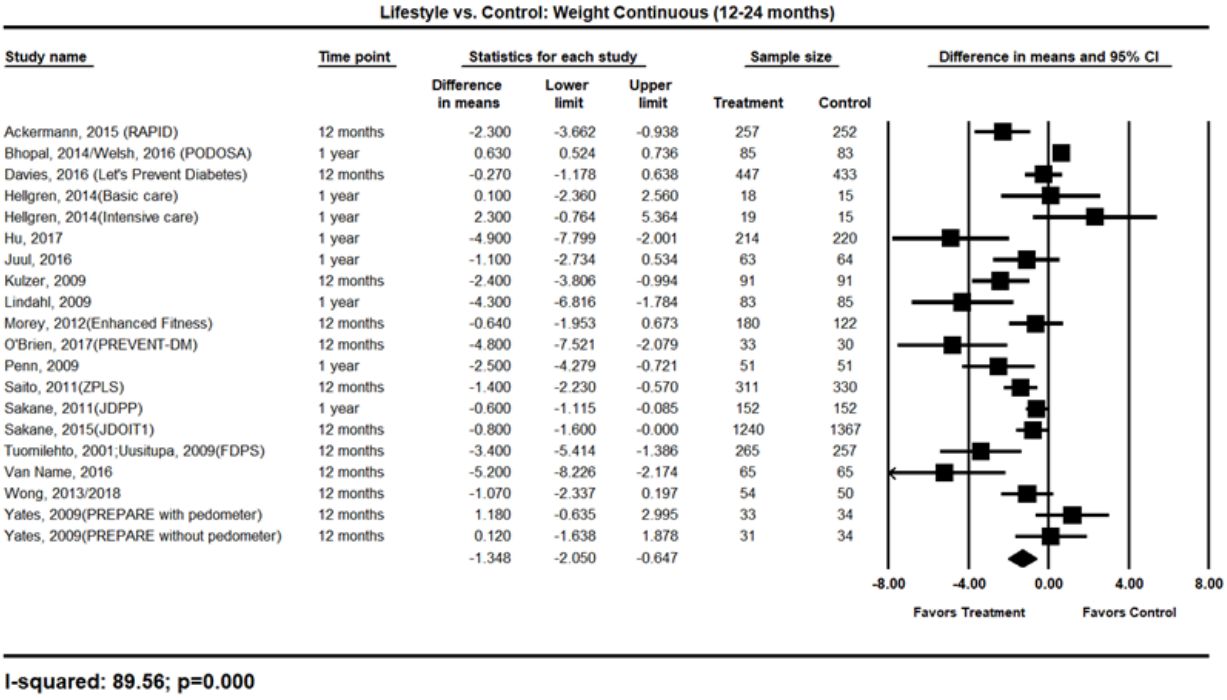
I-squared: 80.84; p=0.000

Appendix F Figure 83. Lifestyle vs. Control: Weight Continuous (>24 Months)



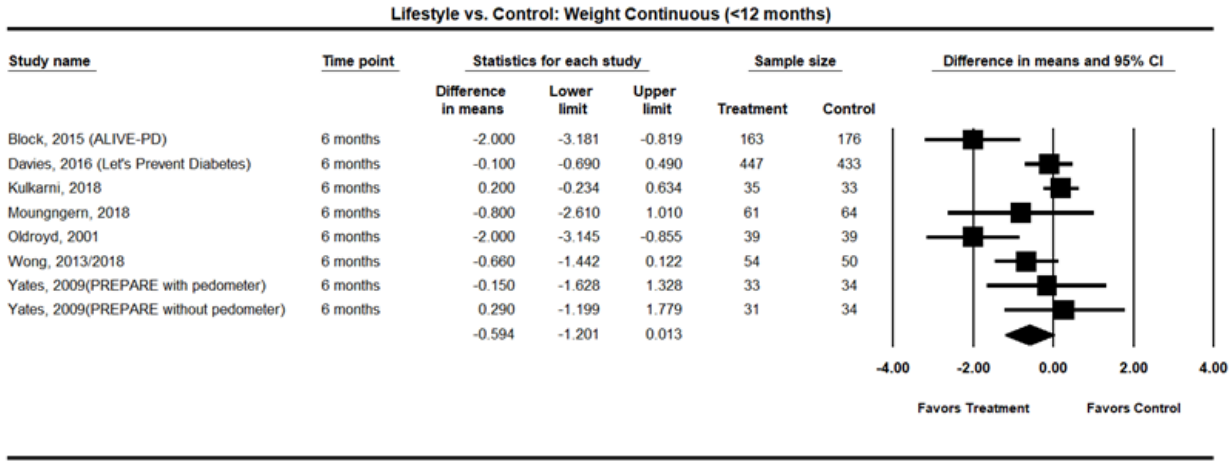
I-squared: 82.05; p=0.000

Appendix F Figure 84. Lifestyle vs. Control: Weight Continuous (12-24 Months)



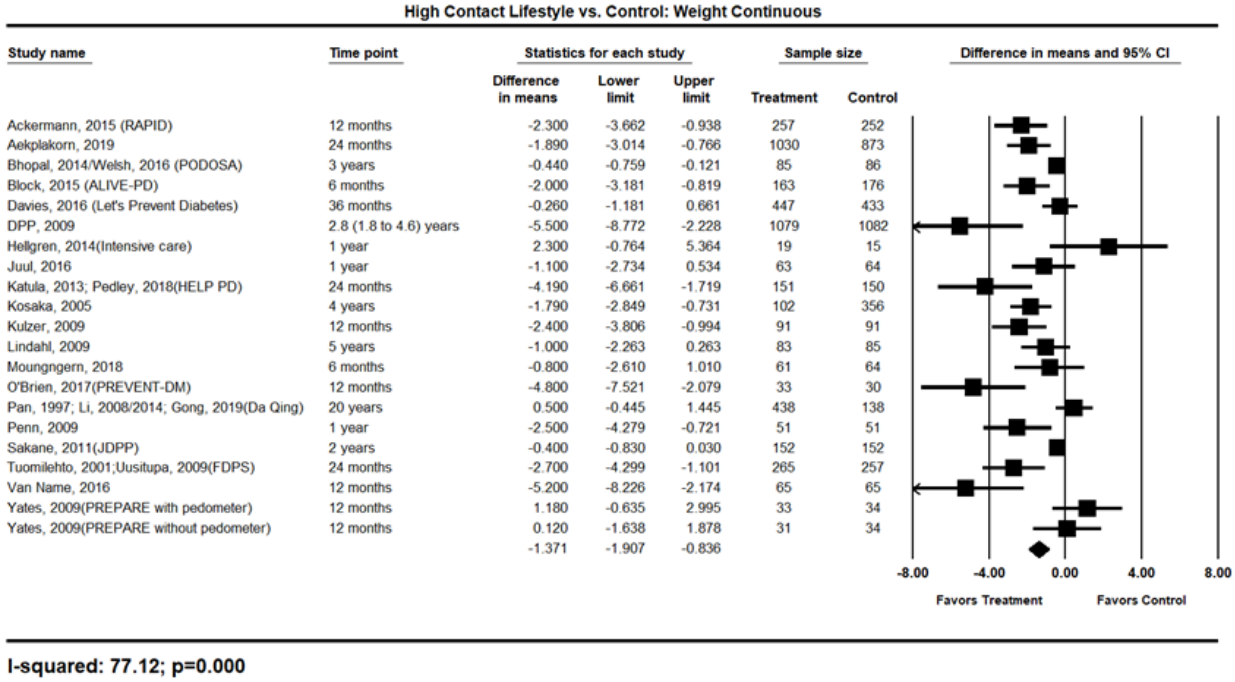
I-squared: 89.56; p=0.000

Appendix F Figure 85. Lifestyle vs. Control: Weight Continuous (<12 Months)



