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Screening for Depression in Adults: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

Background: Depression is relatively common in primary care patients but is not always identified by primary care providers.

Purpose: To systematically review evidence to update the benefits and harms of screening for depression in general and older adults, and to also consider evidence for benefits and harms in pregnant and postpartum women, which was not previously reviewed, to aid the U.S. Preventive Services Task Force (USPSTF) in updating its recommendation on this topic.

Methods: We searched MEDLINE, PubMed, PsycINFO, and the Cochrane Collaboration Registry of Controlled Trials through January 20, 2015, to identify relevant literature published since completion of searching for previous reviews of depression screening in general and older adults (new searches beginning January 1, 2009) and pregnant and postpartum women (new searches beginning January 1, 2012). We also examined references of other existing systematic reviews; searched websites of government agencies, professional organizations, and other organizations for grey literature; and monitored health news websites and journal tables of contents to identify potentially eligible trials. Two investigators independently reviewed identified abstracts and full-text articles against a set of *a priori* inclusion and quality criteria. One investigator abstracted data into an evidence table and a second investigator checked these data. We conducted random effects meta-analyses to estimate the benefit of cognitive behavioral therapy (CBT) in pregnant and postpartum women.

Results: We included 65 studies, reported in 83 publications. Nine trials addressed screening in general (five trials, n=2,924) and older (four trials, n=890) adults, the remaining targeted pregnant and postpartum women, addressing: benefits of screening (six trials, n=11,869); harms of screening (one trial, n=462); benefits of treatment (17 trials, n=1,583); harms of treatment with second generation antidepressants (one systematic review, including 15 studies in depressed pregnant women and 109 studies in general pregnant populations, one trial [n=87], and 12 observational studies [n=4,759,822]); and diagnostic accuracy of selected screening instruments (21 studies, n=6,325). Most studies of antidepressant harms were limited to pregnant women, but evidence for other questions primarily focused on postpartum women.

Trials in postpartum women showed 30 to 59 percent reductions in the risk of depression at 3 to 5 month followup after participating in programs involving depression screening, with or without additional treatment components, compared to usual care. For identifying major depressive disorder using a cutoff of 13 on the English-language Edinburgh Postnatal Depression Scale, sensitivity ranged from 0.67 (95% CI, 0.18 to 0.96) to 0.95 (95% CI, 0.81 to 1.00), and specificity ranged from 0.90 (95% CI, 0.86 to 0.94) to 0.99 (95% CI, 0.97 to 1.00). Pooled results for the benefit of CBT in screen-detected depressed pregnant and postpartum women showed a 35 percent increase in the likelihood of remission with CBT (pooled RR, 1.35 [95% CI, 1.19 to 1.53]; k=9, I^2=18.7%), compared to waitlist or usual care. Observational evidence showed that second generation antidepressant use during pregnancy may be associated with small increases in the risk of preeclampsia, postpartum hemorrhage, miscarriage, perinatal death, preterm birth, serotonin withdrawal syndrome, respiratory distress, pulmonary hypertension, major malformations, cardiac malformations, and being small for gestational age.

Screening programs generally increased the likelihood of remission and treatment response in general adult populations (k=5) experiencing depressive symptoms. None of the trials limited to older adults (k=4) showed a benefit of the screening program, and one showed a statistically non-significant adverse effect on depression remission.

Conclusions: Although direct evidence of the isolated health benefit of depression screening in primary care is weak, the totality of the evidence supports the benefits of screening in pregnant and postpartum and general adult populations, particularly in the presence of additional treatment supports such as treatment protocols, care management, and availability of specially trained depression care providers. Evidence is least supportive of screening in older adults, where direct evidence is most limited.

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Chapter 1. Introduction

Condition Definition

Depression is a term that encompasses many depressive disorders, including major depressive disorder (MDD), persistent depressive disorder (formerly called dysthymia), and minor depression.[1] Individuals with depression often experience not only sadness, but a lack of interest or enjoyment in activities, decreased energy, insomnia, weight changes, feelings of loss and worthlessness, and recurrent thoughts of death or suicide. Postpartum depression describes depressive episodes that occur within 12 months of delivery.[2]

Prevalence and Risk Factors for Depression

Depression is a common mental disorder in the United States. In 2009 to 2012, approximately 7 percent of the U.S. population met the criteria for a current depressive disorder, according to the National Survey on Drug Use and Health (NSDUH) and National Health and Nutrition Examination Survey (NHANES).[3,4] Depression rates are higher in women of reproductive age, at 10.9 percent according to the NSDUH (7.7% among pregnant women, 11.1% among non-pregnant women).[5,6] Data from the 2004 to 2005 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) reported prevalence of 9.1 percent in pregnant women, 10.2 percent in postpartum women, and 13.1 percent in women in childbearing age who were not in the postpartum period.[7] The only estimates of depression available in U.S. primary care settings come from rather outdated meta-analysis of eight studies published between 1987 and 2000, estimating a prevalence of 12.5 percent in primary care in the United States.[8]

In addition to varying by sex, prevalence rates among the general American adult population vary by age, race/ethnicity, education, geographic location, poverty level, and employment. Women, young and middle-aged adults, and non-White individuals had higher rates of depression when compared to their counterparts, as did those who were undereducated, and unemployed (**Table 1**).[9]

Other groups at higher risk for developing depression include those with chronic illnesses (e.g., cancer, cardiovascular disease),[10,11] other mental health disorders (including substance misuse),[12] and those with a family history of psychiatric disorders.[13] A meta-analysis of 84 studies examining risk factors for postpartum depression, for example, identified 13 significant predictors: prenatal depression, poor self-esteem, childcare stress, prenatal anxiety, life stress, decreased social support, single/unpartnered relationship status, history of depression, difficult infant temperament, maternity blues, lower socioeconomic status (SES), and unintended pregnancy.[14] Among older adults, the risk factors for depression include disability and poor health status related to medical-illness-complicated grief, chronic sleep disturbance, loneliness, and a personal history of depression.[15]

Burden of Depression

Globally, MDD is the leading cause of disability among adults in high-income countries. Depression also reaps a significant economic burden as it is associated with decreased work productivity and work absenteeism.[16,17] Depression costs an estimated $23 billion in lost productivity to U.S. employers.[18] In 2009, an estimated $22.8 billion was spent on depression treatment with the largest portion (52.8%) being spent on prescription medications, followed by ambulatory care visits (35.8%).[19]

Depression is also associated with higher mortality[20-23] and greater risk of cardiovascular events.[23] In addition, depression may reduce the likelihood that persons with other health conditions comply with prescribed treatments or manage self-care effectively. This makes depression a particularly important issue within primary care settings, as the presence of depression could impact the effectiveness of care that practitioners are providing for other conditions. A recent study of U.S. veterans, for example, showed depressed patients died younger (71 vs. 76 years) and had more years of potential life lost (13 vs. 10) than non-depressed patients.[24] Depression is an important risk factor for suicide and suicide attempts.[25,26]

Depression has a major impact on quality of life for both the depressed person and his or her family members. The National Comorbidity Survey Replication (NCS-R) has documented substantial role impairments associated with MDD related to work, household responsibilities, social life, and personal relationships.[27] In older adults, depressive disorders were the third-leading cause of loss of quality-adjusted life years in primary care patients over the age of 65, behind only arthritis and heart disease.[28] Family members of depressed patients also experience substantial burden and relational strain[29] as well as more depressive and anxiety disorders than those without a depressed family member.[30,31] Financial difficulties are the most commonly reported family problem in major depression due to lost productivity of the depressed individual (and caregiver) and costs of depression treatment.[31] Children of depressed parents display more emotional and behavioral problems, poorer peer social competence, and poorer school adjustment than those with non-depressed parents.[29,32,33]

Etiology and Natural History

While depression onset can occur at almost any age, the average age of onset among U.S. adults is 32 years.[34] Depression is often a chronic disease characterized by periods of remissions and recurrences, although the course of depression varies widely from person-to-person. A meta-analysis of remission rates among untreated study participants with major depression estimated 23, 32, and 53 percent would remit within 3, 6, and 12 months, respectively.[35] Another systematic review of antidepressant studies with a followup of 10 or more years found 40 to 85 percent of participants experienced a recurrence after approximately 3 years.[36] Among older adults, 8 to 10 percent of those with subthreshold depression developed major depression within a year and only 27 percent entered remission within another year later.[37] While predicting recurrence is difficult, the number of previous episodes and residual symptoms are the strongest predictors for recurrence.[38]

The causes of depression are likely multifactorial and include both biological and environmental factors. While adverse life events increase the likelihood of depression, genetic factors may predispose persons to be affected by environmental factors, such as life events, to a greater or lesser degree.[39] According to the cognitive model of depression, depressed persons have characteristic "depressogenic" ways of acquiring and processing of information from their environment, which implies that the way individuals interpret their experiences directly influences the development of depression.[40] Other factors come into play as well in psychological models of depression, such as social skills, pleasant activities, and other life skills such as problem-solving.[41]

The neurobiology of MDD traditionally focuses on two monoamine neurotransmitters—serotonin and norepinephrine—which are likely to be low in depressed individuals.[42] These neurotransmitters are known for regulating mood and functions such as appetite, sleep, and attention. Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and other second generation antidepressants are commonly used pharmacotherapy for depression. The structure of the brain may also have a role in depression, as evidenced by a meta-analysis of 225 studies comparing brain images of non-depressed individuals and patients with MDD that found significant differences including smaller volumes of the frontal lobe and limbic system in those with depression.[43] Similar findings are also seen in older adults.[44] These structures are responsible for learning, memory, thought processing, and maintaining emotional stability, and their malfunction is considered central to the pathophysiology of depression.[42] It is unclear, however, the degree to which depression results from or causes structural changes in the brain.

Genetics also plays a role in developing depression. Studies have shown that first degree relatives of individuals diagnosed with MDD have a 2- to 3-fold greater risk of developing MDD than the general population. In particular, age at onset in one's 30s or earlier and recurrent episodes of MDD have been identified as genetic characteristics that predict the largest relative risk for first degree relatives to develop MDD. Studies examining the association of MDD with polymorphisms have resulted in mixed evidence, largely due to lack of adequate power to test for genetic susceptibilities as well as limited technological capacity. While studies of genetic association have historically been limited to populations of twins and adopted populations, whole-genome linkage studies have recently become feasible.[45,46]

Current Clinical Practice

Researchers have developed a framework that shows how successful treatment of depression in primary care involves number of steps, including recognition that a patient is depressed, initiation of treatment, and completion of an adequate course of treatment.[47] Estimates of clinician recognition of depression in the United States are wide-ranging, from 21 to 76 percent of depression cases, with about half of the estimates falling above and half below the international pooled average of 47.3 percent.[48] One study reported sensitivity of 49.2 percent and specificity of 81.1 percent for primary care providers in the United States in accurately identifying major depressive episodes.[8] Accuracy may be lower for older adults (age 65 and older) than for younger adults.[49]

If depression is likely to be missed in primary care, one might hypothesize that this would be due to relatively mild symptom severity in patients seen in primary care. However, symptom severity in patients seen in primary care settings was similar to severity of patients seen in mental health specialty settings in earlier research.[50] There were, however, socio-demographic differences in the cases seen in primary and specialty care clinics—depressed patients seen in primary care settings were more likely to be older, female, African American, or unemployed. Notably, suicidality was higher among patients being seen in specialty care settings, despite similar symptom severity.

In terms of typical screening methods, less is known about how often primary care providers use formal screening instruments to identify depression. While some health systems have implemented large-scale formal screening programs, depression screening in other settings may be very limited. According to the 2010 U.S. National Ambulatory Medical Care Survey (NAMCS), depression screening was recorded for only 2.3 percent of visits, although this likely underestimates the true screening of patients over time, since patients may have been screened at other recent visits.[51] These rates have not changed when compared to other cross-sectional studies examining NAMCS data from the previous 5 years.[52,53]

Even among those who are appropriately screened and diagnosed, many patients do not receive treatment. Population-based surveys suggest that only about half of persons with MDD are treated in a given year.[27,54] While most patients with major depressive episodes do eventually get treatment, data from the World Health Organization's (WHO) World Mental Health Survey showed that only 35.4 percent of depressed Americans are treated within a year of depression onset, and the median time to treatment initiation is 4 years.[55] Further, among Americans receiving treatment, only 37.5 percent of patients with MDD received a minimally adequate dose in a given year, according to NCS-R data.[56] A minimally adequate dose was defined as (a) 2 or more months of an appropriate medication plus five or more visits with a physician, or (b) eight or more visits with a health care provider (including mental health specialists) or human services provider (e.g., social worker, religious/spiritual advisor) lasting an average of 30 minutes per visit.

While these data raise concerns that depression is frequently overlooked by primary care providers, there is also growing concern with overtreatment and misdiagnoses, particularly in light of rising rates of antidepressant use in the population.[57] A recent study using data from the 2009 to 2010 NSDUH examined agreement between patient self-report of depression diagnosis from a medical professional in the past 12 months and the presence of Diagnostic and Statistical Manual Fourth Edition (DSM-IV) criteria for a major depressive episode in the past year based on a structured interview.[58] This study found that only 38 percent of surveyed patients reporting a clinician-identified major depressive episode met the DSM-IV criteria, and this rate dropped to 18 percent for older adults (age 65 or older).[49] Forty-three percent of adults (of all ages) not meeting DSM-IV criteria, however, did meet the criteria for minor depression or lifetime minor or major depression. This suggests that some of these patients may have been in a prodromal phase or recovery phase where they were symptomatic, but did not meet full criteria for diagnosis, may have misremembered the timing of their depressive diagnosis, or may have been incompletely treated and potentially in need of treatment despite not meeting current MDD criteria. The use of antidepressant medication is high for primary care clinician-diagnosed

depression and their use was reported by a majority of those receiving treatment whether they met DSM-IV criteria (84%) or not (74%).[58]

We found no information on depression detection rates in postpartum women. One trial of depression treatment during pregnancy examined medical records of participants who volunteered to participate in the study and met DSM-IV criteria for MDD and scored 14 or higher on the Hamilton Rating Scale for Depression (HAM-D).[59] Women in this study were assessed by a wide variety of prenatal care providers and depression was noted in the charts of 56 percent of these pregnant women. Assuming this is typical of community care, identification of depression in pregnant women may be comparable to that in the general adult population, in which estimates average just under 50 percent, but are wide-ranging.

Physician surveys, however, suggest fairly high rates of depression screening in postpartum populations. For example, several surveys of obstetricians-gynecologists, family physicians, and pediatricians show that these providers consider that it is their responsibility, or that it is important, to identify postpartum depression.[60-63] As such, approximately 70 percent of surveyed obstetricians-gynecologists and family physicians reported that they often or always screen patients for postpartum depression.[64,65] Surveys also show that providers generally do not routinely use formal screening tools, but instead use their own clinical methods.[60,64,66,67] For example, while 79 percent of physician surveyed about postpartum screening practices reported that they are unlikely to use a formal screening tool, 43 percent were almost certain to ask whether women felt down, depressed, or hopeless, and 27 percent were almost certain to ask about women's interest in usual activities.[67] Commonly reported barriers to postpartum depression screening included lack of knowledge or training and time constraints.[62-65]

We could find little information on how often treatment was generally recommended and accepted after depression is identified in pregnant and postpartum women.[68] We identified one trial of a depression screening and treatment support intervention that found that 11 percent of postnatal women who were identified by their provider as depressed received counseling in usual care, 35 percent received antidepressants, and a total of 37 percent received either one.[69] Treatment persistence is unknown in pregnant and postpartum women, although discontinuation may be high for antidepressants. This is evidenced by one observational cohort study of Medicaid claims data that identified pregnant women who received a diagnosis of depression and who filled at least two antidepressant prescriptions during pregnancy. The median time to discontinuation of antidepressants was 80 days, well below the generally recommended 6 to 9 months course recommended by the American Psychiatric Association.[70] Only about 20 percent of the women in this study continued their antidepressants for 6 months.[68]

Rationale for Screening for Depression

Screening in primary care may help identify those individuals with undiagnosed depression and could help shorten the typical 4-year lag between depression onset and treatment initiation, which could potentially prevent substantial suffering. Further, screening may help identify patients who have been treated but are still symptomatic and need more effective depression treatment. Indeed, previous studies involving population-based screening in primary care patients

indicated that the majority of identified patients had a history of prior depressive episodes, in both general adult populations[71-73] and older adults.[74] Depression screening also presents an opportunity to identify patients who are suicidal, among those screening positive. While the USPSTF has not recommended universal screening for suicide, they do note that "primary care clinicians should be aware of psychiatric problems in their patients and should consider asking these patients about suicidal ideation and referring them" for treatment.[75]

Screening Instruments

The Patient Health Questionnaire (PHQ) is the most commonly used depression screening instrument in the United States.[76] Other commonly used depression screening instruments include the Hospital Anxiety and Depression Scales (HADS) among adults, the Geriatric Depression Scale (GDS) among older adult, and the Edinburgh Postnatal Depression Scale (EPDS) among pregnant women. **Table 2** provides more detailed descriptions of instruments that can be used for depression screening. Positive screening tests should be followed by a more detailed interview to determine the nature of the depressive for diagnostic and treatment planning purposes, rather than assigning a diagnosis of depression based only on a positive screening test.

Interventions to Treat Depression

There are many available treatments for depression including psychotherapy and pharmacotherapy, both of which are widely available either directly in primary care or through referral from primary care. Over half of patients treated for MDD receive treatment in general medicine settings, with the remaining patients receiving care in mental health specialty settings.[56]

Antidepressant medications are the most commonly used treatment for depression (**Table 3**), with second generation antidepressants accounting for approximately 90 percent of antidepressant utilization in 2009.[77] Approximately one-third of persons with severe symptoms of depression take antidepressant medication, and as much as 23 percent of all women in the United States aged 40 to 59 take antidepressants, according to National Center for Health Statistics data from 2005 to 2008.[78] While serious harms of psychotherapy have not been identified, antidepressants are associated with some serious adverse events, including increased suicidality in adolescents and younger adults, serotonin syndrome, and gastrointestinal bleeding. They are also frequently associated with more minor adverse effects such as weight gain, sedation, and adverse sexual effects.[79,80] Second generation antidepressants have "C" pregnancy ratings, except for paroxetine, which has a "D" rating (**Appendix A Table 1**). A "C" rating means that animal studies at higher than human doses have been shown to harm the fetus, and a "D" rating means there is evidence of human fetal risk based on adverse events reported from investigational or marketing studies. The Food and Drug Administration (FDA) will soon be changing their pregnancy and lactation labeling information for prescription drugs, including antidepressants[81] Second generation antidepressants are excreted into breast milk.[82]

Recent efforts to improve depression outcomes in primary care settings often include collaborative care interventions. These interventions apply a chronic disease care model to

depression and utilize care or case managers to support the primary care clinician, facilitate patients' treatment engagement, and monitor symptoms. Care managers may provide patient education; arrange appointments with specialty providers; monitor treatment adherence, depressive symptoms, and adverse effects; notify providers when patients fail to improve or experience side effects; and provide supportive or psychotherapeutic counseling in some cases. Collaborative care interventions have been recommended by the Community Guide.[83]

Complementary and alternative therapies include yoga, exercise, and dietary supplements such as St. John's Wort are also sometime used for depression, and some interventions are appropriate second-line treatments for severe depression when first-line treatments are not effective, such as polypharmacy, transcranial stimulation, and electroconvulsive therapy (ECT).

Current U.S. Initiatives and Recommendations of Other Organizations

The Healthy People 2020 initiative[84] has published 12 objectives related to mental health and mental disorders, including major depression listed below:

- MHMD-4: Reduce the proportion of persons who experience major depression episodes
- MHMD-10: Increase depression screening by primary care providers

The recommendations for depression screening in clinical practice from other health organizations are listed in **Table 4**.

In addition, some states have passed legislation to mandate screening of women who are pregnant (West Virginia), postpartum (New Jersey), or both (Illinois). Other states have passed legislation to guarantee reimbursement for screening, initiate programs to train providers, or raise awareness about depression in pregnant and postpartum women.[85]

Previous USPSTF Recommendation

In 2009, the USPSTF concluded that there is at least moderate certainty that the net benefit of screening for depression is at least moderate for adults who receive care in clinical practices that have staff-assisted depression care supports in place. The USPTSF recommended screening adults for depression when staff-assisted depression care supports are in place to assure accurate diagnosis, effective treatment, and followup (B recommendation).[86] The USPSTF also concluded that there is at least moderate certainty that the net benefit of screening adults for depression is small for adults who receive care in clinical practices without staff-assisted depression care support in place. The USPSTF recommended against routinely screening adults for depression when staff-assisted depression care supports are not in place; there may be considerations that support screening for depression in the individual patient (C recommendation).[86] This recommendation was based on a combination of results from the 2002 USPSTF review[87] and a targeted update published in 2009.[80]

Chapter 2. Methods

Scope and Purpose

This targeted update review examined the evidence for depression screening in general adult populations (including older adults) and also considered comprehensive evidence for benefits and harms of depression screening in pregnant and postpartum women. The USPSTF will use this review to update their 2009 recommendation for depression screening in primary care in the United States.[86]

We developed separate analytic frameworks for general adult populations and pregnant women, with additional questions that addressed pregnant and postpartum women. In general-adult populations, we examined studies that compared depression and other outcomes in persons who were screened versus not screened (Key Question [KQ] 1 for benefits, KQ2 for harms), or whose providers received screening results versus did not receive screening results (KQ1a for benefits, KQ2 for harms). Evidence related to diagnostic accuracy of depression screening instruments and effectiveness of depression treatment was not included in the current review for general adult populations because they were considered established by the previous reviews. For pregnant and postpartum women, however, we examined direct evidence of benefits (KQ1) and harms (KQ3) of depression screening and the chain of indirect evidence, including the diagnostic accuracy of commonly used screening instruments (KQ2) as well as the benefits (KQ4) and harms (KQ5) of treatment in screen-detected depressed women.

Key Questions and Analytic Framework

We developed analytic frameworks and KQs in consultation with USPSTF members for pregnant and postpartum women (**Figure 1**) and the general adult population, including older adults (**Figure 2**). The KQs are listed below:

Pregnant and Postpartum Women

1. Do primary care depression screening programs in pregnant and postpartum women result in improved health outcomes (decreased depressive symptomatology; decreased suicide deaths, attempts, or ideation; improved functioning; improved quality of life; or improved health status)?
   a. Does sending depression screening test results to providers (with or without additional care management supports) result in improved health outcomes?
   b. Does the effect of screening vary by population characteristics*?
2. What is the test performance of the most commonly used primary care depression screening instruments in pregnant and postpartum women?
   a. Do the test performance characteristics of the screening instruments vary by population characteristics*?

3. What are the harms associated with primary care depression screening programs in pregnant and postpartum women?
   a. Do the harms vary by population characteristics*?
4. Does treatment (psychotherapy, antidepressants, or collaborative care) result in improved health outcomes (decreased depressive symptomatology; decreased suicide deaths, attempts, or ideation; improved functioning; improved quality of life; or improved health status) in pregnant and postpartum women who screen positive for depression in primary care?
   a. Do the effects of the interventions vary by population characteristics*?
5. What are the harms of treatment in pregnant and postpartum women who screen positive for depression in primary care?
   a. Do the harms vary by population characteristics*?
   b. What is the prevalence of other selected serious harms of treatment with antidepressants in the general (i.e., not limited to primary care) population of pregnant and postpartum women?

*Population characteristics include sex, age, race/ethnicity, comorbid conditions, and new-onset depression versus recurrent depression.

General Adult Population, Including Older Adults

1. Do primary care depression screening programs in the general adult population, including older adults, result in improved health outcomes (decreased depressive symptomatology; decreased suicide deaths, attempts, or ideation; improved functioning; improved quality of life; or improved health status)?
   a. Does sending depression screening test results to providers (with or without additional care management supports) result in improved health outcomes?
   b. Does the effect of screening vary by population characteristics*?
2. What are the harms associated with primary care depression screening programs in the general adult population, including older adults?
   a. Do the harms vary by population characteristics*?

Data Sources and Searches

We conducted an initial search for existing synthesized literature and guidelines related to depression screening and treatment in MEDLINE/PubMed, the Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, BMJ Clinical Evidence, Institute of Medicine, the National Institute for Health and Clinical Excellence, PsycINFO, the Agency for Healthcare Research and Quality, the American Psychiatric Association, the American Psychological Association, the Campbell Collaboration, the Canadian Agency for Drugs and Technologies in Health, the National Health Services' Health Technology Assessment Programme, and the Centre for Reviews and Dissemination from 2008 through October 3, 2013. The search strategies are listed in **Appendix B**.

For pregnant and postpartum women, we systematically evaluated all relevant reviews through abstract and full-text review, and identified existing good quality systematic reviews to use as

foundational reviews for benefits and harms of screening and treatment.[88] We selected three good-quality reviews that served as foundational reviews. We chose these reviews based on relevance (i.e., inclusion and exclusion criteria that were at least as inclusive as our review), their having conducted a good-quality search, their having reported good-quality article evaluation methods, and recency.[89-91] For the question of harms of antidepressants (KQ5), the foundational review of sufficient quality and the evidence was base so extensive that we used this review directly as evidence in our report and did not re-evaluate individual studies included in this review.[91] We used the other two foundational reviews as the starting point for study identification for other key questions related to pregnant and postpartum women, and then searched for additional original research published after the search windows of these foundational reviews. We evaluated all studies included in each of these foundational reviews against our *a priori* inclusion/exclusion criteria. Then we searched for newly published literature bridging from these foundational reviews. For general adult populations, we evaluated all included studies in the previous USPSTF review in addition to searching for newly published literature.

We searched for newly published literature in the following databases: MEDLINE/PubMed, PsycINFO, and the Cochrane Central Register of Controlled Trials through January 20, 2015 (**Appendix B**). In general adult populations, we searched from January 1, 2009. We began our bridge search for pregnant and postpartum women from January 1, 2012 since there was at least one foundational review with a search period for each key question for pregnant and postpartum women that extended into 2012. We also reviewed reference lists of relevant studies and reviews to identify additional potentially relevant studies that were not identified by our literature searches. We managed literature search results using the bibliographic management software program Reference Manager® version 12.0 (Thomason Reuters, New York, NY).

Study Selection

Two investigators independently reviewed titles and abstracts using an online platform (Abstrackr)[92] against pre-specified inclusion and exclusion criteria, At least one investigator evaluated each full-text article to determine potential relevancy (**Appendix B Tables 1** and **2**). Full-text articles were reviewed by two investigators for a final inclusion/exclusion decision. Disagreements were resolved through discussion or consultation with the other investigators. A list of excluded studies after full text review, including the reasons for exclusion, is available in **Appendix C**.

We included fair- and good-quality studies published in the English language that were conducted among adult aged ≥ 18 years living in countries ranked as having "very high" human development according to the WHO,[93] including:

- Randomized controlled trials (RCTs) and non-randomized controlled clinical trials (CCTs) examining benefits or harms of screening or treatment (psychotherapy, pharmacotherapy, collaborative care) in pregnant and postpartum women.
- Studies of diagnostic accuracy of the PHQ or EPDS in pregnant and postpartum women.

- Systematic reviews, RCTs, CCTs, or large comparative observational studies that examined harms of antidepressants in pregnant or postpartum women.
- RCTs and CCTs examining benefits or harms of screening in general or older adult populations.

We defined postpartum women as those whose babies were less than 1 year old at study enrollment. We required that studies assessing the benefits and harms of screening for either population be conducted in a primary care setting, including obstetrics/gynecology (OB-GYN) or pediatrics for postpartum depression screening. Studies limited to persons with other medical or mental health conditions were excluded, however we did not exclude studies that included some persons with such conditions, as long as it was not a requirement of participation. Studies of depression screening could also include additional treatment elements, as long as the screening test results were given to the primary care provider. We required that the control group either was not screened or did not have their screening test results sent to their provider.

Studies of psychotherapy (examined only for pregnant and postpartum women) could additionally take place in virtual (i.e., online or computer-based) or mental health clinic settings. We required that studies of depression treatment use population-based screening to identify eligible patients. Thus, we excluded studies in which recruitment was based on referral, recruitment was from populations of known or likely depressed patients (e.g., persons identified as depressed in their medical charts), or volunteers recruited through media or other advertising. Control groups in treatment studies could include usual care, no intervention, waitlist, attention control, or a minimal intervention (e.g., no more than 15 minutes of information, not intended to be a therapeutic dose). We excluded comparative effectiveness studies.

We excluded trials exploring the efficacy of complementary and alternative therapies such as yoga, exercise, transcranial stimulation, and dietary supplements such as St. John's Wort, since they are not widely used in primary care settings. We also excluded trials focused on second-line treatments for severe depression when first-line treatments are not effective, such as polypharmacy and electroconvulsive therapy (ECT).

We required minimum followup of 6 weeks for studies of benefits of screening and treatment, and harms of psychotherapy or collaborative care interventions. We had no minimum followup for harms of antidepressants.

Diagnostic accuracy studies (examined only for pregnant and postpartum women) were required to perform the index and reference tests within 2 weeks of each other, and must have had patients covering a wide spectrum of symptom severity (i.e., case-control designs were excluded). A valid reference standard was a structured or semi-structured diagnostic interview with a trained interviewer, or a non-brief (greater than 5 minutes) unstructured interview with a mental health clinician. Studies that only gave the reference test to a subset of participants had to make appropriate adjustments to their analysis, or provide sufficient data to allow us to adjust the analysis. Studies had to report sensitivity, specificity, positive predictive value (PPV) or negative predictive value (NPV), or the raw data to allow us to calculate diagnostic accuracy.

We included a variety of study designs in examination of harms of antidepressants in pregnant and postpartum women. Our primary data source was one of the foundational reviews that included extensive information on harms of antidepressant treatment.[91] We focused on serious maternal or fetal/infant harms. Maternal harms included suicidality, serotonin syndrome, cardiac effects, seizures (bupropion only), bleeding, cardiometabolic effects, and preeclampsia. Infant harms included neonatal death, major malformations, small for gestational age/low birth weight, cardiopulmonary effects, and other serious events requiring medical attention. Comparative cohort studies had to be large (minimum of 10 cases in each exposure group) and include appropriate controls who were not taking antidepressants.

Quality Assessment and Data Abstraction

Two investigators independently assessed the quality of included studies using criteria defined by the USPSTF[94] and supplemented it with criteria from the Quality Assessment of Diagnostic Accuracy (QUADAS) II,[95] and the Newcastle-Ottawa Scale (NOS)[96] for diagnostic accuracy and observational studies, respectively (**Appendix B Table 3**). We also used the Assessment of Multiple Systematic Reviews (AMSTAR)[97] to assess the quality of the foundational evidence review used for harms of antidepressant treatment in pregnant and postpartum women.[91] Each study was assigned a final quality rating of good, fair, or poor and disagreements were resolved through discussion.

We excluded studies rated as poor quality (i.e., attrition greater than 40%, differential attrition of greater than 20%, other "fatal flaws," or the cumulative effects of multiple minor flaws and/or missing important information significant enough to limit our confidence in the validity of the results). Good-quality studies included all or most of the following: adequate randomization procedures, allocation concealment, blinding of outcome assessors, reliable outcome measures, comparable groups at baseline (with specified eligibility criteria), low attrition, acceptable statistical methods, and adequate and faithful adherence to the intervention. We rated studies as fair quality if they did not meet most of the "good" quality criteria.

One investigator abstracted data from all included studies into a Microsoft Access® database (Microsoft Corporation, Redmond, WA) and a second investigator checked the data for accuracy. We abstracted study design characteristics, population demographics, baseline history of depression and other mental health conditions, screening and intervention details (if applicable), depression outcomes, other health outcomes (e.g., suicidality, mortality, quality of life, functioning, health status, child/infant outcomes, emergency department visits or inpatient stays), adverse events, and diagnostic accuracy outcomes (if applicable).

Data Synthesis and Analysis

We created summary tables for all KQs, showing study characteristics, population characteristics, intervention characteristics (if applicable), and outcomes for qualitative evidence synthesis. We used these tables and forest plots of results to examine data for consistency, precision, and relationship of effect size with key potential modifiers such as treatment contact

time, control group recovery or response, and time to followup. We had sufficient data with acceptable comparability between studies to conduct meta-analysis only for trials examining the benefits of cognitive behavioral therapy (CBT) or related approaches to treat depression in pregnant and postpartum women compared to usual care or other control conditions. We ran a random effects model using the DerSimonian and Laird (DL) pooled estimate, which we felt was acceptable given our body of evidence for this outcome consisting of nine studies, with low statistical heterogeneity and fairly comparable sample sizes among the studies.[98] Because the number of studies was fairly small we also ran a sensitivity analysis using a restricted maximum likelihood model with the Knapp-Hartung modification for small samples. We used Stata version 13.1 (Stata Corp LP, College Station, TX) for all analyses.

For the studies of instrument accuracy, we calculated sensitivity and specificity with Jeffrey's confidence intervals (CIs), using data from 2x2 tables that included true positives, false positives, false negatives, and true negatives. If these data were not reported directly we created 2x2 tables based on the total sample size, number of persons with the diagnosis according to the reference standard, sensitivity, and specificity. Several studies only verified a negative screening result in a random sample of those below a predetermined threshold (which was lower than the typical cutoffs for a positive screener in all cases).[99-101] For these studies we applied the proportion with a depressive disorder according to the reference standard to the full sample of those below the threshold and calculated sensitivity and specificity based on these extrapolated results.[102] In all cases, there were no false negatives, so sensitivity did not change but specificity increased with extrapolation.

USPSTF Involvement

This research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the USPSTF. We consulted with USPSTF liaisons at key points in the review including the development of the research plan (i.e., KQs, analytic framework, and the inclusion/exclusion criteria), as well as finalizing the systematic review. An AHRQ Medical Officer provided project oversight, reviewed the draft and final versions of the review, and assisted with public comment on the research plan and draft review. The USPSTF and AHRQ had no role in the study selection, quality assessment, or the writing of the systematic review.

Chapter 3. Results

Literature Search

We screened 6,519 abstracts and identified 65 included studies that reported results in 83 publications. For pregnant and postpartum women, we included six trials addressing the benefits or harms of screening,[69,99,103-106] 21 diagnostic accuracy studies,[69,99-101,107-123] and 31 studies[91,124-152] that assessed the benefits or harms of treatment. This final group included one recent systematic review on the harms of antidepressants[91] (**Appendix B Figure 1**). In general and older adults, we included nine trials that addressed the benefits or harms of screening (**Appendix B Figure 2**).[72,73,153-159]

Results of Included Studies in Pregnant and Postpartum Women

We used five KQs and related sub-questions to assess depression screening and treatment for pregnant and postpartum women. These KQs addressed benefits of screening (KQ1), accuracy of selected depression screening instruments (KQ2), harms of depression screening (KQ3), benefits of depression treatment in screen-detected patients (KQ4), and harms of depression treatment, particularly antidepressants (KQ5).

Key Question 1. Do Primary Care Depression Screening Programs in Pregnant and Postpartum Women Result in Improved Health Outcomes?

Key Question 1a. Does Sending Depression Screening Test Results to Providers (With or Without Additional Care Management Supports) Result in Improved Health Outcomes?

Study Characteristics

We included six trials that examined the benefits of screening for pregnant and postpartum depression (n=11,869), with or without additional provider training or treatment optimization. These trials were primarily conducted in postpartum women. All of these trials studied women identified through healthcare settings and included both depressed and non-depressed women in their samples (**Table 5**).[69,99,103-106] Two trials included unscreened control groups[104,105] and four trials screened all participants and sent results only to intervention group providers.[69,99,103,106] None of the studies, however, used a straightforward design that compared usual care plus screening (and no additional treatment components) to usual care without screening.

All six of these trials were conducted in primary care settings, including obstetric clinics and routine in-home postpartum services offered in some countries. Only one trial was conducted in the United States.[69] The remaining trials were conducted in northern Europe,[103,106] the United

Kingdom,[99,105] and Hong Kong.[104] While most trials screened women at 1 to 2 months postpartum, one trial screened women during gestational week 25.[106] Followup ranged from 11 weeks[106] to approximately 16.5 months post-baseline.[99]

All studies used the EPDS for screening with variable cutoffs (ranging from 10 to 13). One study used both the EPDS and the PHQ.[69] Screening in these trials took place in the context of clinic or hospital visits or maternal home visits. Acceptance of screening was high in these studies—81 to 93 percent of those invited completed the screening.

Populations

Our six included studies provided few details about sample characteristics (**Table 6**). Few trials reported average age of the mothers or race/ethnicity and only two described participants' depression history. Between 10 and 28 percent of the study samples screened positive for depression, with higher positivity rates generally associated with lower EPDS cutoffs. While two trials were specifically limited to women with live-born children, exclusion criteria were fairly minimal in the remaining studies.[99,103]

Screening Program Interventions

This evidence included six widely differing interventions that accompanied or supplemented screening (**Table 7**; **Appendix D Table 1**). While two trials involved minimal additional intervention beyond screening or feedback of screening results in postpartum[104] and pregnant[106] women, two other trials examined the effects of screening plus provider supports in postpartum women.[69,106] Finally, two trials examined screening strategies that gave providers results feedback plus adjunctive counseling by home health visitors in postpartum women.[99,103]

The two trials that focused primarily on the effects of screening (with few additional treatment components) used EPDS to screen women treated at maternal health centers. The nurses or midwives caring for participants scoring at or above 10 or 12 were notified of their patients' elevated scores.[104,106] One of these studies used the same nurse providers to provide nondirective counseling to women in both the treatment and control groups, and the two groups differed only in the case-finding approach (screening plus usual clinical interview versus usual clinical interview alone). As such, this study provided the purest test of screening in this body of evidence.[104] This study design, however, could also contaminate results because the intervention component was delivered to both groups by the same individual. By holding the intervention component constant, however, it increased the likelihood that differences between groups are due to the effects of adding EPDS screening to usual care.

The two trials that targeted providers involved guidelines, provider materials, and (in one trial) patient handouts.[69,105] Both studies also used screening tests for symptom monitoring and screening. They integrated test results into the treatment algorithms. The U.S.-based study conducted by Yawn and colleagues targeted family medicine practices and provided training in, and tools for, identifying, diagnosing, and treating depression in postpartum women.[69] The intervention included: an immediate action protocol with a treatment algorithm based in part on PHQ-9 test results; a suggested schedule of followup visits and phone calls, along with an outline

for what should be covered at followup; information about antidepressants (including safety for pregnant and breastfeeding mothers); and materials for the patient and her partner. Similarly, the trial from the United Kingdom provided midwives with training, treatment guidelines, materials, and patient hand-outs.[105]

The final two trials tested specific therapeutic approaches delivered by nurses or health visitors in the patient's home, including non-directive/person-centered counseling or cognitive-behavioral therapy.[99,103] These studies administered EPDS to all intervention participants in an attempt to identify those in need of treatment. While control group participants completed the EPDS, these results were not routinely sent to their provider.

Quality Assessment

We rated one trial as good quality[104] and the remaining five as "fair" rating. Among the fair-quality studies, one reported generally good methods (e.g., valid randomization, allocation concealment, good measurement procedures, baseline comparability between groups), but was rated fair for fairly low retention (84% at 5-month followup). The longer-term followup data were excluded because they had very low retention (43% at 11 months).[99] The remaining studies generally had low retention (generally less than 75%) and frequently failed to report valid randomization procedures or allocation concealment. Some of these studies did not clearly demonstrate comparable groups at baseline.[103,106] None of the trials reported blinding of outcomes assessment, but all used self-report questionnaires for primary outcomes, usually collected via mail. One of the trials assigned two comparable municipalities in Norway to be intervention and control areas, but because they did not report random assignment, we considered this study as a CCT.[103]

Findings

Depression outcomes. Five of the six trials reported the proportion of women scoring above a specified cut-off on the EPDS, which we refer to as depression prevalence, at followup ranging from 1.5 to 16 months (**Appendix D Table 2**). Trials in postpartum women showed 28 to 59 percent reductions in the risk of depression at followup, compared to usual care, when babies were aged 4 to 6.5 months (**Figure 3**). This effect was smaller and was not statistically significant in the trial of pregnant women, which included little beyond screening results feedback.[106] Depression prevalence was lower in the screened group in the Hong Kong-based screening-only intervention in the near-term (4 months), but this effect was not sustained at 16 months, compared to usual clinical case-finding.[104] Four studies reported increases in the likelihood that patients no longer screened positive at followup (akin to remission) or showed a pre-determined level of improvement on a scale score (akin to treatment response), among those who screened positive at baseline (**Figure 4**).[69,99,103,106] There was a 21 to 33 percent increase in the likelihood of remission or response in trials of postpartum women at 4.5 to 12 months (6 to 14 months postpartum). While the effect was even larger in the trial of pregnant women, followup was only 2.75 months.[106] **Appendix D Figure 1** shows the prevalence and remission/response results for all intervention groups at all available followup timepoints.

All trials also reported mean or median EPDS scores, except the U.S.-based trial. These data were insufficient to allow us to create forest plots, so we only present these in tabular form (**Table 8**). While the results were typically statistically significant, absolute differences between the groups were very small—on the order of a 1-point mean or median difference between groups on the 30-point EPDS. These studies, however, were in general postpartum or pregnant populations. These studies included both depressed and non-depressed women with low average symptom scores, so the small effect sizes are not surprising. These results also reflect group mean or median differences and not differences in the proportion testing above a depression cutpoint. The largest difference between groups was apparent in a subgroup analysis limited to patients who scored 12 or higher on the EPDS at baseline. Intervention participants reduced their score by an average of 5.9 points, compared to an average 4.1-point reduction in the control group. This result is still a very small, clinically non-significant between-group effect. Of the three intervention groups in this trial, all three had an average in the "mild" depressive symptoms range (below 10) at followup, but the control group was still slightly above the cutoff of 10.[99] Both of the trials that employed few provider supports or depression counseling reported slightly lower scores up to 4-month followup (5.1 to 5.8 in the intervention groups vs. 6.5 to 6.1 in the control groups, $p<0.05$) after a screening intervention.[104,106] These groups, however, did not differ at 16-month followup in one of these studies.[104]

The most applicable results come from a fair-quality trial of screening plus provider supports conducted in the United States.[69] This trial found that 45 percent of intervention participants reported a 5-point or greater drop in their PHQ-9 score, compared to 35 percent with usual care (OR, 1.74 [95% CI, 1.05 to 5.86], adjusted for depression history, marital status, income, education, age, and degree of parenting stress). This trial was rated as "fair" primarily because attrition was over 25% in both groups.

Other beneficial outcomes. A variety of additional outcomes were reported in some trials (**Appendix D Tables 3-6**). The Hong Kong-based screening trial that did not include extra provider supports or counseling found small statistically significant differences in only two of the nine quality of life or child/infant outcomes they reported, covering measures of marital satisfaction, parental stress, general distress, and baby's weight and baby's health care use (doctor visits, hospitalizations).[104] In both cases these effects were only present at 4 months and disappeared at 16 months. In contrast, the U.K.-based study that assigned women to screening plus one of two counseling conditions showed improvements in a most of the quality of life measures they included, such as state and trait anxiety measures, the Short Form (SF-36) mental component scale, parental stress, and a global clinical outcomes measure (CORE-OM) at 5-month followup.[99] No trials reported suicide-related outcomes.

Key Question 1b. Does the Effect of Screening Vary By Population Characteristics?

We were unable to examine variability in benefit by our *a priori* population characteristics. The only subgroup analyses in the included studies examined this effect in the subgroup that screened positive for depression at baseline and were described above.

Key Question 2. What Is the Test Performance of the Most Commonly Used Primary Care Depression Screening Instruments in Pregnant and Postpartum Women?

Study Characteristics

We identified 21 studies[69,99-101,107-123] (n=6,325) that examined the accuracy of the EPDS relative to a diagnostic interview, which was generally a standardized interview such as the Structured Clinical Interview for DSM-IV Disorders (SCID) (**Table 9**; **Appendix C Table 7**). We found no studies that met our inclusion criteria that also examined the performance characteristics of the PHQ-9 or other PHQ instruments in pregnant and postpartum women. Seven of the included studies used the English-language version of the EPDS (n=3,055).[69,99,100,108,115,117,118] The remaining 14 studies explored translations into Chinese,[113,116] French,[107,114] Hungarian,[120,121] Italian,[109,112] Japanese,[122] Lithuanian,[110,111] Spanish,[101,123] and Taiwanese.[119] We focused primarily on the English-language studies.

Most of the English-language studies assessed women between 6 and 12 weeks postpartum, although one assessed women at any point during pregnancy or up to 6 months postpartum.[118] Assessments took place in OBGYN or other primary care clinics[69,100,108,115] or as part of a home-visit program for new mothers.[99,117,118] Almost of the studies of EPDS translations were conducted in the context of primary care settings (including OB-GYN). While most of these also focused on the early post-partum period, three targeted pregnant women.[107,111,120]

Populations

The majority of studies focused on postpartum women (**Table 10**). The average age in most studies of the English-language EPDS was mid-20s. Except for one trial limited to African-American women, racial and ethnic minority populations were either not well represented (30% or less) or a race/ethnicity breakdown was not reported.[118] This single study that only included African-American women enrolled in a home visitation program in a low-income urban community was the only study of the English-language EPDS that included pregnant as well as postpartum women. Only three English-version studies reported on depression history in their sample, with 15 to 30 percent of women in these studies identified as having a previous history of depression.[69,99,108] A history of other mental health or medical conditions were sparsely reported. In studies of EPDS translations, average ages were generally around 30 and racial/ethnic background was rarely reported.

Quality Assessment

We rated a single study good-quality rating [120] and the remaining studies as fair quality. Studies were generally quite small 69 percent of all 2x2 tables had five or fewer false negatives, which was usually the smallest cell of the 2x2 table of true positives, false positives, false negatives, and true negatives. Only 13 percent of all 2x2 tables had more than 10 false negatives. The EPDS was administered as a paper-and-pencil test and the diagnostic interview usually occurred the same day. Two of the English-version studies, however, did not report the time between the EPDS and the interview.[69,99] In one of these the EPDS was likely not administered the same day

since the interviewers began attempting to schedule the assessment after receiving notification that the EPDS was completed.[99] While most studies conducted diagnostic interviews with all participants completing the EPDS, four studies only interviewed a random sample of those who scored below a certain cutoff on the EPDS,[99-101] including three of the English EPDS studies.[99,100] When studies did use a random sample, we extrapolated using the process described above in methods sections. We did not use specificity data from one trial that did not report sufficient data to extrapolate.[99] Only half of the studies described training of diagnostic interviewers, and fidelity or quality assurance procedures for the diagnostic interviews was rarely reported. Most studies completed the diagnostic interview after the EPDS, and most reported that the interviewer was blind to the EPDS results.

Findings

While most studies reported performance characteristics across a wide range of EPDS thresholds (**Appendix D Table 8**), we primarily focus our results on the cutoff of ≥ 10 and ≥ 13, which are most widely cited as usual cutoffs and were among the most widely reported cutoffs in this body of literature. A cutoff of 13 would typically be used for identifying MDD, while the lower cutoff would be useful for picking up minor depression or other depressive disorders in addition to MDD. The sensitivities and specificities, including all cutoffs for any language version of the EPDS, are shown in **Appendix D Figures 2–5** for MDD and minor or major depression.

EPDS cutoff of ≥13. Sensitivity and specificity of the English-language EPDS using the cutoff of ≥ 13 are shown in **Figure 5**. For identifying MDD, sensitivity ranged from 0.67 (95% CI, 0.18 to 0.96) to 0.95 (95% CI, 0.81 to 1.00), with most falling between 0.75 and 0.81. Sensitivity for detecting MDD ranged from 0.78 to 0.81 in the two trials conducted in the United States,[108,118] including the relatively recently-published study in low-income African-American women.[118] The largest study similarly reported sensitivity of 0.79 (95% CI, 0.72 to 0.85).[99] While sensitivities were much lower (less than 0.50) when the target condition was major or minor depression, this finding was based on just two studies. In one study, sensitivity for any MDD (0.79 [95% CI, 0.72 to 0.85]) was similar to that for moderate to severe MDD (0.85 [95% CI, 0.74 to 0.93]).[99] Thus, our best estimate for average sensitivity in the United States with a cut-off of 13 is approximately 0.80.

Specificity ranged from 0.90 (95% CI, 0.86 to 0.94) to 0.99 (95% CI, 0.97 to 1.00) for MDD with the English-language EPDS. Specificities were similar when used to identify major or minor depression. Specificity was similar for MDD and major and minor depression combined. Specificities in the two largest trials ranged from 0.90 to 0.95, with slightly higher values associated with the reference standard of MDD (vs. major or minor depression).

For the English language versions of the EPDS, we estimated PPV for detecting MDD to be 47 to 64 percent, in a population with an MDD prevalence of 10 percent (**Table 11**). This is assuming a sensitivity of 0.80 (consistent with the largest and U.S.-based studies) and specificity of 0.90 or 0.95 (approximate range of all studies, excluding one outlier).[99] PPV would be 59 to 74 percent in a population with MDD prevalence of 15 percent, under the same assumptions. NPV was estimated at 96 percent or greater under all scenarios shown in **Table 11**.

While sensitivity was wide-ranging for non-English versions of the EPDS, the Spanish version showed acceptable performance characteristics. The sensitivity in one study conducted in Spain was 0.85 (95% CI, 0.72 to 0.94),[101] but was only 0.76 (95% CI, 0.61 to 0.81) in a smaller (n=111) study conducted in Chile with a very high depression prevalence (34%).[123] The Hungarian, Italian, and Spanish versions all reported high specificity (usually 0.95 or above) with the cutoff of ≥ 13.

EPDS cutoff of ≥10. Sensitivity and specificity of the English-language EPDS using the cutoff of ≥ 10 are shown in **Figure 6**. Sensitivity for detecting MDD was fairly wide-ranging, from 0.67 (95% CI, 0.18 to 0.96) to 1.00 (95% CI, 0.89 to 1.00). Sensitivity was similar for detecting major or minor depression and ranged from 0.63 (95% CI, 0.44 to 0.79) to 0.84 (95% CI, 0.69 to 0.94). Sensitivity from the two trials conducted in the United States ranged from 0.72 to 0.86.[69,118] Specificity was similar for detecting MDD and detecting major or minor depression and ranged from 0.71 (95% CI, 0.62 to 0.78) to 0.90 (95% CI, 0.86 to 0.93).

Using a cutoff of ≥10 in the English language version of the EPDS, PPV was at 50 percent in only the higher-prevalence (15%) scenario if we assume an optimistic sensitivity of 0.84 (largest study, U.S.-based) and specificity of 0.85 (mid-range of all estimates) (**Table 11**).

While sensitivity was wide-ranging across non-English translations at a cutoff of 10, the Spanish version performed well in Spain with a sensitivity of 0.89 (95% CI, 0.82 to 0.94).[101] Specificity for these tools was usually above 0.90 regardless of language.

Key Question 2a. Do the Test Performance Characteristics of the Screening Instruments Vary By Population Characteristics?

We found no studies that reported performance characteristics separately for subgroups based on age, race/ethnicity, comorbid conditions, or new-onset versus recurrent depression.

Key Question 3. What Are the Harms Associated With Primary Care Depression Screening Programs in Pregnant and Postpartum Women?

Among the trials addressing benefits of screening, the trial that focused most narrowly on the effects of screening alone reported that there were no adverse effects of screening in postpartum women.[104] In addition, none of the KQ1/1a trials showed paradoxical effects of concern. We found no additional trials addressing harms of screening beyond those included for benefits of treatment.

Key Question 3a. Do the Harms Vary By Population Characteristics?

We found no evidence on harms of screening so we could not evaluate variability in harms by population characteristics (e.g., sex, age, race/ethnicity, comorbid conditions, new-onset vs. recurrent depression).

Key Question 4. Does Treatment Result in Improved Health Outcomes in Pregnant and Postpartum Women Who Screen Positive for Depression in Primary Care?

Study Characteristics

We identified 17 trials that examined the benefits of interventions in pregnant or postpartum women who had screened positive for depression in primary care or community settings (**Table 12**), usually compared with usual care. These trials were published between 1989 and 2014. Six of these trials were conducted in North America,[124,129,134,140,149,150] seven were conducted in Europe,[126,128,132,133,138,147] three were conducted in Australia,[141,142,146] and one was conducted in Taiwan.[131] The total number of women randomized across all studies was 1,583. There was only one large trial (n=1,762 randomized).[138] This study, however, combined treatment in depressed women and prevention in women who were not depressed. We only included results related to the depressed subgroup (n=324).The remaining trials were small or moderately sized (fewer than 50 per group, often fewer than 30 per group). The EPDS was the most common instrument used for screening with cutoff scores used for eligibility ranging from 9 to 13. The proportion of women screening positive for depression at recruitment varied from 6 to 61 percent. Followup periods also varied widely, from 6 weeks[131,147] to 18 months.[128]

Populations

Fifteen of the 17 included studies recruited women during the postpartum period, usually 6 to 12 weeks postpartum. Only two studies recruited women during pregnancy.[138,140] All studies reported outcomes during the postpartum period. All but two of the studies reported mean maternal age, which ranged from 22 to 32 years (**Table 13**). Only four studies reported race or ethnicity data and 33 to 69 percent of the participants in these studies were White. Fewer than half of the studies described the participants' depression history, and the type of information on depression history they provided varied considerably across studies. For example, reports of prior history of depression or major depression ranged from 30 to 76 percent, history of recurrent or chronic depression ranged from 21 to 74 percent, and prior treatment for depression ranged from 16 to 46 percent. Two studies described history of anxiety disorders, which was reported in 37 to 48 percent of the study population.[124,150] None of the studies reported other medical conditions or substance abuse history. Many treatment studies excluded women with the most severe depression, such as those with a history of psychosis, current suicidal ideation, or need for crisis management.[124,126,133,140-142,148-150] Two trials also excluded women who were taking psychotropic medications,[124,140] and a few excluded patients with substance abuse disorders.[124,126,149] In addition, a few studies were limited to women with no perinatal complications, preterm birth, or major congenital abnormalities.

Depression Interventions

The included trials utilized several different types of behavioral interventions (**Appendix C Table 9**), and two trials tested multiple approaches in different intervention arms.[128,141] The most commonly studied approach was CBT or related interventions that included traditional CBT components, such as stress management, goal setting, and problem solving. The trials conducted

with pregnant women investigated CBT[140] and CBT-related[138] interventions. Other approaches to psychotherapy included nondirective counseling[128,132,147,149] and psychodynamic therapy.[128,129] One intervention targeted mother-baby interactions with the goal of increasing a mother's responsiveness to her baby's cues.[134] Another trial addressed mother-baby interactions while also providing psychotherapy to the mother.[150] Behavioral interventions were between 1 and 3 months duration, except one intervention that lasted almost 5 months.[124] One trial studied a stepped-care intervention that involved referral to the primary care provider, patient information, a care manager who had regular telephone contact, and, if needed, consultation with or referral to mental health providers, who utilized a variety of psychotherapeutic methods as would be found in typical community-based care, and psychiatry referral for evaluation or medication adjustment, if needed. Only one trial examined antidepressant medication, comparing fluoxetine with placebo, with adjunctive CBT in for both treatment arms.[126]

Interventions were most often delivered by mental health providers (e.g., therapists, psychologists, psychiatrists, or social workers), medical providers (i.e., physicians, nurses, or midwives), or a home health visitor. Treatment intensity, defined as the estimated total hours of exposure to active intervention, varied widely across studies and ranged from printed material only[131] to 21 hours of individual or group contact.[148] Within general therapeutic approach (e.g., CBT, other behaviorally-based), treatment outcome tables and forest plots were organized in order of increasing treatment intensity to better elucidate the potential impact of treatment intensity on outcomes. Fewer than half of the studies reported treatment adherence data. Using the most stringent definition (i.e., completion of all planned sessions), adherence ranged from 49 to 100 percent in the studies reporting that data.[124,128,129,132,133,140,142,146]

Quality Assessment

We rated 15 of the trials as fair quality and two as good quality.[128,138] Two of the fair-quality studies generally had good methods with adequate followup, but were small in size and had one or more concerns about randomization, baseline differences between groups, or differential attrition between groups.[124,140] The remaining studies exhibited multiple methodological concerns, including small sample sizes, followup below 90 percent, poorly described inclusion/exclusion criteria, inadequate allocation concealment or blinding of outcome assessment, intervention not manualized or well described, or inadequate intervention fidelity.

Findings

Depression outcomes. Fourteen of the 17 trials reported an outcome similar to depression remission at followup ranging from 1.5 to 18 months (**Appendix D Table 10**). While most trials reported the proportion below a specified cut-point on a depression symptom scale, two trials conducted diagnostic interviews to confirm clinical remission.[124,128] We grouped these outcomes together and refer to them as "remission." However, we were unable to truly estimate absolute remission rates. **Figure 7** shows a forest plot of remission rates (according the studies' definition), ordered by increasing intensity (estimated hours) of the intervention, grouped by general therapeutic approach.

Results for CBT. All nine trials of CBT or related interventions showed an increased likelihood of remission with treatment in the short term, although not all results were statistically significant. Results were similar for pregnant and postpartum women. Most trials followed participants for only 7.8 months or less, and none showed a benefit beyond 7.8 months followup. Pooled results that used only the longest followup period within 1 year, and selected the treatment arm that adhered most purely to CBT principles if multiple treatment arms were tested, showed a 35 percent increase in the likelihood of remission with CBT (DL pooled relative risk [RR], 1.35 [95% CI, 1.19 to 1.53]; k=9, I^2=18.7%), compared to usual care. Results were almost identical in sensitivity analysis using a more conservative pooling method, with even lower statistical heterogeneity (restricted maximum likelihood [REML] pooled RR, 1.35 [95% CI, 1.17 to 1.55]; k=9, I^2=10.2%). Although most evidence was in postpartum women, both trials in pregnant women (shown with an asterisk in **Figure 7**) were consistent with the trials in postpartum women, with RRs of 1.36 or higher, although only one of these was statistically significant. While it appeared that increased hours of contact may have been associated with larger effect sizes, larger effect sizes were also generally observed in studies with lower control group remission rates and smaller sample sizes. In fact, control group remission rates, contact hours, sample size, and time to followup were all confounded with each other, and we could not draw conclusions about their relative importance.

The two good-quality studies had the smallest[128] and third smallest[138] effects among the CBT intervention arms, although the latter, which was also the largest included study, showed a statistically significant benefit (REML pooled RR, 1.36 [95% CI, 1.13 to 1.65]). Among the studies conducted in the United States, one was a recently published study in high-risk women (unmarried, low income, aged ≤ 18 years, or inadequate prenatal care) who were part of a home visit program and met criteria for MDD at 3 months postpartum.[124] These women also had high rates of comorbid mental health conditions. Women in the CBT arm had a 47 percent increased the likelihood of remission (RR, 1.47 [95% CI, 1.10 to 1.95]) and showed greater improvement in depressive symptoms and global assessment of functioning, at both 4.5 and 7.5 months followup.

Results for other approaches. NonCBT approaches were highly variable in their effects and limited by lack of replication of intervention approaches. None of these trials published enough data to draw firm conclusions, including the trials of fluoxetine and the stepped-care intervention. The U.S.-based study of the stepped care intervention was highly applicable, but did not find beneficial results.[129] Their intervention included biweekly phone followup with a care manager after treatment initiation, decision support for the provider, patient materials, and specialty care available if needed. Although a greater number of the stepped care participants received treatment, no differences were seen in depression symptoms, depression remission, general health and mental health ratings, or functioning. In fact, a greater proportion of the usual care participants no longer screened positive for depression at followup than stepped-care participants (56% remission with stepped care vs. 72% usual care, p=0.48). This was a very small study (n=34), however, with statistically non-significant but potentially important differences at baseline such that the intervention group was more likely to be low income (proportion with family income less than $40,000 was 85% in the intervention group vs. 65% in the control group), on medical assistance (83% vs. 53%) and unmarried (74% vs. 60%).

Several trials also reported changes in depression symptoms or mean depression scores at followup, and are shown in **Figure 8**. Among CBT and related interventions, the control groups generally showed roughly a 4-point greater improvement on symptom scales (usually EPDS, range 0 to 30) with CBT than with usual care; usual care generally showed 1- to 6-point changes on the EPDS, compared with 5- to 10-point changes with CBT. Average baseline EPDS scores were generally above the cutoff of 13 (above screening cutoff for identifying MDD), and at followup most CBT group averages were below 10 (below screening cutoff for identifying minor or major depressive disorder), which put them in the mild depressive symptom range, on average. Many studies also showed average EPDS scores below 10 at followup with usual care treatment; however, a greater proportion of usual care group averages were above 10 at followup than CBT groups. Other instruments showed comparable results.

These outcomes also appeared to be related to intervention intensity, such that participants who received more hours of treatment demonstrated the greatest reduction in depression symptoms, however again we were unable to disentangle the effects of contact hours, study size, and control group response rate (a likely indicator of underlying population risk).

Other beneficial outcomes. Several trials reported other outcomes including measures of general psychological functioning,[124] anxiety,[140] functional health,[129] maternal and infant health care utilization,[129] interpersonal support,[124,141] and mother-infant interactions (**Appendix D Tables 11– 13**).[134] Of these, only two studies reported significant findings, although small sample sizes may have limited power to find group differences in the remaining studies,[124,141] Women in the treatment groups demonstrated better scores on measures of psychological functioning, interpersonal support, and global assessment of functioning at follow-up (data not shown). Although these two studies were also higher in treatment intensity (15 to 18 hours) than most of the other studies, lack of complete reporting for outcomes across varying intensity studies limits any interpretation from this observation.

Key Question 4a. Do the Effects of the Interventions Vary By Population Characteristics?

We were unable to examine variability in benefit by our *a priori* population characteristics. No subgroup analyses were reported by age, race/ethnicity, comorbid conditions, and new-onset depression versus recurrent depression.

Key Question 5. What Are the Harms of Treatment in Pregnant and Postpartum Women Who Screen Positive for Depression in Primary Care?

Behaviorally-Based Interventions

None of the trials addressing benefits of behaviorally-based interventions reported on harms of treatment. In addition, none of the trials showed paradoxical effects of concern. We found no additional trials addressing harms of behaviorally-based beyond those included for benefits of treatment.

Antidepressants

We found only one trial of antidepressants conducted in postpartum women with screen-detected depression that reported adverse events.[126] The remaining evidence was not limited to those whose depression is detected through screening and is discussed below under KQ5b. The trial in screen-detected women compared the short-term effects fluoxetine plus CBT versus placebo plus CBT. At 12 weeks followup, one of the 43 (2.3%) women taking fluoxetine discontinued due to adverse effects, compared to three of the 44 (6.8%) taking the placebo.

Key Question 5a. Do the Harms Vary By Population Characteristics?

We were unable to examine variability in benefit by our *a priori* population characteristics. No subgroup analyses were reported by age, race/ethnicity, comorbid conditions, and now-onset depression versus recurrent depression.

Key Question 5b. What Is the Prevalence of Other Selected Serious Harms of Treatment With Antidepressants in the General Population of Pregnant and Postpartum Women?

Study Characteristics

We identified one good-quality comprehensive AHRQ-sponsored systematic review[91] that included studies published between 1996 and 2013, supplemented with 12 additional unique fair-to-good-quality observational studies published between 2012 and 2014 that examined the harms of antidepressants in pregnant or postpartum women (**Table 14**).[125,127,130,135-137,139,143-145,151,152] The AHRQ review examined the comparative effectiveness and safety of antidepressant treatment for depression in pregnant and postpartum women. This review found no RCTs of harms of antidepressants in pregnant women, but did include 15 observational studies that provided evidence of harms of antidepressants at unknown dosages in pregnant depressed women, considered "direct evidence" in their review. The review included an additional 109 observational studies that provided evidence of harms of antidepressants in pregnant women where depression status in either or both treatment arms was unknown, considered "indirect evidence." They did not find evidence related to harms in postpartum women. One-third of studies in the AHRQ review were conducted in the United States.

We identified 12 additional large fair-to-good observational studies published since the AHRQ review (n=4,759,435). Seven of the 12 new studies were conducted in the United States[130,135,143-145,151,152] and five were conducted in Europe.[125,127,136,137,139] Most were cohort studies that used national register or administrative health data to examine exposures and outcomes retrospectively in pregnant women; three were case-control studies.[145,151,152] Five studies provided evidence of outcomes in pregnant women with depression exposed to antidepressants, compared to pregnant women with depression unexposed to antidepressants;[127,130,135,137,151] the remaining seven studies compared outcomes in exposed versus unexposed pregnant women with unknown depression status, although most of these either adjusted analyses for depressive

symptom level[139] or conducted some analyses that were restricted to depressed women.[136,143,144] Most studies were very large and included hundreds of thousands of women.

Populations

The AHRQ review[91] defined the population of interest as pregnant women and women during the first 12 months after delivery who had major depression or subthreshold depressive symptoms. Based on expert input, they also included studies of pregnant women who received antidepressants for unknown or mixed reasons. In addition, the conception period was included when studying teratogenicity of antidepressants.

All 12 studies identified since the AHRQ review involved women exposed to antidepressants during their pregnancy. Seven of the studies reported mean maternal age, ranging from 23 to 30 years (**Table 15**). Only five studies reported race or ethnicity data; in these studies, 40 to 67 percent of participants were White. Two studies reported a history of pre-pregnancy depression, ranging from 6 to 7 percent.

Interventions and Exposure Definitions

Interventions included in the AHRQ review[91] were commonly used antidepressants, including tricyclic antidepressants. For purposes of this review, we did not include data on tricyclic antidepressants when possible, as our focus was on second generation antidepressants.

In the twelve observational studies identified since the AHRQ review, interventions included SSRIs, SNRIs, bupropion, mirtazapine and trazodone. Timing of antidepressant medication exposure in these studies ranged from first trimester to third trimester, including date of delivery (**Appendix D Table 14**). Three studies examined exposure by defined groups of antidepressant doses (high vs. low in one study;[125] high vs. medium vs. low in two studies[143,144]). One study[130] examined exposure by number of antidepressant medications prescribed and one by duration of exposure.[144] Most assessed exposure by using pharmacy dispensing records,[125,130,135-137,143,144] although one study used only prescriptions[127] and four others used patient report.[139,145,151,152]

Quality Assessment

We rated the quality of the AHRQ review[91] as good using AMSTAR criteria: study design was determined *a priori*, and the authors performed a comprehensive literature search, including grey literature, provided lists of included and excluded studies, included sufficient detail about included studies, and assessed the quality of included studies using standard methods.

In addition, nine of the 12 studies identified since the AHRQ review were rated as good quality.[125,127,130,135-137,143,144,152] These nine studies were all very large population-based studies that used electronic data, generally with extensive adjustment for potentially confounding variables, such as maternal age, race/ethnicity, education, parity, depression history, smoking history, multiple gestation, previous miscarriages, non-antidepressant medication exposures and year of delivery. Among the two fair-rated studies, one reported generally good methods (e.g., appropriate ascertainment of exposed and non-exposed, adequately defined eligibility criteria,

acceptable followup and adjustment for confounders), but was rated fair for low survey response rate (43% for mailed questionnaire), unreported baseline characteristics, and self-reported outcomes.[139] The other fair-rated study reported generally good methods (e.g., appropriate ascertainment of exposed and non-exposed, adequately defined eligibility criteria, and acceptable followup), but was rated fair for changing the measure of exposure over the course of the study, not reporting blinding of interviewers identifying exposure, not adjusting for all potential confounders, and having an insufficient sample size to assess some outcomes.[145] Although most of these added observational studies used good methods, conclusions are still somewhat limited, as it is impossible to avoid the issue of confounding by indication; despite extensive efforts to adjust for confounding variables, there may still be something fundamentally different about women who take antidepressants and women who do not for which the studies could not fully control.

Findings

Detailed results from the included observational studies are shown in **Appendix D Table 15** and a summary of findings are in **Tables 16** and **17**.

Maternal outcomes. None of the included studies, including the AHRQ review,[91] addressed *serotonin syndrome*. Likewise, none assessed *cardiac effects* or *seizures* in pregnant or postpartum women exposed to antidepressants. Evidence for *suicidality* and *metabolic effects* was judged insufficient in the AHRQ review,[91] and the included studies published since the AHRQ review did not address these outcomes.

Preeclampsia. One study that examined risks of preeclampsia in depressed women exposed to antidepressants in the second or third trimester, published since the AHRQ review, reported an increased risk in women exposed to venlafaxine (adjusted RR, 1.57 [95% CI, 1.29 to 1.91]).[144] In this study, 8.9 percent of women exposed to venlafaxine developed preeclampsia, compared to 5.4 percent of women with no exposure. There was no increased risk with SSRIs, mirtazapine, or trazodone.

Vaginal bleeding and postpartum hemorrhage. In an analysis limited to depressed women, one study published after the AHRQ review[91] found an increased risk of postpartum hemorrhage for women taking antidepressants with high serotonin transporter affinity (93% of dispensings were SSRIs, the remaining were primarily venlafaxine).[143] In this analysis, 4.0 percent of the women exposed to these medications experienced postpartum hemorrhage, compared with 2.8 percent without exposure. Risk was also increased with the use of antidepressants with low serotonin transporter affinity (78% of dispensings were bupropion; the remaining were primarily mirtazapine and trazodone; 4.2% with postpartum hemorrhage with exposure vs. 2.8% without exposure).

The same study reported an increased risk for most agents in all women, controlling for number of mood or anxiety diagnoses—adjusted RRs ranged from 1.31 (95% CI, 1.12 to 1.54) for sertraline to 2.24 (95% CI, 1.69 to 2.97) for venlafaxine.[143] Similarly, the AHRQ review[91] identified one case-control study that addressed postpartum hemorrhage and found an increased likelihood of SSRI use in women with unknown depression status who experienced maternal

postpartum hemorrhage, with similar results for 60 and 180 days of SSRI exposure. Another large observational study, however, found no association between use of second generation antidepressants (SSRIs, SNRIs, mirtazapine, or trazodone) and postpartum hemorrhage or vaginal bleeding in women with unknown depression status.[139]

The strongest evidence for women with depression suggests an increased risk of harms for most second-generation antidepressants.

Miscarriage or spontaneous abortion. The AHRQ review[91] included one very large study (n=512,574) limited to women with depression, in which 14.9 percent of those taking SSRIs during the first trimester had a miscarriage, compared with 12.1 percent of women who did not take SSRIs (adjusted RR, 1.4 [95% CI, 1.2 to 1.7]).[160] In contrast, one very large (n=1,005,319) study published after the AHRQ review found no increased risk of miscarriage with SSRI use in women with depression exposed at any point in pregnancy.[137] They did, however, report increases in the risk of miscarriage with the SNRIs venlafaxine (unadjusted RR, 1.80 [95% CI 1.19 to 2.72]) and duloxetine (unadjusted RR, 3.12 [95% CI 1.55 to 6.31]), as well as mirtazapine (unadjusted RR, 2.23, [95% CI 1.34 to 3.70]).

In women with unknown depression status, one study that was included in the AHRQ review found an increased risk of miscarriage in women exposed to SSRIs at any time during pregnancy (adjusted OR, 1.60 [95% CI, 1.28 to 2.04]), and an increased risk with exposure to venlafaxine (adjusted OR, 2.11 [95% CI, 1.34 to 3.30]).[161] In another study published since the AHRQ review, women with unknown depression status had increases in the risk of miscarriage with SSRI use. This study's authors also found an increased risk with prior SSRI use (i.e., discontinued use more than 3 months before pregnancy, and no pregnancy exposure), suggesting that the increased risk may be due to some other issue, perhaps depression-related, rather than specific to SSRIs.[125] This study did not examine SNRIs.

Overall, the evidence suggests a possible increased risk of miscarriage or spontaneous abortion in women exposed to SSRIs and SNRIs in the first trimester.

Infant outcomes.

Perinatal death. The AHRQ review[91] only included evidence for women of unknown depression status. There were no studies subsequent to the review that examined this outcome. In the AHRQ review, one study that addressed perinatal death within a year of birth found an increased risk for infants of women exposed to the SSRIs escitalopram, fluvoxamine and paroxetine, but not citalopram, fluoxetine or sertraline. Four studies examined SSRI use and perinatal death within 28 days of birth. One study found an increased risk with citalopram (adjusted OR, 2.49 [95% CI, 1.33 to 4.65]; 0.83% of babies with exposure *in utero* died within 28 days of birth, vs. 0.34% among unexposed babies). There were no other findings of increased perinatal death within 28 days for any other individual SSRI in any of the four studies. The two studies that also examined perinatal death between 28 to 365 days after birth did not find an increased risk with SSRIs as a class, but did show increased risk for several SSRI agents (escitalopram, fluvoxamine, paroxetine). In all, the evidence suggests a possible association between perinatal death and SSRI use.

Preterm birth. The AHRQ review[91] included two observational studies limited to depressed women that compared infants of women treated with SSRIs during pregnancy to those of untreated women and did not find a statistically significant increased risk of preterm birth, although wide CI suggest lack of precision (pooled OR, 1.87 [95% CI, 0.89 to 3.89]). One study published since the AHRQ review examined this outcome with SSRIs as a class and with any antidepressant use.[130] In analysis limited to depressed women, a small increased risk of preterm birth was identified with any antidepressant use, largely representing SSRIs (12.7% of babies of mothers with three or more SSRI dispensings were born in weeks 32 through 36, vs. 11.5% in the babies of mothers with no dispensings; unadjusted OR, 1.12 [95% CI, 1.03 to 1.23]).

This same study[130] also examined a broader control group with unknown depression status, but controlling for history of depression and other mental health diagnoses. These results varied by trimester of exposure: exposure in the second trimester was associated with preterm labor and delivery, while exposure in the third trimester was not. For each trimester, these associations were strongest in women who had the greatest exposure, as measured by number of prescriptions (**Table 17**). For the second trimester SSRI exposure, gestational age was reduced by 2.6, 5.8, and 6.6 days for one, two, or three or more prescription fills, respectively. In the third trimester, gestational age was increased by 0.9, 1.8, and 6.4 days with one, two, or three or more SSRI prescription fills. Eleven studies of women with unknown depression status in the AHRQ review provided evidence of an increased risk of preterm birth in infants of women exposed to SSRIs as a class at any point in their pregnancy compared to unexposed women (pooled OR not reported), and specifically with exposure to citalopram and escitalopram.[91] Two studies included in the AHRQ review showed an increased risk of preterm birth for infants of mothers with unknown depression status exposed to SNRIs as a class at any point in their pregnancy (pooled adjusted OR, 1.79 [95% CI, 1.46 to 2.19], Q=0.77). However, these results differ from findings in the more recent large cohort studies that showed differential risk by trimester.

Overall, results suggest an increased risk of preterm birth with SSRIs and perhaps SNRIs, but are not conclusive regarding timing of exposure. Similarly, dose-response relationships in these data are mixed and inconsistent.

Low birth weight or small for gestational age. No studies of this outcome reported analysis limited to depressed women. Five studies in the AHRQ review[91] found no association between low birth weight and maternal exposure to SSRIs in infants of women of unknown depression status (pooled OR, 1.04 [95% CI, 0.64 to 1.69], I^2=30%). A sixth study showed an increased risk of smaller head circumference in infants of depressed women on SSRIs compared to women without depression or SSRI exposure (-5.9 millimeters [mm] [95% CI, -11.5 to -0.3]), but no difference between infants of depressed and non-depressed women not exposed to SSRIs, suggesting no independent association with depression. For SNRIs, there was insufficient evidence due to small sample sizes.

We found one additional very large retrospective Danish cohort study that examined SSRI use in all women, controlling for depression status. This study found an increased risk for being small for gestational age in infants born to women who used SSRIs during pregnancy (n=673,853; adjusted HR, 1.22 [95% CI, 1.13 to 1.32]).[136] Absolute rates of low birth weight were not reported.

It is difficult to determine how strongly to weigh this more recent evidence against the five studies in the AHRQ review finding no association; the AHRQ review did not report the total n evaluated, so we cannot determine if the lack of association was due to low power, however the OR was very close to 1.0, suggesting no association. However, given that the recent cohort study was very the large, covered a well-defined population, and controlled for a number important confounders (including depression diagnosis in medical or mental health records), we conclude that an association with SSRIs is possible.

Seizures. Two studies examined this outcome in depressed women. One study in the AHRQ review[91] found no increased risk of neonatal seizures with SSRI use. In contrast, a large retrospective cohort study published since the AHRQ review did report more than a doubling of seizure occurrence in babies of depressed women with exposure to three or more prescription fills of antidepressants of any kind, primarily SSRIs (unadjusted OR, 2.39 [95% CI 1.57 to 3.64], 0.66% among exposed babies vs. 0.28% in unexposed babies).[130] There was no similar association in women with one or two prescription fills.

Seven studies in the AHRQ review examined this outcome in women with unknown depression status, and demonstrated an increased risk of seizures in infants of women exposed to SSRIs (k=7; pooled OR, 4.11 [95% CI, 1.78 to 9.48], I^2=not reported). In the aforementioned study published since the AHRQ review, there was an increased risk of neonatal seizures in women who received two or three prescription fills of SSRIs in the third trimester (adjusted OR for two fills, 2.8 [95% CI, 1.4 to 5.5]), in women with unknown depression status, but controlling for previous depression and other mental health disorders. However, they found no association with SSRI use in the second trimester in this analysis.[130]

Overall, the evidence suggests that there may be an association with SSRIs and neonatal seizures.

Serotonin withdrawal syndrome. No evidence restricted to women with depression was available for this outcome. For women with unknown depression status, the AHRQ review[91] identified five small cohort studies that provided evidence of increased risk of serotonin withdrawal syndrome in infants of women with unknown depression status exposed to SSRIs as a class; the AHRQ review authors were unable to pool these results. Outcomes examined included ratings of neonatal symptoms of withdrawal, such as central nervous system symptoms (e.g., reflexes, tremor, muscle tone, crying) and other indications (e.g., hyperthermia, respiratory rate, yawning, gastrointestinal disturbance). Neonatal seizures, hypertension and respiratory distress were considered separately. In the largest cohort study that adjusted for multiple confounders in the AHRQ review, there was an increased risk of serotonin withdrawal syndrome in infants of women exposed to fluoxetine during the first trimester (adjusted RR, 8.7 [95% CI, 2.9 to 26.6]), while in another cohort study, infants of women exposed to an SSRI or to venlafaxine in the third trimester had an increased risk of this outcome (adjusted OR, 3.1 [95% CI, 1.3 to 7.1]). Two of the remaining small studies found increased risks with SSRIs and SNRIs, while a third found no associated risk with SSRIs. None of the studies published subsequent to the AHRQ review examined this outcome.

In sum, there is a possible association between SSRIs and SNRIs and neonatal serotonin withdrawal syndrome, although evidence limited to depressed women is lacking.

Respiratory distress. Three studies included in the AHRQ review[91] and one published subsequently provide evidence regarding this outcome in women with depression. In the AHRQ review, three studies found evidence of an increased risk of respiratory distress in infants born to women exposed to SSRIs during pregnancy (pooled OR, 1.91 [95% CI, 1.63 to 2.24], I^2=0%). The largest of these studies reported that 7.8 percent of infants not exposed to SSRIs *in utero* experienced neonatal respiratory distress, compared with 13.9 percent of the exposed babies.

Additionally, one large cohort study (n=228,876) published since the AHRQ review[130] showed an increased risk of neonatal respiratory distress in infants of depressed women exposed to antidepressants (primarily SSRIs) when three or more prescriptions were filled (5.4% of exposed babies vs. 4.6% of unexposed babies).

In women with unknown depression status, four studies included in the AHRQ review found evidence of an increased risk of respiratory distress in infants of exposed women (pooled adjusted OR, 1.79 [95% CI, 1.64 to 1.97], I^2=0%). In the previously mentioned study published since the AHRQ review, when the unexposed group was not limited to depressed women, but controlling for depression history, there was an increase in risk in infants of women exposed to SSRIs in the second trimester.[130] Consistent with this study's findings for other harmful outcomes, timing of exposure affected risks, with increased risk with three or more prescriptions in women exposed in the second trimester compared to similar exposure in the third trimester. Timing and dose/duration of exposure (represented by number of prescriptions) cannot be separated across all studies, and thus these data are not definitive.

Overall, these finding suggest a possible association between maternal SSRI use and neonatal respiratory distress.

Pulmonary hypertension. The only evidence available for this outcome was in women with unknown depression status, and limited to the findings included in the AHRQ review.[91] Therein, three studies found an increased risk of pulmonary hypertension in infants of mothers who had exposure to SSRIs at any point in their pregnancy (pooled adjusted OR, 2.41 [95% CI, 1.47 to 3.95], I^2=14%). For maternal exposure to SSRIs early in pregnancy, significant heterogeneity prevented the authors from pooling data from the four studies that examined this outcome. For women exposed to SSRIs late in pregnancy, generally defined as 20 weeks gestation or later, three studies found an increased risk of pulmonary hypertension of the newborn (pooled adjusted OR, 2.72 [95% CI, 1.63 to 4.54], I^2=14%).

The evidence suggests a possible association of pulmonary hypertension with maternal exposure to SSRIs, particularly late in pregnancy.

Major malformations. Two studies examined this outcome in studies of depressed women published since the AHRQ review. The first was a large (n=349,127) retrospective cohort study of depressed women that found no increased risk of major malformations with any SSRI. [127] The second was a case-control study of 622 infants with clubfoot and 2002 infants with

malformations, all born to women with depression. [Yazdy 2014] There was an increased risk of SSRI exposure in the second or third month of pregnancy for mothers of infants born with clubfoot (adjusted OR, 1.8 [95% CI 1.1 to 2.8]). There was an increased risk of escitalopram exposure for infants with clubfoot (adjusted OR, 2.9 [95% CI 1.1 to 7.2]); evidence suggested a possible increased risk of sertraline (adjusted OR, 1.6 [95% CI 0.8 to 3.2]) and paroxetine exposure (adjusted OR, 9.2 [95% CI, 0.7 to 484.6]) as well, but confidence intervals were wide for these two antidepressants due to the small numbers of exposed cases.

Data from the AHRQ review in populations with unknown depression status suggested a small increased risk of major malformations with exposure to fluoxetine (k=7, pooled adjusted OR, 1.14 [95% CI, 1.01 to 1.30], I^2=0%) and paroxetine (k=8, pooled adjusted OR, 1.17 [95% CI, 1.02 to 1.35], I^2=0%), but not other SSRIs. Raw rates of major malformations were not reported.

These findings indicate a possible association of major malformations with maternal use of SSRIs during pregnancy.