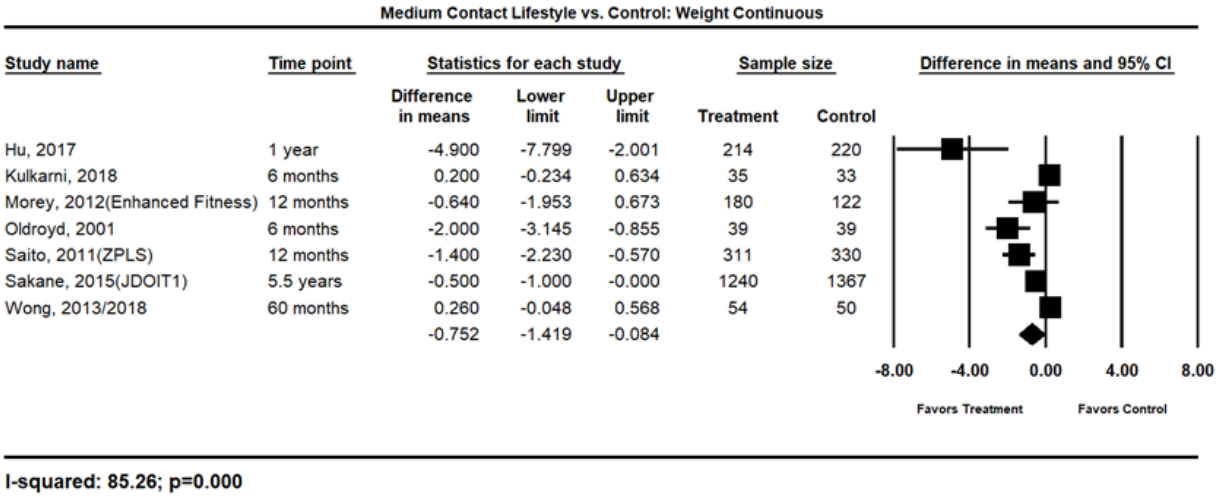
I-squared: 70.44; p=0.001

Appendix F Figure 86. High Contact Lifestyle vs. Control: Weight Continuous



I-squared: 77.12; p=0.000

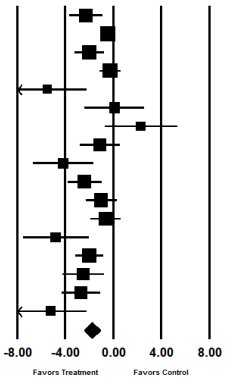
Appendix F Figure 87. Medium Contact Lifestyle vs. Control: Weight Continuous



I-squared: 85.26; p=0.000

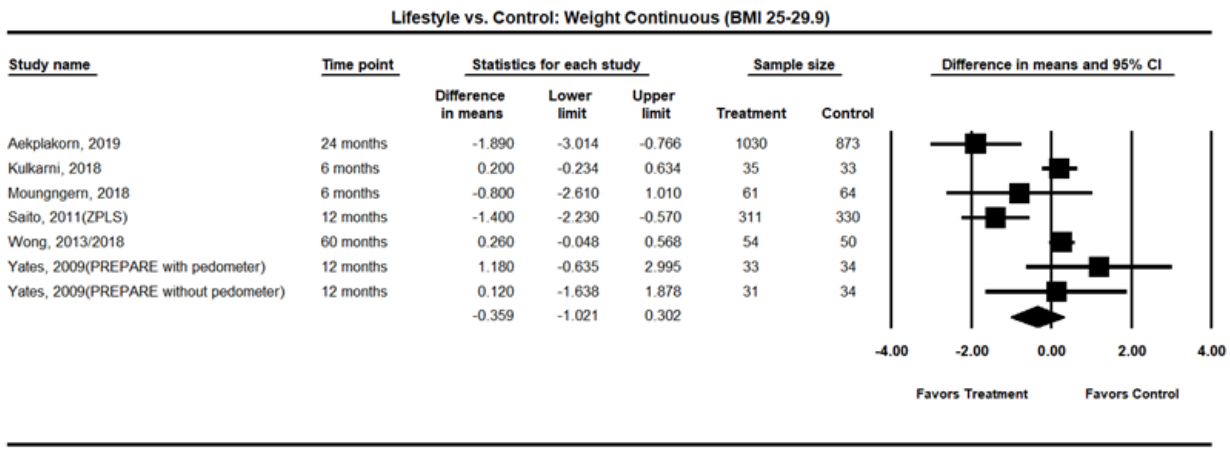
Appendix F Figure 88. Lifestyle vs. Control: Weight Continuous (BMI >30)

Study name	Time point	Statistics for each study			Sample size	
		Difference in means	Lower limit	Upper limit	Treatment	Control
Ackermann, 2015 (RAPID)-ITT	12 months	-2.300	-3.662	-0.938	257	252
Bhopal, 2014/Welsh, 2016 (PODOSA)	3 years	-0.440	-0.759	-0.121	85	86
Block, 2015 (ALIVE-PD)	6 months	-2.000	-3.181	-0.819	163	176
Davies, 2016 (Let's Prevent Diabetes)-36mo	36 months	-0.260	-1.181	0.661	447	433
DPP, 2009	2.8 (1.8 to 4.6) years	-5.500	-8.772	-2.228	1079	1082
Hellgren, 2014(Basic care)-2	1 year	0.100	-2.360	2.560	18	15
Hellgren, 2014(Intensive care)-2	1 year	2.300	-0.764	5.364	19	15
Juul, 2016	1 year	-1.100	-2.734	0.534	63	64
Katula, 2013	24 months	-4.190	-6.661	-1.719	151	150
Kulzer, 2009	12 months	-2.400	-3.806	-0.994	91	91
Lindahl, 2009-5yrs	5 years	-1.000	-2.263	0.263	83	85
Morey, 2012(Enhanced Fitness)	12 months	-0.640	-1.953	0.673	180	122
O'Brien, 2017(PREVENT-DM)	12 months	-4.800	-7.521	-2.079	33	30
Oldroyd, 2001	6 months	-2.000	-3.145	-0.855	39	39
Penn, 2009	1 year	-2.500	-4.279	-0.721	51	51
Tuomilehto, 2001; Uusitupa, 2009(FDPS)-24mo	24 months	-2.700	-4.299	-1.101	265	257
Van Name, 2016	12 months	-5.200	-8.226	-2.174	65	65
		-1.793	-2.478	-1.108		



I-squared:76.53; p=0.00

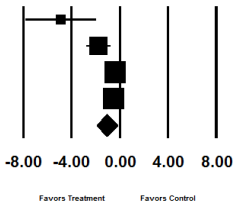
Appendix F Figure 89. Lifestyle vs. Control: Weight Continuous (BMI 25-29.9)



I-squared: 78.34; p=0.000

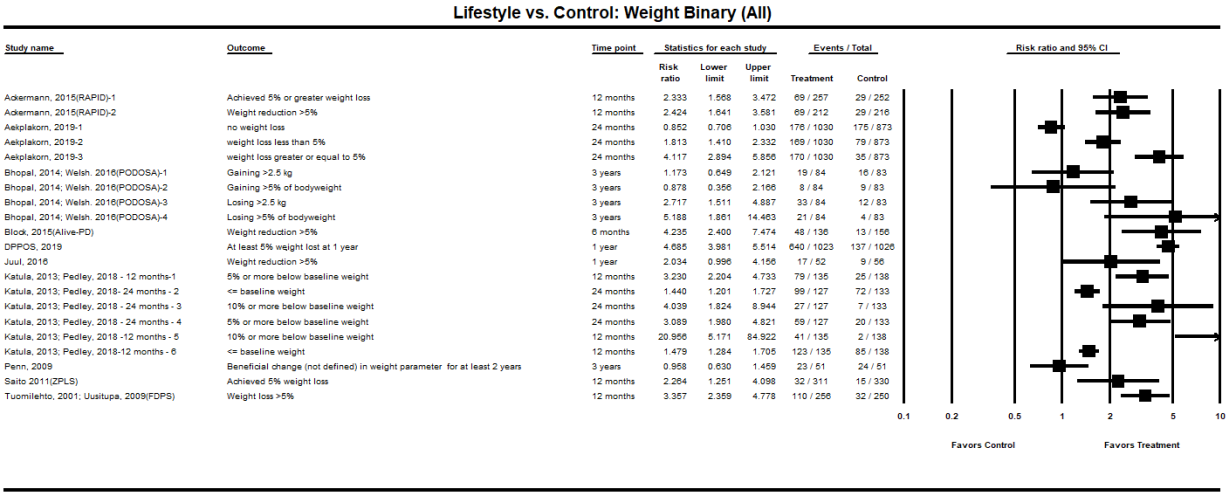
Appendix F Figure 90. Lifestyle vs. Control: Weight Continuous (<BMI 25)

Study name	Time point	Statistics for each study			Sample size		Difference in means and 95% CI
		Difference in means	Lower limit	Upper limit	Treatment	Control	
Hu, 2017	1 year	-4.900	-7.799	-2.001	214	220	
Kosaka, 2005-1	4 years	-1.790	-2.849	-0.731	102	356	
Sakane, 2011(JDPP)	2 years	-0.400	-0.830	0.030	152	152	
Sakane, 2015(JDOIT1)	5.5 years	-0.500	-1.000	-0.000	1240	1367	
		-1.085	-1.934	-0.235			



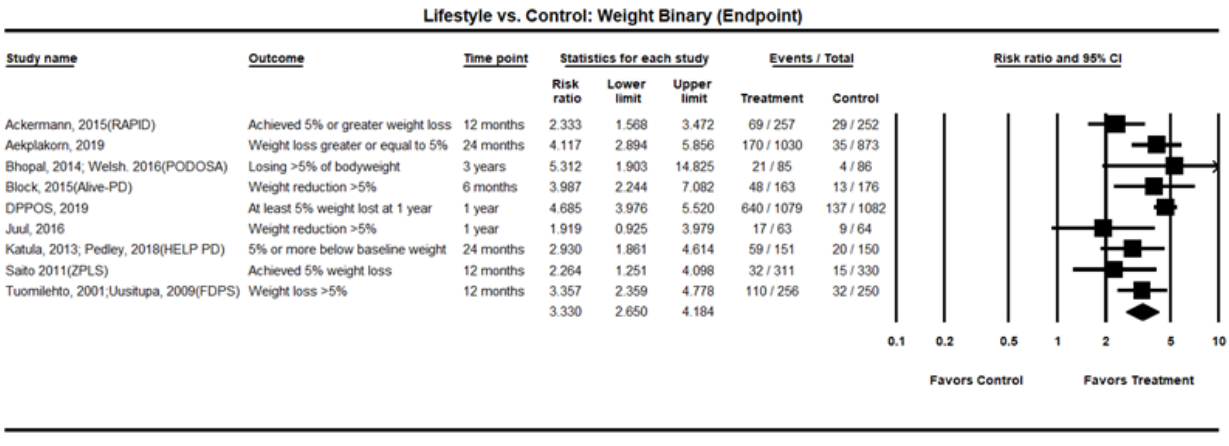
I-squared:79.0; p=0.00

Appendix F Figure 91. Lifestyle vs. Control: Weight Binary



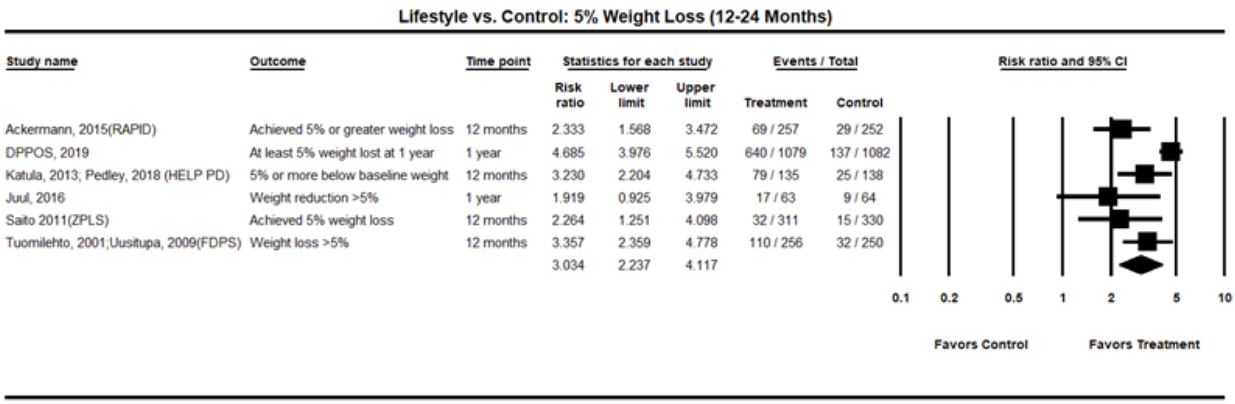
I-squared: N/A; p=N/A

Appendix F Figure 92. Lifestyle vs. Control: Weight Binary (Endpoint)



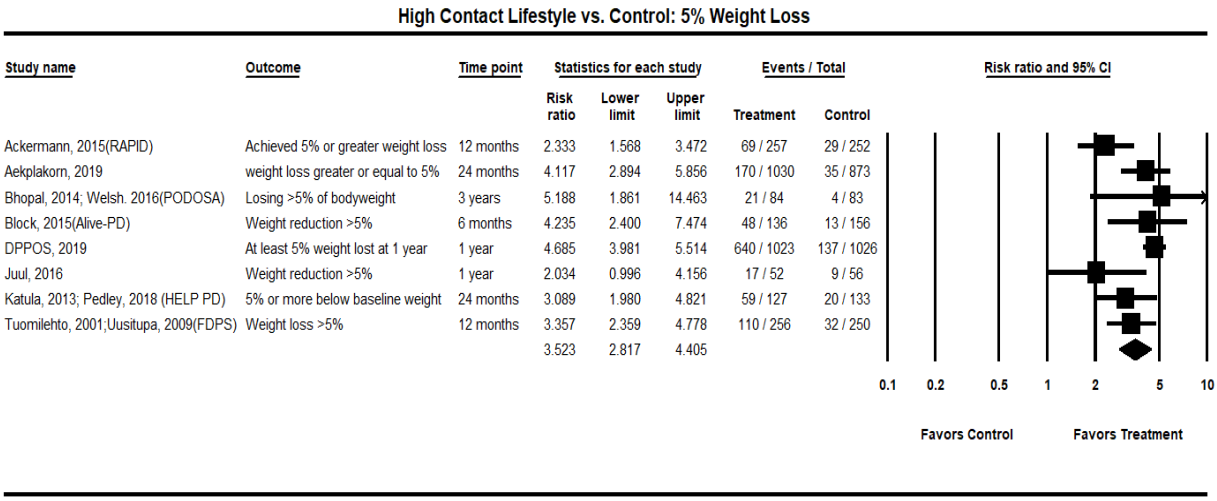
I-squared: 61.29; p=0.008

Appendix F Figure 93. Lifestyle vs. Control: 5% Weight Loss (12-24 Months)



I-squared: 74.36; p=0.002

Appendix F Figure 94. High Contact Lifestyle vs. Control: Weight Loss Binary

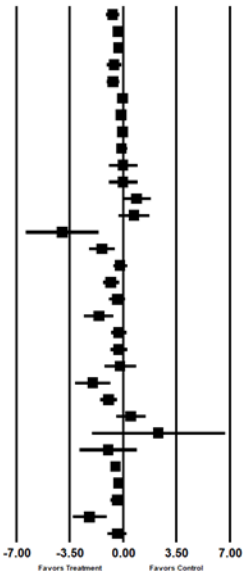


I-squared: 57.94; p=0.020

Appendix F Figure 95. Lifestyle vs. Control: BMI (All)