Cardiac malformations. Evidence on this outcome in women with known depression was found in two large retrospective cohort studies (combined n=1,280,386) published since the AHRQ review.[127,135] These studies found no increased risk of neonatal cardiac malformations in women exposed to classes of SSRIs or SNRIs, or to individual ADs, including bupropion, with the possible exception of paroxetine, for which there were mixed findings: one study identified an increased risk in infants of women exposed to paroxetine in the first trimester (adjusted OR, 1.67 [95% CI, 1.00 to 2.80], 3.0% in exposed babies, vs. 2.8% in unexposed);[127] the other found no increased risk associated with maternal paroxetine exposure at any point during pregnancy (adjusted OR, 0.9 [95% CI, 0.7 to 1.2]).[135]

For women with unknown depression status, five studies in the AHRQ review found no increased risk of cardiac malformations in infants of women who took SSRIs as a class during pregnancy.[91] However, five studies in the AHRQ review did find that paroxetine increases the risk of infant cardiac malformations (pooled OR, 1.45 [95% CI, 1.13 to 1.85], I^2=0%). Additionally, a large (n=27,045) case-control study published since the AHRQ review found an increased risk of venlafaxine exposure at any point from 1 month preconception through the third month of pregnancy for mothers of infants born with atrial septal defects (adjusted OR, 3.1 [95% CI, 1.4 to 7.4]).[145] A second large (n=16,524) case-control study published since the AHRQ review found an increased risk of bupropion exposure in the first trimester for mothers of infants born with ventricular septal defects (adjusted OR, 2.5 [95% CI, 1.3 to 5.0]).[152] Neither of these case-control studies was limited to depressed women, and it is recognized that case-control methodology may overestimate relative risks compared with cohort designs.

Overall, the evidence regarding infant cardiac malformations suggests a possible association with maternal use of bupropion, paroxetine and venlafaxine.

Results of Included Studies in General and Older Adults

Key Question 1. Do Primary Care Depression Screening Programs in the General Adult Population, Including Older Adults, Result in Improved Health Outcomes?

Key Question 1a. Does Sending Depression Screening Test Results to Providers (With or Without Additional Care Management Supports) Result in Improved Health Outcomes?

Study Characteristics

We found nine trials addressing benefits of screening (n=3,814);[72,73,153-159] five in general adult populations[72,73,154,155,157] and four targeting older adults (**Table 18**).[153,156,158,159] All studies except one in older adults were available for our previous systematic review. As in that review, only one study met criteria for KQ1, comparing screening with usual care case-finding.[154] The remaining studies met criteria for KQ1a, in which all patients in both groups were screened for depression, patients screening positive were enrolled in the study, but results were returned only to providers in the intervention group.[72,73,153,155-159] Additional treatment components were included along with screening results feedback in these studies, ranging from brief education about the screening test[72] to an extensive quality improvement program.[155]

The single KQ1 trial, by Williams and colleagues, randomized participants to screening or usual care and retained participants who screened negative as well as positive in the analysis, comparable to a typical primary care population.[154] All included participants, however, completed a diagnostic interview via phone, so none were truly naïve to being asked about depressive symptoms. In addition, followup for depression outcomes was limited to one of the two study sites and further to only those who met criteria for MDD at the diagnostic interview, with a subset of those who did not meet MDD criteria, oversampling those with depression symptoms. For all remaining (KQ1a) trials, samples were limited to patients with depressive symptomatology. Some studies included patients who screened positive on a single depression screening instrument while other required either an additional screening instrument or a confirmed diagnosis of depression after a diagnostic interview.

Most of the trials were cluster randomized, at the level of the providers or clinics rather than individuals, and three were individually randomized trials, including the KQ1 study.[72,154,157] Followup ranged from 3 months to almost 5 years.

Two studies were conducted in the Netherlands[158,159] and the remainder were conducted in the United States, all in primary care settings. This is an older body of literature; the most recent trial was published within the past 5 years,[158] however, the rest were published in the 1990s through early 2000s.

Studies used a variety of screening instruments. Most of the trials targeting older adults used the GDS, and others used the Center for Epidemiologic Studies Depression (CES-D), various forms

of the PHQ or the Primary Care Evaluation of Mental Disorder (PRIME-MD), and the WHO Composite International Diagnostic Interview (CIDI). In most cases screening occurred in conjunction with a primary care clinic visit; however, one of the studies conducted in the Netherlands either invited participants to complete a home-based screening or sent the screening instrument by mail, with just over 50 percent completing the screening in both cases. Where reported, screening was completed by 53 to 90 percent of those invited to be screened.

Populations

Population characteristics are presented in **Table 19**. Five trials (n=2,924) included general adult populations with wide age ranges (i.e. 18 years and older), and average ages were generally in the mid-40s.[72,73,154,155,157] Four trials targeted older adults,[153,156,158,159] including both trials from the Netherlands; minimum ages ranged from 55 to 75 years. In all cases women outnumbered men; across the entire body of evidence, 72 percent of participants were women. Only four of the trials reported substantial racial or ethnic minority representation, all conducted in the 1990s. Most trials included a substantial number of participants who had recently been treated for depression, or had depression previously documented. Two trials (one in general adults and one in older adults), however, specifically targeted persons with untreated depression who were not seeking treatment for mental health issues,[157,158] another trial in 145 older adults excluded persons already taking antidepressants,[159] and a fourth trial in general adults made the *a priori* decision to report results separately for those with newly-identified depression versus previously known depression, and reported some results only for those with newly-identified depression.[73]

Although there was a wide range of screening positivity rates (**Table 18**), in most trials between 14 and 17 percent of the sample screened positive for depression. The screen positive rate was lowest (5.9%) in one large multi-site trial that included a mix of urban and rural clinics,[73] and highest (45%) in a trial of persons with Medicaid or who were below the federal poverty line and without health insurance.[157]

Interventions

Interventions were extremely variable, with no apparent replication across trials. Detailed descriptions of the interventions are available in **Appendix D Table 16**, and a compiled list of selected components offered in each intervention is shown in **Table 20**, roughly ordered by increasing intensity of the intervention within the two age-based strata. At the low end, one trial in general adults tested screening versus usual case-finding,[154] while another in the same population offered very little beyond feedback of screening test results.[72] Two trials primarily focused on making specialist treatment more easily available without extensive training or support directly to the provider.[156,158] Three trials attempted to help improve the primary care clinician's depression care, by providing training,[159] or a standardized treatment protocol with every patient screening positive,[153,157] along with patient hand-outs and patient-specific evaluation of current medications, in one case.[153] The final two trials provided quite extensive training to primary care providers, and had dedicated staff to help with referrals as well as patient followup for symptom and medication monitoring.[73,155] The trial with the most extensive intervention beyond screening results feedback included day-long or multi-day training of "leader" primary care providers, nurses, and mental health providers at each site; treatment

manuals, monthly lectures, and academic detailing for other site providers; printed materials for patients and providers; and either extra support for mediation adherence or low-cost CBT with specially trained mental health clinicians.[155]

Quality

We rated only two of the studies as good quality,[73,158] but one these had higher attrition after the initial 6-month followup, more consistent with a fair rating at longer followup.[73] Most trials reported followup between 80 and 90 percent. Most trials did not explicitly report allocation concealment and few provided information about intervention fidelity. Several studies reported generally good methods (all or most of: adequate randomization methods, baseline comparability between groups, blinding of outcomes assessment, conservative handling of missing data, acceptable statistical methods, no apparent selective reporting of outcomes), but were graded as fair primarily due to the small sample size[157] or attrition.[155,156]

Findings

Depression outcomes. All but two of the trials reported the proportion of the population with depressive symptoms at baseline who were below some pre-specified level of symptomatology at followup, such as no depressive symptoms or below a certain threshold on a screening instrument (**Appendix C Table 17**). We refer to these as remission outcomes.[72,73,153-156,159] Both trials that failed to report remission did report the proportion whose symptoms scores were reduced by a specific amount, to indicate treatment response.[157,158] **Figure 9** shows a forest plot of remission and response (where remission was not reported), ordered by increasing level of provider support beyond screening or results feedback, with general adult populations shown separately from trials targeting older adults.

General adult populations. Screening programs generally increased the likelihood of remission and treatment response in general adult populations experiencing depressive symptoms. All studies showed greater remission or response in the intervention groups, but results were statistically significant only in the two studies with greatest additional supports beyond simple screening or results feedback.[73,155] However, these studies were also the two largest in this population. One of these only found a benefit for those with newly-identified depression, and did not provide data for the whole sample or the complementary subgroup with previously-known depression.[73] This trial reported 47 percent remission in the intervention group after 12 months, compared with 28 percent in the control group, among those with newly-identified depression (RR, 1.71 [95% CI, 1.13 to 2.57]), with a very similar effect size at 24 months.[73] The largest study, with an extensive quality improvement program in a mixed population of persons with newly and previously-identified depression, reported 58 percent remission in the intervention group compared with 49 percent in the control group at 12 months (RR, 1.19 [95% CI, 1.06 to 1.34]).[155] This single study provided repeated followup over 5 years. Group differences were diminished at 24- and 57-month followup, although results were statistically significant at 57-month followup. Although the effect in this study was relatively small, this could be considered an effectiveness trial of a relatively comprehensive depression screening and care support system, conducted in naturalistic managed care settings, with minimal participant exclusion criteria, and free choice of treatment by patients and providers.

Other studies were smaller and underpowered for statistical significance of even fairly large group differences (e.g., 48% remission in intervention group vs. 27% in control group; RR, 1.79 [95% CI, 0.94 to 3.41]).[154] Three studies in general adult populations also reported depression symptom measures, although data were insufficient for creating forest plots so are presented in tabular form only (**Table 21**). Statistically significant benefits on depression symptoms were found in one of the two smallest trials,[72,157] and only in the subgroup with newly-identified depression in one of the larger trials.[73]

Older adult populations. Screening programs were not successful in reducing depression in older adults, and even had a clinically significant (but not statistically significant) paradoxically negative effect in one new study for this body of evidence conducted in the Netherlands. As discussed below, issues specific to the Dutch health care system and the study designs could be factors explaining these results. Evidence specific to the United States was limited to two trials, neither or which showed a benefit of screening programs, and neither had substantial added provider supports beyond screening results feedback. These studies are also quite small and therefore could be underpowered.

Other beneficial outcomes. A few studies reported additional beneficial outcomes, such as improved quality of life[155,157,159] or functioning (**Appendix D Tables 18** and **19**).[153] The large trial in general adult populations reported improvement in the mental component scale of the SF-36 but not the physical component, but others generally showed no greater improvement in intervention participants on various other beneficial outcomes. None of the trials reported suicide-related outcomes.

Key Question 1b. Does the Effect of Screening Vary By Population Characteristics?

Two studies (one in general and one in older adults) were limited to persons with untreated, presumably newly identified depression,[157,158] and one reported results separately for general adults with newly identified and previously known depression, which was planned *a priori*.[73] In this study, the intervention was only beneficial for those with newly-identified depression. Neither of the studies that were entirely limited to those with untreated depression showed a statistically significant benefit or harm, but point estimates were widely discrepant between these two studies suggesting a large potential benefit in general adults (RR, 1.87 [95% CI, 0.74 to 4.73])[157] and large potential detrimental effect in older adults (RR, 0.62 [95% CI, 0.39 to 1.01]); complicating interpretation, these studies also varied in screening and intervention approaches and population characteristics.[158] For example, the Dutch study showing a potential detrimental effect had fewer low-income individuals (under 20%) than the U.S. study showing large potential benefit (100% below poverty line), but almost half (44%) of the population in the Dutch study had a DSM-IV diagnosis, although none were being treated for depression. Finally, as discussed next, studies conducted in the Netherlands appear to differ qualitatively from the rest of the body of evidence and results may reflect a different health care system.

One study reported effects in separate subgroups by age[158] and one study did so by race/ethnicity.[155] There was some suggestion that benefits were greater in African-American and Latino populations than in European-Americans; however, data were limited to a single study.

Evidence was even more limited or completely absent to evaluate differential effects on age, sex, and comorbid conditions.

Key Question 2. What Are the Harms Associated With Primary Care Depression Screening Programs in the General Adult Population, Including Older Adults?

One KQ1 trial reported that no adverse events were attributable to the intervention; however, this was only reported for the subset with newly-identified depression.[73] None of the other KQ1 trials reported on harms, and we found no additional studies addressing harms of screening beyond the trials included for KQ1 and KQ1a.

Control groups showed greater likelihood of remission in both of the trials conducted in older adults in the Netherlands. Results were not statistically significant in either study, but differences were fairly large in one of the studies.[158] The recent, good-quality trial by van der Weele and colleagues reported that 33 percent of their control participants showed a 50 percent or greater decrease on the MADRS, compared with 21 percent in the intervention group. This study was limited to adults aged 75 and older who were not already being treated for depression. They conducted home-based screening for half of the sample, and the other half were screened by mail or phone followup to the mailed questionnaire. Those who screened positive were referred to a community mental health clinic, which offered individual counseling and a 10-week course about coping with depression. While most of the participants who were referred "accepted" the referral (it is unclear what "accepted" meant), only 19 percent participated in the 10-week course, and only 70 percent of those completed the course. The authors of this study point out that in the Dutch healthcare system, primary care providers often have longstanding, close relationships with their older patients, and continuity of care is the norm. They speculated that while their aim was to improve depression care with minimal extra burden to the provider, perhaps "the marginal role of the [general practitioner in the study design] gave a breach in continuity of care that was not beneficial."

Key Question 2a. Do the Harms Vary By Population Characteristics?

We found no data addressing variability in harms by population characteristics.

Chapter 4. Discussion

Summary of Evidence

Data related to pregnant and postpartum populations primarily targeted postpartum women, except for harms of antidepressants, which was usually limited to antidepressant use during pregnancy (**Table 22**). We found moderate evidence suggesting that programs involving depression screening of pregnant and postpartum women, with or without additional treatment-related supports, reduce depression prevalence and increase remission or treatment response. Most included trials, however, included additional treatment elements beyond screening. Low-to-moderate strength evidence suggests that the English-language version of the EPDS has acceptable sensitivity and specificity for detecting postpartum MDD. This evidence also showed that psychotherapy can help increase remission in women with postpartum depression. Data was insufficient on benefits of antidepressant use in pregnant and postpartum women. We found moderate-strength evidence suggesting second-generation antidepressant use during pregnancy may be associated with increased risk of some serious harms. Important limitations to the evidence, however, were noted for all key questions related to pregnant and postpartum women, including relatively small number of studies, few trials with good applicability to primary care in the United States, many studies with very small study sizes, as well as other concerns. Information on harms was almost entirely limited to observational studies. Effect sizes in trials of treatment benefit may slightly overestimate the effect sizes found in typical primary care populations.

In general-adult primary care populations, the current review found low-to-moderate evidence suggesting that programs that include screening, or screening results feedback, improve the likelihood of remission or treatment response. This particularly true for patients with newly-identified depression and when screening is combined with other depression care supports for providers (**Table 23**). We found insufficient data to determine whether these programs are beneficial when targeted specifically at older adults. It may be reasonable to generalize findings in general adults to older adults, however, given that they were not specifically excluded in many general adult studies and the relative paucity of specific evidence in older adults that is applicable to US primary care.

Pregnant and Postpartum Women

Direct evidence on effects of screening pregnant and postpartum women for depression is somewhat limited, but suggests that programs that include screening reduce overall depression prevalence and increase likelihood of remission or treatment response by 23 to 30 percent in depressed postpartum women. This evidence base is relatively small, however, including only six trials with relatively short followup, but more than 10,000 women. Most of the research was conducted outside of the United States in health care systems very different from that in United States. For example, several studies on the benefits of screening were conducted as part of home visit programs,[99,103,105] which are not typical of the care in the United States. These studies also included treatment components beyond screening. Two trials provided minimal additional

components beyond screening and these showed a benefit for either reduced depression prevalence[104] or increased treatment response.[106] The most applicable study, conducted in U.S primary care, included screening results feedback along with care supports, such as treatment guidelines, scripts for monitoring calls from nurses, and patient self-help materials.[69] This study reported a 33 percent increase in the likelihood of treatment response in the intervention group, among women who screened positive at baseline.

Our results are consistent with two recent comprehensive reviews of depression identification in pregnant and postpartum women, which included overlapping, but not identical, evidence bases.[89,90] One review concluded that their included studies showed using the EPDS had beneficial effects, although it was difficult to disentangle the effects of using an identification strategy from the effects of subsequent interventions provided.[90] The other review concluded that screening was associated with modest improvement in depression across a variety of low-intensity interventions.[89]

The English-language version of the EPDS appears to have acceptable properties for identifying women with MDD. While the range of sensitivities and specificities were quite wide, the largest and most applicable studies reported sensitivities of around 0.80 and specificities of 0.90 or higher, for a cutoff of 13 to detect MDD, primarily examined in postnatal women. While this body of evidence was fairly large (k=21), only seven studies addressed the English-language version of the EPDS. Likewise, only three of these were conducted in the United States. Further, the literature on the English-language version of the EPDS was hampered by small study sizes, usually including fewer than 30 persons meeting criteria for MDD. Some of these trials had fewer than 10 cases either overall or for reported subgroups, which resulted in low precision and very few false negatives.[100,117,118] On the other hand, the broad application of the EPDS with relatively acceptable results in various languages and populations can be seen as reassuring as to its applicability to a diverse U.S. perinatal population. Other reviews drew similar conclusions, which included a broader range of screening instruments.[89,90] When considering all the translated versions of the EPDS, one group concluded that the EPDS performs reasonably well, with sensitivity ranging from 0.60 to 0.96 and specificity ranging from 0.45 to 0.97 for MDD.[90] This group further noted that while the identification tools that were not specific to pregnant and postpartum women, such as the Beck Depression Index (BDI) and HAM-D, may be less sensitive but more specific than the EPDS for pregnant and postpartum women. Similarly, the other review concluded that both sensitivity and specificity generally were in the 0.80 to 0.90 range for most screening tests.[89]

One could argue that sensitivity is more important than specificity for depression screening because depression often co-occurs with other mental health disorders, particularly anxiety-spectrum and substance use disorders. One third of women with post-partum anxiety disorders, for example, also met criteria for depression.[162] The principle components of most behaviorally-based treatments were not developed specifically for depression or are expected to only benefit persons meeting full diagnostic criteria for MDD. Rather, behaviorally-based treatments are well-suited to treating a wide range of mental health issues, including anxiety and substance misuse, and very unlikely to cause harm to persons whose symptoms do not meet criteria for MDD, but who are distressed, overwhelmed, or unhappy nevertheless. Thus, highly sensitive but

not specific instruments are likely to identify some women where depression is not the primary diagnosis, but who would likely benefit from further evaluation and treatment.

Counseling pregnant and postpartum women with screen-detected depression using CBT or related behaviorally-based approaches reduced postpartum depression symptomatology and increased the likelihood of remission over usual care. We found insufficient data to determine whether the use of other treatment modalities was beneficial in either pregnant or postpartum women, including antidepressants. Although most of the studies of CBT and related interventions were conducted outside of the United States, one study that was conducted in the United States found a benefit of CBT at both 4.5 and 7.5 month followups.[124] Another highly applicable U.S.-based study that assessed a stepped-care approach with high-risk, low-income postpartum women found the intervention was not beneficial, although the study was hampered by very small sample size.[129] Additionally, lack of benefit in a stepped-care approach does not provide evidence against expected benefit from provision of effective therapies, such as CBT, to all screen-detected women.

Typically, studies generally reported that the intervention groups improved more than usual care, although both groups improved. Women in the usual care group generally showed improvements on the EPDS of one to six points on a 30-point scale, compared with 5- to 10-point improvements with CBT or related therapies. One group explored the relationship between depressive symptoms and assessments of functional impairment and emotional well-being.[163] They found that a change of three points on the HAM-D (a 52-point scale) was associated with clinically important changes in these other areas. While it is difficult to directly translate this finding to the EPDS, the improvements reported in the intervention groups were very likely to represent clinically important changes, as did changes seen in many of the usual care groups. We could not find information on the availability of CBT in the United States or ease of accessibility. Unfortunately, this treatment is unlikely to be universally accessible. On the other hand, antidepressants, which do not have evidence to support them in pregnant or postpartum women, are widely available.

Other reviews have also concluded that that behaviorally-based treatment of depression is beneficial during the postpartum period. They have also reported that data are lacking on the use of antidepressants. These reviews were not limited to studies of women with screen-detected depression.[164,165] For example, based on 27 studies, including open trials, quasi-randomized trials, and randomized controlled trials of pharmacologic and psychological interventions, one review concluded that women undergoing treatment for postpartum depression showed substantial reductions in depressive symptoms, with an estimated standardized effect size of 0.65, compared with control groups (Hedge's g, 0.65 [95% CI, 0.45 to 0.86], I^2=43%, after excluding an outlier with large beneficial effect).[164] Symptom levels at post-treatment were generally below cutoffs indicative of clinically important symptoms.[164]

In addition to the lack of applicability to the United States, some concerns exist about generalizability and overestimation of effect size in the broader depression treatment literature. Some (but not all) of these concern apply to the trials included in this review. Some researchers have found that generalizability of clinical trial treatment results in general may be reduced by restrictive inclusion and exclusion criteria. In general, most real-world patients (not limited to

pregnant and postpartum women) with depression do not meet typical criteria for inclusion in clinical trials.[166] In a large observational study of individuals with a major depressive episode, 75.8 percent would have met at least one of the typical exclusion criteria for clinical trials of depression treatment. The criteria that would lead to the greatest number of exclusions include: presence of comorbid non-depressive non-substance-related Axis I disorders (e.g., anxiety disorders) (47.4% of sample), the duration of the depressive episode (less than 4 weeks or greater than 2 years, 40.3% of sample).[166] This finding was confirmed by the Sequenced Treatment Alternative to Relieve Depression (STAR*D) study of stepped-care treatment for depression in primary care (not limited to peripartum women), which had minimal exclusion criteria. This study found that patients meeting inclusion criteria for typical efficacy trials had shorter average duration of illness and lower rates of family history of substance abuse, prior suicide attempts, and anxious and atypical features.[167] The treatment studies included in this review generally excluded women with greatest disease severity, such as history of psychosis, current suicidal ideation, or need for crisis management. Some also excluded women taking psychotropic medications, and a few excluded patients with substance abuse disorders and perinatal complications. The included trials, however, rarely excluded patients for long duration of depression and none excluded women with any other Axis I disorder. As such, most women with co-morbid anxiety disorders, for example, would have been included.

The STAR*D study also found higher response and remission rates in the subgroup that met typical trial inclusion criteria (even after controlling for baseline factors),[167] suggesting trial evidence may overestimate effects of treatment. Further, a review of psychotherapy trials found that high-quality studies consistently found smaller effects than lower -quality trials, even after controlling for a number of study characteristics (including control group type). This finding is consistent with our finding of relatively smaller effects in good quality studies.[168] Indeed, the two good-quality studies included for this KQ had two of the three smallest effect sizes for remission/response in the CBT group. One of these trials did show a statistically significant benefit,[138] which was very similar to the pooled estimate. While the other trial did not show a benefit of CBT at 4.5, 9, or 18 months, it did show a benefit for psychodynamic therapy at 4.5 months only.[128]

Also, while small studies' bias have been reported in psychotherapy literature,[169,170] one analysis suggested that the statistical significance of pooled results may be only minimally affected.[170] Many of our included studies had very small sample sizes. The largest study was a good-quality Hungarian trial of women identified and treated with CBT during pregnancy. This trial reported a benefit of CBT therapy at 6 week postpartum. Not surprisingly, the effect size of this study was almost identical to the pooled estimate, suggesting that overestimation of effect was probably less of a concern in the current review than in other meta-analyses.[138]

Our belief that overestimation of effect size is likely limited in this review is further supported by the fact that other reviewers have shown that trials that recruited through screening generally found smaller effect sizes than those enrolling self-selected volunteers from broad-based community recruitment through media ads and other means.[171] Since we limited our included studies to those that used screening to identify eligible participants, this likely limited the degree to which our pooled effect size overestimates real-world results.

We found very little evidence related to the harms of behaviorally-based treatment in pregnant or postpartum women. We found no study that suggested that these treatments could be harmful. We found evidence suggesting use of some specific agents or classes of antidepressants, particularly SSRIs and venlafaxine, during pregnancy may be associated with increases in the risk of preeclampsia, postpartum hemorrhage, miscarriage, as well as a number of adverse infant outcomes (e.g. preterm birth, neonatal seizures). For antidepressants, there is an imbalance of evidence such that most available studies suggest potential harms when used during pregnancy while showing very little evidence for benefits. Data on harms from antidepressants were exclusively observational, however, so we could not definitively determine whether these agents were the direct cause of these adverse events. Indeed, one large observational study that noted increases in miscarriage with SSRI use also found increases when women had discontinued the SSRIs more than 3 months before they got pregnant.[125] This suggests that the increased risk may be due to some other confounding factor, perhaps related to depression itself, because this study was not limited to depressed women.

In summary, available data suggests caution in prescribing antidepressants during pregnancy, especially since we found no evidence related to treatment efficacy in pregnant women. Indeed, many women express a preference for nonpharmacologic treatment during pregnancy.[172-175]

The only evidence we included related to harm of antidepressant treatment in *postpartum* women, on the other hand, was the small efficacy trial of fluoxetine in screen-detected women. This trial reported no differences in discontinuation due to side effects. Postpartum women may have concerns about breastfeeding, since antidepressants are detected in breast milk. However, not all are found in infant serum.[176] For example, paroxetine and sertraline tend to be undetectable in infant blood levels, while, levels of citalopram and fluoxetine can sometimes exceed recommended maximum levels.

In adults in general, serious adverse events can include suicidality (particularly in younger adults), hyponatremia, seizures, gastrointestinal (GI) bleeding and serotonin syndrome.[177,178] Other studies have commonly reported adverse effects include discontinuation syndrome, GI upset, sexual side effects, agitation, anxiety, and weight gain.[179,180]

Acceptability of Screening in Pregnant and Postpartum Women to Patients and Providers

In the included screening studies, screening was completed on 81 to 93 percent of women they attempted to screen, suggesting high feasibility and low refusal rates. None of the included studies, however, specifically reported participants' feelings about depression screening. In a recent study of 145 postpartum American women screened during a pediatric visit, the majority (95.7%) found discussing symptoms of depression with their pediatrician to be acceptable and welcome.[181] Similarly, in an Australian study of 479 postpartum women who were screened with the EPDS, nearly all women (96.7%) thought it would be a good idea to screen new mothers for postnatal depression.[182] Although not limited to pregnant and postpartum women, universal screening in an OB-GYN service was generally seen in a positive light among participants in a collaborative-care RCT. Many patients reported that while participants had been feeling depressed, they would not have brought it up with their providers if they had not been specifically asked.[63]

Studies from Australia and the United Kingdom, however, suggest that women with depressive symptoms may feel some discomfort with depression screening.[182-184] For example, 29 percent of women in an Australian study who were informed that they had screened positive reported feeling upset or a little upset.[183] Also, a small qualitative study conducted in the United Kingdom of postnatal screening in the home found some women felt anxious about the consequence of the results and were reluctant to answer the questions or answer them truthfully; others felt it was intrusive and felt a diagnosis of depression would be stigmatizing.[184] These results suggest sensitive screening procedures and handling of positive screening results are important.

One Australian study also evaluated the general practitioners', maternal child health nurses', and midwives' level of comfort and perceived usefulness of the EPDS after 3 years of routine perinatal use.[183] Almost all providers reported an intent to keep using the EPDS (97 to 99%) and most rated it as "certainly/very" useful (55% of general practitioners, 75% of maternal child health nurses, and 57% of midwives). Similarly, most of the remaining providers rated the EPDS as "somewhat" useful. Midwives were more likely to experience discomfort in explaining the EPDS than physicians and nurses.[183]

Acceptability of Treatment in Pregnant and Postpartum Women

None of our included treatment studies in pregnant and postpartum women reported on acceptability of depression treatment. Women in six qualitative studies of women participating in psychosocial groups for postpartum depression reported that the groups helped them develop better relationships with their babies and assess their roles of partner and mother. They reported they were better able to understand their feelings associated with post-partum depression, appreciated the support and decreased isolation, and benefited from normalizing/social comparisons with other women suffering from post-partum depression. Some participants, however, reported difficulty applying CBT principles, difficulty talking openly in group settings, negative social comparisons, and being distressed by other women's stress and dysfunction.[185] Descriptive studies among postpartum women—either diagnosed with postpartum depression or not—showed they are more accepting of psychotherapy as treatment for depression than using antidepressants.[172-175] The women's main concerns with antidepressant treatment included their effects on parenting and breastfeeding as well as a fear of dependence and the stigma associated with their use.[172] Postpartum depressed women who are prescribed antidepressants tend to have poor compliance.[186]

Estimated Effect of Screening Alone

It is difficult to isolate the effect of screening using available data. Therefore, we are unable to translate these results into downstream clinical benefits. The usual care for identifying depression in postpartum women is not well understood and varies considerably across settings. A few states have mandated depression screening in pregnant or postpartum women and some others have funded programs to guarantee reimbursement for screening, train providers, or raise awareness about depression in pregnant and postpartum women.[85] Most states, however, do not have such programs and the standard of care varies considerably even within states with related legislation. Previous observational cohort studies that assessed the implementation of systematic screening without further care supports reported mixed findings—some reported continued low

rates of screening or care initiation while other did not.[187-190] Among the trials included in our review, the proportion of depressed women who recovered or responded to treatment varied widely, undoubtedly fueled at least in part by different outcome definitions. The U.S.-based study of screening included in this review found that 41 percent of postpartum women with elevated EPDS scores had been correctly identified by providers as being depressed with usual clinical practice. Sixty-six percent of these women were identified with EPDS results, which is a 61 percent increase in correct identification of depression.[191] This seems to support the likelihood that the 23 to 30 percent reduction in prevalence in mostly non-U.S.-based screening studies would be plausible in the United States.

General and Older Adult Populations

We found that evidence generally supported the benefits of depression screening programs in general adult populations, with the most robust findings in programs that included substantial care supports beyond simple screening, in persons with newly-identified depression. We found no evidence of benefit of screening in older adults, but data with high applicability to the United States were limited to only two older studies.

One trial conducted in older adults hinted that a program of home-based screening and referral to specialty care with limited role for the primary care provider may have a harmful effect on older adults. This result must be interpreted with great caution, however, given that it was only found in a single study, was not statistically significant, and was conducted in the context of a healthcare system that may be quite different from what many experience in the United States. Older adults, however, may have unique needs with regards to depression identification and care for a number of reasons. First, older adults have an increased likelihood of serious comorbid illness, which may both make it difficult to diagnose depression and increase the risk of harmful drug interactions with antidepressant use. Older adults may have recognized or unrecognized cognitive impairment that can increase their risk for depression and decrease their odds of responding to treatment, in part due to either difficulty engaging in therapy and/or decreased adherence to treatment recommendations due to cognitive issues. In addition, older adults may be more likely to endorse a high level of stigma associated with depression (particularly African-Americans), a preference for depression treatment from primary care providers (versus specialty care), and preference for nonactive treatments, such as supportive care and watchful waiting over active treatments.[192-195]

The current body of evidence was almost the same as the evidence included in the previous review. These reviews differed by only two trials, both of which were in older adults: we excluded one previously included trial[196] due to a slight change in inclusion criteria in the current review and we also identified one newly published study.[158] The excluded study did not report remission, so the data on remission was identical in the previous and current reviews, except for the addition of the newly published study. However, the excluded study did report a 1-point statistically significant greater improvement in depressive symptoms on a 30-point scale. We excluded this study because depression screening results were not directly returned to providers. Instead, providers received the results of a thorough geriatric assessment that was triggered by the positive screening test. We used a more narrow interpretation of screening test results in this review than what was used in the previous review.

As with the previous review, the number of studies that examined screening programs in general and older adults was limited, and most screening interventions provided additional treatment support components, at times quite extensive, making it impossible to isolate the effects of screening alone. In addition, several trials included only a small number of participants, limiting statistical power and precision of effects. An important strength of the subset of studies that were not limited to older adults was that they had good applicability to the U.S. primary care system as all were conducted in the United States and were conducted in a wide variety of primary care settings.

Previous reviews supporting the USPSTF recommendations on depression screening have examined the complete chain of evidence in an expanded analytic framework.[87,177] The USPSTF previously concluded that brief, accurate, and feasible screening tests are available for detecting depressive disorders in adults (good evidence) and older adults (fair-to-good evidence), and that effective pharmacologic (good evidence) and psychotherapeutic treatments (fair evidence) are available for adult primary care patients with major depression.[87] Further, the 2009 review clarified that the benefits to older adults from antidepressants and/or psychotherapy was comparable to younger adults. However, one group of researchers requested unpublished results of antidepressant trials from the FDA and found that published results reported larger effect sizes than unpublished data and raised concerns that reported benefits of antidepressant treatment may be overstated.[197] Regarding serious harms of antidepressants, the 2009 review found that older adults have a higher risk for upper gastrointestinal bleeding with antidepressant use.[177] The 2009 review also concluded that data linking antidepressant use to suicide deaths was inconclusive, but may be elevated in younger adults, particularly with the use of paroxetine for major depressive disorder.

Since the current review only assessed the direct effects of screening programs in general adult populations, and some information on benefits of treatment and screening instrument accuracy were last examined in the 2002 review, we non-systematically examined current evidence for these two areas.

For benefits of treatment, recent reviews reported that collaborative care interventions, SSRIs, venlafaxine, and certain psychological treatments are effective in reducing depressive symptoms in studies of patients recruited through from primary care settings, even without systematic screening.[83,198,199] For example, the Community Guide found that collaborative care interventions improve depressive symptoms, adherence to treatment, response to treatment, and remission and recovery from depression. Many of these interventions involved screening.[83] We were unable to include most of these collaborative care trials in our review since screening (or results feedback) alone were typical control groups in these trials.

Further, we searched for studies in adults or older adults whose depression was identified through screening in primary care. We found 18 trials that were published between 1983 and 2013. Details of these studies can be found in **Appendix E**.[200-217] We found seven trials of collaborative care or other system-level approaches,[201,204,209-211,214,218] and five of these showed beneficial results after 6 or more months, including both trials that were limited to older adults.[204,214] For example, the Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT) found greater declines in suicidal ideation, earlier treatment response, and higher

depression remission rates at 24-month followup.[204] Eleven trials tested behavioral interventions in the general or older adult populations,[200,202,203,205,206,208,212,216,217,219,220] and results were mixed. In general, studies that utilized more intensive (e.g., greater number of sessions) behaviorally-based treatments were more likely to report positive effects than less intensive approaches. Some studies noted that participants with more severe depression symptoms at baseline showed greater treatment effects[200,212] and that treatment effects tended to diminish over longer followup periods.[209,214] One trial studied the effect of an antidepressant in a screened population, and reported a beneficial effect after 8 months of treatment.[202]

For screening instrument accuracy, we focused on the examination of the GDS (for older adult populations) and PHQ family of instruments, which are widely used in current practice. These instruments were largely not represented in published studies until after the 2002 review was completed. Authors of a recent review of the PHQ-9 concluded that it had acceptable diagnostic properties for detecting major depressive disorder for cutoff scores between 8 and 11, with a pooled specificity from 0.83 (95% CI, 0.69 to 0.92) for a cutoff score of 8, to 0.89 (95% CI, 0.79 to 0.94) for a cutoff score of 11. Corresponding pooled sensitivity estimates ranged from 0.82 (95% CI, 0.66 to 0.92) for a cutoff score of 8, to 0.89 (95% CI, 0.75 to 0.96) for a cutoff score of 11. While a cutoff score of 11 appeared to have the optimal trade-off between sensitivity and specificity, this may vary according to clinical setting.[221] An individual-level pooled data analysis is underway to examine the PHQ family of instruments, which can overcome some important limitations of the study-level data, including the risk of overestimation of accuracy due to reporting of optimal cutoffs (rather than the full range).[222] In a separate review, studies evaluating the GDS-15 (k=7) used cutoffs ranging from 3 to 7, which resulted in an adjusted sensitivity of 81.3 percent (95% CI, 77.2 to 85.2) and a specificity of 78.4 percent (95% CI, 71.2 to 84.8).[223] Authors concluded that the GDS-15 had adequate diagnostic value. Furthermore, they concluded that the use of the GDS-15 by general practitioners could increase unassisted case detection by 8 percent. Similarly, Chilean researchers found that self-administered screening tools were much more sensitive than general practitioners in identifying depression, but with comparable specificity.[224] A more detailed write-up of instrument accuracy of the PHQ and GDS is available in **Appendix F**. Ultimately, sensitivity may be more important than specificity for patients with depressive symptoms. As many as half of persons with mood disorders are likely to also have anxiety disorders, and both antidepressants and behaviorally-based interventions are also likely to benefit those with anxiety symptoms in addition to depressive symptoms.[225-227]

Acceptability of Screening Programs to Patients and Providers

In most of the included studies that reported screening completion rates, 80 to 90 percent of persons invited to screen completed the screening test, which suggests depression screening was both feasible and generally acceptable to patients. One Dutch study used mail or phone for screening rather than incorporating the screening into a clinic visit and had a substantially lower completion rate (53%).[158] Two of the included screening studies—one in U.S. adults[154] and one in Dutch older adults[159]—determined screening did not affect the patient's satisfaction with care. In a recent patient satisfaction survey among 107 U.S. geriatric patients, 62.9 percent found mental health screening questions acceptable.[228] Less than 3 percent of respondents found the questions very difficult, stressful, intrusive, embarrassing, upsetting, or uncomfortable as it raised difficult emotions and an awareness of their current mental health status. In another U.S.

study, patients reported that they appreciated learning how to help themselves with their depression after being screened with the PHQ-9.[229]

Only two of the included screening trials evaluated the physician's perception of the utility of screening for depression in adults.[72,154] In one study, physicians found the PHQ-9 useful in 78 percent of baseline patient visits regardless of depression status.[72] In the other study, 433 physicians randomized to use a case-finding instrument (1-item or 20-item) returned a questionnaire regarding its helpfulness.[154] The majority (76%) found the instrument to be very or somewhat helpful, while only 4 percent found it unhelpful.

One depression-screening implementation study surveyed providers 1 year after implementation of a program in a United States Army medical clinic. This intervention involved staff training, depression screening, automatic entry of results in the chart, automatic scheduling of a followup appointment with the primary care provider, and an offer for a mental health referral. This study reported 54 percent of primary care providers and 95 percent of nurses strongly agreed that screening for depression enhanced quality of care.[230] An implementation effort in three U.S. non-profit and county agencies that provided case management to older adults revealed some challenges.[231] In this intervention, older adults screening positive for depression and their families received education on depression and printed materials. Case managers facilitated referrals and helped clients communicate with a medical or mental health provider. Case managers also provided behavioral activation counseling. Challenges included clients' reluctance to acknowledge depressive symptoms and difficulty engaging in behavioral activation; differences among case managers' mental health knowledge, skills, and "buy-in"; limited time for case managers' intervention and referral activities; and agency cultures that don't foster in-agency supervision. The screening and patient education components of the intervention were rated "easy" by 90 percent of case managers; most of the challenges came with implementation of the referrals and behavioral activation counseling.

Estimated Effect of Screening Alone

As with pregnant and postpartum women, correct identification of depression by primary care providers is undoubtedly variable across different settings. Reviews examining correct identification rates estimate an average rate of approximately 47 percent.[47,48] This result is consistent with a recently conducted trial in Spain that reported 48 percent of depressed primary care patients were correctly identified as depressed by their providers.[232] This trial reported a 21 percent increase in identification after training providers in screening and implementing a screening program.[232] Similarly, after implementing a screening program in a U.S. Army clinic, the number of depression cases identified increased from approximately 100 per month to 130 to 140 per month.[230] Assuming that all other parts of the treatment process are constant, a 20 to 40 percent increase in recognition of depression would translate to a 20 to 40 percent increase in remission of depressed cases. This result is consistent with the effect sizes reported by studies of screening programs in general adult populations. As the work by Pence and colleagues makes clear, improvements in other steps in the process after recognition of depression have the potential for additional gains in depression remission.[47] Indeed, failure to deliver effective treatment negates the benefits of greater depression identification. As a result, it appears that the most active area of research is in testing collaborative care and care management models for

screen-detected or otherwise identified depression, rather than examining the specific effects of screening in the absence of other treatment supports.

Concerns About Routine Depression Screening

Other reviewers have questioned the evidence supporting a recommendation favoring a depression screening.[233-235] These reviewers cite a number of concerns, including the lack of true direct evidence to support depression screening; the concern that most cases identified through screening will not be newly-identified persons with previously unknown depression, but will primarily be persons already known to be depressed and treated for depression; and the concern that those who are newly identified through screening will have milder cases of depression that may not warrant treatment, thus increasing the risk of unnecessary treatment and direct harms of treatment. The Canadian Task Force and Preventive Health Care (CTFPHC) has recently recommended not routinely screening for depression in either average- or increased-risk adults in primary care setting, due to lack of direct evidence on benefit and harms of screening.[236] The CTFPHC review required an unscreened control group and only included five quasi-experimental studies of community screening programs conducted in Japan as their evidence base. We excluded these studies because they examined public health interventions, not healthcare-based interventions. The CTFPHC did not consider any of our included KQ1a studies because they did not include unscreened control groups (even though providers did not receive the screening results). They also excluded the studies we included in KQ1 that included unscreened control groups. In the KQ1 study that was conducted in a population of general adults, control-group participants underwent a diagnostic interview as part of the study process, which may have been the reason for exclusion by the CTFPHC reviewers.[154] They also excluded two KQ1 trials that were conducted in postpartum women—one due to lack of appropriate compartor[104] (perhaps because both groups were treated by the same study-trained providers, if treatment was recommended) and one because it was not an eligible population[105] (perhaps because they were recruited from midwives' postnatal care practices, rather than general primary care).