Lifestyle vs. Control: BMI (All)

Study name	Time point	Statistics for each study				Sample size		Difference in means and 95% CI
		Difference in means	Lower limit	Upper limit	p-Value	Treatment	Control	
Aekplakorn, 2019	24 months	-0.690	-1.100	-0.280	0.001	1030	873	
Bhopal, 2014; Welsh, 2016(PODOSA) -2yr	2 years	-0.360	-0.473	-0.247	0.000	85	86	
Bhopal, 2014; Welsh, 2016(PODOSA)-1yr	1 year	-0.310	-0.423	-0.197	0.000	85	86	
Bhopal, 2014; Welsh, 2016(PODOSA)-3yr	3 years	-0.600	-1.059	-0.141	0.010	85	86	
Block, 2015(Alive-PD)	6 months	-0.660	-1.050	-0.270	0.001	163	176	
Davies, 2016 (Let's Prevent Diabetes) - 6mo	6 months	-0.030	-0.274	0.214	0.810	447	433	
Davies, 2016 (Let's Prevent Diabetes)- 24mo	24 months	-0.140	-0.480	0.200	0.420	447	433	
Davies, 2016 (Let's Prevent Diabetes) -36mo	36 months	-0.050	-0.357	0.257	0.750	447	433	
Davies, 2016 (Let's Prevent Diabetes)-12mo	12 months	-0.110	-0.437	0.217	0.510	447	433	
Hellgren, 2014 (Basic Care)	1 year	-0.010	-0.922	0.902	0.983	18	15	
Hellgren, 2014 (Basic Care)2	1 year	-0.010	-0.922	0.902	0.983	18	15	
Hellgren, 2014 (Intensive Care)	1 year	0.890	-0.030	1.810	0.058	19	15	
Hellgren, 2014 (Intensive Care)2	1 year	0.700	-0.273	1.673	0.158	19	15	
Hu, 2017	1 year	-4.000	-6.366	-1.634	0.001	214	220	
Katula, 2013; Pedley, 2018(HELP PD)	2 years	-1.400	-2.226	-0.574	0.001	151	150	
Kulkarni, 2018	6 months	-0.200	-0.625	0.225	0.357	35	33	
Kulzer, 2009(PREDIAS)	12 months	-0.800	-1.300	-0.300	0.002	91	91	
Lindahl, 2009 -5yr	5 years	-0.400	-0.896	0.096	0.114	83	85	
Lindahl, 2009-1yr	1 year	-1.600	-2.536	-0.664	0.001	83	85	
Lindahl, 2009-3yr	3 years	-0.300	-0.796	0.196	0.236	83	85	
Morey, 2012(Enhanced Fitness)	12 months	-0.280	-0.820	0.260	0.309	180	122	
Moungngern, 2018	6 months	-0.200	-1.204	0.804	0.696	61	64	
O'Brien, 2017(PREVENT-DM)	12 months	-2.000	-3.134	-0.866	0.001	33	30	
Oldroyd, 2001	6 months	-0.950	-1.494	-0.406	0.001	39	39	
Pan, 1997; Li, 2008/2014; Gong, 2019(Da Qing)-20yr	20 years	0.500	-0.445	1.445	0.300	438	138	
Pan, 1997; Li, 2008/2014; Gong, 2019(Da Qing)-30yr	30 years	2.300	-2.046	6.646	0.300	438	138	
Pan, 1997; Li, 2008/2014; Gong, 2019(Da Qing)-6yr	6 years	-0.990	-2.860	0.880	0.300	438	138	
Saito, 2011(ZPLS)	12 months	-0.500	-0.796	-0.204	0.001	311	330	
Sakane, 2011(JDPP)-1yr	1 year	-0.300	-0.555	-0.045	0.021	152	152	
Sakane, 2011(JDPP)-3yrs	3 years	-0.400	-0.800	0.000	0.050	152	152	
Van Name, 2016	12 months	-2.200	-3.273	-1.127	0.000	65	65	
Wong, 2013/2018	12 months	-0.400	-1.016	0.216	0.203	54	50	

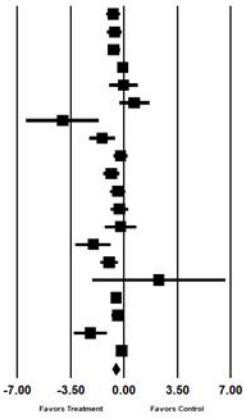


I-squared: N/A; p=N/A

Appendix F Figure 97. Lifestyle vs. Control: BMI (>24 Months)

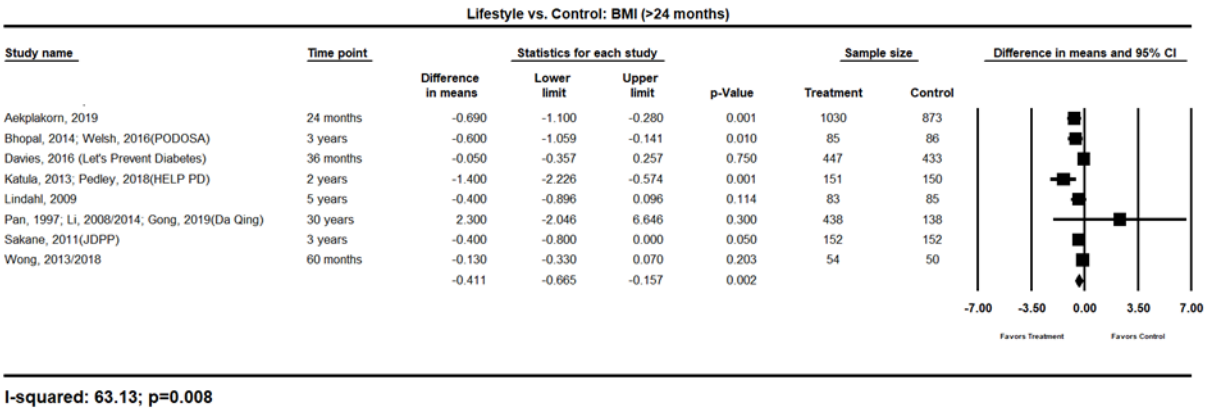
Lifestyle vs. Control: BMI (Endpoint)

Study name	Time point	Difference in means	Statistics for each study: Lower limit	Upper limit	p-Value	Sample size: Treatment	Control
Aekplakorn, 2019	24 months	-0.690	-1.100	-0.280	0.001	1030	873
Bhopal, 2014; Welsh, 2016(PODOSA)	3 years	-0.600	-1.059	-0.141	0.010	85	86
Block, 2015(Alive-PD)	6 months	-0.660	-1.050	-0.270	0.001	163	176
Davies, 2016 (Let's Prevent Diabetes)	36 months	-0.050	-0.357	0.257	0.750	447	433
Hellgren, 2014 (Basic Care)	1 year	-0.010	-0.922	0.902	0.983	18	15
Hellgren, 2014 (Intensive Care)	1 year	0.700	-0.273	1.673	0.158	19	15
Hu, 2017	1 year	-4.000	-6.366	-1.634	0.001	214	220
Katula, 2013; Pedley, 2018(HELP PD)	2 years	-1.400	-2.226	-0.574	0.001	151	150
Kulkarni, 2018	6 months	-0.200	-0.625	0.225	0.357	35	33
Kulzer, 2009(PREDIAS)	12 months	-0.800	-1.300	-0.300	0.002	91	91
Lindahl, 2009	5 years	-0.400	-0.896	0.096	0.114	83	85
Morey, 2012(Enhanced Fitness)	12 months	-0.280	-0.820	0.260	0.309	180	122
Moungngern, 2018	6 months	-0.200	-1.204	0.804	0.696	61	64
O'Brien, 2017(PREVENT-DM)	12 months	-2.000	-3.134	-0.866	0.001	33	30
Oldroyd, 2001	6 months	-0.950	-1.494	-0.406	0.001	39	39
Pan, 1997; Li, 2008/2014; Gong, 2019(Da Qing)	30 years	2.300	-2.046	6.646	0.300	438	138
Saito, 2011(ZPLS)	12 months	-0.500	-0.796	-0.204	0.001	311	330
Sakane, 2011(JDPP)	3 years	-0.400	-0.800	0.000	0.050	152	152
Van Name, 2016	12 months	-2.200	-3.273	-1.127	0.000	65	65
Wong, 2013/2018	60 months	-0.130	-0.330	0.070	0.203	54	50
		-0.541	-0.757	-0.325	0.000		



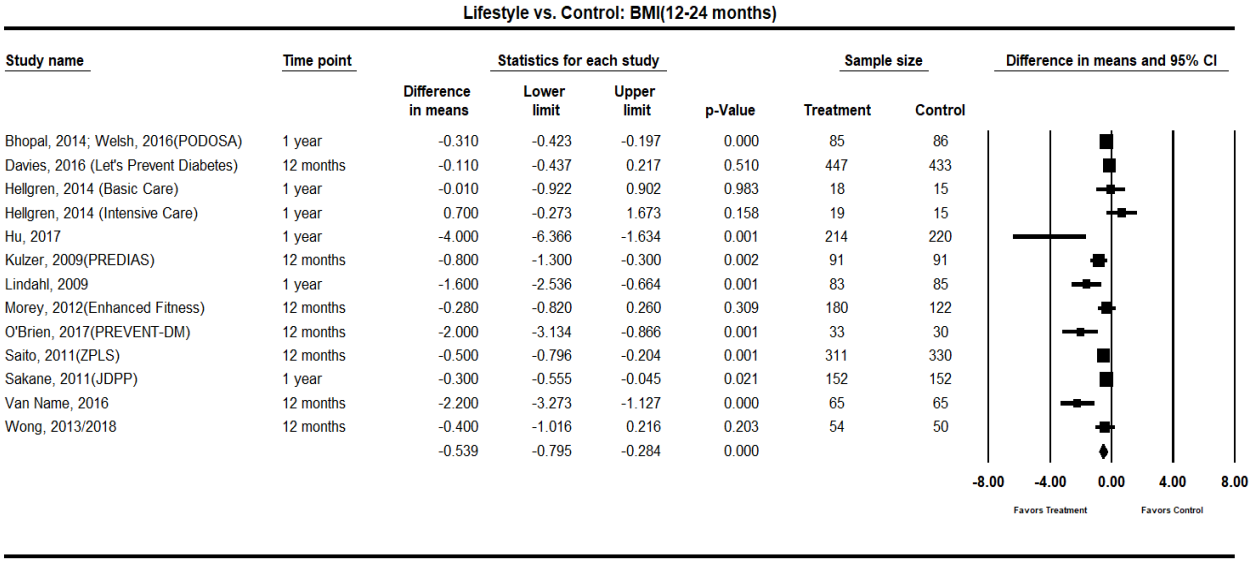
I-squared: 70.50; p=0.000

Appendix F Figure 97. Lifestyle vs. Control: BMI (>24 Months)



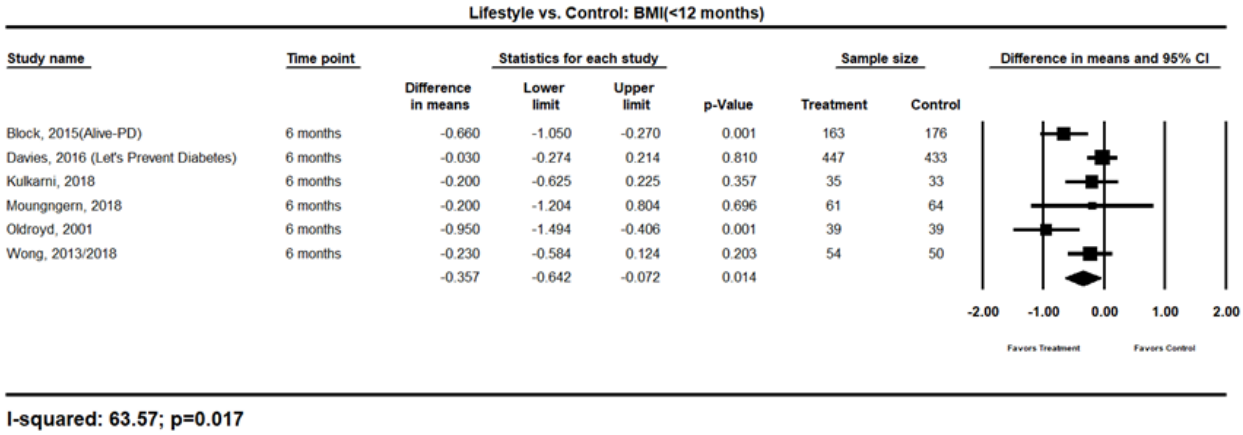
I-squared: 63.13; p=0.008

Appendix F Figure 98. Lifestyle vs. Control: BMI (12-24 Months)



I-squared: 74.69; p=0.000

Appendix F Figure 99. Lifestyle vs. Control: BMI (<12 Months)

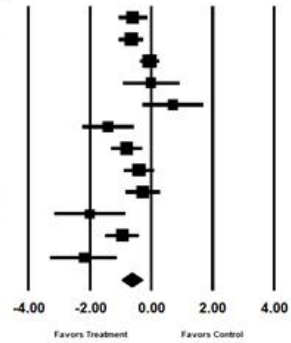


I-squared: 63.57; p=0.017

Appendix F Figure 100. Lifestyle vs. Control: BMI (BMI >30)

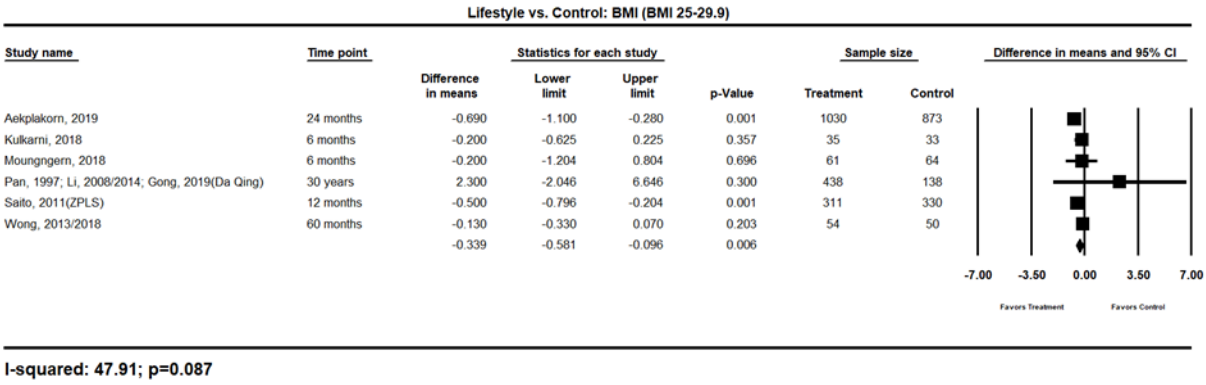
Lifestyle vs. Control: BMI (BMI >30)