We agree that very little data exists that allows us to determine the effects of screening alone compared with no screening. Instead, most KQ1/KQ1a interventions included screening and additional treatment elements. Thombs and colleagues likened this to testing usual-case finding for cancer plus less-than-ideal cancer care versus screening plus state-of-the-art treatment.[237] Unfortunately, depression is a condition that is plagued by both under identification and less-than-ideal care.[56,68]

While limited, we did have one trial conducted in a general-adult population and one conducted in a postpartum population that looked specifically at the addition of systematic use of a screening instrument versus usual case-identification, either without further enhancements to depression care[154] or with the same treatment offered to both groups, if depression treatment was indicated.[104] The latter, which was conducted in a population of postpartum women, reported reduced depression prevalence at 4 months, although this effect disappeared at 16 months followup. The other trial, which was conducted in a general adult population, reported increased likelihood of remission at 3-month followup among those depressed at baseline. This study,

however, did not find statistically significant group differences in overall depression prevalence (37% in the intervention group vs. 46% in the control group, p=0.19).[154]

While this is very minimal data that is directly on point, it is further supported by two streams of indirect evidence. First, critics have not acknowledged that there is a complete chain of indirect evidence showing that that screening instruments can identify depression, and that treatment with net benefits is available for persons with depression, as determined by the previous USPSTF reviews on this topic. Our updated, nonsystematic examination of this evidence clarifies that depression treatment can be effective in persons whose depression is detected by screening in primary care settings, further solidifying the indirect chain. Second, screening trials with additional supports may be interpreted as providing evidence for a complete system of care in which the sum is more important than the parts.

While few trials had unscreened control groups, we believe that screening in the control group that did not provide results feedback to the provider would be most likely to attenuate results. This is because screened persons may have heightened awareness of their depression and, therefore, be more likely to bring it up with their provider. Thus, we believe effects seen in studies of screening results feedback versus no feedback may, if anything, underestimate the true effect of screening.

A second concern is that few new cases of depression will be found with screening. In most of the included studies, a high proportion of persons who screened positive had already been identified by health providers as depressed, unless patients with previously known or treated depression were specifically excluded. Since depression is often inadequately treated,[56,68] however, we believe it is also important for persons who are still depressed despite previous treatment efforts to be identified so their provider can continue to help them until they are able to find a successful treatment. Further, depression screening presents an opportunity to query suicidal ideation among those who screen positive. While the USPSTF has not recommended routine screening for suicide risk, they did note that "primary care clinicians should be aware of psychiatric problems in their patients and should consider asking these patients about suicidal ideation and referring them" for treatment.[75] Thus, pragmatically, identifying incompletely treated patients could be considered an added benefit of routine depression screening, although falls more in the realm of depression management than prevention through early detection, which is the traditional definition of screening.

A third concern is that additional cases found through screening are more likely to have very mild depression. Critics note that treatment may not be necessary or even beneficial with mild depression, and could lead to overuse of antidepressants and unnecessary harms associated with them. Indeed, studies of antidepressants do show larger beneficial effects in patients with more severe depression than those with mild depression.[238,239] In fact, an analysis of data submitted to the FDA found that efficacy of second generation antidepressants only met criteria for clinical significance at highest depression severity levels.[239] A review of psychological treatments for depression, however, did not find an association between baseline depression severity and effect size, and although within-study results suggested larger effects with greater severity, differences between subgroups were not statistically significant and the pooled effect was statistically significant for those with lower baseline severity.[240] Thus, if the only or primary treatment

available is antidepressants, this argument has merit. If behaviorally-based treatment is available, however, this concern is diminished. The U.K.'s National Institute for Health and Care Excellence recommends active monitoring, low-intensity psychosocial interventions, or advice on sleep and anxiety management as initial strategies in persons with newly-identified mild or sub-threshold depression, rather than antidepressants.[241]

To examine this further and focus on screen-detected depression, we identified nine RCTs, published between 1997 and 2014 that examined the effectiveness of behaviorally-based and/or pharmacologic treatments for relatively mild depression (sub-threshold depression, sub-syndromal depression, minor depression, dysthymia, and major depressive disorder with mild-to-moderate symptoms) in patients who had screened positive for depression in primary care settings.[204,207,208,212,242-246] Two trials had both medication and behaviorally-based treatment arms.[244,246] Two other trials examined a stepped-care approach that may have included options for both behaviorally-based and pharmacologic interventions.[204,207] All but one of these trials excluded participants with current or recent treatment for depression.[208] We found limited empirical support for the effectiveness of behavioral interventions in the treatment of mild depression and three of the seven behaviorally-based treatment arms showed a benefit of treatment. Both of the treatment arms that tested antidepressants (paroxetine and sertraline) showed a benefit of treatment.[244,246] Both of the stepped-care approaches, however, did not show group differences in the subgroup of patients with minor depression.[204,207] Both intervention and control groups showed substantial improvement in the two stepped-care studies, including a large U.S.-based study in older adults.[204] This evidence strengthens the concern that there may be limited down-stream benefits for persons with relatively mild depression whose depression is detected through screening. This is consistent with a review of psychological therapies, which showed smaller effects in primary care-based trials of screen-detected depression compared with referral-based recruitment.[247]

Although simple logic supports the notion that screen-detected depression would be milder, on average, than depression identified through usual clinical care, we found very limited evidence to clarify whether this is the case. One collaborative care trial examined PHQ-9 scores in depressed women in an OB-GYN practice who were identified through systematic screening versus usual case-finding and found no differences in depression severity.[248]

Limitations of the Review

In addition to limitations of the evidence discussed above, this review did not cover areas of research that may be pertinent. For example, we limited our examination of screening instrument accuracy in pregnant and postpartum women to only two instruments, the PHQ and the EPDS, which we believe are most widely used in clinical practice. We found no data related to the PHQ. We also did not include nontrial evidence related to harms of screening or behaviorally-based treatment. We believe the risks for these treatments are minimal. We did consider pertinent observational evidence in the discussion, primarily associated with acceptability of these treatments. Further, we limited our evidence of antidepressant harms in pregnant and postpartum women to a prespecified list of serious harms. We did not examine other harms that may be important, if not life-threatening, such as developmental outcomes and behavioral outcomes in

babies, such as crying and sleeping. In addition, we only examined evidence limited to pregnant and postpartum women, rather than providing a comprehensive examination of all harms in adults. Also, we did not review effectiveness of interventions in pregnant and postpartum women that are generally offered outside of the healthcare setting but are widely available, such as yoga, exercise, and light therapy. We did not examine benefits of screening or treatment in pregnant or postpartum adolescents.

We did not systematically review the accuracy of depression screening instruments or benefits and harms of treatment for general and older adult populations. Thus, while we did not complete the entire chain of indirect evidence, we instead focused only on direct evidence of screening benefits and harms. This indirect data was previously systematically reviewed and found to adequately support a screening recommendation, and we did informally review data published in these areas since the previous reviews. A systematic update may have revealed more data than we found.

Future Research Needs

In general, the field of depression screening and treatment research would benefit from standardized definitions of important outcomes, such as depression remission or depression prevalence. Cross-study comparisons would also be enhanced by adopting a small number of depression symptom measures, such as the PHQ instruments, the GDS, and the EPDS. Evidence with high applicability to the United States was limited for most KQs. Specific needs include:

- Large trials conducted in the United States of screening alone, compared with usual care-finding, in pregnant and postpartum women, general adult populations, and older adults, covering a variety of primary care settings.
- Trials that examine the relative importance of screening and other treatment support components, such as treatment guidelines and training, staff-assisted symptom monitoring, ease of referral, and role of the primary care provider.
- Large-scale good-quality U.S.-based trials of depression treatment in pregnant and postpartum women.
- More information on screening instrument accuracy of the PHQ family of instruments, likely the most widely used instrument in practice (underway, protocol published).[222]

Ghio and colleagues[249] discuss unmet needs and research challenges for late-life mood disorders, including "critical aspects of clinical trials in late-life mood disorders that limit our knowledge about diagnosis/treatment of depression in older adults", with which we concur. These include heterogeneous age ranges used in inclusion criteria, exclusion of very old patients, atypical presentation of late-life depression, few rating scales specific for geriatric population, lack of evidence in patients with more than one comorbidity, high frequency of suboptimal prescribing, heterogeneity of secondary outcomes, high attrition rates, uncertainty about optimal trial duration, among others.

We identified a number of additional ongoing studies that may be relevant for updates of this review, primarily trials of behavioral treatment in pregnant and postpartum women (**Appendix G**).

Conclusion

Although direct evidence of the isolated health benefit of depression screening in primary care is weak, the totality of the evidence supports the benefits of screening in pregnant and postpartum and general adult populations, particularly in the presence of additional treatment supports, such as treatment protocols, care management, and availability of specially trained depression care providers. The indirect evidence shows that depression screening instruments can identify adults, including older adults as well as pregnant and postpartum women, who need further evaluation and may need treatment for depression, and depression treatment is likely to be effective. The only risk of harm we identified was with the use of antidepressants during pregnancy, although the risks appear to be small and alternative treatment options are available in most settings. Evidence is the least supportive of screening in older adults, where direct evidence is most limited and did not demonstrate a beneficial effect. Generalizing from evidence in all adults to older adults may be reasonable.

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Figure 1. Analytic Framework, Pregnant and Postpartum Women

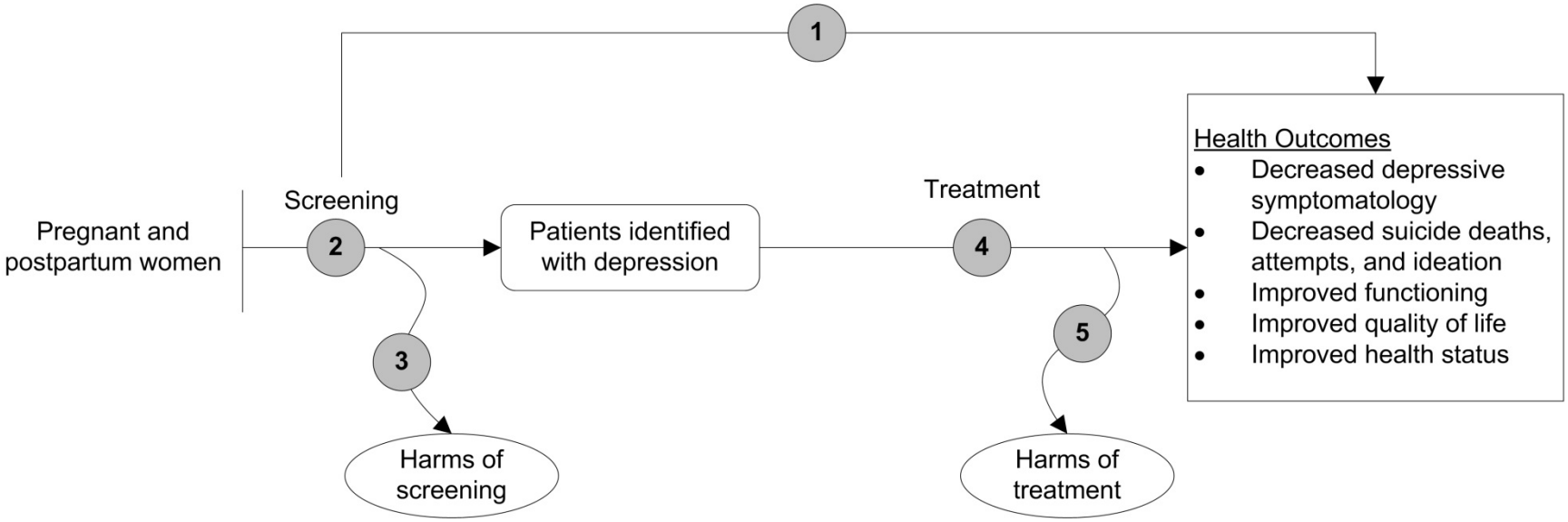


Figure 2. Analytic Framework, General and Older Adults

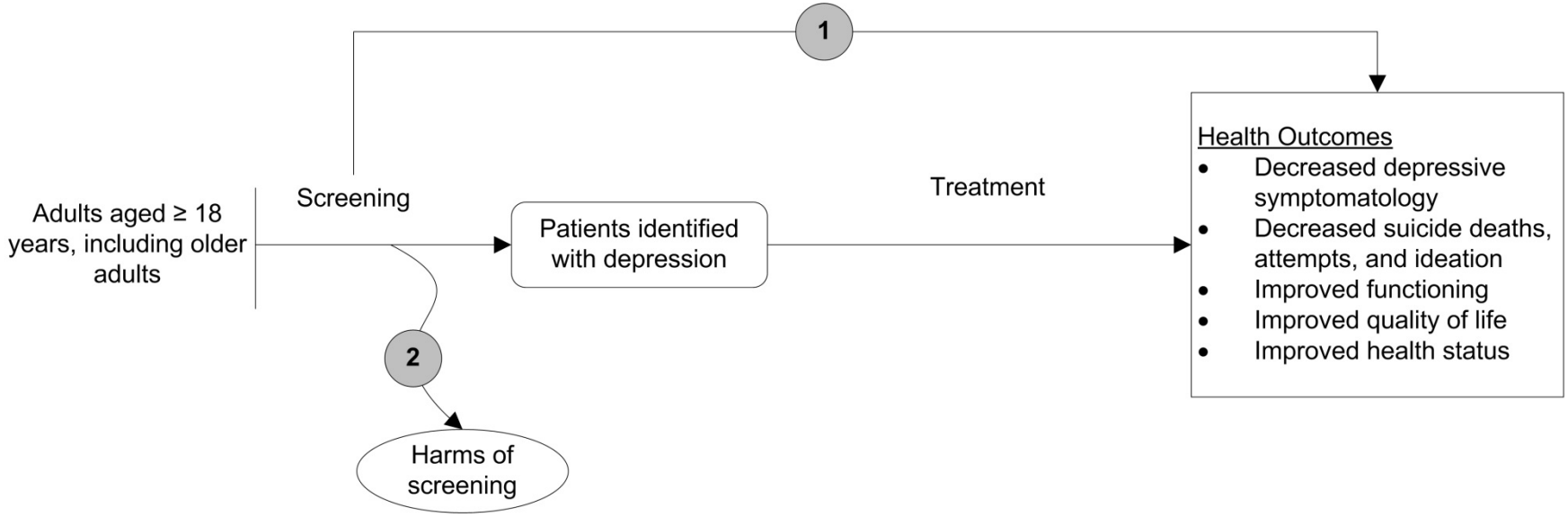
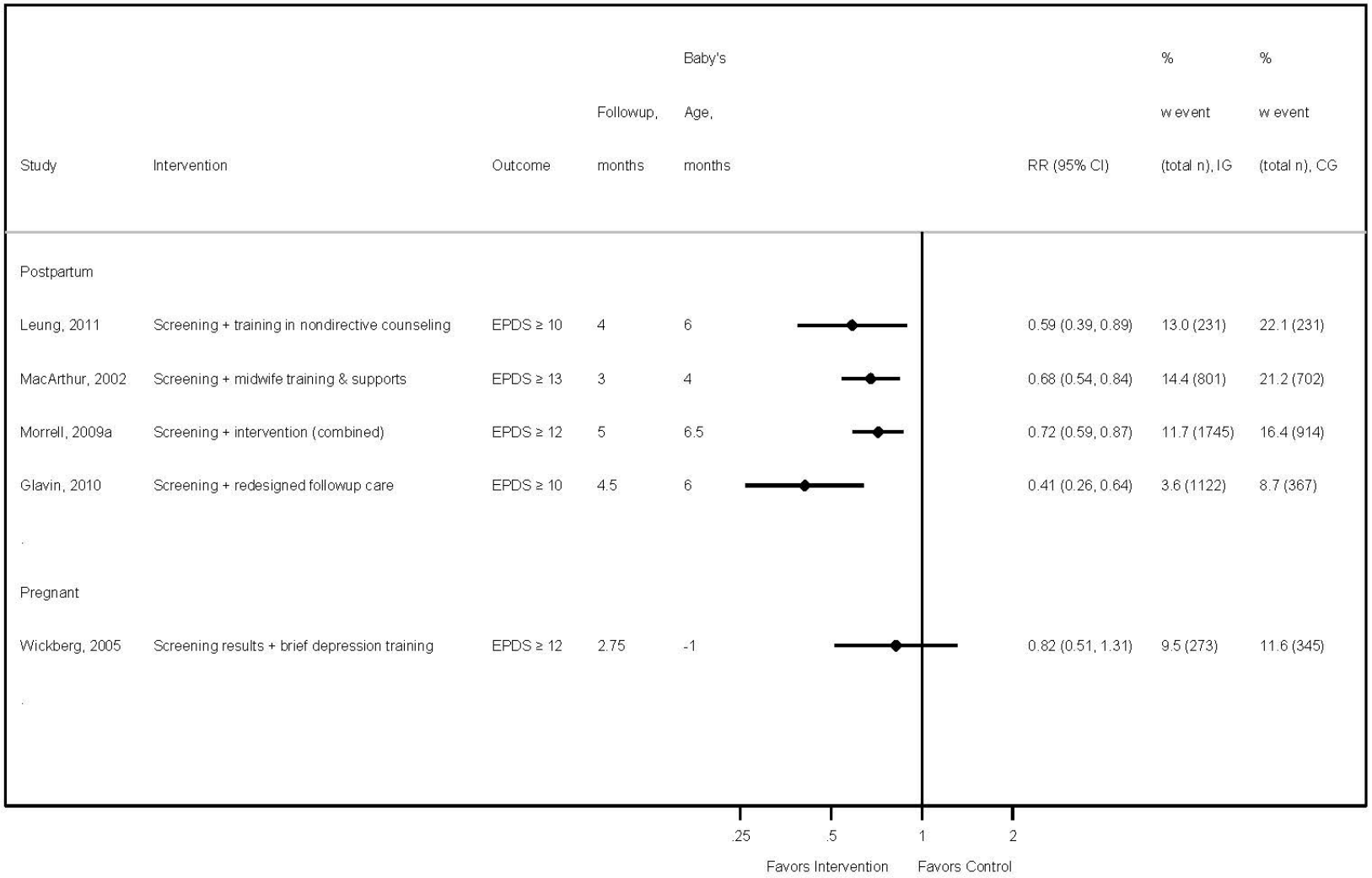
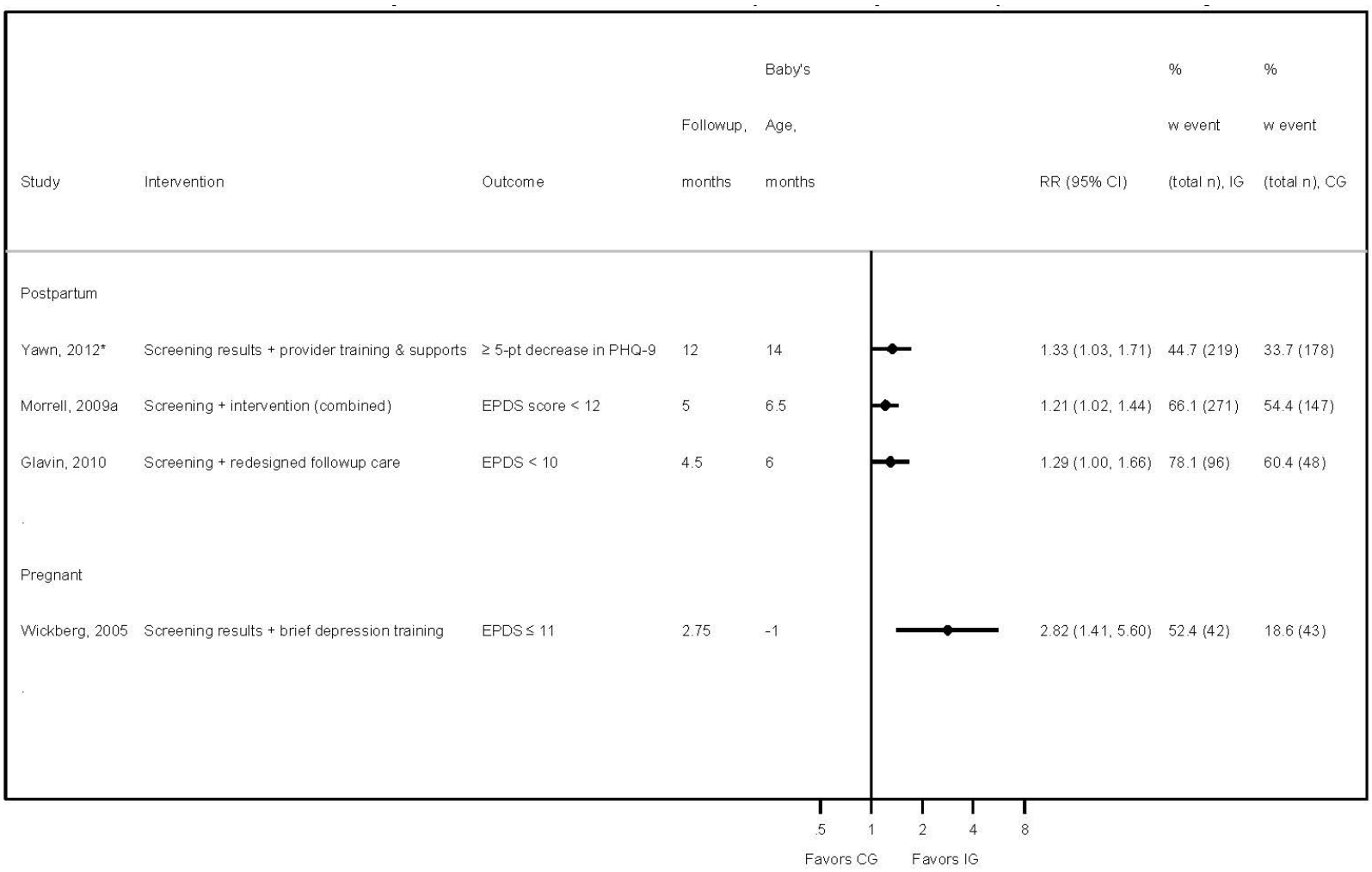


Figure 3. Forest Plot of Depression Prevalence in Pregnant and Postpartum Women (Key Question 1)



Abbreviations: CG = control group; CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale; IG = intervention group; RR = relative risk.

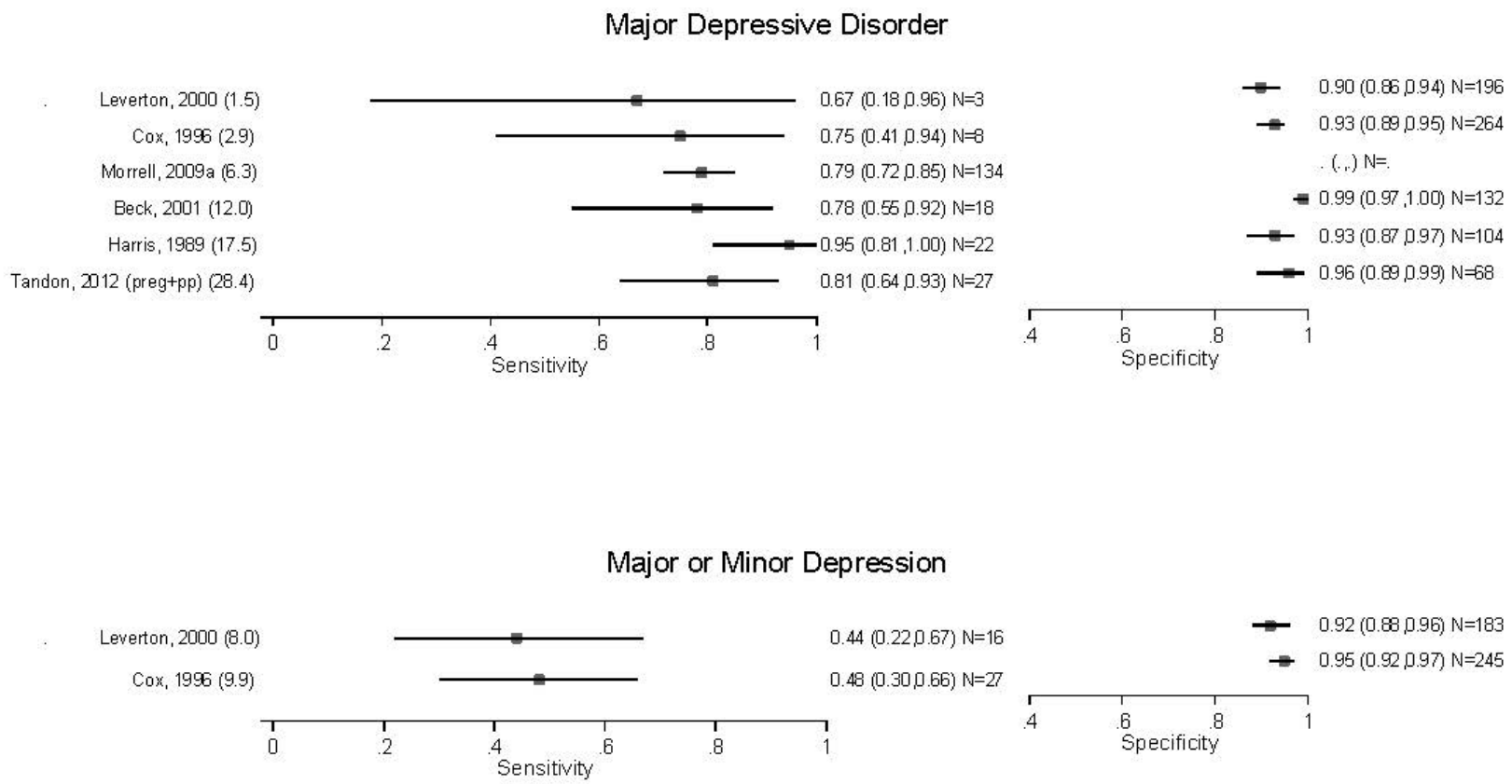
Figure 4. Forest Plot of Depression Remission in Pregnant and Postpartum Women (Key Question 1)



*Response to treatment (rather than remission).

Abbreviations: CG = control group; CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale; IG = intervention group; PHQ = Patient Health Questionnaire; pt = point; RR = relative risk.

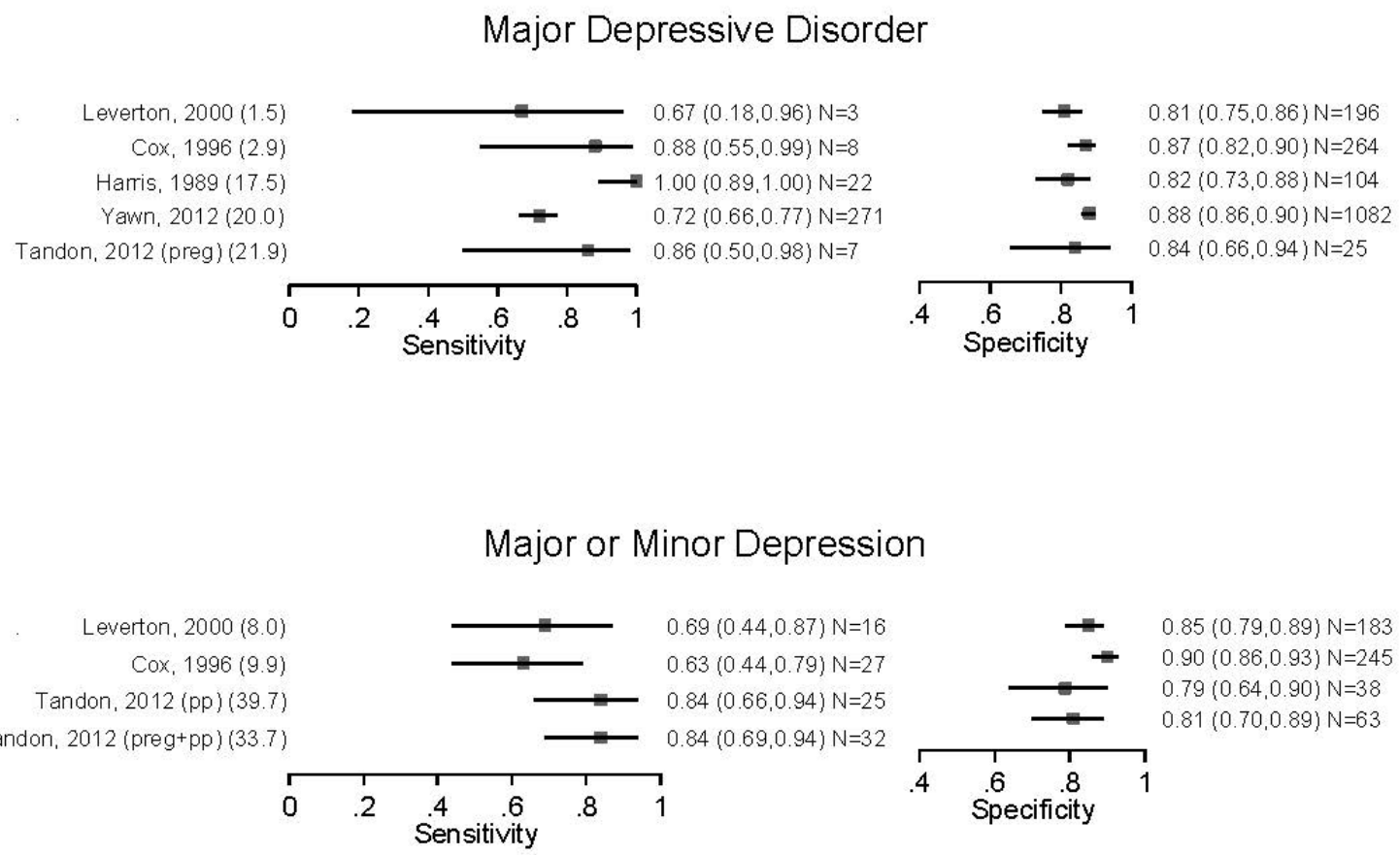
Figure 5. Sensitivity and Specificity of the EPDS Using a Cutoff of ≥13, English-Version Only (Key Question 2)



*Data are extrapolated from partial verification.

Abbreviations: CI = confidence interval; N = number; PP = postpartum; preg = pregnant.

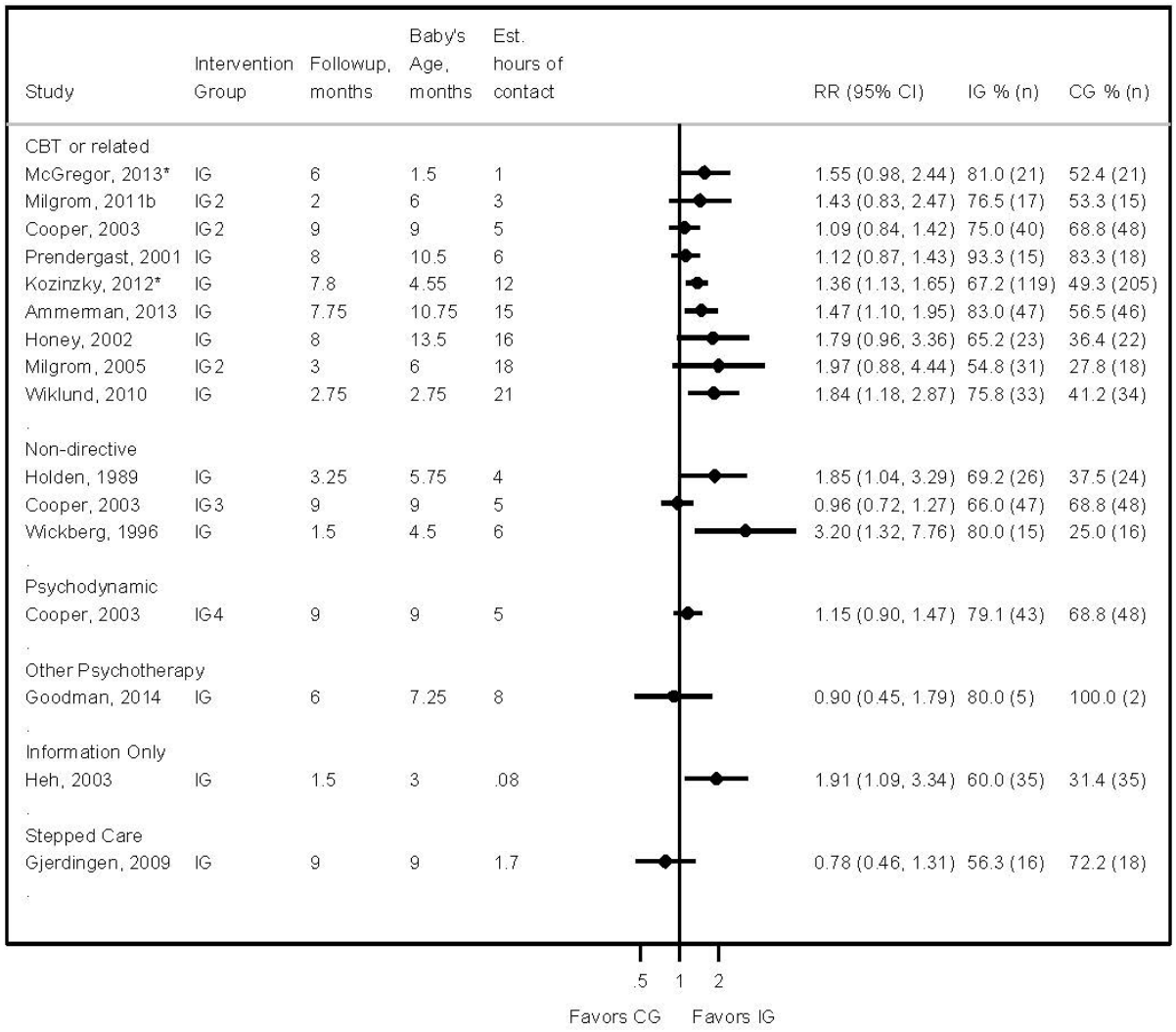
Figure 6. Sensitivity and Specificity of the EPDS Using a Cutoff of ≥10, English-Version Only (Key Question 2)



*Data are extrapolated from partial verification.

Abbreviations: CI = confidence interval; N = number; PP = postpartum; preg = pregnant.

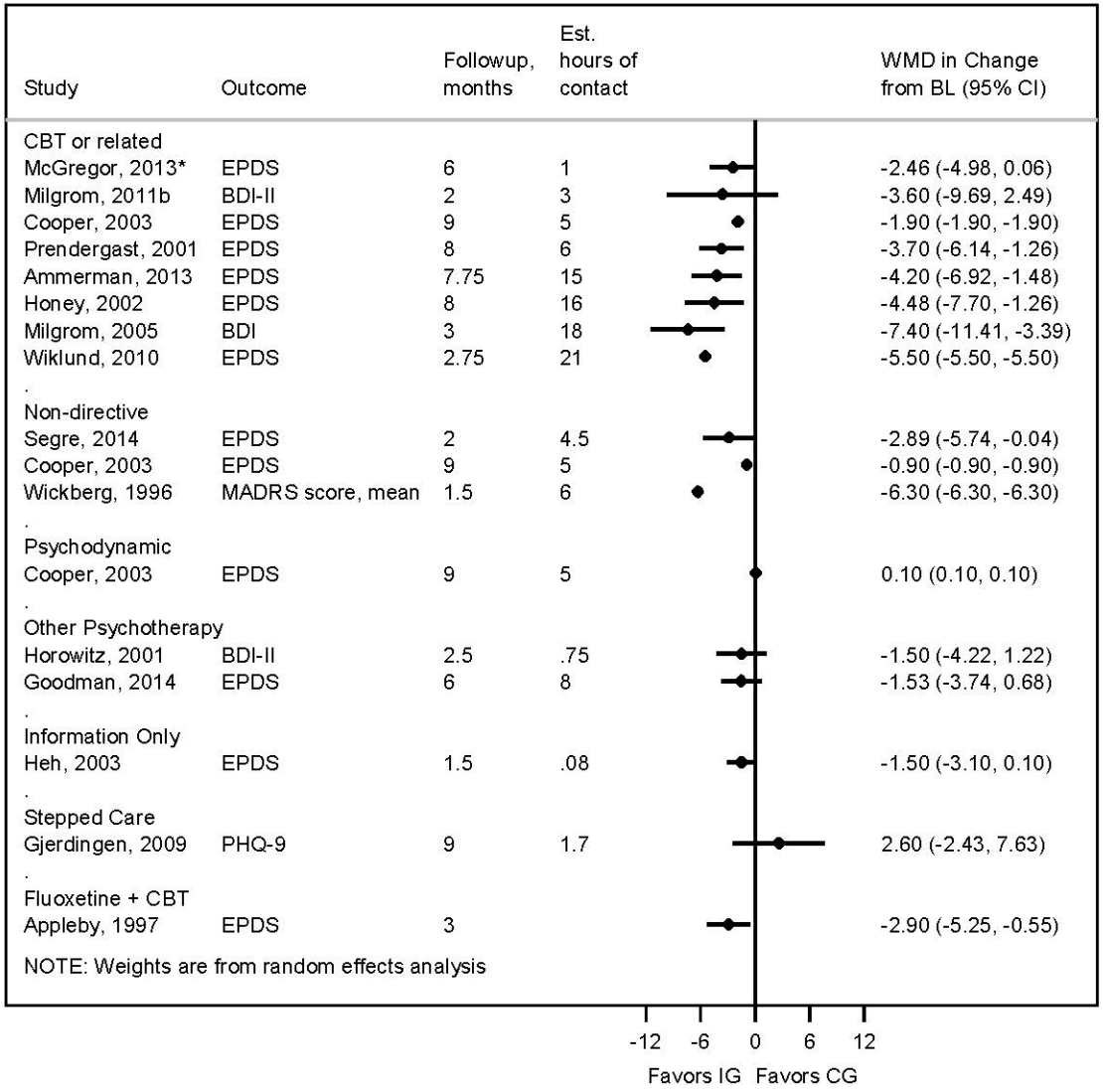
Figure 7. Forest Plot of Depression Remission or Response in Pregnant and Postpartum Women (Key Question 4)



*Pregnant women only.

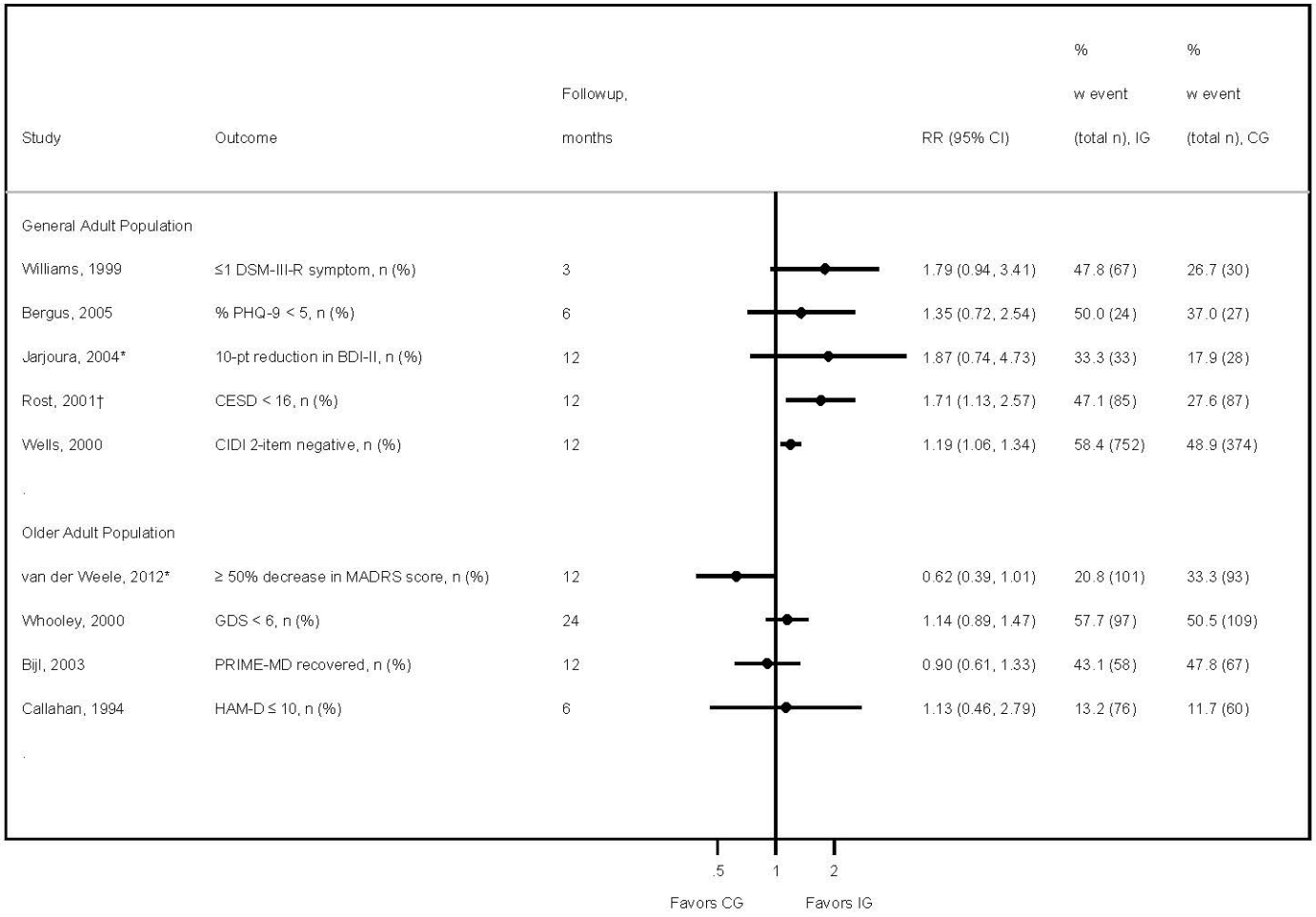
Abbreviations: CBT = cognitive behavioral therapy; CG = control group; CI = confidence interval; est = estimated; IG = intervention group; RR = relative risk.