Study name	Time point	Statistics for each study				Sample size		Difference in means and 95% CI
		Difference in means	Lower limit	Upper limit	p-Value	Treatment	Control	
Bhopal, 2014; Welsh, 2016(PODOSA)	3 years	-0.600	-1.059	-0.141	0.010	85	86	
Block, 2015(Alive-PD)	6 months	-0.660	-1.050	-0.270	0.001	163	176	
Davies, 2016 (Let's Prevent Diabetes)	36 months	-0.050	-0.357	0.257	0.750	447	433	
Hellgren, 2014 (Basic Care)	1 year	-0.010	-0.922	0.902	0.983	18	15	
Hellgren, 2014 (Intensive Care)	1 year	0.700	-0.273	1.673	0.158	19	15	
Katula, 2013; Pedley, 2018(HELP PD)	2 years	-1.400	-2.226	-0.574	0.001	151	150	
Kulzer, 2009(PREDIAS)	12 months	-0.800	-1.300	-0.300	0.002	91	91	
Lindahl, 2009	5 years	-0.400	-0.896	0.096	0.114	83	85	
Morey, 2012(Enhanced Fitness)	12 months	-0.280	-0.820	0.260	0.309	180	122	
O'Brien, 2017(PREVENT-DM)	12 months	-2.000	-3.134	-0.866	0.001	33	30	
Oldroyd, 2001	6 months	-0.950	-1.494	-0.406	0.001	39	39	
Van Name, 2016	12 months	-2.200	-3.273	-1.127	0.000	65	65	
		-0.643	-0.969	-0.317	0.000			



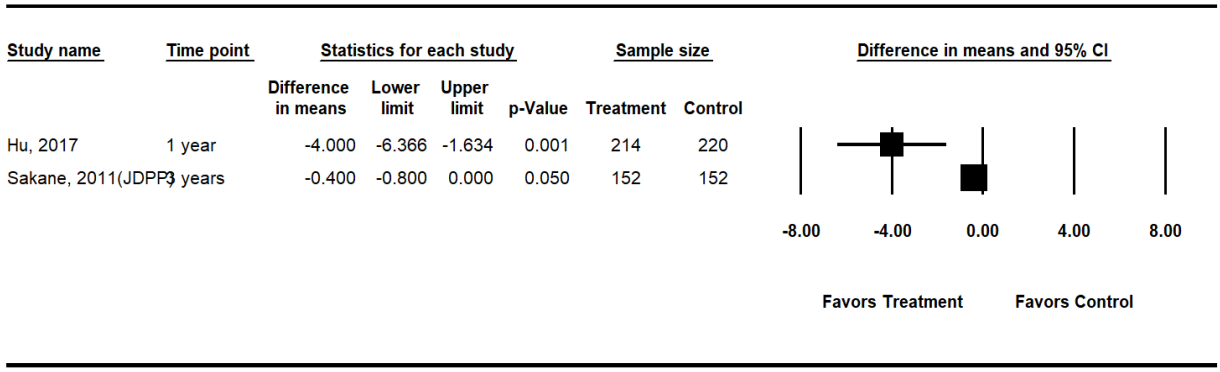
I-squared: 73.64; p=0.000

Appendix F Figure 101. Lifestyle vs. Control: BMI (BMI 25-29.9)



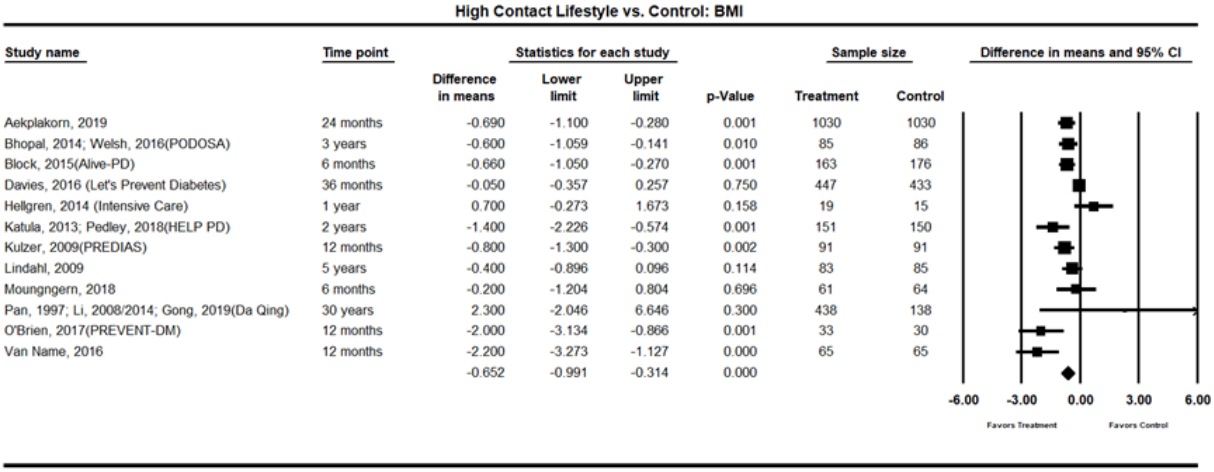
I-squared: 47.91; p=0.087

Appendix F Figure 102. Lifestyle vs. Control: BMI (BMI <25)



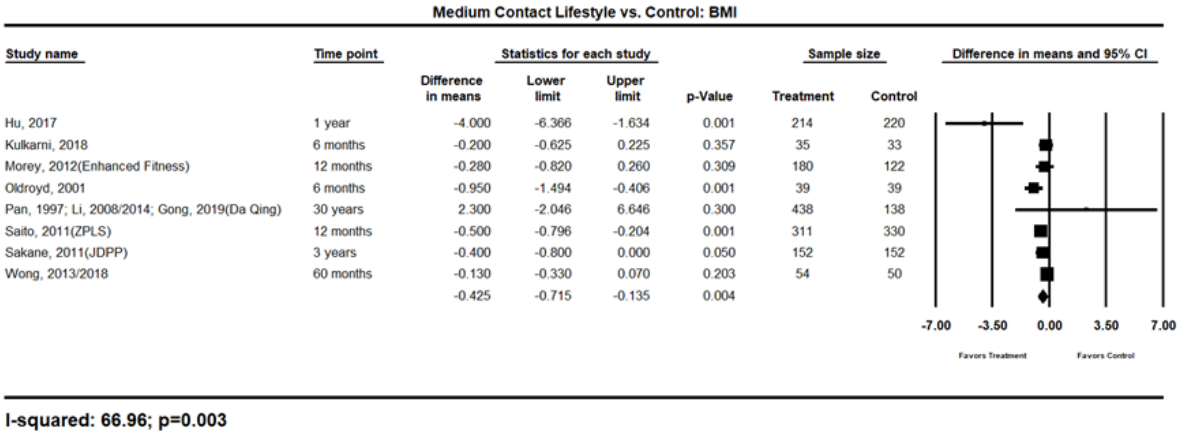
I-squared:N/A; p=N/A

Appendix F Figure 103. High Contact Lifestyle vs. Control: BMI



I-squared: 72.53; p=0.000

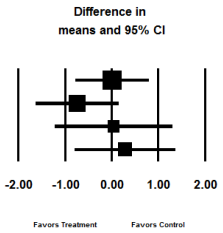
Appendix F Figure 104. Medium Contact Lifestyle vs. Control: BMI



I-squared: 66.96; p=0.003

Appendix F Figure 105. Lifestyle vs. Control: 10-Year CVD Risk

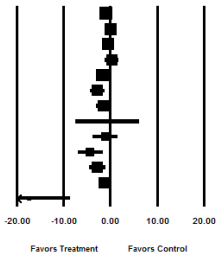
Study name	Comparison	Time point	Statistics for each study			Sample size	
			Difference in means	Lower limit	Upper limit	Treatment	Control
Davies, 2016-12 months	Let's Prevent Diabetes	12 months	0.010	-0.772	0.792	447	433
Davies, 2016-24 months	Let's Prevent Diabetes	24 months	-0.740	-1.621	0.141	447	433
Davies, 2016-36 months	Let's Prevent Diabetes	36 months	0.040	-1.210	1.290	447	433
Davies, 2016-6 months	Let's Prevent Diabetes	6 months	0.280	-0.796	1.356	447	433



I-squared:N/A; p=N/A

Appendix F Figure 106. Pharmacological or Combo vs. Control: Systolic Blood Pressure