Figure 8. Forest Plot of Changes in Depression Scores in Pregnant and Postpartum Women (Key Question 4)



Abbreviations: BDI = Beck Depression Inventory; BL = baseline; CBT = cognitive behavioral therapy; CG = control group; CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale; est = estimated; IG = intervention group; PHQ = Patient Health Questionnaire; SD = standard deviation; SE = standard error; WMD = weighted mean difference.

Figure 9. Forest Plot of Depression Remission or Response in General and Older Adults (Key Question 1)



*Response rather than remission reported.
†Subgroup with newly diagnosed depression only; results not reported for entire sample or for subgroup with previously known depression.

Abbreviations: BDI = Beck Depression Inventory; CES-D=Center for Epidemiologic Studies Depression; CG = control group; CI = confidence interval; CIDI = Composite International Diagnostic Interview; DSM = Diagnostic and Statistical Manual; GDS = Geriatric Depression Scale; HAM-D = Hamilton Depression Rating Scale; IG = intervention group; MADRS = Montgomery Asberg Depression Rating Scale; PHQ = Patient Health Questionnaire; PRIME-MD = Primary Care Evaluation of Mental Disorders; pt = point; RR = relative risk.

Table 1. Percentage of U.S. Adults With at Least One Major Depressive Episode in the Past Year, NSDUH 2013[9]

Category	Characteristics	≥1 Major Depression Episode in Past Year (%)
Age (years)	18-25	8.7
	26-29	8.1
	30-34	7.8
	35-39	7.1
	40-44	7.5
	45-49	7.4
	50-54	7.9
	55-59	6.6
	50-65	6.1
	≥ 65 years	2.6
Sex	Men	5.1
	Women	8.1
Race/Ethnicity	White	7.3
	Black	4.6
	Hispanic	5.8
	American Indian or Native American	8.9
	Native Hawaiian or Other Pacific Islander	1.6
	Asian	4.0
	Multiracial	11.4
Education	Less than high school	6.3
	High school graduate	6.0
	Some college	7.8
	College graduate	6.5
Poverty level	Less than 100%	8.9
	100-199%	7.9
	≥ 200%	5.8
Employment status	Full-time	5.3
	Part-time	7.8
	Unemployed	9.5
	Other (e.g., student, retired or disable)	8.0

Abbreviation: NSDUH = National Survey on Drug Use and Health.

Table 2. Depression Symptoms Rating Scales

Instrument	Number of Items	Scoring Range	Administration Time	Typical Cut-Points
Beck Depression Inventory (BDI/BDI-II)	21	0-63	10 minutes	11 = mild 17 = borderline clinical 21 = moderate 31 = severe 40 = extreme
Center for Epidemiologic Studies Depression Scale (CES-D)	20	0-60	10 minutes	16
Edinburgh Postnatal Depression Scale (EPDS)	10	0-30	5 minutes	0-9 = mild distress 10-12 = moderate distress 13 = high likelihood of diagnosis
Geriatric Depression Scale (GDS Long Form)	30	0-30	5 minutes	0-9 = normal 10-19 = mild 20-30 = severe
Geriatric Depression Scale, 15 item (GDS Short Form)	15	0-15	5-7 minutes	≥ 6
Hamilton Depression Rating Scale (HDRS/HAM-D)	17	0-54	15 minutes	7-17 = mild 18-24 = moderate ≥24 = severe
Hospital Anxiety and Depression Scale (HADS)	14 (7 specific to depression)	0-21	2-5 minutes	≥ 8
Montgomery-Asberg Depression Rating Scale (MADRS)	10	0-60	15 minutes	15 = mild 25 = moderate 31 = severe 44 = very severe
Patient Health Questionnaire– Depression (PHQ-9)	9	0-27	5-10 minutes	<5 = minimal 5-9 = mild 10-14 = moderate 15-19 = moderately severe 20-27 = severe

Table 3. FDA-Approved Pharmacotherapy for Depression in Adults

Category	Drug Class	Generic Names (Brand Name)
First-Generation	Tricyclic Antidepressants (TCAs)	Amitriptyline Amoxapine Clomipramine Desipramine (Norpramin) Doxepin (Sinequan) Imipramine (Tofranil) Maprotiline Nirtriptyline Nortriptyline (Pamelor) Protriptyline (Vivactil) Trimipramine (Surmontil)
	Monoamine Oxidase Inhibitors (MAOIs)	Isocarboxazid (Marplan) Phenelzine (Nardil) Selegiline (Emsam [transdermal patch]) Tranylcypromine (Parnate)
Second-Generation	Selective Serotonin Re-Uptake Inhibitors (SSRIs)*	Citalopram (Celexa) Escitalopram (Lexapro) Fluoxetine (Prozac) Fluvoxamine Paroxetine* (Paxil, Pexeva) Sertraline* (Zoloft)
	Selective Serotonin/Norepinephrine Re-uptake Inhibitors (SNRIs)	Desvenlafaxine (Pristiq) Duloxetine (Cymbalta) Venlafaxine (Effexor)
	Dopamine Re-Uptake Inhibitors (DRIs)	Bupropion (Wellbutrin)
	5-HT_{2A} Receptor Antagonists	Nefazodone
	Serotonin Re-Uptake Inhibitors (SRIs)	Trazadone
	Tetracyclic Antidepressants (TeCAs)	Mirtazapine

*SSRIs are the first-choice medicine for treating postpartum depression; sertraline and paroxetine are recommended for breast-feeding women.

Table 4. Recommendations of Other Organizations for Depression Screening in Adults

Organization, Year	Recommendation
American Academy of Family Physicians (AAFP), 2012	The AAFP recommends screening adults for depression when staff-assisted depression care supports are in place to assure accurate diagnosis, effective treatment, and follow-up.[250] The AAFP recommends against routinely screening adults for depression when staff-assisted depression care supports are not in place.[250] These recommendations are based on the 2009 USPSTF recommendation.
American Academy of Pediatrics (AAP), 2010	The AAP recommends that pediatricians screen mothers for postpartum depression at baby's one-, two- and four-month visits.[251]
American College of Physicians (ACP), 2009	The ACP recommends that primary care providers should screen all adults for depression and that all primary care providers should have systems in place, either within the primary care setting itself or through collaborations with mental health professionals, to ensure the accurate diagnosis and treatment of this condition.[252] The ACP supports the 2009 USPSTF recommendation.
American Congress of Obstetricians and Gynecologists (ACOG), 2010	There is insufficient evidence to support a firm recommendation for universal antepartum or postpartum screening, screening for depression has the potential to benefit a woman and her family and should be strongly considered.[253]
Canadian Task Force on Preventive Health Care (CTFPHC), 2013	The CTFPHC does not recommend routinely screening for depression in adults at average risk of depression or in adults in subgroups of the population who may be at an increased risk of depression.[236]
Institute for Clinical Systems Improvement, 2013	Clinician should use a standardized instrument to screen for depression if it is suspected based on risk factors or presentation. Clinicians should use DSM-5 criteria to determine a diagnosis of major depression, persistent depressive disorder, and unspecified depressive disorder. Clinicians should assess and treat for depression in patients with some comorbidities. Clinicians should acknowledge the impact of culture and cultural differences on physician and mental health. When using pharmacotherapy in elderly patients, the clinician should carefully consider how the metabolism of the drug may be affected by physiologic changes, their comorbid illnesses and the medications used for them. Clinicians should screen and monitor depression in pregnant and post-partum women. A collaborative care approach is recommended for patients with depression in primary care. A written and mutually agreed-upon treatment plan engaging the patient and family is recommended. Clinicians should provide antidepressant medications and/or referral for psychotherapy as treatment for major depression. Clinicians should establish and maintain follow-up with patients.[254]
Community Preventive Services Task Force (CPSTF), 2009	The CPSTF recommends collaborative care for the management of depressive disorders based on strong evidence of effectiveness in improving depression symptoms, adherence to treatment, response to treatment, and remission and recovery from depression. This collaboration is designed to improve the routine screening and diagnosis of depressive disorders, as well as the management of diagnosed depression.[255]

Abbreviations: DSM = Diagnostic and Statistical Manual; USPSTF = U.S. Preventive Services Task Force.

Table 5. Study Characteristics of Included Studies for Key Questions 1 and 1a (Pregnant and Postpartum Women)

Author, Year and Quality	KQ1	Study Design	N	Intervention	Weeks Postpartum at Baseline	Followup (m)	Country	Setting	Invited to Screen (% Screened)	% Screened Positive for Depression	Definition of Screened Positive
Leung, 2011[104] Good	KQ1	RCT	462	Screening	8	4, 16	Hong Kong	Primary care	NR	25.1	EPDS ≥ 10
Wickberg, 2005[106] Fair	KQ1a	Cluster RCT	669	Screening results + brief depression training	25 weeks gestation	2.75	Sweden	Primary care	717 (93.3%)	13.9	EPDS ≥ 12 at gestational week 25
Yawn, 2012[69,256] Fair	KQ1a	Cluster RCT	2343	Screening results + provider training & supports	8	6, 12	United States	Primary care	2398 (97.7%)	27.9	EPDS ≥ 10 or PHQ-9 ≥ 10
MacArthur, 2002[105] Fair	KQ1	Cluster RCT	2064	Screening + midwife training & supports	4	3	United Kingdom	Primary care/home visits	NR	12.8	EPDS ≥ 13 at 4 months postpartum
Morrell, 2009a[99,257] Fair	KQ1a	Cluster RCT	4084	Screening results + CBT or person-centered counseling	6	5	United Kingdom	Primary care/home visits	NR	17.3	EPDS ≥ 12 at 6 weeks postpartum
Glavin, 2010[103] Fair	KQ1a	CCT	2247	Screening results + redesigned followup care	6	1.5, 4.5	Norway	Primary care/home visits	2508 (89.6%)	10.1	EPDS ≥ 10 at 6 weeks postpartum

Abbreviations: CBT = cognitive behavioral therapy; CCT = controlled clinical trial; EPDS = Edinburgh Postnatal Depression Scale; KQ = Key Question; m = months; NR = not reported; PHQ = Patient Health Questionnaire; RCT = randomized controlled trial.

Table 6. Population Characteristics of Included Studies for Key Questions 1 and 1a (Pregnant and Postpartum Women)

Author, Year and Quality	Mean Age and Range (years)	Race/Ethnicity (%)	SES	Depression History, n (%)
Leung, 2011[104] Good	NR	NR	Family income ≤ HK$19,999, n (%): 233 (50.4)	NR
Wickberg, 2005[106] Fair	NR	NR	NR	NR
Yawn, 2012[69] Fair	26.4 (≥ 18)	Black: 18 Hispanic: 12 White: NR	Uninsured at 2 months postpartum, n (%): 862 (36.8)	History of depression: 709 (30.3%)
MacArthur, 2002[105] Fair	NR	NR	Most deprived Townsend quartile, n (%): 503 (24.4)	NR
Morrell, 2009a[99] Fair	NR (≥ 18)	Black: NR Hispanic: NR White: 95.3	Rent council or housing association, n (%): 547 (13.4)	Previous pregnancy w/ postnatal depression: 617 (15.1%)
Glavin, 2010[103] Fair	32.5 (≥ 18)	NR	NR	NR

Abbreviations: NR = not reported; HK = Hong Kong; SES = socioeconomic status.

Table 7. Intervention Characteristics of Included Studies for Key Questions 1 and 1a (Pregnant and Postpartum Women)

Author, Year Quality	Intervention	Train PCP in Screening	Train PCP in Depression Diagnosis	Train PCP in Depression Treatment	Treatment Guidance Provided	Patient Materials Provided	Patient-specific Treatment Recommendations	Referral Support for PCP	Symptom Monitoring by Support Staff	Treatment Adherence Monitoring by Support Staff	Counseling to Support Adherence	Behavioral Counseling Approach	Estimated Hours of Behavioral Counseling	Target Provider
Leung, 2011[104] Good	Screening + training in nondirective counseling	✓		✓								NA	NA	Nurse
Wickberg, 2005[106] Fair	Screening results + brief depression training		✓	✓								NA	NA	Midwife
Yawn, 2012[69] Fair	Screening results + provider training & supports	✓	✓	✓	✓	✓		✓	✓	✓	✓	NR	0.25	Physician
MacArthur, 2002[105] Fair	Screening + midwife training & supports			✓	✓							NA	NA	Midwife
Morrell, 2009a[99] Fair	Screening + person-centered counseling or CBT		✓	✓	✓							Person-centered or CBT	8	Health visitor
Glavin, 2010[103] Fair	Screening + redesigned followup care		✓	✓	✓	✓						Non-directive counseling	NR	Public health nurse visitor

Abbreviations: CBT = cognitive behavioral therapy; NA = not applicable; PCP = primary care provider.

Table 8. Results of Included Studies for Key Questions 1 and 1a (Pregnant and Postpartum Women): Depressive Symptoms

Author, Year Quality	Intervention	Subgroup	F/U (mo)	IG n	BL IG Mean	BL IG SD	F/U IG Mean	F/U IG SD	IG Mean Change	IG SD Change	CG n	BL CG Mean	BL CG Mean SD	F/U CG Mean	F/U CG SD	CG Mean Change	CG SD Change	Between Group Difference (p-value)
Leung, 2011[104]	Screening + training in nondirective counseling	All participants	4	231	NR	NR	5.1	3.6	NR	NR	231	NR	NR	6.5	4.4	NR	NR	<0.001
Good			16	231	NR	NR	5.8	3.9	NR	NR	231	NR	NR	5.8	3.6	NR	NR	0.819
Wickberg, 2005[106]	Screening results + brief depression training	All participants	2.75	226	6.4	NR	5.4	NR	-1.0	NR	231	6.1	NR	6.1	NR	0.0	NR	<0.05
Fair																		
MacArthur, 2002[105]	Screening + community-based postnatal care	All participants	3	801	NR	NR	6.4	NR	NR	NR	702	NR	NR	8.1	NR	NR	NR	NR
Fair																		
Morrell, 2009a[99]	Screening + intervention (combined)	All participants	5	1745	6.6	4.8	5.5	4.7	-1.1	4.8	914	6.8	5.0	6.4	5.2	-0.4	5.1	0
Fair		EPDS ≥12 at 6 weeks postpartum	5	271	15.1	2.9	9.2	5.4	-5.9	4.7	147	15.4	3.2	11.3	5.8	-4.1	5.0	0.004
Glavin, 2010[103]	Screening + redesigned followup care	All participants	1.5	1516	4.0	NR	2.9	NR	NR	NR	405	5.1	NR	4.0	NR	NR	NR	NR
Fair			4.5	1516	4.0	NR	2.0	NR	NR	NR	367	5.1	NR	4.1	NR	NR	NR	NR

Abbreviations: BL = baseline; CG = control group; EPDS = Edinburgh Postnatal Depression Scale; F/U = followup; IG = intervention group; n = number; NR = not reported; SD = standard deviation.

Table 9. Study Characteristics of Included Studies for Key Question 2 (Pregnant and Postpartum Women)

Author, Year and Quality	N	Reference Standard	Pregnant or Postpartum	Weeks Postpartum	Country (Language)	Setting	% Positive for Depression per Reference Standard
English EPDS							
Yawn, 2012[69] Fair	1353	PHQ-9 and physician evaluation for depression	Postpartum	5-12	United States	Primary Care	20.0
Beck, 2001[108] Fair	150	DSM-IV diagnosis of MDD	Postpartum	2-12	United States	Primary Care	12.0
Tandon, 2012[118] Fair	95	SCID-I/NP diagnosis of MDD	Both	Pregnant-26 weeks postpartum	United States	Other Community/ Home Visits	28.4
Morrell, 2009a[99,257] Fair	860	SCAN interview diagnosis of moderate or severe depression	Postpartum	6	United Kingdom	Primary Care/ Home Visits	6.3
Cox, 1996[100,258] Fair	272	SPI interview criteria for MDD	Postpartum	24	United Kingdom	OB-GYN	6.2
Leverton, 2000[117,259] Fair	199	PSE interview and Bedford College diagnosis of case depression	Postpartum	12	United Kingdom	OB-GYN/ Home Visits	1.5
Harris, 1989[115] Fair	126	DSM-II criteria for MDD	Postpartum	6	United Kingdom	Other Clinical	17.4
Non-English EPDS							
Chen, 2013[113] Fair	487	DSM-IV-TR clinical interview diagnosis of any depression	Postpartum	1-22	Singapore (Chinese)	OB-GYN	6.2
Lee, 2001[116] Fair	145	SCID-NP diagnosis of major or minor depression	Postpartum	6	Hong Kong (Chinese)	OB-GYN	11.7
Guedeney, 1998[114] Fair	87	RDC diagnosis of major or minor depressive disorder	Postpartum	16	France (French)	Other Community	51.7
Adouard, 2005[107] Fair	60	MINI DSM-IV criteria for MDD	Pregnant	28-34 gestation	France (French)	OB-GYN	25
Toreki, 2013[120] Good	219	SCID DSM-IV criteria for MDD	Pregnant	12 gestation	Hungary (Hungarian)	OB-GYN	3.2
Toreki, 2014[121] Fair	266	SCID diagnosis of MDD	Postpartum	6	Hungary (Hungarian)	OB-GYN	3.0

Table 9. Study Characteristics of Included Studies for Key Question 2 (Pregnant and Postpartum Women)

Author, Year and Quality	N	Reference Standard	Pregnant or Postpartum	Weeks Postpartum	Country (Language)	Setting	% Positive for Depression per Reference Standard
Carpiniello, 1997[112] Fair	61	Clinically depressed by the PSE interview	Postpartum	4-6	Italy (Italian)	Other Community	14.8
Benvenuti, 1999[109] Fair	113	MINI DSM-III-R criteria for any depression	Postpartum	0.5	Italy (Italian)	OB-GYN	15.9
Yamashita, 2000[122] Fair	75	SADS diagnostic interview for minor or major depression	Postpartum	4	Japan (Japanese)	Primary Care	14.7
Bunevicius, 2009b[111] Fair	230	SCID-NP diagnosis of MDD during 1st trimester	Pregnant	1st, 2nd, 3rd trimester	Lithuania (Lithuanian)	OB-GYN	5
Bunevicius, 2009a[110] Fair	94	CIDI-SF diagnosis of depressive disorder	Postpartum	2	Lithuania (Lithuanian)	NR	14
Garcia-Esteve, 2003[101] Fair	1123	SCID diagnosis of MDD	Postpartum	6	Spain (Spanish)	OB-GYN	3.2
Alvarado, 2014[123] Fair	111	DSM-IV or ICD-9 diagnosis of MDD based on MINI interview	Pregnant	28 weeks gestation	Chile (Spanish)	Primary Care	34.2
Teng, 2005[119] Fair	199	MINI DSM-IV diagnosis of any depressive disorder	Postpartum	6	Taiwan (Taiwanese)	Other Community	11.8

Abbreviations: CIDI = Composite International Diagnostic Interview; DSM = Diagnostic and Statistical Manual; EPDS = Edinburgh Postnatal Depression Scale; MDD = major depressive disorder; MINI = Mini International Neuropsychiatric Interview; NP = non-patient; OB-GYN = obstetrics and gynecology; PHQ = Patient Health Questionnaire; PSE = Present State Examination; RDC = Research Diagnostic Criteria; SADS = Schedule for Affective Disorder and Schizophrenia; SCAN = Schedules for Clinical Assessment in Neuropsychiatry; SCID = Structured Clinical Interview for DSM Disorder; SPI = Standardized Psychiatric Interview.

Table 10. Population Characteristics of Included Studies for Key Question 2 (Pregnant and Postpartum Women)

Author, Year and Quality	Mean Age and Range (years)	Race/ Ethnicity (%)	SES	Depression History, n (%)
English EPDS				
Yawn, 2012[69] Fair	26.4 (≥ 18)	Black: 18 Hispanic: 12 White: NR	Uninsured at 2 months postpartum, n (%): 862 (36.8)	History of depression: 709 (30.3%)
Beck, 2001[108] Fair	31 (18-46)	Black: 8 Hispanic: 3.3 White: 86.7	No HS diploma, n (%): 3 (2)	Previous history of depression: 25 (16.7%)
Tandon, 2012[118] Fair	24.4 (NR)	Black: 100 Hispanic: NR White: NR	Single, n (%): 83 (95)	NR
Morrell, 2009a[99] Fair	NR (≥ 18)	Black: NR Hispanic: NR White: 95.3	Rent council or housing association, n (%): 547 (13.4)	Previous pregnancy w/ postnatal depression: 617 (15.1%)
Cox, 1996[100] Fair	25.4 (NR)	NR	Partner unemployed, n (%): 24 (10.3)	NR
Leverton, 2000[117] Fair	NR	NR	NR	NR
Harris, 1989[115] Fair	24.6 (17-40)	NR	NR	NR
Non-English EPDS				
Chen, 2013[113] Fair	30.4 (19-43)	Black: 0 Hispanic: 0 White: 0	Live in public housing, n (%): 469 (96)	NR
Lee, 2001[116] Fair	29 (16-42)	Black: 0 Hispanic: 0 White: 0	Unemployed, n (%): 13 (6)	NR
Guedeney, 1998[114] Fair	30.4 (20-42)	NR	Poor SES, n (%): 8 (9.19)	NR
Adouard, 2005[107] Fair	31.5 (23-46)	NR	Unemployed, n (%): 9 (15)	Past MDD episode: 3 (5%)
Toreki, 2013[120] Good	30.0 (17-42)	NR	Single, n (%): 2 (0.9)	NR
Toreki, 2014[121] Fair	30.5 (18-42)	NR	NR	NR
Carpiniello, 1997[112] Fair	31.6 (22-43)	NR	NR	Previous depressive episode: 1 (1.6%)
Benvenuti, 1999[109] Fair	31.9 (NR)	NR	Single, n (%): 3 (2.7)	NR
Yamashita, 2000[122] Fair	31 (19-41)	NR	III, IV, and V manual or unemployed partner occupation classification, n (%): 20 (23)	NR

Table 10. Population Characteristics of Included Studies for Key Question 2 (Pregnant and Postpartum Women)

Author, Year and Quality	Mean Age and Range (years)	Race/ Ethnicity (%)	SES	Depression History, n (%)
Bunevicius, 2009b[111] Fair	29 (18-43)	NR	Unemployed, n (%): 37 (16.1)	History of depression: 24 (10.4%)
Bunevicius, 2009a[110] Fair	29 (20-43)	NR	Employed or in school, n (%): 94 (100)	History of depression: 8 (8.5%)
Garcia-Esteve, 2003[101] Fair	30.2 (NR)	NR	NR	NR
Alvarado, 2014[123] Fair	25 (18-43)	NR	Unstable job, n (%): 9 (8.1)	NR
Teng, 2005[119] Fair	29 (16-41)	NR	Annual income < $300k NT, n (%): 6 (3.4)	NR

Abbreviations: EPDS = Edinburgh Postnatal Depression Scale; HS = high school; MDD = major depressive disorder; NR = not reported; NT = New Taiwan; SES = socioeconomic status.

Table 11. Calculated Positive and Negative Predictive Values of Included Studies for Key Question 2 (Pregnant and Postpartum Women), Based on Best Estimates for Sensitivity and Specificity of English-Language EPDS

EPDS Cutoff	Sensitivity	Specificity	Prevalence‡	PPV	NPV
13 (MDD)*	0.80	0.90	0.10	0.47	0.98
	0.80	0.95	0.10	0.64	0.98
	0.80	0.90	0.15	0.59	0.96
	0.80	0.95	0.15	0.74	0.96
10 (major or minor depression)†	0.63	0.85	0.10	0.32	0.95
	0.84	0.85	0.10	0.38	0.98
	0.63	0.85	0.15	0.43	0.93
	0.84	0.85	0.15	0.50	0.97

*For a cutoff of ≥13 (MDD): a) sensitivity of 0.80 chosen based on three studies that include the two largest studies and the two conducted in the United States[99,108,118]; b) specificity chosen as estimated range across all studies, largest study was an outlier with very low specificity, remaining studies all in the range of 0.90 to 0.99.
†For cutoff of ≥10 (major or minor depression): a) sensitivity estimates are highest and lowest reported among those used to detect major or minor depression; b) specificity chosen as mid-range of all studies, which ranged from 0.79 to 0.90 and was fairly evenly distributed.
‡Lower prevalence estimate chosen based on MDD prevalence in 2004–2005 NESARC data in postpartum women, high estimate based on 50% increase from that.

Abbreviations: EPDS = Edinburgh Postnatal Depression Scale; MDD = major depressive disorder; NPV = negative predictive value; PPV = positive predictive value.

Table 12. Study Characteristics of Included Studies for Key Question 4 (Pregnant and Postpartum Women)

Author, Year Quality	Design	N	Intervention	Weeks Postpartum at Baseline	Followup (mo)	Country	Setting	Invited to Screen (% Screened)	% Screened Positive for Depression	Definition of Screened Positive
CBT or Related Interventions										
McGregor, 2013[140] Fair	CCT	42	CBT	22 weeks gestation	4, 6	Canada	Primary Care	153 (96.1%)	30.6	EPDS > 9
Milgrom, 2011b[142] Fair	RCT	68	CBT	16	2	Australia	Primary Care + Psychology Clinic	NR	9.4	EPDS ≥ 13
Cooper, 2003[128,260] Good	RCT	193	CBT or psychodynamic or non-directive counseling	0	4, 9, 18	United Kingdom	Other Community	NR	6.4	EPDS ≥12 and systematically assessed as depressed
Prendergast, 2001[146] Fair	RCT	37	CBT	10	1.5, 8	Australia	Primary Care	NR	NR	EPDS >12 and meeting DSM-IV major and minor depression criteria
Kozinzky, 2012[138] Good	RCT	324	CBT - Related	27 weeks gestation	4.75	Hungary	Primary Care	2160 (81.6%)	18.4	Leverton Questionnaire score ≥11/12
Ammerman, 2013[124,261-264] Fair	RCT	93	CBT - Related	12	4.75, 7.75	United States	Other Community	1768 (70.1%)	24.7	EPDS ≥11
Honey, 2002[133] Fair	RCT	45	CBT - Related	22	2, 8	United Kingdom	Primary Care	NR	NR	EPDS >12
Milgrom, 2005[141] Fair	RCT	192	CBT (Coping with Depression Course) or CBT - Related	12	12	Australia	Other Community	NR	12.8	EPDS ≥12
Wiklund, 2010[148] Fair	RCT	67	CBT	0	2.75	Sweden	Primary Care	437 (67.3%)	22.8	EPDS ≥12 at 4 weeks postpartum

Table 12. Study Characteristics of Included Studies for Key Question 4 (Pregnant and Postpartum Women)

Author, Year Quality	Design	N	Intervention	Weeks Postpartum at Baseline	Followup (mo)	Country	Setting	Invited to Screen (% Screened)	% Screened Positive for Depression	Definition of Screened Positive
Other Behaviorally-Based Interventions										
Holden, 1989[132] Fair	RCT	55	Non-directive counseling	10	3.25	United Kingdom	Primary Care	NR	8.2	EPDS >12/13 6 weeks after delivery and met diagnostic criteria about 12 weeks after delivery
Wickberg, 1996[147] Fair	RCT	41	Non-directive counseling	12	1.5	Sweden	Primary Care	1874 (88.3%)	60.6	EPDS ≥12 twice (2 and 3 months postpartum), MADRS ≥10 and diagnosed according to DSM-III-R criteria for major depression
Segre, 2014[149] Fair	RCT	66	Non-directive counseling	NR	2	United States	Primary Care/Home Visits	NR	NR	EPDS score ≥12
Goodman, 2014[150] Fair	RCT	42	Perinatal dyadic psychotherapy	5	3, 6	United States	Home Visits	NR	7.3	EPDS score 10-19 at 4-6 weeks postpartum
Heh, 2003[131] Fair	RCT	70	Information support	6	1.5	Taiwan	Primary Care	500 (81.4%)	20	EPDS ≥10
Horowitz, 2001[134] Fair	RCT	122	Interaction coaching	6	1.5, 2.5	United States	Other Community	NR	10.0	EPDS ≥10 at 2-4 weeks postpartum
Stepped Care										
Gjerdingen, 2009[129] Fair	RCT	39	Stepped care	0	9	United States	Primary Care	1556 (32.5%)	8.9	SCID within 2 weeks of the 0-1 month survey; either a positive 2-question depression screen or 9-item PHQ-9 at a later interval; SCID-positive 0-6 months postpartum
Antidepressants										
Appleby, 1997[126] Fair	RCT	87	Fluoxetine + CBT	7	3	United Kingdom	Other Community	2978 (80.4%)	21	EPDS ≥10

Abbreviations: CBT = cognitive behavioral therapy; DSM = Diagnostic and Statistical Manual; EPDS = Edinburgh Postnatal Depression Scale; MADRS = Montgomery Asberg Depression Rating Scale; PHQ = Patient Health Questionnaire; RCT = randomized controlled trial; SCID = Structured Clinical Interview.

Table 13. Population Characteristics of Included Studies for Key Question 4 (Pregnant and Postpartum Women)

Author, Year Quality	Mean Age and Range (years)	Race/ Ethnicity (%)	SES	Depression History including Medication Use, n (%)
CBT or Related Interventions				
McGregor, 2013[140] Fair	NR (≥ 16)	NR	Annual household income $0-$19,999, n (%): 3 (7.1)	Past depression: 18 (42.9%) Current use of antidepressants: 0 (0%)
Milgrom, 2011b[142] Fair	31.5 (NR)	NR	Income < $40k, n (%): 13 (19.1)	NR
Cooper, 2003[128] Good	27.7 (17-42)	NR	High social disadvantage, n (%): 47 (24.7)	NR
Prendergast, 2001[146] Fair	32.2 (NR)	NR	Married, n (%): 34 (92)	Past treatment (had some form of counseling): 17 (45.9%) SSRI (not specified) use: 1 (2.7%)
Kozinzky, 2012[138] Good	27.3 (NR)	NR	Primary education, n (%): 230 (13.1)	NR
Ammerman, 2013[124] Fair	21.9 (16-37)	Black: 32.2 Hispanic: 7.5 White: 62.4	Income < $10k, n (%): 52 (55.9)	Recurrent depression: 69 (74.2%)
Honey, 2002[133] Fair	27.9 (NR)	NR	Married/cohabiting, n (%): 35 (77.8)	NR
Milgrom, 2005[141] Fair	29.7 (NR)	NR	Family income, mean (SD): 41400 (20500)	NR
Wiklund, 2010[148] Fair	NR	NR	Married, n (%): 64 (95.5)	Treatment for depression (not specified): 11 (16.4%)
Other Behaviorally- Based Interventions				
Holden, 1989[132] Fair	26.2 (NR)	NR	Single, n (%): 3 (6)	Previous depression: 21 (42%)
Wickberg, 1996[147] Fair	28.4 (NR)	NR	Educational level on Hollingshead Scale, mean: 3.5	Previous depression: 15 (36.6%)
Segre, 2014[149] Fair	26.3 (≥ 14)	Black: 33.3 Hispanic: 40.9 White: 33.3	Annual income < $5k, n (%): 10 (15.1)	MDD diagnosis: 20 (30.3%) Medication use for mood management: 11 (16.7%)
Goodman, 2014[150] Fair	30.7 (NR)	Black: NR Hispanic: 23.8 White: 59.5	Income < $40k, n (%): 5 (11.9)	Major or minor depression, n (%): 13 (31%) Depression treatment, n (%): 0 (0%)

Table 13. Population Characteristics of Included Studies for Key Question 4 (Pregnant and Postpartum Women)

Author, Year Quality	Mean Age and Range (years)	Race/ Ethnicity (%)	SES	Depression History including Medication Use, n (%)
Heh, 2003[131] Fair	27.1 (20-35)	NR	Monthly family income $30,000-$60,000, n (%): 9 (12.9)	NR
Horowitz, 2001[134] Fair	31 (17-41)	Black: 7.4 Hispanic: 7.4 White: 68.9	Annual household income < $50k, n (%): 35 (29)	NR
Stepped Care				
Gjerdingen, 2009[129] Fair	27.6 (≥ 16)	NR	Total family income < $40,000, n (%): 29 (74.4)	NR
Antidepressants				
Appleby, 1997[126] Fair	25.3 (NR)	NR	Unemployed, n (%): 66 (75.9)	History of postnatal depression: 30 (34.5%)

Abbreviations: CBT = cognitive behavior therapy; NR = not reported; SD = standard deviation; SES = socioeconomic status.

Table 14. Study Characteristics of Included Observational Studies for Key Question 5 (Pregnant Women)

Author, Year Quality	Study Design	N	Country	Pertinent Outcomes	Pertinent Agents	Exposure Groups	Exposure Group Description
Palmsten, 2013a[144] Good	Cohort	85,326	United States	Preeclampsia	2nd generation AD	Exposed (n=26,107)	AD dispensing between gestational days 90-225
						Nonexposed (n=59,219)	No AD dispensed between LMP and gestational day 225, *OR* first preeclampsia diagnosis occurred before first AD dispensing
Palmsten, 2013b[143] Good	Cohort	102,722	United States	Postpartum hemorrhage	2nd generation AD	Current exposure (n=14,205)	Women w/ a supply of antidepressants that overlapped w/ delivery date
						Recent exposure (n=6,925)	Women w/ a supply of AD on at least 1 day in the month before delivery date but not on a delivery date
						Past exposure (n=12,548)	Women w/ a supply of AD ending between 5 and 1 months before delivery
						Nonexposed (n=69,044)	Women who had no supply of AD in the 5 months before delivery
Lupattelli, 2014[139] Fair	Cohort	57,279	Norway	Postpartum hemorrhage, vaginal bleeding	2nd generation AD	Exposed (first trimester) (n=427)	Women who used SSRI or SNRI during first trimester
						Exposed (second trimester) (n=222)	Women who used SSRI or SNRI during second trimester
						Exposed (week 30 to birth) (n=123)	Women exposed to SSRI or SNRI from week 30 to childbirth
						Depressed-nonexposed (n=1,282)	Depressed women as assessed at both 17 and 30 weeks gestation with no AD use during any trimester of pregnancy
						Not depressed-nonexposed (n=55,411)	Women without diagnosed depression during pregnancy and no AD use during pregnancy
						Nonexposed (first trimester) (n=55,533)	Women with no AD use during the first trimester of pregnancy; may have had exposure in 2nd and 3rd trimesters
						Nonexposed (second trimester) (n=55,750)	Women with no AD use during the second trimester of pregnancy; may have had exposure during 1st and 3rd trimesters
						Nonexposed (week 30 to birth) (n=55,862)	Women not exposed to AD from week 30 of pregnancy to childbirth

Table 14. Study Characteristics of Included Observational Studies for Key Question 5 (Pregnant Women)

Author, Year Quality	Study Design	N	Country	Pertinent Outcomes	Pertinent Agents	Exposure Groups	Exposure Group Description
Andersen, 2014[125] Good	Cohort	1,279,840	Denmark	Miscarriage	SSRI	Exposed (n=22,884)	Pregnant women exposed to any SSRI during the first 35 days of pregnancy and with continuous exposure pre-pregnancy.
						Nonexposed (n=1,256,956)	Pregnant women not exposed to SSRIs during the first 35 days of pregnancy
						Previous exposure (n=14,016)	Women exposed to SSRIs 3-12 months before pregnancy but not during pregnancy or 3 months pre-pregnancy
Kjaersgaard, 2013[137] Good	Cohort	1,005,319	Denmark	Spontaneous abortion	2nd generation AD	Depressed-exposed (n=1,674)	AD prescription redeemed at any time from 30 days before conception to 1 day before end of pregnancy; depression diagnosis anytime between 6 months prior to conception and 1 day before end of pregnancy
						Not depressed-exposed (n=13,789)	AD prescription redeemed from 6 months before conception to 1 day before pregnancy; not depressed
						Exposed (n=15,463)	Combines depressed and non-depressed with AD prescriptions
						Depressed-nonexposed (n=820)	No AD prescription redeemed from 6 months before conception to 1 day before pregnancy end; depression diagnosis anytime between 6 months prior to conception and 1 day before end of pregnancy
						Not depressed-nonexposed (n=818,426)	No prescription redeemed from 6 months before conception up to 1 day before pregnancy end; not depressed
						Nonexposed (n=819,246)	Combines depressed and non-depressed with no AD prescriptions
Hayes, 2012[130] Good	Cohort	228,876	United States	Gestational age, neonatal convulsions, respiratory distress	2nd generation AD	Depressed- Any prescriptions (n=16,896)	Depressed women w/ at least 1 prescription during pregnancy
						Depressed- 1 prescription (n=NR)	Depressed women w/ 1 prescription filled during pregnancy
						Depressed- 2 prescriptions (n=NR)	Depressed women w/ 2 prescriptions filled during pregnancy
						Depressed- ≥ 3 prescriptions (n=6,196)	Depressed women who filled at least 3 AD prescriptions during pregnancy
						Depressed-nonexposed (n=16,901)	Depressed women w/out AD prescriptions during pregnancy

Table 14. Study Characteristics of Included Observational Studies for Key Question 5 (Pregnant Women)

Author, Year Quality	Study Design	N	Country	Pertinent Outcomes	Pertinent Agents	Exposure Groups	Exposure Group Description
						Not depressed-nonexposed (n=195,079)	Non-depressed women w/out AD prescriptions during pregnancy
						Nonexposed (n=NR)	All women, depressed and non-depressed, who did not have any AD prescriptions during pregnancy
Jensen, 2013a[136] Good	Cohort	673,853	Denmark	Small for gestational age	2nd generation AD	Depressed-exposed (n=166)	Women with diagnosis of depression during pregnancy and who used AD during pregnancy, but not pre-pregnancy
						Depressed-exposed (pre- and during pregnancy) (n=1,134)	Women w/ diagnosis of depression during pregnancy and who used AD both pre- and during pregnancy
						Exposed (n=8,511)	Cashed a prescription of AD during pregnancy, 1st trimester (n=7,510), 2nd trimester (n=3,837), and 3rd trimester (n=3,300)
						Exposed- SSRI (n=NR)	Filled a prescription for an SSRI during pregnancy
						Depressed-nonexposed (n=1,926)	Women diagnosed w/ depression during pregnancy but who did not use any AD during pregnancy, but who did use AD pre-pregnancy; risk group 6
						Depressed-nonexposed (pre- or during pregnancy) (n=740)	Women diagnosed w/ depression during pregnancy but who did not use any AD either pre- or during pregnancy; risk group 5
						Not depressed-nonexposed (n=638,116)	All pregnancies where there was no maternal diagnosis of depression before pregnancy end and no AD use either pre- or during pregnancy, risk group 1
Ban, 2014[127] Good	Cohort	349,127	United Kingdom	Major congenital malformations	SSRI	Depressed-exposed (n=7,683)	Women who were depressed and had an SSRI prescription recorded in their medical record between 4 weeks before and 12 weeks after the first day of the LMP (first trimester)
						Depressed-nonexposed (n=13,432)	Women who had a diagnosis of depression but no documented prescriptions for AD in first trimester
						Not depressed-nonexposed (n=325,294)	Women who had no depression diagnosis recorded and no AD prescriptions in first trimester

Table 14. Study Characteristics of Included Observational Studies for Key Question 5 (Pregnant Women)

Author, Year Quality	Study Design	N	Country	Pertinent Outcomes	Pertinent Agents	Exposure Groups	Exposure Group Description
Polen, 2013[145] Fair	Case-control	27,045	United States	Birth defects (anencephaly, cleft palate, gastroschisis, specified heart defects)	Venlafaxine	Cases (n=91)	Mothers w/ pregnancies affected by one of 30 selected birth defects
						Cases (2003-2007) (n=69)	Mothers w/ pregnancies affected by one of 30 selected birth defects in years 2003-2007
						Controls (n=26,954)	Mothers of babies w/out birth defects
						Controls (2003-2007) (n=13,462)	Mothers of babies w/out birth defects in years 2003-2007
Yazdy, 2014[151]	Case-control	2,624	United States	Clubfoot	SSRI	Cases-Depressed, Exposed > 30 days (n=33)	Depressed cases exposed to SSRI for more than 30 days during lunar months 2-3 of pregnancy
						Cases- Not Depressed, Nonexposed (n=477)	Non-depressed cases, not exposed to SSRI during pregnancy
						Controls-Depressed, Exposed > 30 days (n=58)	Depressed controls exposed to SSRI for more than 30 days during lunar months 2-3 of pregnancy
						Controls- Not Depressed, Nonexposed (n=1,650)	Non-depressed controls, not exposed to SSRI during pregnancy
Louik, 2014[152] Good	Case-control	16,524	United States	Cardiac malformations	SSRI	Cases- exposed (n=NR)	Among cases, any exposure with or without other antidepressants occurring between 28 days prior to LMP to the fourth lunar month
						Cases-nonexposed (n=NR)	Among cases, women with no exposure to any antidepressant at any time from 56 days prior to LMP to the end of pregnancy
						Controls-exposed (n=NR)	Among controls, any exposure with or without other antidepressants occurring between 28 days prior to LMP to the fourth lunar month which includes 39 exposed to bupropion, 290 to SSRIs, and 81 to other antidepressants
						Controls-nonexposed (n=NR)	Among cases, women with no exposure to any antidepressant at any time from 56 days prior to LMP to the end of pregnancy

Table 14. Study Characteristics of Included Observational Studies for Key Question 5 (Pregnant Women)

Author, Year Quality	Study Design	N	Country	Pertinent Outcomes	Pertinent Agents	Exposure Groups	Exposure Group Description
Huybrechts, 2014[135] Good	Cohort	931,259	United States	Cardiac malformations	2nd generation AD	Depressed-exposed (n=36,783)	Exposed from LMP through 90 days pregnancy (1st trimester); depressed patients using SSRIs.
						Exposed (n=46,144)	Exposed to SSRI from LMP through 90 days pregnancy (1st trimester)
						Depressed-nonexposed (n=180,561)	Depressed, No exposure to ADs during 1st trimester of pregnancy
						Nonexposed (n=885,115)	No exposure to ADs during 1st trimester

Abbreviations: AD = antidepressants; ICD = International Classification of Disease; LMP = last menstrual period; MoBa = Norwegian Mother and Child Cohort Study; NR = not reported; SNRI = selective norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; w/ = with.