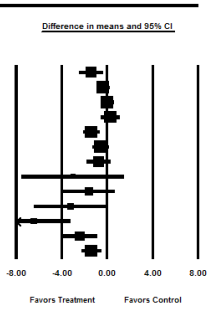
Study name	Comparison	Time point	Statistics for each study			Sample size	
			Difference in means	Lower limit	Upper limit	Treatment	Control
Chiasson, 2002, 2003(STOP-NIDDM)	Acarbose	3.3 years	-0.920	-1.467	-0.373	714	715
DPP, 2002/2005-1yr	Metformin	1 years	-0.010	-1.119	1.099	1073	1082
DPP, 2002/2005-2yrs	Metformin	2 years	-0.420	-1.529	0.689	1073	1082
DPP, 2002/2005-3yrs	Metformin	3 years	0.280	-1.106	1.666	1073	1082
DREAM Trial, 2006, 2006, and 2008-Rosiglitazone	Rosiglitazone	Final Visit	-1.700	-2.556	-0.844	2635	2635
le Roux, 2017(SCALE)-160weks	Liraglutide	160 weeks	-2.800	-4.208	-1.392	1505	749
le Roux, 2017(SCALE)-172wks	Liraglutide	172 weeks	-1.500	-3.062	0.062	1505	749
O'Brien, 2017(PREVENT-DM)	Metformin	12 months	-0.700	-7.348	5.948	29	30
Ramadrandran, 2009(IDPP-2)	Pioglitazone	36 months	-1.100	-3.665	1.465	204	203
DREAM Trial, 2006, 2006, and 2008-Ramipril	Ramipril	Median 3 years	-4.300	-6.860	-1.740	2623	2646
NAVIGATOR, 2010/2010; Currie, 2017-Valsartan	Valsartan	Median 5 years	-2.800	-4.467	-1.133	4631	4675
Gokulakrishnan, 2017(D-CLIP)	Stepwise intervention of DPP lifestyle classes plus metformin	12 months	-1.200	-2.390	-0.010	75	75
Lu, 2011	Intensive integrated intervention	2 years	-17.260	-25.787	-8.733	106	104



I-squared:N/A; p=N/A

Appendix F Figure 107. Pharmacological or Combo vs. Control: Diastolic Blood Pressure

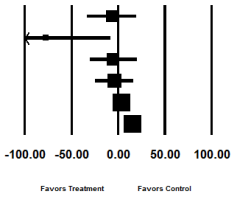
Study name	Comparison	Time point	Statistics for each study			Sample size	
			Difference in means	Lower limit	Upper limit	Treatment	Control
Chiasson, 2002; Chiasson, 2003(STOP-NIDDM)	Acarbose	3.3 years	-1.400	-2.433	-0.367	714	715
DPP, 2002/2005-1yr	Metformin	1 years	-0.370	-0.924	0.184	1073	1082
DPP, 2002/2005-2yrs	Metformin	2 years	0.010	-0.544	0.564	1073	1082
DPP, 2002/2005-3yrs	Metformin	3 years	0.290	-0.542	1.122	1073	1082
DREAM Trial, 2006, 2006, and 2008	Rosiglitazone	Final visit	-1.400	-2.105	-0.695	2635	2634
le Roux, 2017(SCALE)-160wks	Liraglutide 3.0mg, with lifestyle counseling	160 weeks	-0.600	-1.300	0.100	1505	749
le Roux, 2017(SCALE)-172wks	Liraglutide 3.0mg, with lifestyle counseling	172 weeks	-0.740	-1.789	0.309	1505	749
O'Brien, 2017(PREVENT-DM)	Metformin	12 months	-3.000	-7.501	1.501	29	30
Ramadrandran, 2009(IDPP-2)	pioglitazone, 30 mg, with lifestyle	36 months	-1.600	-3.844	0.644	204	203
Gokulakrishnan, 2017 (D-CLIP)	Stepwise intervention of DPP lifestyle plus metformin	12 months	-3.200	-6.374	-0.026	75	75
Lu, 2011	Intensive integrated intervention	2 years	-6.440	-9.621	-3.259	106	104
DREAM Trial, 2006/2006/2009	Ramapiril	Median: 3 years	-2.400	-3.921	-0.879	2623	2646
NAVIGATOR Trial, 2010/2017	Valsartan	Median: 5 years	-1.400	-2.234	-0.566	4631	4675



I-squared:N/A; p=N/A

Appendix F Figure 108. Pharmacological or Combo vs. Control: Total Cholesterol

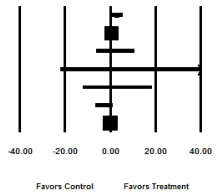
Study name	Comparison	Time point	Statistics for each study			Sample size		Difference in means and 95% CI
			Difference in means	Lower limit	Upper limit	Treatment	Control	
Gokulakrishnan, 2017(D-CLIP)	Lifestyle plus metformin	12 months	-7.000	-33.106	19.106	75	75	
le Roux, 2017 (SCALE)	Liraglutide	160 weeks	-77.340	-146.017	-8.663	1505	749	
Lu, 2011	Intensive integrated intervention	2 years	-5.410	-30.337	19.517	106	104	
O'Brien, 2017(PREVENT-DM)	Metformin	12 months	-4.100	-24.145	15.945	29	30	
Ramadrandran, 2009 (IDPP-2)	Pioglitazone	36 months	3.860	-4.440	12.160	204	203	
Zinman, 2010 (CANOE)	Rosiglitazone plus metformin	3.9 years	15.460	6.467	24.453	103	104	



I-squared:N/A; p=N/A

Appendix F Figure 109. Pharmacological or Combo vs. Control: High Density Lipoprotein

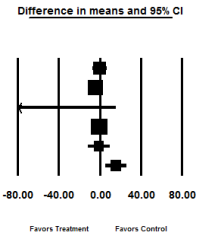
Study name	Comparison	Time point	Statistics for each study			Sample size	
			Difference in means	Lower limit	Upper limit	Treatment	Control
DeFronzo, 2011 (ACTNOW)	Pioglitazone	Mean: 2.2 years	2.920	0.705	5.135	303	299
DPP, 2002/2005	Metformin	3 years	0.400	0.147	0.653	1073	1082
Gokulakrishnan, 2017 (D-CLIP)	Stepwise intervention of DPP lifestyle classes plus metformin	12 months	2.200	-6.005	10.405	75	75
le Roux, 2017(SCALE)	Liraglutide	160 weeks	34.803	-22.008	91.614	1505	749
Lu, 2011	Intensive integrated intervention	2 years	3.100	-11.958	18.158	106	104
O'Brien, 2017(PREVENT-DM)	Metformin	12 months	-2.900	-6.629	0.829	29	30
Zinman, 2010	Rosiglitazone plus metformin	3.9 years	0.000	0.000	0.000	103	104



I-squared:N/A; p=N/A

Appendix F Figure 110. Pharmacological or Combo vs. Control: Low Density Lipoprotein

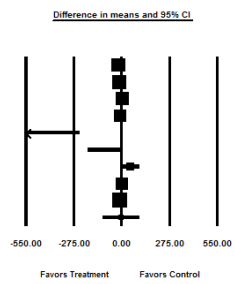
Study name	Comparison	Time point	Statistics for each study			Sample size	
			Difference in means	Lower limit	Upper limit	Treatment	Control
DeFronzo, 2011; Espinoza, 2016 (ACTNOW)	Pioglitazone	Mean: 2.2 years	-0.390	-7.149	6.369	303	299
Gokulakrishnan, 2017(D-CLIP)	Stepwise intervention plus metformin	12 months	-4.000	-7.967	-0.033	75	75
le Roux, 2017(SCALE)	Liraglutide	160 weeks	-77.340	-169.458	14.778	1505	749
Lu, 2011	Intensive integrated intervention	2 years	-0.780	-2.869	1.309	106	104
O'Brien, 2017(PREVENT-DM)	Metformin	12 months	-1.000	-11.526	9.526	29	30
Zinman, 2010(CANOE)	Rosiglitazone plus metformin	3.9 years	15.470	5.565	25.375	103	104



I-squared:N/A; p=N/A

Appendix F Figure 111. Pharmacological or Combo vs. Control: Triglycerides

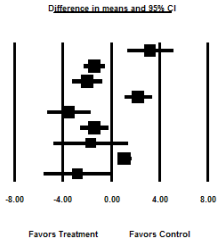
Study name	Comparison	Time point	Statistics for each study			Sample size	
			Difference in means	Lower limit	Upper limit	Treatment	Control
Chiasson, 2002; Chiasson, 2003(STOP-NIDDM)	Acarbose	3.3 years	-19.490	-34.300	-4.680	714	715
DeFronzo, 2011; Espinoza, 2016(ACT NOW)	Pioglitazone	Mean: 2.2 years	-12.280	-23.345	-1.215	303	299
DPP, 2002/2005	Metformin	3 years	4.500	-12.316	21.316	1073	1082
Gokulakrishnan, 2017(D-CLIP)	Stepwise intervention of DPP lifestyle classes plus metformin	12 months	-6.000	-28.377	16.377	75	75
le Roux, 2017(SCALE)	Liraglutide	160 weeks	-531.420	-819.069	-243.771	1505	749
Lu, 2011	Intensive integrated intervention	2 years	-100.970	-195.741	-6.199	106	104
Nijpels, 2018(DAISI)	Acarbose	37 months	51.370	0.536	102.204	60	58
O'Brien, 2017(PREVENT-DM)	Metformin	12 months	1.100	-21.689	23.889	29	30
Ramachandran, 2009(IDPP-2)	Pioglitazone	36 months	-10.630	-21.673	0.413	181	186
Zinman, 2010(CANOE)	Rosiglitaazone plus metformin	3.9 years	-2.660	-106.484	101.164	103	104



I-squared:N/A; p=N/A

Appendix F Figure 112. Pharmacological or Combo vs. Control: Weight Continuous (All)

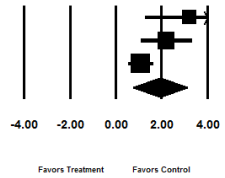
Study name	Comparison	Time point	Statistics for each study			Sample size	
			Difference in means	Lower limit	Upper limit	Treatment	Control
DeFronzo, 2011; Espinoza, 2016 (ACT NOW)	Pioglitazone	"Mean: 2.2 years	3.200	1.303	5.097	303	299
Chiasson, 2002; Chiasson, 2003(STOP-NIDDM)	Acarbose	3.3 years	-1.410	-2.248	-0.572	714	715
DPP, 2009	Metformin	2.8 (1.8 to 4.6)	-2.000	-3.190	-0.810	1073	1082
DREAM Trial/The DREAM Trial Investigators, 2006, 2006, and 2006	Rosiglitazone	Final visit	2.200	1.093	3.307	2635	2634
le Roux, 2017(SCALE)	Liraglutide 3.0mg once-daily for 160 weeks, with lifestyle counseling	172 weeks	-3.500	-5.260	-1.740	1505	749
Lu, 2011	Intensive integrated intervention	2 years	-1.430	-2.549	-0.311	106	104
O'Brien, 2017(PREVENT-DM)	Metformin	12 months	-1.700	-4.729	1.329	29	30
Ramadrandran, 2009(IDPP-2)	Pioglitazone	36 months	1.080	0.552	1.608	204	203
Gokulakrishnan, 2017 (D-CLIP subgroup)	Stepwise intervention of DPP lifestyle classes plus metformin	12 months	-2.800	-5.577	-0.023	75	75



I-squared:N/A; p=N/A

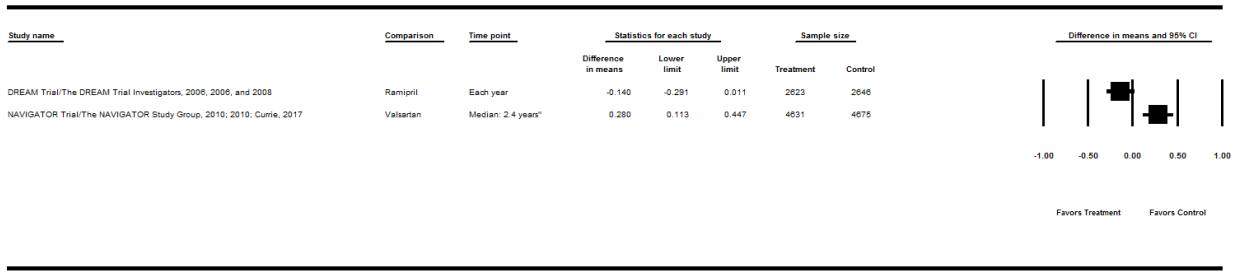
Appendix F Figure 113. Thiazolidinedione vs. Control: Weight Continuous

Study name	Comparison	Time point	Statistics for each study			Sample size	
			Difference in means	Lower limit	Upper limit	Treatment	Control
DeFronzo, 2011; Espinoza, 2016 (ACT NOW)	Pioglitazone	Mean: 2.2 years	3.200	1.303	5.097	303	299
DREAM Trial/The DREAM Trial Investigators, 2006; 2006; 2006	Rosiglitazone	Final visit	2.200	1.093	3.307	2635	2634
Ramadrandran, 2009(IDPP-2)	Pioglitazone	36 months	1.080	0.552	1.608	204	203
			1.913	0.750	3.076		



I-squared:70.91; p=0.32

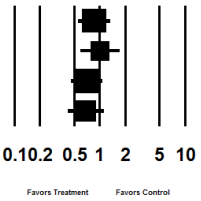
Appendix F Figure 114. Hypertension Treatment vs. Control: Weight Continuous



I-squared:N/A; p=N/A

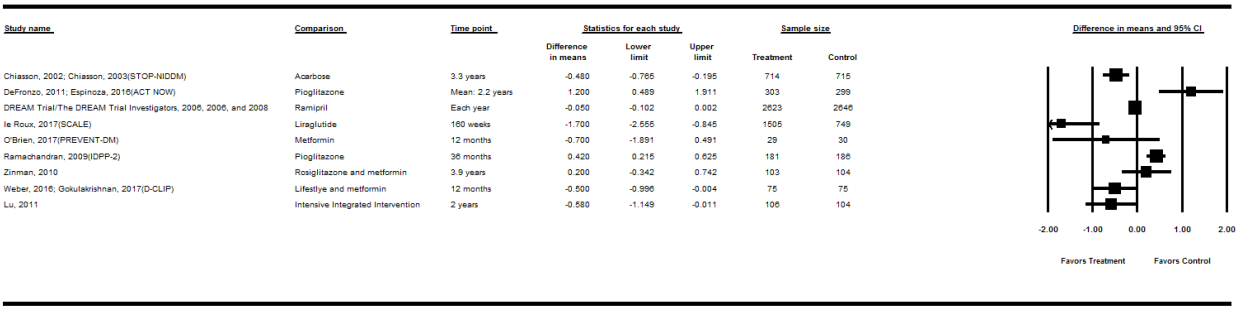
Appendix F Figure 115. Rosiglitazone Plus Metformin vs. Control: Weight Loss or Weight Gain Binary

Study name	Outcome	Time point	Statistics for each study			Events / Total		Risk ratio and 95% CI
			Risk ratio	Lower limit	Upper limit	Treatment	Control	
Zinman, 2010-1	Weight gain >2 kg	3.9 years	0.857	0.561	1.308	28 / 103	33 / 104	
Zinman, 2010-2	Weight gain >3 kg	3.9 years	1.010	0.598	1.706	22 / 103	22 / 104	
Zinman, 2010-3	Weight loss >2 kg	3.9 years	0.699	0.465	1.051	27 / 103	39 / 104	
Zinman, 2010-4	Weight loss >3 kg	3.9 years	0.684	0.422	1.108	21 / 103	31 / 104	



I-squared:N/A; p=N/A

Appendix F Figure 116. Pharmacological or Combo vs. Control: BMI



I-squared:N/A; p=N/A

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