Table 15. Population Characteristics of Included Observational Studies for Key Question 5 (Pregnant Women)

Author, Year Quality	Mean Age and Range (years)	Race/Ethnicity (%)	SES	Depression History, n (%)	Antidepressant Use, n (%)
Palmsten, 2013a[144] Good	23.7 (12-55)	Black: 22.5 Hispanic: 11.8 White: 58.9	Medicaid, n (%): 85326 (100)	Inpatient depression diagnosis: 5598 (6.6%), Depression diagnosis: 85326 (100%)	Antidepressant: 26107 (30.6%)
Palmsten, 2013b[143] Good	23.5 (12-55)	Black: 19.2 Hispanic: 10.3 White: 63.9	Medicaid enrollee, n (%): 102722 (100)	NR	Current antidepressant use: 14205 (13.8%)
Lupattelli, 2014[139] Fair	NR (NR)	NR	Primary education, n (%): 1390 (2.4)	Lifetime history of depression: 18597 (32.5%)	AD use during pregnancy: 527 (0.9%)
Andersen, 2014[125] Good	NR (NR)	NR	Income, Lowest quartile, n (%): 313747 (25)	NR	AD use during first 35 days of pregnancy: 22884 (1.8%)
Kjaersgaard, 2013[137] Good	30.2 (NR)	NR	Income 0-20%, n (%): 199318 (19.9)	NR	Use of AD: 22061 (2.2%)
Hayes, 2012[130] Good	23.2 (15-44)	Black: 41.7 Hispanic: NR White: 55.7	Education < 12 years, n (%): 96170 (42.1)	Depression diagnosis pre-pregnancy: 13593 (5.9%)	Used AD on date of delivery through date of deliver + 90 days: 17773 (7.8%)
Jensen, 2013a[136] Good	29 (NR)	NR	NR	Documented diagnosis of depression: 3966 (0.6%)	AD use during pregnancy: 8511 (1.3%)
Ban, 2014[127] Good	30 (14-45)	NR	Townsend deprivation index (1- least deprived), n (%): 85160 (24.4)	NR	NR
Polen, 2013[145] Fair	NR (NR)	Black: NR Hispanic: NR White: 58.6	≤ HS education, n (%): 11613 (42.9)	NR	Venlafaxine during pregnancy: 91 (0.3%)
Yazdy, 2014[151]	NR (NR)	Black: 15.8 Hispanic: 11.9 White: 67	Education < 12 years, n (%): 355 (13.5)	Self-reported depression 1 month pre- or during pregnancy: 497 (18.9%)	NR
Louik, 2014[152] Good	NR (NR)	NR	NR	NR	NR
Huybrechts, 2014[135] Good	24.0 (NR)	Black: 34.2 Hispanic: 18.1 White: 40.1	NR	Diagnosed depression: 217347 (23.3%)	NR

Abbreviations: AD = antidepressants; HS = high school; NR = not reported; SES = socioeconomic status.

Table 16. Summary of Adjusted* Results of Maternal Harms With Second-Generation Antidepressant Use During Pregnancy for Key Question 5 (Pregnant Women)

Outcome Conclusion	AHRQ Review[91]	Included Observational Studies
Serotonin syndrome	Not addressed	Not addressed
Cardiac effects	Not addressed	Not addressed
Seizures (bupropion only)	Not addressed	Not addressed
Suicidality	Insufficient evidence	Not addressed
Gestational diabetes / metabolic effects	Weight gain: insufficient evidence Other metabolic outcomes: not addressed	Not addressed
Preeclampsia *Conclusion: Possible association with venlafaxine*	Not addressed	Depressed Women (Palmsten 2013a)[144] Increased risk • Venlafaxine (n=1,113): RR, 1.57 (95% CI, 1.29 to 1.91) No association: citalopram (n=1,680), escitalopram (n=1,936), fluoxetine (n=299), paroxetine (n=3,517), sertraline (n=7,143), duloxetine (n=NR), mirtazapine (n=253), trazodone (n=339)

Table 16. Summary of Adjusted* Results of Maternal Harms With Second-Generation Antidepressant Use During Pregnancy for Key Question 5 (Pregnant Women)

Outcome Conclusion	AHRQ Review[91]	Included Observational Studies

Vaginal bleeding / postpartum hemorrhage
 	
Conclusion: Possible association with SSRIs and SNRIs
	Depressed Women: No evidence
	
	Unknown Depression Status (k=1, n=26,403)
	Increased risk
	• SSRIs
	  • 60-day exposure (n=423): OR, 1.40 (95% CI, 1.04 to 1.88)
	  • 180-day exposure (n=626): OR, 1.32 (95% CI, 1.03 to 1.70)
	
	No association:
	• SSRIs, 30-day exposure (n=310) or 90-day exposure (n=501)
	• Non-SSRIs, 30-day exposure (n=64), 60-day exposure (n=92), 90-day exposure (n=123), or 180-day exposure (n=167)
		Depressed Women (Palmsten 2013b)[143]
		Increased risk
		• SSRI+venlafaxine, current (n=8,917): RR, 1.46 (95% CI, 1.29 to 1.65)
		• SSRI+venlafaxine, recent (n=4,344): RR, 1.28 (95% CI, 1.08 to 1.52)
		• Atypical antidepressant, current (n=1,012): RR, 1.52 (95% CI, 1.12 to 2.06)
		
		No association
		• SSRI+venlafaxine, past (n=7,432)
		• Atypical antidepressant, recent (n=616)
		• Atypical antidepressant, past (n=1460)
		
		All women Control Group, controlling for depression status
		Increased risk (Palmsten 2013b)[143]
		• Citalopram, current (n=891): RR, 1.48 (95% CI, 1.07 to 2.04)
		• Escitalopram, current (n=1,022): RR, 1.56 (95% CI, 1.16 to 2.09)
		• Fluoxetine, current (n=3,322): RR, 1.51 (95% CI, 1.27 to 1.79)
		• Paroxetine, current (n=2,055): RR, 1.36 (95% CI, 1.09 to 1.71); recent (n=962): adjusted RR, 1.52 (95% CI, 1.12 to 2.07)
		• Sertraline, current (n=4,526): RR, 1.31 (95% CI, 1.12 to 1.54); recent (n=2,266): RR, 1.27 (95% CI, 1.01 to 1.59)
		• Venlafaxine, current (n=763): RR, 2.24 (95% CI, 1.69 to 2.97)
		• Bupropion, past (n=1,666): RR, 1.33 (95% CI, 1.03 to 1.71)
		
		No association: (Lupatelli 2014;[139] Palmsten 2013b[143])
		• SSRI+SNRI, week 30 or later (n=122)[139], second trimester (n=222)[139], first trimester (n=427)[139]
		• Mirtazapine, current (n=129) or past (n=135)[143]
		• Trazodone, current (n=139), recent (n=73), or past (n=226)[143,143]

Table 16. Summary of Adjusted* Results of Maternal Harms With Second-Generation Antidepressant Use During Pregnancy for Key Question 5 (Pregnant Women)

Outcome Conclusion	AHRQ Review[91]	Included Observational Studies
Miscarriage/ spontaneous abortion *Conclusion: Possible association with SNRIs, SSRIs in 1st trimester, particularly paroxetine*	Depressed Women (k=1, n=512,574) Increased risk • SSRIs, first trimester (n=1,539): RR, 1.4 (99% CI, 1.2 to 1.7) Unknown Depression Status (k=1, n=5,124) Increased risk • SSRIs (n=NR): OR, 1.60 (95% CI, 1.28 to 2.04) • Paroxetine (n=569): OR, 1.75 (95% CI, 1.31 to 2.34) • Venlafaxine (n=161): OR, 2.11 (95% CI, 1.34 to 3.30) No association: citalopram (k=1, n=NR), fluvoxamine (k=1, n=NR), fluoxetine (k=1, n=NR), sertraline (k=1, n=NR).	Depression Women (Kjaersgaard 2013)[137] Increased risk • Venlafaxine (n=NR): RR, 1.80* (95% CI, 1.19 to 2.72) • Duloxetine (n=NR): RR, 3.12* (95% CI, 1.55 to 6.31) • Mirtazapine (n=NR): RR, 2.23* (95% CI, 1.34 to 3.70) No association (n=NR for all): fluoxetine, citalopram, escitalopram, paroxetine, sertraline, Unknown Depression Status (Andersen 2014)[125] Increased risk (exposure during first 35 days of pregnancy) • Citalopram (n=9,927): HR, 1.29 (95% CI, 1.21 to 1.27) • Escitalopram (n=2,377): HR, 1.25 (95% CI, 1.09 to 1.42) • Fluoxetine (n=4,111): HR, 1.10 (95% CI, 1.01 to 1.21) • Paroxetine (n=2,739): HR, 1.27 (95% CI, 1.14 to 1.42) • Sertraline (n=4,453): HR, 1.45 (95% CI, 1.33 to 1.58) • For all SSRIs above, risk was also increased with use ≥3 months pre-pregnancy (and discontinued ≥3 months before pregnancy)

*Unadjusted results.

Abbreviations: AHRQ = Agency for Healthcare Research and Quality; CI = confidence interval; HR = hazard ratio; NR = not reported; OR = odds ratio; RR = relative risk; SNRI = selective norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors.

Table 17. Summary of Adjusted* Results of Infant Harms With Second-Generation Antidepressant Use During Pregnancy for Key Question 5 (Pregnant Women)

Outcome Conclusion	AHRQ Review[91]	Included Observational Studies
Perinatal death *Conclusion: Possible association with SSRIs*	Unknown Depression Status Increased risk Within first year of life (k=1, n=98,325): • Escitalopram (n=NR): OR, 3.52 (95% CI, 1.30 to 9.49) • Fluvoxamine (n=NR): OR, 4.52 (95% CI, 1.44 to 14.24) • Paroxetine (n=NR): OR, 2.18 (95% CI, 1.03 to 4.61) Within 28 days of birth (k=1, n=920,620): • Citalopram (n=1,800): OR, 2.49 [1.33 to 4.65] No association: • Within first year of life: citalopram (n=NR), fluoxetine (n=NR), sertraline (n=NR) • Within 28 days of birth escitalopram (n=NR), fluoxetine (n=NR), paroxetine (n=NR), sertraline (n=NR); 28-365 days after birth (k=2, n=NR): SSRIs as class	Not addressed
Pre-term birth / gestational age *Conclusion: Possible association with SSRIs in first two trimesters and SNRIs*	Depressed Women No association: SSRIs (k=2, n=NR): pooled OR*, 1.87 (95% CI, 0.89 to 3.89) Unknown Depression Status Increased risk: • SSRIs (k=11, n=NR, OR NR) • SSRIs in 1st trimester (k=1, n=NR): OR, 11.7 (95% CI, 2.2 to 60.70) • SSRIs in 3rd trimester (k=1, n=NR): OR, 2.46 (95% CI, 1.75 to 3.50) • Citalopram (k=4, n=NR): OR, NR • Escitalopram (k=4, n=NR): OR, NR • SNRIs, bupropion (k=2, n=NR): pooled OR, 1.79 (95% CI, 1.46 to 2.19), I^2=NR No association: fluoxetine (k=4, n=NR), paroxetine (k=8, n=NR), sertraline (k=2,n=NR)	Depressed Women: (Hayes 2012)[130] Increased risk: • Any antidepressant (mostly SSRIs), % born gestational weeks 32-36: 1-2 prescriptions (n=10,700): OR 1.91*, (95% CI, 1.77 to 2.07) 3+ prescriptions (n=6,196): OR 1.12*, 95% CI, 1.03 to 1.23) Unknown Depression Status in Control Group (Hayes 2012, N=228,876)[130] Increased risk: • SSRIs in 2nd trimester (mean difference in days, n=NR for all, nulliparous women): ▪ 1 prescription: -2.6 (95% CI, -1.3 to -3.9) ▪ 2 prescriptions: -5.8 (95% CI, -3.8 to -7.8) ▪ 3+ prescriptions: -6.6 (95% CI, -4.6 to -8.6) Decreased risk: • SSRIs in 3rd trimester (mean difference in days, n=NR for all, nulliparous women): ▪ 1 prescription: 0.9 (95% CI, 0.3 to 1.6) ▪ 2 prescriptions: 1.8 (95% CI, 0.9 to 2.7) ▪ 3+ prescriptions: 6.4 (95% CI, 5.5 to 7.3)

Table 17. Summary of Adjusted* Results of Infant Harms With Second-Generation Antidepressant Use During Pregnancy for Key Question 5 (Pregnant Women)

Outcome Conclusion	AHRQ Review[91]	Included Observational Studies
Low birth weight / Small for gestational age (SGA) *Conclusion: Possible association with SSRIs*	Depressed Women: No evidence Depressed Women vs. Not Depressed + No SSRI Increased risk • SSRIs: increased risk of smaller head circumference (k=1, n=5,502, n=NR): -5.9 mm (95% CI, -11.5 to -0.3) Unknown Depression Status No association with low birth weight: SSRIs:(k=5, n=NR) Insufficient evidence: SNRIs/NRIs	Depressed Women: No evidence All Women, Controlling for Depression Status (Jensen 2013)[136] Increased risk • SSRIs during pregnancy (n=NR): HR, 1.22 (95% CI, 1.13 to 1.32) • 2nd generation non-SSRIs before pregnancy (n=NR): HR, 1.14 (95% CI, 1.05 to 1.24) No association: • SSRIs before pregnancy (n=NR), • 2nd generation non-SSRIs during pregnancy (n=NR)
Seizures/ convulsions *Conclusion: Possible association with SSRIs*	Depressed Women No association: • SSRIs (k=1, n=NR): 0.14% exposed vs. 0.09%, risk difference 0.0005 (95% CI, -0.0015 to 0.0025); RR*, 1.56 (95% CI, NR) Unknown Depression Status Increased risk: • SSRIs (k=7, n=NR): pooled OR*, 4.11 (95% CI, 1.78 to 9.48, I^2=NR)	Depressed Women: (Hayes 2012)[130] Increased risk: • Any antidepressant (mostly SSRIs): 3+ prescriptions (n=6,196): OR 2.39*, (95% CI, 1.57 to 3.64) No association: 1-2 prescriptions (n=10,700) Unknown Depression Status in Control Group (Hayes 2012, N=228,876)[130] Increased risk: • SSRIs 3rd trimester: 2 prescriptions (n=NR): OR, 2.8 (95% CI, 1.4 to 5.5); 3+ prescriptions (n=NR): OR, 4.9 (95% CI, 2.6 to 9.5) No association • SSRIs 3rd trimester, 1 prescription (n=NR)
Serotonin withdrawal (discontinuation) syndrome *Conclusion: Possible association with SSRIs and SNRIs*	Depressed Women: No evidence Unknown Depression Status Increased risk: • SSRI (k=1, n=120): increased risk of Finnegan severe score of ≥8 (13% vs. 0%, p=NR); increased risk of any symptoms of withdrawal (30% vs. 0%, p=NR) • Fluoxetine (k=1, n=482): increased risk of poor neonatal adaptation, RR, 8.7 (95% CI, 2.9 to 26.6) • SSRI or venlafaxine during 3rd trimester (k=1, n=166): increased risk of neonatal behavioral signs, OR, 3.1 (95% CI, 1.3 to 7.1) • SSRI or SNRI (k=1, n=56): increased risk of elevated Finnegan neonatal abstinence score (2 vs. 0, p<0.05) No association: SSRIs as class (k=1, n=108)[265]	Not addressed

Table 17. Summary of Adjusted* Results of Infant Harms With Second-Generation Antidepressant Use During Pregnancy for Key Question 5 (Pregnant Women)

Outcome Conclusion	AHRQ Review[91]	Included Observational Studies
Neonatal respiratory distress *Conclusion: Possible association with SSRIs*	Depressed Women Increased risk: • SSRIs (k=3, n=NR): pooled OR*, 1.91 (95% CI, 1.63 to 2.24), I^2=0% Unknown Depression Status Increased risk: • SSRIs (k=4, n=748,658): pooled OR, 1.79 (95% CI, 1.64 to 1.97), I^2=0%	Depressed Women: (Hayes 2012)[130] Increased risk: • Any antidepressant (mostly SSRIs): 3+ prescriptions (n=6,196): OR 1.18*, (95% CI, 1.04 to 1.35) No association: 1-2 prescriptions (n=10,700) Unknown Depression Status in Control Group (Hayes 2012)[130] Increased risk: • SSRIs, 2nd trimester: 2 prescriptions (n=NR): OR, 1.4 (95% CI, 1.1 to 1.8); 3+ prescriptions (n=NR): OR, 1.6 (95% CI, 1.2 to 2.0) Decreased risk: • SSRIs, 3rd trimester, 3+ prescriptions (n=NR): OR, 0.6 (95% CI, 0.5 to 0.8) No association: • SSRIs, 2nd trimester, 1 prescription (n=NR); 3rd trimester, 1 or 2 prescriptions (n=NR)
Pulmonary hypertension *Conclusion: Possible association with SSRIs, particularly late in pregnancy*	Unknown Depression Status Increased risk: • SSRIs o Any time during pregnancy (k=3, n=NR): pooled OR, 2.41 (95% CI, 1.47 to 3.95), I^2=14% o Late exposure (generally ≥20 weeks) (k=3, n=NR): pooled OR, 2.72 (95% CI, 1.63 to 4.54), I^2=14% No association (but high heterogeneity in pooled estimate): • SSRIs, early exposure (not defined) (k=4, n=NR)	Not addressed
Major Malformations *Conclusion: Possible association with SSRIs*	Depressed Women Insufficient evidence (k=3, n=NR) Unknown Depression Status Increased risk: • Fluoxetine (k=7, n=NR): pooled OR, 1.14 (95% CI, 1.01 to 1.30), I^2=0% • Paroxetine (k=8, n=NR): pooled OR, 1.17 (95% CI, 1.02 to 1.35), I^2=0% No association: SSRIs (k=6, n=NR), citalopram or escitalopram (k=8, n=NR), fluvoxamine (k=2, n=NR), sertraline (k=7, n=NR)	Depressed Women (Ban 2014; Yazdy)[127,151] Increased risk (Yazdy 2014; n=2,624): • SSRIs: increased risk of SSRI use in the 2nd or 3rd month of pregnancy for mothers of infants born with clubfoot: adjusted OR, 1.8 (95% CI, 1.1 to 2.8). • Escitalopram: increased risk of use in 2nd or 3rd month of pregnancy for mothers of infants born with clubfoot: adjusted OR, 2.9 (95% CI, 1.1 to 7.2) No association: citalopram (n=1,946), escitalopram (n=333), fluoxetine (n=3,189), paroxetine (n=1,200), sertraline (n=757)

Table 17. Summary of Adjusted* Results of Infant Harms With Second-Generation Antidepressant Use During Pregnancy for Key Question 5 (Pregnant Women)

Outcome Conclusion	AHRQ Review[91]	Included Observational Studies
Cardiac malformations *Conclusion: Possible association with bupropion, paroxetine and venlafaxine*	Depressed Women: No evidence Unknown Depression Status Increased risk: • Paroxetine (k=5, n=NR): pooled OR, 1.45 (95% CI, 1.13 to 1.85), I^2=0% No association: SSRIs (k=5, n=NR), citalopram or escitalopram (k=6, n=NR), fluoxetine (k=5, n=NR), fluvoxamine (k=3, n=NR), sertraline (k=4, n=NR)	Depressed Women (Ban 2014;[127] Huybrechts 2014[135]) Increased risk: • Paroxetine in 1st trimester (n=1,200): adjusted OR, 1.67 (95% CI, 1.00 to 2.80)[127] No association: SSRIs (k=2; N=44,461), citalopram (n=1,946),[127] escitalopram (n=333),[127] fluoxetine (k=2; n=11,853),[127] paroxetine (n=8,748),[135] sertraline (k=2; n=11,813),[135] SNRIs (n= 6,010),[135] bupropion (n=8,748)[135] Unknown Depression Status (Polen 2013; Louik 2014)[145,152] Increased risk: • Bupropion: Increased risk of bupropion use in 1st trimester for mothers of infants with ventricular septal defects (n=16,524): adjusted OR, 2.5 (95% CI, 1.3 to 5.0)[152] • Venlafaxine: Increased risk of venlafaxine use pre- and in early pregnancy for mothers of infants with atrial septal defects: adjusted OR, 3.1 (95% CI, 1.3 to 7.4)[145]

*Unadjusted results.

Abbreviations: AHRQ = Agency for Healthcare Research and Quality; CI = confidence interval; HR = hazard ratio; NR = not reported; OR = odds ratio; RR = relative risk; SNRI = selective norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors.

Table 18. Study Characteristics of Included Studies for Key Questions 1 and 2 (General and Older Adults)

Author, Year and Quality	KQ1	Study Design	N	Intervention	Followup (mo)	Country	Setting	Invited to Screen (% Screened)	% Screened Positive for Depression	Definition of Screened Positive
General Adults										
Williams, 1999[154] Fair	KQ1	RCT	969	Case-finding (20-item or 1 item)	3	United States	Primary Care	NR	37.1	"Yes" on single-item screen or CES-D ≥ 16
Bergus, 2005[72] Fair	KQ1a	RCT	59	Screening results to provider	2, 6	United States	Primary Care	951 (90.5%)	13.8	Positive on either of first 2 items of PHQ-9
Jarjoura, 2004[157] Fair	KQ1a	RCT	61	Screening results + treatment protocol	12	United States	Primary Care	NR	45.4	Positive response on either of two PRIME-MD depression items
Rost, 2001[73,266,267] Good	KQ1a	Cluster RCT	479	Screening results + provider training & supports	6, 12, 24	United States	Primary Care	11006 (84.4%)	5.9	WHO-CIDI-positive and IDD ≥ 5
Wells, 2000[155,268,269] Fair	KQ1a	RCT	1356	Screening results, provider training & support, CBT or medication support	6, 12, 24, 57	United States	Primary Care	33932 (80.5%)	14.3	Positive on WHO CIDI-2
Older Adults										
van der Weele, 2012[158] Good	KQ1a	Cluster RCT	239	Screening results + referral for stepped care	6, 12	Netherlands	Primary Care/Home-based Screening	10681 (52.8%)	9.4	GDS-15 ≥ 5
Whooley, 2000[156] Fair	KQ1a	Cluster RCT	331	Screening results + provider training + psycho-education course	24	United States	Primary Care	2896 (81.0%)	14.1	GDS ≥ 6
Bijl, 2003[159,270] Fair	KQ1a	Cluster RCT	145	Screening results + provider training	6, 12	Netherlands	Primary Care	NR	17.2	GDS ≥ 5
Callahan, 1994[153] Fair	KQ1a	Cluster RCT	175	Screening results + provider support	6, 9	United States	Primary Care	4413 (85.4%)	16.2	CES-D ≥ 16 + HAM-D ≥ 15

Abbreviations: CBT = cognitive behavioral therapy; CES-D: Center for Epidemiologic Studies Depression; CIDI = Composite International Diagnostic Interview GDS = Geriatric Depression Scale; HAM-D: Hamilton Depression Rating Scale; IDD = Inventory to Diagnose Depression; KQ = Key Question; NR = not reported; RCT = randomized controlled trial; PHQ = Patient Health Questionnaire; PRIME-MD: Primary Care Evaluation of Mental Disorders; WHO = World Health Organization.

Table 19. Population Characteristics of Included Studies for Key Questions 1 and 2 (General and Older Adults)

Author, Year and Quality	Mean Age and Range (years)	% Female	Race/Ethnicity (%)	SES	Depression History including Treatment, n (%)
General Adults					
Williams, 1999[154] Fair	58 (≥ 18)	71	Black: 10.4 Hispanic: 59.3 White: 29	Annual income < $7,200, n (%): 339 (39.3)	Known depressed at BL: 115 (13.3%)
Bergus, 2005[72] Fair	41.0 (NR)	66.7	Black: NR Hispanic: NR White: 94.1	Some college, n (%): 26 (51.0)	Prior treatment for depression: 31 (60.8%) Current medication for depression or anxiety: 17 (33.3%)
Jarjoura, 2004[157] Fair	45 (24-67)	68.9	NR	Medicaid or uninsured + below poverty line, n (%): 61 (100)	Treated for depression or other MH issue at BL: 0 (0%)
Rost, 2001[73] Good	42.6 (> 18)	83.9	Black: NR Hispanic: NR White: 84.3	Income, mean: 10408	Recently treated: 243 (50.7%) On antidepressants in the month preceding index visit: 177 (56%)
Wells, 2000[155] Fair	43.7 (> 18)	72.3	Black: 6.9 Hispanic: 29.2 White: 57.4	< HS education, n (%): 220 (16.2)	Lifetime depressive disorder status: 1093 (80.6%) Antidepressant use at BL: 372 (27.4%)
Older Adults					
van der Weele, 2012[158] Good	80 (≥ 75)	72.4	NR	Income only social security, n (%): 40 (16.7)	DSM-IV diagnosis presented: 105 (43.9%) Treated for depression: 0 (0%)
Whooley, 2000[156] Fair	75.8 (≥ 65)	60.7	Black: 32.6 Hispanic: 4.5 White: 43.9	HS graduate, n (%): 167 (81.3)	Antidepressant use past 12 months: 66 (19.9%)
Bijl, 2003[159] Fair	65.6 (≥ 55)	57.2	NR	Education none-low, n (%): 90 (62)	Previous depression: 120 (82.8%) Current use of antidepressants: 0 (0%)
Callahan, 1994[153] Fair	65.3 (≥ 60)	76	Black: 51.4 Hispanic: NR White: NR	Education (years), mean: 8.8	Depression diagnosis (recorded as outpatient diagnosis): 36 (20.6%) On antidepressant: 20 (11.4%)

Abbreviations: BL = baseline; DSM=Diagnostic and Statistical Manual; HS = high school; MH = mental health; NR = not reported; SES = socioeconomic status.

Table 20. Intervention Characteristics of Included Studies for Key Questions 1 and 2 (General and Older Adults)

Author, Year Quality	Intervention	Train PCP in Screening	Train PCP in Depression Diagnosis	Train PCP in Depression Treatment	Treatment Guidance Provided	Patient Materials Provided	Patient-specific Treatment Recomm-endations	Referral Support for PCP	Symptom Monitoring by Support Staff	Treatment Adherence Monitoring by Support Staff	Counseling to Support Adherence	Behavioral Counseling Approach	Estimated Hours of Behavioral Counseling	Target Provider
General Adults														
Williams, 1999[154] Fair	Case-finding (1 item or 20-item)											NA	NA	Physician
Bergus, 2005[72] Fair	Screening results to provider	✓										NA	NA	Medical provider
Jarjoura, 2004[157] Fair	Screening results + treatment protocol			✓	✓	✓		✓				NA	NA	Resident physicians
Rost, 2001[73] Good	Screening results + provider training & supports	✓	✓	✓	✓	✓		✓	✓	✓	✓	NA	NA	Physician, nurse
Wells, 2000[155] Fair	Screening results, provider training & support, CBT or medication support		✓	✓	✓	✓		✓	✓	✓	✓	CBT or related or medication manage-ment	NR	Psycho-therapist, nurse specialist, physician
Older Adults														
van der Weele, 2012[158] Good	Screening results + referral for stepped care										✓	CBT or related	NR	General practitioner, mental health professional
Whooley, 2000[156] Fair	Screening results + provider training + psycho-education course		✓	✓								General education	7	Primary care physician, psychiatric nurse
Bijl, 2003[159] Fair	Screening results + provider training	✓	✓	✓								NA	NA	General practitioner

Table 20. Intervention Characteristics of Included Studies for Key Questions 1 and 2 (General and Older Adults)

Author, Year Quality	Intervention	Train PCP in Screening	Train PCP in Depression Diagnosis	Train PCP in Depression Treatment	Treatment Guidance Provided	Patient Materials Provided	Patient-specific Treatment Recomm-endations	Referral Support for PCP	Symptom Monitoring by Support Staff	Treatment Adherence Monitoring by Support Staff	Counseling to Support Adherence	Behavioral Counseling Approach	Estimated Hours of Behavioral Counseling	Target Provider
Callahan, 1994[153] Fair	Screening results + provider support				✓	✓	✓					NA	NA	Physicians

Abbreviations: CBT = cognitive behavior therapy; NA = not applicable; PCP = primary care physician.

Table 21. Results of Included Studies for Key Question 1 (General and Older Adults): Depressive Symptoms

Author, Year Quality	Subgroup	Instrument	Followup, months	IG N	IG Mean Change	IGSD	CG N	CG Mean Change	CG SD	Between Group Difference (p-value)
General Adults										
Bergus, 2005[72] Fair	All participants	PHQ-9	2	24	-5.8	NR	27	-5.8	NR	NR
			6	24	-5.7	NR	27	-5.0	NR	0.45
Jarjoura, 2004[157] Fair	All participants	BDI-II	6	33	NR	NR	28	NR	NR	NR
			12	33	NR	NR	33	NR	NR	0.05
Rost, 2001[73] Good	New treatment episode	CES-D	6	97	-21.7	NR	92	-13.7	NR	0.04
	Recently treated	CES-D	6	NR	-14.5	NR	NR	-11.0	NR	NS
Older Adults										
van der Weele, 2012[158] Good	All participants	MADRS	6	107	-1.1	6.1	103	-2.9	6.3	0.056
			12	101	-3.1	6.7	93	-4.6	7.0	0.088
Whooley, 2000[156] Fair	All participants	GDS	24	76	-1.8	5.1	97	-2.2	5.2	0.41
Bijl, 2003[159] Fair	All participants	MADRS	2	70	-2.1	26.1	75	-1.4	26.9	NR
			6	70	-12.4	23.8	75	-9.5	21.7	<0.05
			12	70	-10.9	23.9	75	-10.9	21.6	NR
Callahan, 1994[153] Fair	All participants	HAM-D	6	76	-4.2	NR	60	-4.9	NR	NSD
			9	76	-6.1	NR	60	-7.0	NR	NSD

Abbreviations: BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies Depression; CG = control group; GDS = Geriatric Depression Scale; HAM-D = Hamilton Rating Scale for Depression; IG = intervention group; MADRS = Montgomery Asberg Depression Rating Scale; NR = not reported; NS = not significant; PHQ = Patient Health Questionnaire; SD = standard deviation.

Table 22. Summary of Evidence in Pregnant and Postpartum Women

Key Question	No. of Studies, No. of Observations (n), Design	Summary of Findings	Consistency/ Precision	Reporting Bias	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
Key Question 1 *Benefits of screening*	k=6 n=11,869 5 RCTs, 1 CCT	Trials reported approximately 20% to 60% reductions in prevalence of depression with depression screening (+/- additional components), and approximately 20-30% increases in remission or treatment response in those with depressive symptoms at baseline. Two interventions that focused on screening without additional supports or counseling showed reductions in depression in the near-term (up to 4 months); 4 interventions providing additional provider supports or counseling consistently showed improvement in depression outcomes; one of these also reported numerous quality of life outcomes that largely showed improvement with screening + CBT or person-centered counseling	Reasonably consistent, Imprecise	None detected	Fair	Limited number of studies, wide range of intervention approaches with no replication of any interventions, minimal descriptions of samples (e.g., age, race/ethnicity, previous depression); minimal information on the role of screening in the beneficial results	Moderate. We are moderately confident that the estimate of effect lies close to the true effect for remission or response.	All conducted in maternal health or other primary care settings, however only one conducted in the United States, three involved home visits, which are rarely used in the United States.
Key Question 2 *Performance characteristics of the EPDS*	k=21 (k=7, English language version) n= 6,325 (n=3,055, English language version) Studies reporting performance characteristics	For detecting MDD, sensitivity of the English language EPDS likely approximately 0.80 and specificity likely 0.90 or above with a cutoff of 13 in the first 3 months postpartum. Sensitivity substantially lower if detecting both major and minor depression. In a population with 10% MDD prevalence, PPV estimated at 47% to 64% for detecting MDD. Results more variable with cutoff of 10, but relevant for detecting MDD or minor depression: sensitivity estimated between 0.63 to 0.84, specificity likely between 0.80 and 0.90. Positive predictive values were below 50% in all but the most optimistic scenario with cutoff of 10.	English version: Cutoff 13: Reasonably consistent for detecting MDD, reasonably precise Cutoff 10: Somewhat inconsistent for detecting MDD or minor depression, imprecise	Possible; some studies reported optimal cutoff, but most English language version studies reported commonly used cutoffs of 10 and 13.	Fair	Limited data on English-language version, much of it collected 15-25 years ago, small ns. Training and fidelity associated with the reference standard were rarely reported, two English-version studies did not report the interval between the EPDS and the reference test.	Low-to-moderate. We have limited confidence that the estimate of effect lies close to the true effect for remission or response.	Uncertain, only three of the studies of the English-language version were conducted in the United States. However, study with best applicability reported relatively good performance characteristics.

Table 22. Summary of Evidence in Pregnant and Postpartum Women

Key Question	No. of Studies, No. of Observations (n), Design	Summary of Findings	Consistency/ Precision	Reporting Bias	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
Key Question 3 *Harms of Screening*	Reported harms: k=1, n=462	One of the included studies reported no adverse. We found no additional data addressing harms of screening beyond trials of screening's benefit. No evidence of paradoxical deleterious effects.	NA	NA	NA	No evidence directly examined harms.	Insufficient	NA
Key Question 4 *Benefits of Treatment*	k=17 n=1,583 16 RCTs, 1 CCT	CBT and related therapeutic approaches are likely to increase the likelihood of remission (RR, 1.35 [95% CI 1.19 to 1.53]) in the short term (<8 months) and reduce symptom severity. Larger effects were generally associated with greater contact hours. Data were insufficient to evaluate other treatment approaches, including stepped care (k=1) and fluoxetine (k=1).	CBT: Reasonably consistent, Reasonably precise for remission/ response	Possible; variety of definitions used for remission, possibility that definition with largest effect was presented in some studies.	Fair	Mostly small studies with one or more methodological limitations	CBT: Moderate. We are moderately confident that the estimate of effect lies close to the true effect for remission/ response.	Limited to studies of screen-detected depression conducted in or recruited from primary care, but only 3 conducted in the United States with little information about population characteristics, particularly racial/ethnic background.
Key Question 5 *Harms of Treatment (Behaviorally -based)*	k=0	None of the included studies reported on adverse events or other specific harms. We found no additional data addressing harms of screening beyond trials of screening's benefit. No evidence of paradoxical deleterious effects.	NA	N NA	NA	No evidence directly examined harms.	Insufficient	NA

Table 22. Summary of Evidence in Pregnant and Postpartum Women

Key Question	No. of Studies, No. of Observations (n), Design	Summary of Findings	Consistency/ Precision	Reporting Bias	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
Key Question 5 *Harms of Treatment (anti-depressants)*	k=14 1 SER 1 RCT 9 large cohort studies 3 large case-control study N=4,759,822	2nd gen. AD are associated w/ an increased risk of some serious AEs. Positive associations between AD & harms for preeclampsia (venlafaxine), postpartum hemorrhage (SSRIs [≥60d exposure], SNRIs), miscarriage (SSRIs 1st tri.; SNRIs), perinatal death (SSRIs); preterm birth (SSRIs in 1st and 2nd tri., SNRIs), small for gestational age (SSRIs), infant seizures (SSRIs), serotonin withdrawal syndrome (SSRIs, SNRIs), neonatal respiratory distress (SSRIs), pulmonary HTN (SSRIs, particularly late in pregnancy), major malformations (SSRIs), and cardiac malformations (paroxetine, venlafaxine, bupropion). Negative studies are not summarized here, but for most outcomes w/ studies showing a positive association, other studies showed no association.	Consistent direction of effect for most outcomes Reasonably precise.	Unlikely, most included limited number of outcomes and used medical records to ascertain exposure and outcomes.	Good	No RCTs; only observational evidence, so causality cannot be clearly determined. Many studies compared harms in groups of women with unknown depression status, exaggerating the potential confounding by indication. No data was available to examine harms by dose; some did examine harms by length of exposure. Most used pharmacy fills to examine exposure, but did not verify women were actually taking antidepressants as prescribed.	Moderate. We are moderately confident that the estimates of effect lies close to the true effect for most reported harms.	Only approximately one-third of studies were conducted in the United States, but the majority of the remaining was conducted in Europe, and applicability is likely moderately good.

Abbreviations: AD = antidepressants; AE = adverse effects; CBT = cognitive behavioral therapy; CI = confidence interval; EPC = Evidence-based Practice Center; EPDS = Edinburgh Postnatal Depression Scale; gen = generation; HTN = hypertension; MDD = major depressive disorder; NA = not applicable; PE = preeclampsia; PPH = postpartum hemorrhage; RCT = randomized controlled trial; RDS = respiratory distress; RR = relative risk; SER = systematic evidence review; SGA = small for gestational age; SNRI = selective norepinephrine reuptake inhibitors; SS = serotonin syndrome; SSRI = selective serotonin reuptake inhibitors; tri = trimester; ven = venlafaxine; vs = versus; w/ = with.

Table 23. Summary of Evidence in General and Older Adults

Key Question	No. of Studies (k), No. of Observations (n), Design	Summary of Findings	Consistency/ Precision	Reporting Bias	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
Key Question 1 *Benefits of screening* *General Adult Population*	k=5 RCTs n=2,924	Screening programs were likely to increase the likelihood of remission and treatment response in general adult populations experiencing depressive symptoms, particularly programs with greater provider supports and those focused on newly-identified depression. Remission or treatment response was increased by approximately 20-80% with screening (+/- additional components), but results were statistically significant in only two of the largest studies with greatest additional supports beyond simple screening results feedback, one of which only found a benefit for those with newly-identified depression. Other studies were smaller and underpowered for statistical significance of even fairly large group differences (e.g., 48% remission in IG vs. 27% in CG).	Reasonably consistent, Imprecise	Possible, some studies reported response to treatment instead of remission, other beneficial outcomes sparsely reported	Fair	Only one trial had an unscreened control group; most trials provided components in addition to screening results feedback so cannot isolate importance of screening component; many studies had small n with limited power and were studied only patients who screened positive (so cannot assess population-based impact assess); Few studies altogether, all conducted 10+ years ago.	Low-to-Moderate. We are moderately confident that the estimate of effect lies close to the true effect for remission or response.	All conducted in primary care settings in the United States, with geographic and economic diversity among the studies.
Key Question 1 *Benefits of screening* *Older Adults*	k=4 RCTs n=890	Screening programs were not successful in older adults, and even had a paradoxically negative (but not statistically significant) effect in two studies conducted in The Netherlands. Evidence specific to the United States were limited to two trials, neither or which showed a benefit of screening programs, and neither had substantial added provider supports beyond screening results feedback.	Inconsistent, Imprecise	Same as general adult populations	Fair	Very limited data relevant to the United States, and smaller total n, with conflicting results.	Low. We have limited confidence that the estimate of effect lies close to the true effect for remission or response.	2 of 4 conducted in The Netherlands, where usual care may be quite different from United States.

Table 23. Summary of Evidence in General and Older Adults

Key Question	No. of Studies (k), No. of Observations (n), Design	Summary of Findings	Consistency/ Precision	Reporting Bias	Overall Study Quality	Body of Evidence Limitations	EPC Assessment of Overall Strength of Evidence	Applicability
Key Question 2 *Harms of screening*	Reported harms: k=1, n=211 Paradoxical effect: k=1, n=239	One trial reported that no adverse events were attributable to the intervention in the subset with newly-identified depression. We found no additional data addressing harms of screening beyond trials of screening's benefit; One trial from The Netherlands in older adults showed a non-statistically significant deleterious effect, with questionable applicability to the United States.	NA	NA	Fair	No evidence directly examined harms.	Insufficient	Low

Abbreviations: EPC = Evidence-based Practice Center; NA = not applicable; RCT = randomized controlled trial; vs = versus.

Appendix A. FDA Antidepressant Drug Labels for Pregnant and Postpartum Women

On October 7, 2014, we searched for the current drug label information of brand name antidepressants on the Drugs@FDA website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/). We also examined drug approval and labeling revision documents for any medical or statistical reviews associated with labeling considerations for pregnant or postpartum women. Discontinued drugs were not evaluated.

Generic (Brand Name)	FDA Pregnancy Category*	Drug Label: Fetal/Neonate Complications	Drug Label: Nursing Considerations	Other Nursing Considerations[82]
SSRIs				
Sertraline (Zoloft)	C	Nonteratogenic effects include complications requiring prolonged hospitalization, respiratory support, and tube feeding upon delivery. Other clinical findings include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying; infants exposed to SSRIs in pregnancy may have an increased risk PPHN and is associated with substantial neonatal morbidity and mortality. Several recent studies suggest a positive statistical association between SSRI use in pregnancy and PPHN	It is not known whether, and in what amount, sertraline or its metabolites are excreted in human milk. Caution should be exercised when administered to nursing women	Studies generally confirm that the transfer of sertraline and its metabolite to the infant is minimal and attaining clinically relevant plasma levels in infants is remote
Paroxetine (Pereva, Paxil)	D	Epidemiological studies have shown that infants exposed to paroxetine in the first trimester have an increased risk of congenital malformations, particularly cardiovascular malformations; nonteratogenic effects include complications requiring prolonged hospitalization, respiratory support, and tube feeding upon delivery. Other clinical findings include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying; infants exposed to SSRIs in pregnancy may have an increased risk for PPHN and is associated with substantial neonatal morbidity and mortality. Several recent studies suggest a positive statistical association between SSRI use in pregnancy and PPHN	Paroxetine is secreted in human milk and caution should be exercised when administering to nursing women	Studies suggest minimal to no effect on breastfed infants. Most studies show minimal to no plasma levels in breastfed infants

Appendix A. FDA Antidepressant Drug Labels for Pregnant and Postpartum Women

Generic (Brand Name)	FDA Pregnancy Category*	Drug Label: Fetal/Neonate Complications	Drug Label: Nursing Considerations	Other Nursing Considerations[82]
Fluvoxamine (Luvox)	C	Increased embryofetal death, increased incidences of fetal eye abnormalities, decreased fetal body weight; nonteratogenic effects include complications requiring prolonged hospitalization, respiratory support, and tube feeding upon delivery. Other clinical findings include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying; infants exposed to SSRIs in pregnancy may have an increased risk for PPHN and is associated with substantial neonatal morbidity and mortality. Several recent studies suggest a positive statistical association between SSRI use in pregnancy and PPHN	Fluvoxamine is secreted in human breast milk, potential for serious adverse effects from exposure in the nursing infant should be taken into consideration when the decision to continue or discontinue use is made	Data from studies suggests only minuscule amounts of fluvoxamine are transferred to infants, plasma levels in infants are too low to be detected, and no adverse effects have been noted
Fluoxetine (Prozac)	C	Fetal cardiovascular malformations; nonteratogenic effects include complications requiring prolonged hospitalization, respiratory support, and tube feeding upon delivery. Other clinical findings include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying; infants exposed to SSRIs in pregnancy may have an increased risk for PPHN and is associated with substantial neonatal morbidity and mortality. Several recent studies suggest a positive statistical association between SSRI use in pregnancy and PPHN	Because Prozac is excreted in human milk, nursing while on Prozac is not recommended. Studies show mixed results in nursing infants; some show no adverse effects and others reporting increased crying, sleep disturbance, vomiting, and watery stools in exposed infants.	Women taking fluoxetine should be advised to continue breastfeeding and observe the infant for side effects. Severe colic, fussiness, and crying have been reported.
Escitalopram (Lexapro)	C	Nonteratogenic effects include complications requiring prolonged hospitalization, respiratory support, and tube feeding upon delivery. Other clinical findings include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying; infants exposed to SSRIs in pregnancy may have an increased risk for PPHN and is associated with substantial neonatal morbidity and mortality. Several recent studies suggest a positive statistical association between SSRI use in pregnancy and PPHN	Escitalopram is excreted in human breast milk, so caution should be exercised and breastfeeding infants should be observed for adverse reactions when administering to nursing women. Some reports of infants experiencing excessive somnolence, decreased feedings, and weight loss	Recent data concerning use in breastfeeding mothers suggests the relative infant dose is low and plasma levels in breastfed infants are largely undetectable. No adverse events in infants were reported

Appendix A. FDA Antidepressant Drug Labels for Pregnant and Postpartum Women

Generic (Brand Name)	FDA Pregnancy Category*	Drug Label: Fetal/Neonate Complications	Drug Label: Nursing Considerations	Other Nursing Considerations[82]
Citalopram (Celexa)	C	Nonteratogenic effects include complications requiring prolonged hospitalization, respiratory support, and tube feeding upon delivery. Other clinical findings include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying; infants exposed to SSRIs in pregnancy may have an increased risk for PPHN and is associated with substantial neonatal morbidity and mortality. Several recent studies suggest a positive statistical association between SSRI use in pregnancy and PPHN-Serotonin syndrome	Citalopram is excreted in human breast milk, caution should be exercised and breastfeeding infants should be observed for adverse reactions when administering to nursing women. Some reports of infants experiencing excessive somnolence, decreased feedings, and weight loss	Reports of excessive somnolence, decreased feeding, and weight loss in breastfed infants. However, majority of studies show no or limited side effects in breastfed infants. Risks of this product are quite low
SNRIs				
Venlafaxine*	C	No teratogenic effects reported; non-teratogenic effects included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia , tremor, jitteriness, irritability, and constant crying	Venlafaxine has been reported to be excreted in milk, potential for serious adverse reactions in nursing infants. A decision should be made to discontinue nursing or to discontinue the drug	Venlafaxine does enter the milk in moderate amounts, however no side-effects have been reported following its lactational exposure
Duloxetine (Cymbalta)	C	Non-teratogenic effects included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia , tremor, jitteriness, irritability, and constant crying	The safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended	Milk levels in one study (6 mothers) are low and the relative infant dose is low. Subsequent study suggests weight-adjusted infant dose of 0.14% of the maternal dose
Desvenlafaxine (Pristiq)	C	Neonates exposed to SNRIs or SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Non-teratogenic effects included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia , tremor, jitteriness, irritability, and constant crying	Potential for serious adverse reactions in nursing infants from PRISTIQ	Desvenlafaxine does enter the milk in moderate amounts, however no side-effects have been reported following its lactational exposure
DRIs				
Bupropion (Wellbutrin)	C	No increased risk of congenital malformations overall	Bupropion and its metabolites are present in human milk, exercise caution when administering to nursing women	Plasma levels in breastfed infants are undetectable, one case of seizure in 6-month old infant

Appendix A. FDA Antidepressant Drug Labels for Pregnant and Postpartum Women

Generic (Brand Name)	FDA Pregnancy Category*	Drug Label: Fetal/Neonate Complications	Drug Label: Nursing Considerations	Other Nursing Considerations[82]
5-HT$_{2A}$ Receptor Antagonists				
Nefazodone *	C	Premature birth, infants drowsiness and lethargy, infant failure to thrive, and poor temperature control	It is not known whether Nefazodone or its metabolites are excreted in human milk, caution should be exercised when administered to nursing women	Medication should not be used in breastfeeding mothers with young infants, premature infants, infants subject to apnea, or other weakened infants
SRIs				
Trazodone (Oleptro)	C	Increased fetal resorption, increase in congenital anomalies, may cause fetal harm	Oleptro use in pregnant and nursing women is not recommended	Milk levels are probably too low to be clinically relevant in the breastfed infant, did not report any pediatric concerns in breastfeeding infants
TeCAs				
Miratazapine (Remeron)	C	No evidence of teratogenic effects	Remeron may be excreted into breast milk, caution should be exercised in administering to nursing women	Two studies found no adverse effects among infants of nursing mothers and suggest breastfeeding is safe during Miratazapine therapy

Note: No Black Box Warnings for Pregnant.
*FDA Pregnancy Categories: Category C = Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of drug in pregnant women despite potential risks; Category D = There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Abbreviations: DRI = dopamine reuptake inhibitors; FDA = U.S. Food and Drug Administration; PPHN = persistent pulmonary hypertension of the newborn; SNRI = serotonin-norepinephrine reuptake inhibitors; SRI = serotonin reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; TeCA = tricyclic antidepressants.

Systematic Reviews Literature Search Strategies

Cochrane Database of Systematic Reviews Issue 10 of 12, October 2013
#1 [mh ^depression] from 2008 to 2013, in Cochrane Reviews
#2 [mh ^"depression, postpartum"] from 2008 to 2013, in Cochrane Reviews
#3 [mh ^"depressive disorder, major"] from 2008 to 2013, in Cochrane Reviews
#4 [mh ^"dysthymic disorder"] from 2008 to 2013, in Cochrane Reviews
#5 [mh ^"depressive disorder"] from 2008 to 2013, in Cochrane Reviews
#6 [mh ^"seasonal affective disorder"] from 2008 to 2013, in Cochrane Reviews
#7 [mh ^"Depressive Disorder, Treatment-Resistant"] from 2008 to 2013, in Cochrane Reviews
#8 (depress*.ti or dysthymi*.ti or antidepress*.ti or mood.ti) from 2008 to 2013, in Cochrane Reviews
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 from 2008 to 2013, in Cochrane Reviews

Database of Abstracts of Reviews of Effects (Via CRD)
((depression or depressed or depressive or mood)):TI OR (dysthimi*):TI OR (antidepress*):TI IN DARE FROM 2008 TO 2013

Health Technology Assessment
((depression or depressed or depressive or mood)):TI OR (dysthimi*):TI OR (antidepress*):TI IN HTA FROM 2008 TO 2013

Medline
Database: Ovid MEDLINE(R) without Revisions <1996 to September Week 4 2013>, Ovid MEDLINE(R) Daily Update <October 01, 2013>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <October 01, 2013>
Search Strategy:
---
1 Depression/dh, dt, pc, rh, su, th [Diet Therapy, Drug Therapy, Prevention & Control, Rehabilitation, Surgery, Therapy] ()
2 Depression, Postpartum/dh, dt, pc, rh, su, th ()
3 Depressive Disorder, Major/dh, dt, pc, rh, su, th ()
4 Dysthymic Disorder/dh, dt, pc, rh, su, th ()
5 Depressive Disorder/dh, dt, pc, rh, su, th ()
6 Depressive Disorder, Treatment-Resistant/dh, dt, pc, rh, su, th ()
7 Depression/ ()
8 Depression, Postpartum/ ()
9 Depressive Disorder, Major/ ()
10 Dysthymic Disorder/ ()
11 Depressive Disorder/ ()
12 Depressive Disorder, Treatment-Resistant/ ()
13 Mass screening/ ()
14 screen$.ti,ab. ()
15 13 or 14 ()
16 7 or 8 or 9 or 10 or 11 or 12 ()
17 15 and 16 ()

18 1 or 2 or 3 or 4 or 5 or 6 or 17 ()
19 limit 18 to "all adult (19 plus years)" ()
20 limit 19 to systematic reviews ()
21 limit 20 to (english language and yr="2008 -Current") ()
22 depression.ti. ()
23 depressed.ti. ()
24 depressive.ti. ()
25 dysthymi$.ti. ()
26 antidepress$.ti. ()
27 mood.ti. ()
28 22 or 23 or 24 or 25 or 26 or 27 ()
29 limit 28 to systematic reviews ()
30 limit 29 to ("in data review" or in process or "pubmed not medline") ()
31 limit 30 to (english language and yr="2008 -Current") ()
32 21 or 31 ()
33 remove duplicates from 32 ()

PubMed
#3 Search #2 AND publisher[sb] Filters: Publication date from 2008/01/01 to 2013/12/31; English
#2 Search #1 AND systematic[sb]
#1 Search depression[ti] OR depressive[ti] OR depressed[ti] OR antidepress*[ti] OR dysthymi*[ti] OR mood[ti]

PsycINFO <1806 to October Week 1 2013>
Search Strategy:
---
1 major depression/ ()
2 dysthymic disorder/ ()
3 Postpartum Depression/ ()
4 Recurrent Depression/ ()
5 Treatment Resistant Depression/ ()
6 "Depression (Emotion)"/ ()
7 1 or 2 or 3 or 4 or 5 or 6 ()
8 limit 7 to "300 adulthood <age 18 yrs and older>" ()
9 limit 8 to "0830 systematic review" ()
10 limit 8 to 1200 meta analysis ()
11 9 or 10 ()
12 limit 11 to (english language and yr="2008 -Current") ()

Literature Search Strategies for Primary Literature

Ovid Medline

General adult population - screening

Database: Ovid MEDLINE(R) without Revisions <1996 to January Week 2 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <January 19, 2015>, Ovid MEDLINE(R) Daily Update < January 19, 2015>
Search Strategy:
---
1 Depression/ ()
2 Depressive Disorder/ ()
3 Depressive Disorder, Major/ ()
4 Dysthymic Disorder/ ()
5 depress$.ti,ab. ()
6 dysthym$.ti,ab. ()
7 1 or 2 or 3 or 4 or 5 or 6 ()
8 Mass screening/ ()
9 screen$.ti,ab. ()
10 casefinding.ti,ab. ()
11 case finding.ti,ab. ()
12 (diagnos$ or detect$ or identif$).ti. ()
13 8 or 9 or 10 or 11 or 12 ()
14 7 and 13 ()
15 Mental disorders/di ()
16 depress$.ti,ab. ()
17 15 and 16 ()
18 14 or 17 ()
19 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/ ()
20 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt. ()
21 (random$ or placebo$).ti,ab. ()
22 control groups/ or double-blind method/ or single-blind method/ ()
23 clinical trial$.ti,ab. ()
24 controlled trial$.ti,ab. ()
25 (meta analy$ or metaanaly$).ti,ab. ()
26 19 or 20 or 21 or 22 or 23 or 24 or 25 ()
27 18 and 26 ()
28 limit 27 to "all child (0 to 18 years)" ()
29 limit 27 to "all adult (19 plus years)" ()
30 28 not 29 ()
31 27 not 30 ()
32 limit 31 to (english language and yr="2009 -Current") ()
33 remove duplicates from 32 ()

Pregnant and postpartum women – screening and test performance

Database: Ovid MEDLINE(R) without Revisions <1996 to January Week 2 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations < January 19, 2015>, Ovid MEDLINE(R) Daily Update < January 19, 2015>
Search Strategy:
---
1 Pregnancy/ ()
2 Pregnant women/ ()
3 Prenatal care/ ()
4 Perinatal care/ ()
5 Postnatal care/ ()
6 Postpartum period/ ()
7 Peripartum period/ ()
8 Maternal Health Services/ ()
9 Puerperal Disorders/ ()
10 pregnan$.ti,ab. ()
11 prenatal.ti,ab. ()
12 pre natal.ti,ab. ()
13 perinatal.ti,ab. ()
14 peri natal.ti,ab. ()
15 antenatal.ti,ab. ()
16 ante natal.ti,ab. ()
17 antepartum.ti,ab. ()
18 ante partum.ti,ab. ()
19 postnatal.ti,ab. ()
20 post natal.ti,ab. ()
21 postpartum.ti,ab. ()
22 post partum.ti,ab. ()
23 new mother$.ti,ab. ()
24 puerperal.ti,ab. ()
25 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 ()
26 Depression/ ()
27 Depressive Disorder/ ()
28 Depressive Disorder, Major/ ()
29 Dysthymic Disorder/ ()
30 Anxiety/ ()
31 depress$.ti,ab. ()
32 dysthym$.ti,ab. ()
33 (anxiety or anxious).ti,ab. ()
34 blues.ti,ab. ()
35 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 ()
36 25 and 35 ()
37 Depression, Postpartum/ ()
38 36 or 37 ()

39 Mass screening/ ()
40 Questionnaires/ ()
41 Interview/ ()
42 Psychiatric Status Rating Scales/ ()
43 Self Report/ ()
44 screen$.ti,ab. ()
45 casefinding.ti,ab. ()
46 case finding.ti,ab. ()
47 self report$.ti,ab. ()
48 (depress$ adj5 (scale$ or inventor$ or questionnaire$ or survey$ or index$ or checklist$ or interview$)).ti,ab. ()
49 Patient Health Questionnaire.ti,ab. ()
50 PHQ-2.ti,ab. ()
51 PHQ-9.ti,ab. ()
52 "Hospital Anxiety and Depression Scale".ti,ab. ()
53 Geriatric Depression Scale.ti,ab. ()
54 Beck Depression Inventory.ti,ab. ()
55 Center for Epidemiologic Studies Depression Scale.ti,ab. ()
56 Hamilton Depression Rating Scale.ti,ab. ()
57 Hamilton Rating Scale for Depression.ti,ab. ()
58 Montgomery-Asberg Depression Rating Scale.ti,ab. ()
59 Zung Self-Rating Depression Scale.ti,ab. ()
60 Quick Inventory of Depressive Symptoms.ti,ab. ()
61 Mini-Neuropsychiatric Interview.ti,ab. ()
62 Composite International Diagnostic Interview.ti,ab. ()
63 Primary Care Evaluation of Mental Disorders.ti,ab. ()
64 PRIME-MD.ti,ab. ()
65 Center for Epidemiologic Studies Depression Scale.ti,ab. ()
66 CES-D.ti,ab. ()
67 General Health Questionnaire.ti,ab. ()
68 GHQ-D.ti,ab. ()
69 Generalized Contentment Scale.ti,ab. ()
70 Edinburgh Postpartum Depression Scale.ti,ab. ()
71 EPDS.ti,ab. ()
72 Bromley Postnatal Depression Scale.ti,ab. ()
73 Postpartum Depression Screening Scale.ti,ab. ()
74 PDSS.ti,ab. ()
75 Leverton Questionnaire.ti,ab. ()
76 Postpartum Depression Predictors Inventory.ti,ab. ()
77 PDPI$.ti,ab. ()
78 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 ()
79 38 and 78 ()
80 Postpartum Depression/di ()
81 79 or 80 ()

82 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/ ()
83 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt. ()
84 (random$ or placebo$).ti,ab. ()
85 control groups/ or double-blind method/ or single-blind method/ ()
86 clinical trial$.ti,ab. ()
87 controlled trial$.ti,ab. ()
88 (meta analy$ or metaanaly$).ti,ab. ()
89 82 or 83 or 84 or 85 or 86 or 87 or 88 ()
90 81 and 89 ()
91 limit 90 to (english language and yr="2012 -Current") ()
92 "Sensitivity and Specificity"/ ()
93 "Predictive Value of Tests"/ ()
94 ROC Curve/ ()
95 False Negative Reactions/ ()
96 False Positive Reactions/ ()
97 Diagnostic Errors/ ()
98 "Reproducibility of Results"/ ()
99 Reference Values/ ()
100 Reference Standards/ ()
101 Observer Variation/ ()
102 Receiver operat$.ti,ab. ()
103 ROC curve$.ti,ab. ()
104 sensitivit$.ti,ab. ()
105 specificit$.ti,ab. ()
106 predictive value.ti,ab. ()
107 accuracy.ti,ab. ()
108 false positive$.ti,ab. ()
109 false negative$.ti,ab. ()
110 miss rate$.ti,ab. ()
111 error rate$.ti,ab. ()
112 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 ()
113 81 and 112 ()
114 limit 113 to (english language and yr="2012 -Current") ()
115 91 or 114 ()
116 remove duplicates from 115 ()

Pregnant and postpartum women – drug treatment and harms

Database: Ovid MEDLINE(R) without Revisions <1996 to January Week 2 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations < January 19, 2015>, Ovid MEDLINE(R) Daily Update < January 19, 2015>
Search Strategy:
---
1 Pregnancy/ ()

2 Pregnant women/ ()
3 Prenatal care/ ()
4 Perinatal care/ ()
5 Postnatal care/ ()
6 Postpartum period/ ()
7 Peripartum Period/ ()
8 Maternal Health Services/ ()
9 Puerperal Disorders/ ()
10 pregnan$.ti,ab. ()
11 prenatal.ti,ab. ()
12 pre natal.ti,ab. ()
13 perinatal.ti,ab. ()
14 peri natal.ti,ab. ()
15 antenatal.ti,ab. ()
16 ante natal.ti,ab. ()
17 antepartum.ti,ab. ()
18 ante partum.ti,ab. ()
19 postnatal.ti,ab. ()
20 post natal.ti,ab. ()
21 postpartum.ti,ab. ()
22 post partum.ti,ab. ()
23 new mother$.ti,ab. ()
24 puerperal.ti,ab. ()
25 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 ()
26 Depression/ ()
27 Depressive Disorder/ ()
28 Depressive Disorder, Major/ ()
29 Dysthymic Disorder/ ()
30 Anxiety/ ()
31 depress$.ti,ab. ()
32 dysthym$.ti,ab. ()
33 (anxiety or anxious).ti,ab. ()
34 blues.ti,ab. ()
35 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 ()
36 25 and 35 ()
37 Depression, Postpartum/ ()
38 36 or 37 ()
39 Antidepressive Agents/ ()
40 Antidepressive Agents, Second-Generation/ ()
41 Serotonin Uptake Inhibitors/ ()
42 Neurotransmitter Uptake Inhibitors/ ()
43 Adrenergic Uptake Inhibitors/ ()
44 Dopamine Uptake Inhibitors/ ()
45 Citalopram/ ()
46 Fluoxetine/ ()

47 Fluvoxamine/ ()
48 Paroxetine/ ()
49 Sertraline/ ()
50 Bupropion/ ()
51 (antidepress$ or anti depress$).ti,ab. ()
52 pharmacotherap$.ti,ab. ()
53 (psychotropic adj (drug$ or agent$ or medicat$ or medicine$)).ti,ab. ()
54 Serotonin$ Uptake Inhib$.ti,ab. ()
55 Serotonin$ Re uptake Inhib$.ti,ab. ()
56 Serotonin$ Reuptake Inhib$.ti,ab. ()
57 (serotonergic adj (drug$ or agent$ or medicat$)).ti,ab. ()
58 SSRI$.ti,ab. ()
59 SNRI$.ti,ab. ()
60 Neurotransmitter Uptake Inhib$.ti,ab. ()
61 Neurotransmitter Re uptake Inhib$.ti,ab. ()
62 Neurotransmitter Reuptake Inhib$.ti,ab. ()
63 Adrenergic Uptake Inhib$.ti,ab. ()
64 Adrenergic Re uptake Inhib$.ti,ab. ()
65 Adrenergic Reuptake Inhib$.ti,ab. ()
66 Norepinephrine Uptake Inhib$.ti,ab. ()
67 Norepinephrine Re uptake Inhib$.ti,ab. ()
68 Norepinephrine Reuptake Inhib$.ti,ab. ()
69 Dopamine Uptake Inhib$.ti,ab. ()
70 Dopamine Re uptake Inhib$.ti,ab. ()
71 Dopamine Reuptake Inhib$.ti,ab. ()
72 Bupropion.ti,ab. ()
73 Celexa.ti,ab. ()
74 Citalopram.ti,ab. ()
75 Cymbalta.ti,ab. ()
76 Desvenlafaxine.ti,ab. ()
77 Duloxetine.ti,ab. ()
78 Effexor.ti,ab. ()
79 Escitalopram.ti,ab. ()
80 Fluoxetine.ti,ab. ()
81 Fluvoxamine.ti,ab. ()
82 Lexapro.ti,ab. ()
83 Mirtazapine.ti,ab. ()
84 Nefazodone.ti,ab. ()
85 Paroxetine.ti,ab. ()
86 Paxil.ti,ab. ()
87 Pexeva.ti,ab. ()
88 Pristiq.ti,ab. ()
89 Prozac.ti,ab. ()
90 Remeron.ti,ab. ()
91 Sertraline.ti,ab. ()
92 Trazadone.ti,ab. ()

93 Venlafaxine.ti,ab. ()
94 Wellbutrin.ti,ab. ()
95 Zoloft.ti,ab. ()
96 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 ()
97 38 and 96 ()
98 Depression, Postpartum/dt [Drug Therapy] ()
99 97 or 98 ()
100 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/ ()
101 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt. ()
102 (random$ or placebo$).ti,ab. ()
103 control groups/ or double-blind method/ or single-blind method/ ()
104 clinical trial$.ti,ab. ()
105 controlled trial$.ti,ab. ()
106 (meta analy$ or metaanaly$).ti,ab. ()
107 100 or 101 or 102 or 103 or 104 or 105 or 106 ()
108 99 and 107 ()
109 limit 108 to (english language and yr="2012 -Current") ()
110 Mortality/ ()
111 Morbidity/ ()
112 Death/ ()
113 "Drug-Related Side Effects and Adverse Reactions"/ ()
114 safety.ti,ab. ()
115 harm$.ti,ab. ()
116 mortality.ti,ab. ()
117 toxicity.ti,ab. ()
118 complication$.ti,ab. ()
119 (death or deaths).ti,ab. ()
120 (adverse adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab. ()
121 adverse effects.fs. ()
122 toxicity.fs. ()
123 mortality.fs. ()
124 Prenatal Injuries/ ()
125 Prenatal Exposure Delayed Effects/ ()
126 Fetal Development/ ()
127 Congenital Abnormalities/ ()
128 Abnormalities, Drug-Induced/ ()
129 (deform$ or malform$).ti,ab. ()
130 (congenital adj (defect$ or abnormality)).ti,ab. ()
131 birth defect$.ti,ab. ()
132 teratogen$.ti,ab. ()
133 birth outcome$.ti,ab. ()

134 Infant, Low Birth Weight/ ()
135 Infant, Small for Gestational Age/ ()
136 Infant, Very Low Birth Weight/ ()
137 Infant, Extremely Low Birth Weight/ ()
138 low birth weight$.ti,ab. ()
139 small for gestational age.ti,ab. ()
140 fetal growth.ti,ab. ()
141 Maternal Exposure/ ()
142 maternal exposure.ti,ab. ()
143 Pregnancy Outcome/ ()
144 pregnancy outcome$.ti,ab. ()
145 Pregnancy Complications/ ()
146 Pregnancy Complications, Cardiovascular/ ()
147 (cardiac or cardiovascular).ti,ab. ()
148 Suicide/ ()
149 Suicidal Ideation/ ()
150 Suicide, Attempted/ ()
151 suicid$.ti,ab. ()
152 Seizures/ ()
153 seizure$.ti,ab. ()
154 Hyponatremia/ ()
155 hyponatremi$.ti,ab. ()
156 Drug-Induced Liver Injury/ ()
157 hepatoxicity.ti,ab. ()
158 Serotonin Syndrome/ ()
159 serotonin syndrome.ti,ab. ()
160 Hypertension/ ()
161 (blood pressure$ or hypertens$).ti,ab. ()
162 Sexual Dysfunction, Physiological/ ()
163 (sexual adj (function$ or disorder$ or dysfunction$)).ti,ab. ()
164 (libido adj3 (decrease$ or loss)).ti,ab. ()
165 Nausea/ ()
166 Vomiting/ ()
167 (nausea$ or nauseous or vomit$).ti,ab. ()
168 Diarrhea/ ()
169 diarr$.ti,ab. ()
170 Dizziness/ ()
171 (dizzy or dizziness).ti,ab. ()
172 Headache/ ()
173 headache$.ti,ab. ()
174 Xerostomia/ ()
175 xerostomia$.ti,ab. ()
176 (dry$ adj3 mouth).ti,ab. ()
177 Weight Gain/ ()
178 (weight adj3 (gain$ or increase$)).ti,ab. ()
179 Metabolic Syndrome X/ ()

180 metabolic syndrome.ti,ab. ()
181 withdrawal$.ti,ab. ()
182 discontinu$.ti,ab. ()
183 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 ()
184 99 and 183 ()
185 Milk, human/ ()
186 Lactation/ ()
187 Breast Feeding/ ()
188 Breast Milk Expression/ ()
189 (breast feed$ or breastfeed$ or breast fed or breastfed or lactat$).ti,ab. ()
190 185 or 186 or 187 or 188 or 189 ()
191 (96 or 98) and 190 ()
192 184 or 191 ()
193 limit 192 to (english language and yr="2012 -Current") ()
194 109 or 193 ()
195 Animal/ not (Animal/ and Human/) ()
196 194 not 195 ()
197 remove duplicates from 196 ()

Pregnant and postpartum women – psychotherapy treatment

Database: Ovid MEDLINE(R) without Revisions <1996 to January Week 2 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <January 19, 2015>, Ovid MEDLINE(R) Daily Update < January 19, 2015>
Search Strategy:
---
1 Pregnancy/ ()
2 Pregnant women/ ()
3 Prenatal care/ ()
4 Perinatal care/ ()
5 Postnatal care/ ()
6 Postpartum period/ ()
7 Peripartum period/ ()
8 Maternal Health Services/ ()
9 Puerperal Disorders/ ()
10 pregnan$.ti,ab. ()
11 prenatal.ti,ab. ()
12 pre natal.ti,ab. ()
13 perinatal.ti,ab. ()
14 peri natal.ti,ab. ()
15 antenatal.ti,ab. ()

16 ante natal.ti,ab. ()
17 antepartum.ti,ab. ()
18 ante partum.ti,ab. ()
19 postnatal.ti,ab. ()
20 post natal.ti,ab. ()
21 postpartum.ti,ab. ()
22 post partum.ti,ab. ()
23 new mother$.ti,ab. ()
24 puerperal.ti,ab. ()
25 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 ()
26 Depression/ ()
27 Depressive Disorder/ ()
28 Depressive Disorder, Major/ ()
29 Dysthymic Disorder/ ()
30 Anxiety/ ()
31 depress$.ti,ab. ()
32 dysthym$.ti,ab. ()
33 (anxiety or anxious).ti,ab. ()
34 blues.ti,ab. ()
35 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 ()
36 25 and 35 ()
37 Depression, Postpartum/ ()
38 36 or 37 ()
39 Psychotherapy/ ()
40 Psychotherapy, Brief/ ()
41 Psychotherapy, Group/ ()
42 Behavior Therapy/ ()
43 Cognitive Therapy/ ()
44 Counseling/ ()
45 Directive Counseling/ ()
46 Nondirective Therapy/ ()
47 Problem Solving/ ()
48 psychotherap$.ti,ab. ()
49 (psychological adj5 (therap$ or treatment$ or intervention$)).ti,ab. ()
50 (psychosocial adj5 (therap$ or treatment$ or intervention$)).ti,ab. ()
51 (behavi$ adj5 (therap$ or treatment$ or intervention$)).ti,ab. ()
52 (cognitive adj5 (therap$ or treatment$ or intervention$)).ti,ab. ()
53 cbt.ti,ab. ()
54 (psychodynamic adj5 (therap$ or treatment$ or intervention$)).ti,ab. ()
55 (nondirective adj5 (therap$ or treatment$ or intervention$)).ti,ab. ()
56 (non directive adj5 (therap$ or treatment$ or intervention$)).ti,ab. ()
57 interpersonal therap$.ti,ab. ()
58 interpersonal psychotherap$.ti,ab. ()
59 interpersonal intervention$.ti,ab. ()
60 supportive therap$.ti,ab. ()

61 group therap$.ti,ab. ()
62 counsel$.ti,ab. ()
63 problem solving.ti,ab. ()
64 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 ()
65 38 and 64 ()
66 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/ ()
67 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt. ()
68 (random$ or placebo$).ti,ab. ()
69 control groups/ or double-blind method/ or single-blind method/ ()
70 clinical trial$.ti,ab. ()
71 controlled trial$.ti,ab. ()
72 (meta analy$ or metaanaly$).ti,ab. ()
73 66 or 67 or 68 or 69 or 70 or 71 or 72 ()
74 65 and 73 ()
75 limit 74 to (english language and yr="2012 -Current") ()

Pregnant and postpartum women – collaborative care

Database: Ovid MEDLINE(R) without Revisions <1996 to January Week 2 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations < January 19, 2015>, Ovid MEDLINE(R) Daily Update < January 19, 2015>
Search Strategy:
---
1 Pregnancy/ ()
2 Pregnant women/ ()
3 Prenatal care/ ()
4 Perinatal care/ ()
5 Postnatal care/ ()
6 Postpartum period/ ()
7 Peripartum period/ ()
8 Maternal Health Services/ ()
9 Puerperal Disorders/ ()
10 pregnan$.ti,ab. ()
11 prenatal.ti,ab. ()
12 pre natal.ti,ab. ()
13 perinatal.ti,ab. ()
14 peri natal.ti,ab. ()
15 antenatal.ti,ab. ()
16 ante natal.ti,ab. ()
17 antepartum.ti,ab. ()
18 ante partum.ti,ab. ()
19 postnatal.ti,ab. ()
20 post natal.ti,ab. ()
21 postpartum.ti,ab. ()

22 post partum.ti,ab. ()
23 new mother$.ti,ab. ()
24 puerperal.ti,ab. ()
25 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 ()
26 Depression/ ()
27 Depressive Disorder/ ()
28 Depressive Disorder, Major/ ()
29 Dysthymic Disorder/ ()
30 Anxiety/ ()
31 depress$.ti,ab. ()
32 dysthym$.ti,ab. ()
33 (anxiety or anxious).ti,ab. ()
34 blues.ti,ab. ()
35 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 ()
36 25 and 35 ()
37 Depression, Postpartum/ ()
38 36 or 37 ()
39 Case management/ ()
40 Patient care team/ ()
41 Cooperative behavior/ ()
42 Community mental health services/ ()
43 Interprofessional Relations/ ()
44 Continuity of patient care/ ()
45 Patient-centered care/ ()
46 Patient care management/ ()
47 Delivery of Health Care, Integrated/ ()
48 collaborat$.ti,ab. ()
49 interdisciplinary.ti,ab. ()
50 multidisciplinary.ti,ab. ()
51 (integrated adj5 (healthcare or care)).ti,ab. ()
52 care manag$.ti,ab. ()
53 case manag$.ti,ab. ()
54 cooperative care.ti,ab. ()
55 patient centered care.ti,ab. ()
56 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 ()
57 38 and 56 ()
58 Depression, Postpartum/dh, pc, rh, th [Diet Therapy, Prevention & Control, Rehabilitation, Therapy] ()
59 57 or 58 ()
60 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/ ()
61 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt. ()
62 (random$ or placebo$).ti,ab. ()
63 control groups/ or double-blind method/ or single-blind method/ ()

64 clinical trial$.ti,ab. ()
65 controlled trial$.ti,ab. ()
66 (meta analy$ or metaanaly$).ti,ab. ()
67 60 or 61 or 62 or 63 or 64 or 65 or 66 ()
68 59 and 67 ()
69 limit 68 to (english language and yr="2009 -Current") ()

PsycInfo

Adult population – screening

Database: PsycINFO <1806 to January Week 2 2015>
Search Strategy:
---
1 Major depression/ ()
2 Dysthymic disorder/ ()
3 depress$.ti,ab,id. ()
4 dysthym$.ti,ab,id. ()
5 1 or 2 or 3 or 4 ()
6 Screening/ ()
7 Health Screening/ ()
8 Screening Tests/ ()
9 Intake Interview/ ()
10 Symptom Checklists/ ()
11 Interviews/ ()
12 Questionnaires/ ()
13 Rating Scales/ ()
14 Psychological Screening Inventory/ ()
15 Psychodiagnostic Interview/ ()
16 General Health Questionnaire/ ()
17 Beck Depression Inventory/ ()
18 Zungs Self Rating Depression Scale/ ()
19 screen$.ti,ab,id. ()
20 casefinding.ti,ab,id. ()
21 case finding.ti,ab,id. ()
22 (diagnos$ or detect$ or identif$).ti. ()
23 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 ()
24 5 and 23 ()
25 random$.ti,ab,id,hw. ()
26 placebo$.ti,ab,hw,id. ()
27 controlled trial$.ti,ab,id,hw. ()
28 clinical trial$.ti,ab,id,hw. ()
29 meta analy$.ti,ab,hw,id. ()
30 metaanaly$.ti,ab,hw,id. ()
31 treatment outcome clinical trial.md. ()
32 25 or 26 or 27 or 28 or 29 or 30 or 31 ()

33 24 and 32 ()
34 limit 33 to (100 childhood <birth to age 12 yrs> or 120 neonatal <birth to age 1 mo> or 140 infancy <2 to 23 mo> or 160 preschool age <age 2 to 5 yrs> or 180 school age <age 6 to 12 yrs> or 200 adolescence <age 13 to 17 yrs>) ()
35 limit 33 to "300 adulthood <age 18 yrs and older>" ()
36 34 not 35 ()
37 33 not 36 ()
38 limit 37 to (english language and yr="2009 -Current") ()

PsycInfo

Pregnant and postpartum women – screening and test performance

Database: PsycINFO <1806 to January Week 2 2015>
Search Strategy:
---
1 Pregnancy/ ()
2 Expectant Mothers/ ()
3 Prenatal Care/ ()
4 Perinatal Period/ ()
5 Postnatal Period/ ()
6 Mother Child Relations/ ()
7 pregnan$.ti,ab,id. ()
8 prenatal.ti,ab,id. ()
9 pre natal.ti,ab,id. ()
10 perinatal.ti,ab,id. ()
11 peri natal.ti,ab,id. ()
12 antenatal.ti,ab,id. ()
13 ante natal.ti,ab,id. ()
14 antepartum.ti,ab,id. ()
15 ante partum.ti,ab,id. ()
16 postnatal.ti,ab,id. ()
17 post natal.ti,ab,id. ()
18 postpartum.ti,ab,id. ()
19 post partum.ti,ab,id. ()
20 new mother$.ti,ab,id. ()
21 puerperal.ti,ab,id. ()
22 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 ()
23 Major Depression/ ()
24 Dysthymic disorder/ ()
25 Anxiety/ ()
26 depress$.ti,ab,id. ()
27 dysthym$.ti,ab,id. ()
28 (anxiety or anxious).ti,ab,id. ()
29 blues.ti,ab,id. ()

30 23 or 24 or 25 or 26 or 27 or 28 or 29 ()
31 22 and 30 ()
32 Postpartum Depression/ ()
33 Postpartum Psychosis/ ()
34 31 or 32 or 33 ()
35 Screening/ ()
36 Health Screening/ ()
37 Screening Tests/ ()
38 Intake Interview/ ()
39 Symptom Checklists/ ()
40 Interviews/ ()
41 Questionnaires/ ()
42 Rating Scales/ ()
43 Psychological Screening Inventory/ ()
44 Psychodiagnostic Interview/ ()
45 Self Report/ ()
46 General Health Questionnaire/ ()
47 Beck Depression Inventory/ ()
48 Zungs Self Rating Depression Scale/ ()
49 screen$.ti,ab,id. ()
50 casefinding.ti,ab,id. ()
51 case finding.ti,ab,id. ()
52 self report$.ti,ab,id. ()
53 (depress$ adj5 (scale$ or inventor$ or questionnaire$ or survey$ or index$ or checklist$ or interview$)).ti,ab,id. ()
54 Patient Health Questionnaire.ti,ab,id. ()
55 PHQ-2.ti,ab,id. ()
56 PHQ-9.ti,ab,id. ()
57 "Hospital Anxiety and Depression Scale".ti,ab,id. ()
58 Geriatric Depression Scale.ti,ab,id. ()
59 Beck Depression Inventory.ti,ab,id. ()
60 Center for Epidemiologic Studies Depression Scale.ti,ab,id. ()
61 Hamilton Depression Rating Scale.ti,ab,id. ()
62 Hamilton Rating Scale for Depression.ti,ab,id. ()
63 Montgomery-Asberg Depression Rating Scale.ti,ab,id. ()
64 Zung Self-Rating Depression Scale.ti,ab,id. ()
65 Quick Inventory of Depressive Symptoms.ti,ab,id. ()
66 Mini-Neuropsychiatric Interview.ti,ab,id. ()
67 Composite International Diagnostic Interview.ti,ab,id. ()
68 Primary Care Evaluation of Mental Disorders.ti,ab,id. ()
69 PRIME-MD.ti,ab,id. ()
70 Center for Epidemiologic Studies Depression Scale.ti,ab,id. ()
71 CES-D.ti,ab,id. ()
72 General Health Questionnaire.ti,ab,id. ()
73 GHQ-D.ti,ab,id. ()
74 Generalized Contentment Scale.ti,ab,id. ()

75 Edinburgh Postpartum Depression Scale.ti,ab,id. ()
76 EPDS.ti,ab,id. ()
77 Bromley Postnatal Depression Scale.ti,ab,id. ()
78 Postpartum Depression Screening Scale.ti,ab,id. ()
79 PDSS.ti,ab,id. ()
80 Leverton Questionnaire.ti,ab,id. ()
81 Postpartum Depression Predictors Inventory.ti,ab,id. ()
82 PDPI$.ti,ab,id. ()
83 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 ()
84 34 and 83 ()
85 random$.ti,ab,id,hw. ()
86 placebo$.ti,ab,hw,id. ()
87 controlled trial$.ti,ab,id,hw. ()
88 clinical trial$.ti,ab,id,hw. ()
89 meta analy$.ti,ab,hw,id. ()
90 metaanaly$.ti,ab,hw,id. ()
91 treatment outcome clinical trial.md. ()
92 85 or 86 or 87 or 88 or 89 or 90 or 91 ()
93 84 and 92 ()
94 limit 93 to (english language and yr="2012 -Current") ()
95 ROC curve/ ()
96 Psychometrics/ ()
97 Test Validity/ ()
98 Interrater Reliability/ ()
99 validity.ti,ab,id. ()
100 reliability.ti,ab,id. ()
101 psychometrics.ti,ab,id. ()
102 Receiver operat$.ti,ab,id. ()
103 ROC curve$.ti,ab,id. ()
104 sensitivit$.ti,ab,id. ()
105 specificit$.ti,ab,id. ()
106 predictive value.ti,ab,id. ()
107 accuracy.ti,ab,id. ()
108 false positive$.ti,ab,id. ()
109 false negative$.ti,ab,id. ()
110 miss rate$.ti,ab,id. ()
111 error rate$.ti,ab,id. ()
112 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 ()
113 84 and 112 ()
114 limit 113 to (english language and yr="2012 -Current") ()
115 94 or 114 ()

Pregnant and postpartum women – drug treatment

Database: PsycINFO <1806 to January Week 2 2015>
Search Strategy:
---
1 Pregnancy/ ()
2 Expectant Mothers/ ()
3 Prenatal Care/ ()
4 Perinatal Period/ ()
5 Postnatal Period/ ()
6 Mother Child Relations/ ()
7 pregnan$.ti,ab,id. ()
8 prenatal.ti,ab,id. ()
9 pre natal.ti,ab,id. ()
10 perinatal.ti,ab,id. ()
11 peri natal.ti,ab,id. ()
12 antenatal.ti,ab,id. ()
13 ante natal.ti,ab,id. ()
14 antepartum.ti,ab,id. ()
15 ante partum.ti,ab,id. ()
16 postnatal.ti,ab,id. ()
17 post natal.ti,ab,id. ()
18 postpartum.ti,ab,id. ()
19 post partum.ti,ab,id. ()
20 new mother$.ti,ab,id. ()
21 puerperal.ti,ab,id. ()
22 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 ()
23 Major Depression/ ()
24 Dysthymic disorder/ ()
25 Anxiety/ ()
26 depress$.ti,ab,id. ()
27 dysthym$.ti,ab,id. ()
28 (anxiety or anxious).ti,ab,id. ()
29 blues.ti,ab,id. ()
30 23 or 24 or 25 or 26 or 27 or 28 or 29 ()
31 22 and 30 ()
32 Postpartum Depression/ ()
33 Postpartum Psychosis/ ()
34 31 or 32 or 33 ()
35 Drug Therapy/ ()
36 Antidepressant Drugs/ ()
37 Serotonin Reuptake Inhibitors/ ()
38 Serotonin Norepinephrine Reuptake Inhibitors/ ()
39 Neurotransmitter Uptake Inhibitors/ ()
40 Bupropion/ ()

41 Citalopram/ ()
42 Fluoxetine/ ()
43 Fluvoxamine/ ()
44 Nefazodone/ ()
45 Paroxetine/ ()
46 Sertraline/ ()
47 Trazodone/ ()
48 Venlafaxine/ ()
49 (antidepress$ or anti depress$).ti,ab,id. ()
50 pharmacotherap$.ti,ab,id. ()
51 (psychotropic adj (drug$ or agent$ or medicat$ or medicine$)).ti,ab,id. ()
52 Serotonin$ Uptake Inhib$.ti,ab,id. ()
53 Serotonin$ Re uptake Inhib$.ti,ab,id. ()
54 Serotonin$ Reuptake Inhib$.ti,ab,id. ()
55 (serotonergic adj (drug$ or agent$ or medicat$)).ti,ab,id. ()
56 SSRI$.ti,ab,id. ()
57 SNRI$.ti,ab,id. ()
58 Neurotransmitter Uptake Inhib$.ti,ab,id. ()
59 Neurotransmitter Re uptake Inhib$.ti,ab,id. ()
60 Neurotransmitter Reuptake Inhib$.ti,ab,id. ()
61 Adrenergic Uptake Inhib$.ti,ab,id. ()
62 Adrenergic Re uptake Inhib$.ti,ab,id. ()
63 Adrenergic Reuptake Inhib$.ti,ab,id. ()
64 Norepinephrine Uptake Inhib$.ti,ab,id. ()
65 Norepinephrine Re uptake Inhib$.ti,ab,id. ()
66 Norepinephrine Reuptake Inhib$.ti,ab,id. ()
67 Dopamine Uptake Inhib$.ti,ab,id. ()
68 Dopamine Re uptake Inhib$.ti,ab,id. ()
69 Dopamine Reuptake Inhib$.ti,ab,id. ()
70 Bupropion.ti,ab,id. ()
71 Celexa.ti,ab,id. ()
72 Citalopram.ti,ab,id. ()
73 Cymbalta.ti,ab,id. ()
74 Desvenlafaxine.ti,ab,id. ()
75 Duloxetine.ti,ab,id. ()
76 Effexor.ti,ab,id. ()
77 Escitalopram.ti,ab,id. ()
78 Fluoxetine.ti,ab,id. ()
79 Fluvoxamine.ti,ab,id. ()
80 Lexapro.ti,ab,id. ()
81 Mirtazapine.ti,ab,id. ()
82 Nefazodone.ti,ab,id. ()
83 Paroxetine.ti,ab,id. ()
84 Paxil.ti,ab,id. ()
85 Pexeva.ti,ab,id. ()
86 Pristiq.ti,ab,id. ()

87 Prozac.ti,ab,id. ()
88 Remeron.ti,ab,id. ()
89 Sertraline.ti,ab,id. ()
90 Trazadone.ti,ab,id. ()
91 Venlafaxine.ti,ab,id. ()
92 Wellbutrin.ti,ab,id. ()
93 Zoloft.ti,ab,id. ()
94 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 ()
95 34 and 94 ()
96 limit 95 to animal ()
97 limit 95 to human ()
98 96 not 97 ()
99 95 not 98 ()
100 limit 99 to (english language and yr="2012 -Current") ()

Pregnancy/post-partum – psychotherapy treatment

Database: PsycINFO <1806 to January Week 2 2015>
Search Strategy:
---
1 Pregnancy/ ()
2 Expectant Mothers/ ()
3 Prenatal Care/ ()
4 Perinatal Period/ ()
5 Postnatal Period/ ()
6 Mother Child Relations/ ()
7 pregnan$.ti,ab,id. ()
8 prenatal.ti,ab,id. ()
9 pre natal.ti,ab,id. ()
10 perinatal.ti,ab,id. ()
11 peri natal.ti,ab,id. ()
12 antenatal.ti,ab,id. ()
13 ante natal.ti,ab,id. ()
14 antepartum.ti,ab,id. ()
15 ante partum.ti,ab,id. ()
16 postnatal.ti,ab,id. ()
17 post natal.ti,ab,id. ()
18 postpartum.ti,ab,id. ()
19 post partum.ti,ab,id. ()
20 new mother$.ti,ab,id. ()
21 puerperal.ti,ab,id. ()
22 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 ()

23 Major Depression/ ()
24 Dysthymic disorder/ ()
25 Anxiety/ ()
26 depress$.ti,ab,id. ()
27 dysthym$.ti,ab,id. ()
28 (anxiety or anxious).ti,ab,id. ()
29 blues.ti,ab,id. ()
30 23 or 24 or 25 or 26 or 27 or 28 or 29 ()
31 22 and 30 ()
32 Postpartum Depression/ ()
33 Postpartum Psychosis/ ()
34 31 or 32 or 33 ()
35 Psychotherapy.hw. ()
36 Counseling.hw. ()
37 Therapy.hw. ()
38 Behavior Therapy/ ()
39 Cognitive Therapy/ ()
40 Cognitive Behavior Therapy/ ()
41 Cognitive Restructuring/ ()
42 Problem Solving/ ()
43 psychotherap$.ti,ab,id. ()
44 (psychological adj5 (therap$ or treatment$ or intervention$)).ti,ab,id. ()
45 (psychosocial adj5 (therap$ or treatment$ or intervention$)).ti,ab,id. ()
46 (behavi$ adj5 (therap$ or treatment$ or intervention$)).ti,ab,id. ()
47 (cognitive adj5 (therap$ or treatment$ or intervention$)).ti,ab,id. ()
48 cbt.ti,ab,id. ()
49 (psychodynamic adj5 (therap$ or treatment$ or intervention$)).ti,ab. ()
50 (nondirective adj5 (therap$ or treatment$ or intervention$)).ti,ab,id. ()
51 (non directive adj5 (therap$ or treatment$ or intervention$)).ti,ab,id. ()
52 interpersonal therap$.ti,ab,id. ()
53 interpersonal psychotherap$.ti,ab,id. ()
54 interpersonal intervention$.ti,ab,id. ()
55 supportive therap$.ti,ab,id. ()
56 group therap$.ti,ab,id. ()
57 counsel$.ti,ab,id. ()
58 problem solving.ti,ab,id. ()
59 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 ()
60 34 and 59 ()
61 random$.ti,ab,id,hw. ()
62 placebo$.ti,ab,hw,id. ()
63 controlled trial$.ti,ab,id,hw. ()
64 clinical trial$.ti,ab,id,hw. ()
65 meta analy$.ti,ab,hw,id. ()
66 treatment outcome clinical trial.md. ()
67 61 or 62 or 63 or 64 or 65 or 66 ()

68 60 and 67 ()
69 limit 68 to (english language and yr="2012 -Current") ()

Pregnancy/post-partum – collaborative care

Database: PsycINFO <1806 to January Week 2 2015>
Search Strategy:
---
1 Pregnancy/ ()
2 Expectant Mothers/ ()
3 Prenatal Care/ ()
4 Perinatal Period/ ()
5 Postnatal Period/ ()
6 Mother Child Relations/ ()
7 pregnan$.ti,ab,id. ()
8 prenatal.ti,ab,id. ()
9 pre natal.ti,ab,id. ()
10 perinatal.ti,ab,id. ()
11 peri natal.ti,ab,id. ()
12 antenatal.ti,ab,id. ()
13 ante natal.ti,ab,id. ()
14 antepartum.ti,ab,id. ()
15 ante partum.ti,ab,id. ()
16 postnatal.ti,ab,id. ()
17 post natal.ti,ab,id. ()
18 postpartum.ti,ab,id. ()
19 post partum.ti,ab,id. ()
20 new mother$.ti,ab,id. ()
21 puerperal.ti,ab,id. ()
22 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 ()
23 Major Depression/ ()
24 Dysthymic disorder/ ()
25 Anxiety/ ()
26 depress$.ti,ab,id. ()
27 dysthym$.ti,ab,id. ()
28 (anxiety or anxious).ti,ab,id. ()
29 blues.ti,ab,id. ()
30 23 or 24 or 25 or 26 or 27 or 28 or 29 ()
31 22 and 30 ()
32 Postpartum Depression/ ()
33 Postpartum Psychosis/ ()
34 31 or 32 or 33 ()
35 Interdisciplinary Treatment Approach/ ()
36 Integrated Services/ ()
37 Collaboration/ ()

38 Cooperation/ ()
39 Case Management/ ()
40 Work Teams/ ()
41 Community Mental Health Services/ ()
42 Health Care Delivery/ ()
43 Community Psychology/ ()
44 Community Psychiatry/ ()
45 collaborat$.ti,ab,id. ()
46 interdisciplinary.ti,ab,id. ()
47 multidisciplinary.ti,ab,id. ()
48 (integrated adj5 (healthcare or care)).ti,ab,id. ()
49 care manag$.ti,ab,id. ()
50 case manag$.ti,ab,id. ()
51 cooperative care.ti,ab,id. ()
52 patient centered care.ti,ab,id. ()
53 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 48 or 49 or 50 or 51 or 52 ()
54 34 and 53 ()
55 random$.ti,ab,id,hw. ()
56 placebo$.ti,ab,hw,id. ()
57 controlled trial$.ti,ab,id,hw. ()
58 clinical trial$.ti,ab,id,hw. ()
59 meta analy$.ti,ab,hw,id. ()
60 metaanaly$.ti,ab,hw,id. ()
61 treatment outcome clinical trial.md. ()
62 55 or 56 or 57 or 58 or 59 or 60 or 61 ()
63 54 and 62 ()
64 limit 63 to (english language and yr="2009 -Current") ()

PubMed, publisher-supplied

General adult population

#5 Search #1 AND (#2 OR #3) AND #4 AND publisher[sb] AND English[Language] AND ("2009"[Date - Publication] : "2015"[Date - Publication])
#4 Search random*[tiab] OR placebo*[tiab] OR trial[tiab] OR trials[tiab] OR metaanaly*[tiab] OR "meta analysis"[tiab] OR "meta analyses"[tiab] OR "meta analytic"[tiab]
#3 Search diagnos*[title] OR detect*[title] OR identif*[title]
#2 Search screen*[tiab] OR casefinding[tiab] OR "case finding"[tiab]
#1 Search depress*[title] OR dysthym*[title] OR mental[title] OR mood[title] OR psycholog*[title] OR psychiat*[title]

Pregnant/postpartum population

#9 Search #4 OR #6 OR #8

#8 Search #1 AND #2 AND #7 AND publisher[sb] AND English[Language] AND ("2012"[Date - Publication] : "2015"[Date - Publication]
#7 Search treat*[tiab] OR therap*[tiab] OR antidepress*[tiab] OR pharmacotherap*[tiab] OR psychotropic*[tiab] OR drug*[tiab] OR medicat*[tiab] OR medicine*[tiab]
#6 Search #1 AND #2 AND #5 AND publisher[sb] AND English[Language] AND "2012"[Date - Publication] : "2014"[Date - Publication]
#5 Search screen*[tiab] OR casefinding[tiab] OR "case finding"[tiab] OR scale*[tiab] OR inventor*[tiab] OR questionnaire*[tiab] OR survey*[tiab] OR index*[tiab] OR checklist*[tiab] OR interview*[tiab] OR diagnos*[title] OR detect*[title] OR identif*[title]
#4 Search #1 AND #2 AND #3 AND publisher[sb] AND English[Language] AND "2009"[Date - Publication] : "2014"[Date - Publication]
#3 Search random*[tiab] OR placebo*[tiab] OR trial[tiab] OR trials[tiab] OR metaanaly*[tiab] OR "meta analysis"[tiab] OR "meta analyses"[tiab] OR "meta analytic"[tiab]
#2 Search depress*[title] OR dysthym*[title] OR anxiety[title] OR anxious[title] OR blues[title] OR mental[title] OR mood[title] OR psycholog*[title] OR psychiat*[title]
#1 Search pregnan*[title] OR prenatal[title] OR pre natal[title] OR perinatal[title] OR peri natal[title] OR antenatal[title] OR ante natal[title] OR antepartum[title] OR ante partum[title] OR postnatal[title] OR post natal[title] OR postpartum[title] OR post partum[title] OR mother*[title] OR maternal[title] OR puerperal[title]

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Adult population – Screening

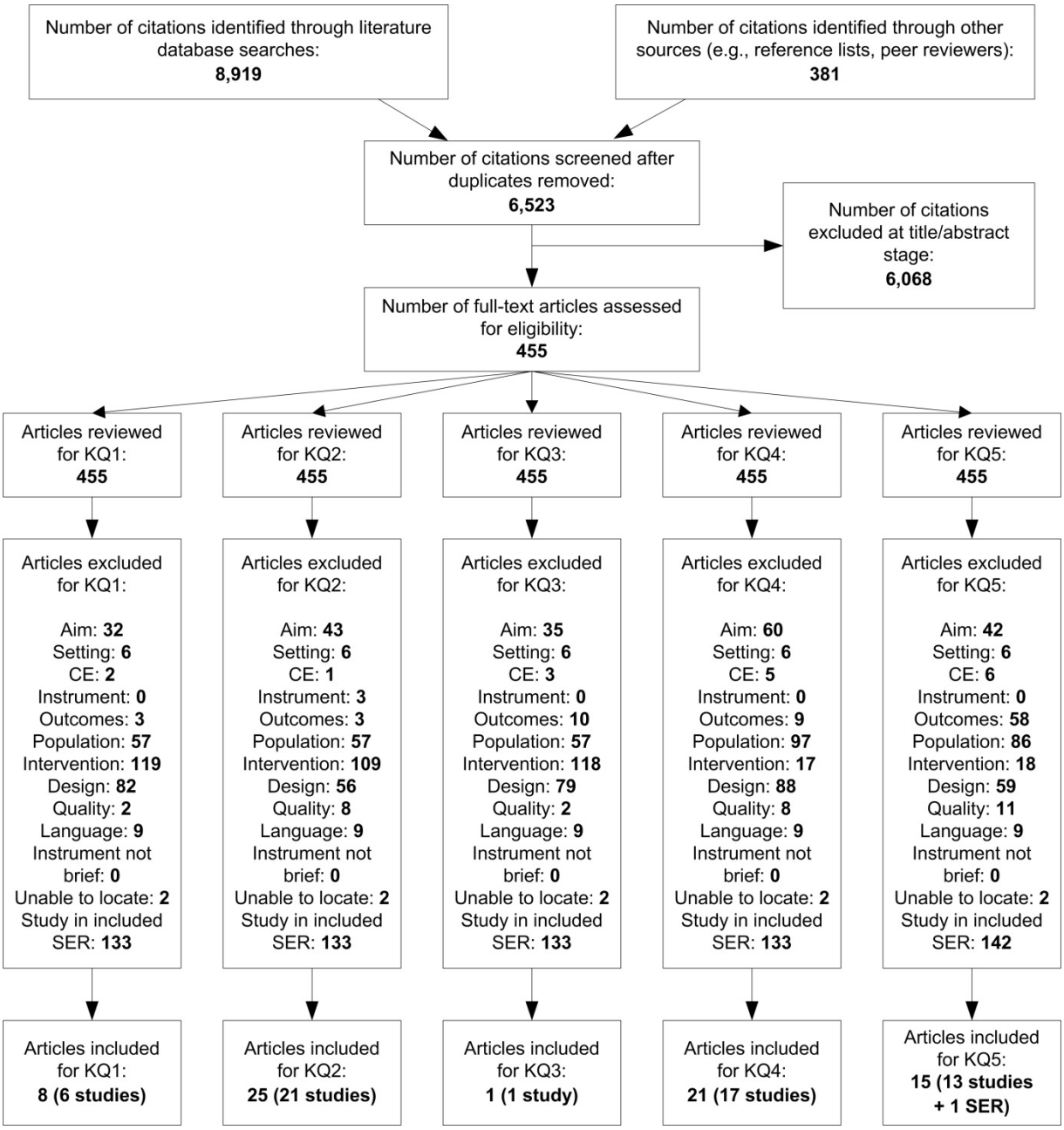
#1 (depress* or dysthym*):ti,ab,kw
#2 screen*:ti,ab,kw
#3 (casefinding or "case finding"):ti,ab,kw
#4 (detect* or identif*):ti,ab,kw
#5 diagnos*:ti
#6 #2 or #3 or #4 or #5
#7 #1 and #6 Publication Year from 2009 to 2015, in Trials

Pregnant/postpartum population - screening

#1 pregnan*:ti,ab,kw
#2 prenatal:ti,ab,kw
#3 pre natal:ti,ab,kw
#4 perinatal:ti,ab,kw
#5 peri natal:ti,ab,kw
#6 antenatal:ti,ab,kw
#7 ante natal:ti,ab,kw
#8 antepartum:ti,ab,kw
#9 ante partum:ti,ab,kw
#10 postnatal:ti,ab,kw
#11 post natal:ti,ab,kw
#12 postpartum:ti,ab,kw

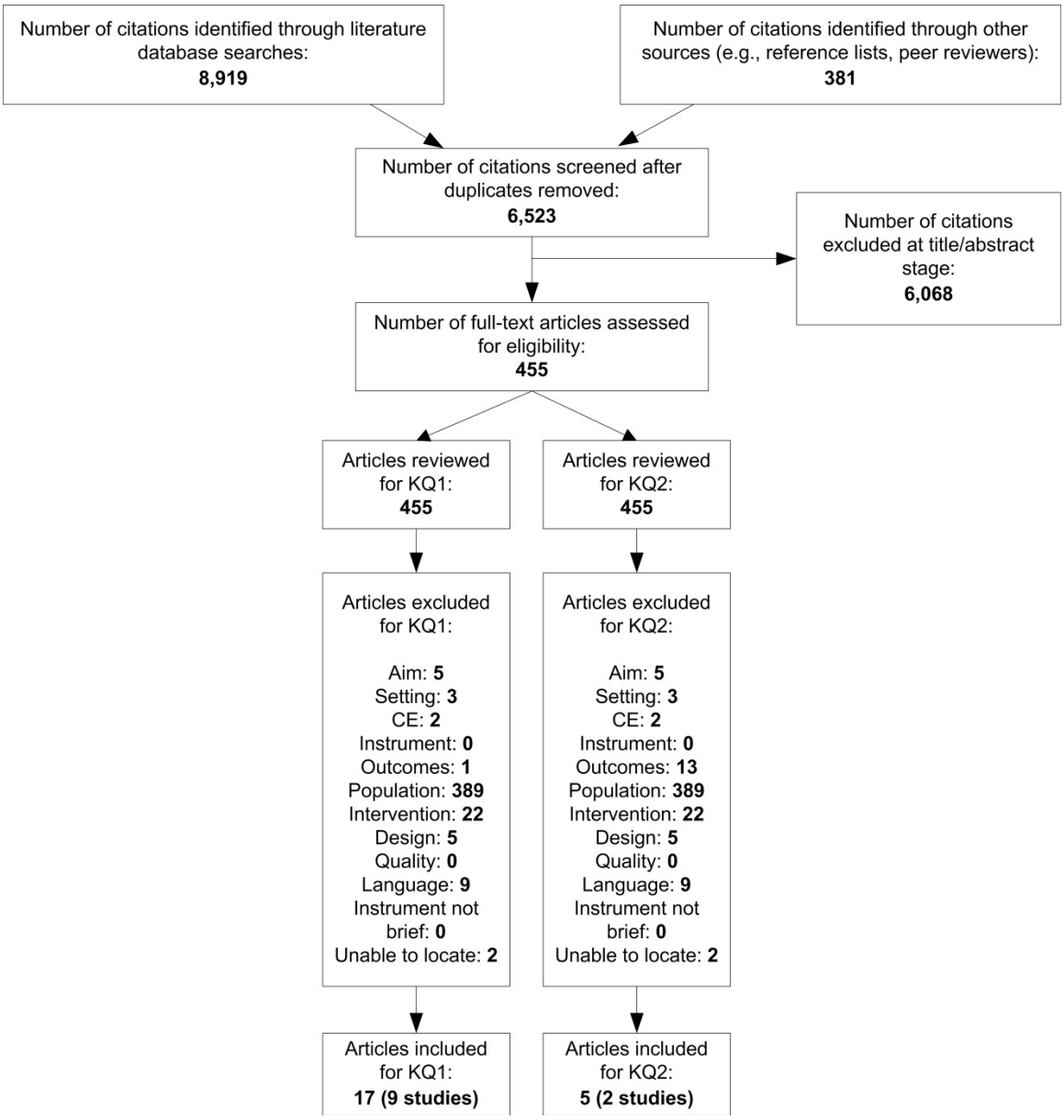
#13 post partum:ti,ab,kw
#14 (new next mother*):ti,ab,kw
#15 puerperal:ti,ab,kw
#16 or #1-#15
#17 depress$:ti,ab,kw
#18 dysthym*:ti,ab,kw
#19 (anxiety or anxious):ti,ab,kw
#20 blues:ti,ab,kw
#21 #17 or #18 or #19 or #20
#22 #16 and #21 Publication Year from 2009 to 2015, in Trials

Appendix B Figure 1. Literature Flow Diagram: Pregnant and Postpartum Women



Abbreviations: CE = comparative effectiveness; KQ = Key Question.

Appendix B Figure 2. Literature Flow Diagram: General Adult Population, Including Older Adults



Abbreviations: CE = comparative effectiveness; KQ = Key Question; SER = systematic evidence review.

Appendix B Table 1. Inclusion and Exclusion Criteria: General Adult Population, Including Older Adults

Category	Inclusion criteria	Exclusion criteria
Condition definition	Focus on major depressive disorder, persistent depressive disorder/dysthymia, and depression not otherwise specified, or "depression" with no further diagnostic specificity	Trials restricted only to persons with bipolar disorder, schizoaffective disorder, seasonal affective disorder, cyclothymia, substance-induced mood disorder, minor depression, or adjustment disorder with depressed mood
Aim	Studies targeting depression screening	Studies restricted to screening or treatment of suicidality, bipolar disorder, or treatment-resistant depression
Population	Adults, including older adults, age 18 years and older	• Nonhuman populations • Children and adolescents (age <18 years), except when related to harms of antidepressants in pregnant women • Persons in institutions (e.g., psychiatric inpatients or prison inmates) • Persons in long-term care (e.g., nursing homes) • Trials limited to persons with comorbid conditions • Trials within closed preexisting social networks (e.g., church, worksite programs)
Intervention	Brief standardized instrument designed to identify persons with depression (no more than 15 minutes if completed prior to visit, no more than 5 minutes if completed during visit); self-report, clinician-administered, or electronically delivered	Trials primarily using treatment modalities other than psychotherapy or FDA-approved antidepressants (e.g., exercise, electroshock treatment, St. John's wort, social marketing, policy, system-level interventions, or adjunctive agents to enhance the effects of antidepressants)
Comparator	Usual care, no screening, and screening with no feedback of results to providers	
Outcomes	**Benefits of screening (KQ 1):** *Primary health outcomes* • Depression symptoms • Depression remission • *Other health outcomes* • Depression response • Suicide deaths, attempts, or ideation • All-cause mortality • Quality of life • Functioning (including days of missed work) • Change in health status (e.g., improvement in comorbid conditions or reduction in physical complaints) • Emergency department visits or inpatient stays **Harms of screening (KQ 2):** • Treatment avoidance • Deterioration in patient-provider relationship • Other harms reported by screening trials • Labeling or stigma • Inappropriate/unnecessary treatment	
Timing of outcome assessment	≥6 weeks after baseline	

Appendix B Table 1. Inclusion and Exclusion Criteria: General Adult Population, Including Older Adults

Category	Inclusion criteria	Exclusion criteria
Setting	• Primary care settings (e.g., internal medicine, family medicine, obstetrics/gynecology, family planning, military health clinics, university-based health clinics) • Virtual (e.g., online screening tools), if patients are identified through screening in primary care or other population-based screening • Psychotherapy: Mental health clinic setting acceptable only if patients are identified through screening in primary care or other population-based screening	• Community/university research laboratories or other nonmedical centers • Mental health clinics (unless recruitment is through primary care screening) • Correctional facilities • School classrooms • Worksites • Inpatient/residential facilities • Emergency departments
Study design	RCTs, CCTs	All other study designs
Country	Countries categorized as "Very High" on the Human Development Index (as defined by the World Health Organization): Andorra, Argentina, Australia, Austria, Barbados, Belgium, Brunei, Canada, Chile, Croatia, Cyprus , Czech Republic , Denmark , Estonia, Finland, France , Germany, Greece, Hong Kong, Hungary, Iceland, Ireland, Israel, Italy , Japan, Korea Rep , Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, New Zealand , Norway, Poland , Portugal, Qatar, Seychelles, Singapore, Slovakia/Slovak Republic, Slovenia, Spain, Sweden, Switzerland, United Arab Emirates, United Kingdom, United States + Taiwan.	Countries not categorized as "Very High" on the Human Development Index
Language	English	Languages other than English
Study quality	Fair or good	Poor, according to design-specific USPSTF criteria

Abbreviations: FDA = Food and Drug Administration; KQ = Key Question; RCT = randomized, controlled trial; CCT = controlled clinical trial.

Appendix B Table 2. Inclusion and Exclusion Criteria: Pregnant and Postpartum Women

Category	Inclusion criteria	Exclusion criteria
Condition definition	Focus on major depressive disorder, persistent depressive disorder/dysthymia, and depression not otherwise specified, or "depression" with no further diagnostic specificity	Trials restricted only to persons with bipolar disorder, schizoaffective disorder, seasonal affective disorder, cyclothymia, substance-induced mood disorder, minor depression, or adjustment disorder with depressed mood
Aim	**Screening (KQs 1, 3) and treatment (KQs 4, 5):** Studies targeting depression screening and treatment **Diagnostic accuracy of screening (KQ 2):** Studies addressing accuracy of depression screening instruments **Harms of antidepressants (KQ 5):** Studies addressing harms of antidepressants	Studies restricted to screening or treatment of suicidality, bipolar disorder, or resistant depression
Population	**Screening (KQs 1, 3):** Pregnant and postpartum women age 18 years and older **Treatment (KQs 4, 5):** Pregnant and postpartum women who screen positive for depression in a primary care setting or are identified through other population-based screening	• Nonhuman populations • Children and adolescents (age <18 years), except when related to harms of antidepressants in pregnant women • Persons in institutions (e.g., psychiatric inpatients or prison inmates) • Persons in long-term care (e.g., nursing homes) • Trials limited to persons with comorbid conditions • Trials within closed preexisting social networks (e.g., church, worksite programs)
Intervention	**Screening (KQs 1, 3):** Brief standardized instrument designed to identify persons with depression (no more than 15 minutes if completed prior to visit, no more than 5 minutes if completed during visit); self-report, clinician-administered, or electronically delivered **Instrument accuracy (KQ 2):** Limited to the most widely used screening tools in this population—the Patient Health Questionnaire (PHQ), in any form, including the related Primary Care Evaluation of Mental Disorders Patient Questionnaire (PRIME-MD, depression section), and the Edinburgh Postpartum Depression Scale (EPDS) **Treatment (KQs 4, 5):** Primary care–relevant interventions, including psychotherapy, FDA-approved antidepressants (except tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors[MAOIs], and collaborative care	Treatment modalities other than psychotherapy or FDA-approved antidepressants (e.g., exercise, electroshock treatment, St. John's wort, social marketing, policy, system-level interventions, or adjunctive agents to enhance the effects of antidepressants); TCAs and MAOIs

Appendix B Table 2. Inclusion and Exclusion Criteria: Pregnant and Postpartum Women

Category	Inclusion criteria	Exclusion criteria
Comparator	**Screening (KQs 1, 3):** Usual care, no screening, and screening with no feedback of results to providers **Treatment (KQs 4, 5):** *Psychotherapy* • No intervention • Usual care • Waitlist • Attention control • Minimal intervention (e.g., usual care limited to no more than 15 minutes of information) *Antidepressants* • No intervention • Placebo • Waitlist *Collaborative care* • Usual care	**Treatment (KQs 4, 5):** Active intervention (i.e., comparative effectiveness)

Appendix B Table 2. Inclusion and Exclusion Criteria: Pregnant and Postpartum Women

Category	Inclusion criteria	Exclusion criteria
Outcomes	**Benefits of screening (KQ 1) and treatment (KQ 4):** *Primary health outcomes* • Depression symptoms • Depression remission *Other health outcomes* • Depression response • Suicide deaths, attempts, or ideation • All-cause mortality • Quality of life • Functioning (including days of missed work) • Change in health status (e.g., improvement in comorbid conditions or reduction in physical complaints) • Child/infant outcomes (continuation of breastfeeding, achievement of recognized developmental milestones, reduced abuse or neglect) • Emergency department visits or inpatient stays **Diagnostic accuracy of screening (KQ 2):** • Sensitivity • Specificity • Positive predictive value • Negative predictive value • Equivalent data to make such calculations (i.e., 2 x 2 table) **Harms of screening (KQ 3):** • Treatment avoidance • Deterioration in patient-provider relationship • Other harms reported by screening trials • Labeling or stigma • Inappropriate/unnecessary treatment **Harms of antidepressant treatment (KQ 5):** • Suicidality • Serotonin syndrome • Cardiac effects • Seizures (bupropion only) • Fetal/infant harms (neonatal death, major malformations, small for gestational age/low birth weight, preeclampsia)	
Timing of outcome assessment	**Screening (KQs 1, 3):** ≥6 weeks after baseline **Diagnostic accuracy of screening (KQ 2):** Maximum of 2 weeks between screening and reference standard **Treatment (KQs 4, 5):** • ≥6 weeks after baseline for treatment and harms of psychotherapy or collaborative care • No minimum followup for harms of antidepressants	

Appendix B Table 2. Inclusion and Exclusion Criteria: Pregnant and Postpartum Women

Category	Inclusion criteria	Exclusion criteria
Setting	• Primary care settings (e.g., internal medicine, family medicine, obstetrics/gynecology, pediatrics [for postpartum screening], family planning, military health clinics, university-based health clinics) • Virtual (e.g., online screening tools), if patients are identified through screening in primary care or other population-based screening • Psychotherapy: Mental health clinic setting acceptable only if patients are identified through screening in primary care or other population-based screening **Harms of antidepressant treatment (KQ 5):** Any outpatient clinical setting	• Community/university research laboratories or other nonmedical centers • Mental health clinics (unless recruitment is through primary care screening) • Correctional facilities • School classrooms • Worksites • Inpatient/residential facilities • Emergency departments
Study design	**Benefits of screening (KQ 1), harms of screening (KQ 3), and benefits of treatment (KQ 4):** RCTs, CCTs **Diagnostic accuracy (KQ 2):** Comparison with gold standard (structured or semistructured diagnostic interview or a nonbrief [>5 minutes] unstructured interview with mental health clinician) within 2 weeks of screening in populations that include a full spectrum of patient severity for the given setting (i.e., studies cannot limit the patient pool to only nondepressed and known/highly likely depressed patients) **Harms of antidepressant treatment (KQ 5):** Systematic reviews; large comparative cohort or case-control observational studies published after identified systematic reviews that include observational studies. "Large" is operationalized as: • n ≥10,000 with at least 6 months of followup for suicide attempts and deaths • n ≥1,000 with at least 3 months of followup for other outcomes	All other study designs
Country	Countries categorized as "Very High" on the Human Development Index (as defined by the World Health Organization): Andorra, Argentina, Australia, Austria, Barbados, Belgium, Brunei, Canada, Chile, Croatia, Cyprus , Czech Republic , Denmark , Estonia, Finland, France , Germany, Greece, Hong Kong, Hungary, Iceland, Ireland, Israel, Italy , Japan, Korea Rep , Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, New Zealand , Norway, Poland , Portugal, Qatar, Seychelles, Singapore, Slovakia/Slovak Republic, Slovenia, Spain, Sweden, Switzerland, United Arab Emirates, United Kingdom, United States + Taiwan.	Countries not categorized as "Very High" on the Human Development Index
Language	English	Languages other than English
Study quality	Fair or good	Poor, according to design-specific USPSTF criteria

Abbreviations: FDA = Food and Drug Administration; KQ = Key Question; RCT = randomized, controlled trial; CCT = controlled clinical trial.

Appendix B Table 3. Quality Assessment Criteria

Study Design	Adapted Quality Criteria
Randomized controlled trials, adapted from the U.S. Preventive Services Task Force methods[94]	• Valid random assignment? • Was allocation concealed? • Was eligibility criteria specified? • Were groups similar at baseline? • Was there a difference in attrition between groups? • Were outcome assessors blinded? • Were measurements equal, valid and reliable? • Was there intervention fidelity? • Was there risk of contamination? • Was there adequate adherence to the intervention? • Were the statistical methods acceptable? • Was the handling of missing data appropriate? • Was there acceptable followup? • Was there evidence of selective reporting of outcomes?
Observational studies (e.g., prospective cohort studies), adapted from the Newcastle-Ottawa Scale (NOS)[96]	• Was there representativeness of the exposed cohort? • Was the non-exposed systematically selected? • Was the ascertainment of exposure reported? • Was eligibility criteria specified? • Were groups similar at baseline? • Was the outcome of interest not present at baseline? • Were measurements equal, valid and reliable? • Were outcome assessors blinded? • Was followup long enough for the outcome to occur? • Was there acceptable followup? • Was there adjustment for confounders? • Were the statistical methods acceptable? • Was the handling of missing data appropriate?

Diagnostic accuracy studies, adapted from the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) II instrument[95]	• Could the selection of patients have introduced bias?
	  o Was a consecutive or random sample of patients enrolled?
	  o Was a case-control design avoided?
	  o Did the study avoid inappropriate exclusions?
	• Could the conduct or interpretation of the index test have introduced bias?
	  o Was the index test interpreted without knowledge of the reference standard results?
	  o If a threshold was use, was it pre-specified?
	  o Was staff trained in the use of the index test?
	  o Was the fidelity of the index test monitored and/or reported?
	• Could the conduct or interpretation of the reference standard have introduced bias?
	  o Is the reference standard likely to correctly classify the target condition?
	  o Was the reference standard interpreted without knowledge of the index test results?
	  o Was staff trained in the assessment of the reference standard?
	  o Was the fidelity of the reference test monitored and/or reported?
	• Could the patient flow have introduced bias?
	  o Was there an appropriate interval between the index test and reference standard?
	  o Did all patients receive the same reference standard?
	  o Did the whole or partial selection of patients receive the reference standard? If so, was it adjusted?
	  o Was the order of tests randomized among patients?
	  o Did all participants complete both the index test and reference standard?
	  o Were all patients included in the analysis?

Appendix B Table 3. Quality Assessment Criteria

Study Design	Adapted Quality Criteria
Assessment of Multiple Systematic Reviews (AMSTAR)[97]	• Was an 'a priori' design provided? • Was there dual study selection? • Was there dual data extraction? • Was a comprehensive literature search performed? • Was a list of studies included provided? • Was a list of excluded studies provided? • Were the characteristics of the included studies provided? • Was the scientific quality of the included studies assessed and documented? • Was the scientific quality of the included studies used appropriately in formulating conclusions? • Were the methods used to combine the findings of studies appropriate? • Was the likelihood of publication bias assessed? • Were potential conflicts of interest/source(s) of support of the systematic review stated? • Were potential conflicts of interest/source(s) of support of the included studies stated?

Appendix C. Excluded Studies

Reason for Exclusion
E1. Study relevance a. Not a trial of depression screening, treatment, or a study of instrument accuracy b. Other
E2. Setting (e.g., schools or classroom-based; inpatient; institutional/residential; workplace; churches; military; other closed social networks or institutional) a. Non-HDI country
E3. Comparative effectiveness
E4. KQ2: Screening instrument (or section of instrument) does not target depression specifically a. Did not use the PHQ or EPDS
E5. No relevant outcomes
E6. Population a. Limited to those with chronic psychotic disorder (e.g., schizophrenia); mental health condition other than depression, substance abuse, PTSD, bipolar, borderline personality disorder; medical condition b. No data specific to the population of interest c. For KQ4p: non-depressed population d. For KQ4p: no population-based screening for recruitment
E7. Intervention a. Not one of the specified interventions b. Not primary care feasible or referable c. Not a screening study d. Only intervention group was screened
E8. Study design
E9. Study quality a. High or differential attrition b. Other quality issue c. Cohort/case-control studies of harms of antidepressants: Fewer than 10 cases among exposed or unexposed (or few than 10 with exposure among cases or controls)
E10. Non-English
E11. Instrument not brief (>15 min self-report instrument to complete in waiting room, >5 min to complete with clinician), or otherwise not feasible for primary-care-based screening
E12. Unable to locate article
E13. SER included in the McDonagh 2014 review
E14. Study included in the McDonagh 2014 review

Abbreviations: EPDS = Edinburgh Postnatal Depression Scale; HDI = human development index; KQ = Key Question; PHQ = Patient Health Questionnaire; PTSD = post-traumatic stress disorder; SER = systematic evidence review

1. Adouard F, Glangeaud-Freudenthal NM, Golse B. Validation of the Edinburgh postnatal depression scale (EPDS) in a sample of women with high-risk pregnancies in France. Arch Womens Ment Health 2005 Jun;8(2):89-95. PMID: 15883653. **KQ1gE6b, KQ2gE6b, KQ1pE8, KQ3pE8, KQ4pE1, KQ5pE1.**
2. Aguado J, Campbell A, Ascaso C, et al. Examining the factor structure and discriminant validity of the 12-item General Health Questionnaire (GHQ-12) among Spanish postpartum women. Assessment 2012 Dec;19(4):517-25. PMID: 21075958. **KQ1gE6b, KQ2gE6b, KQ1pE8, KQ2pE8, KQ3pE8, KQ4pE8, KQ5pE8.**
3. Alexopoulos GS, Reynolds CF, III, Bruce ML, et al. Reducing suicidal ideation and depression in older primary care patients: 24-month outcomes of the PROSPECT study. Am J Psychiatry 2009 Aug;166(8):882-90. PMID: 19528195. **KQ1gE7c, KQ2gE7c, KQ1pE6b, KQ2pE6b, KQ3pE6b, KQ4pE6b, KQ5pE6b.**
4. Almeida OP, Pirkis J, Kerse N, et al. A randomized trial to reduce the prevalence of depression and self-harm behavior in older primary care patients. Ann Fam Med 2012 Jul;10(4):347-56. PMID: 22778123. **KQ1gE7c, KQ2gE7c, KQ1pE6b, KQ2pE6b, KQ3pE6b, KQ4pE6b, KQ5pE6b.**

5. Altamura AC, De Gaspari IF, Rovera C, et al. Safety of SSRIs during pregnancy: a controlled study. Hum Psychopharmacol 2013 Jan;28(1):25-8. PMID: 23166037. **KQ1gE6b, KQ2gE6b, KQ1pE7c, KQ2pE7c, KQ3pE7c, KQ4pE8, KQ5pE5.**
6. Alvarado-Esquivel C, Sifuentes-Alvarez A, Salas-Martinez C. Validation of the edinburgh postpartum depression scale in a population of adult pregnant women in Mexico. J Clin Med Res 2014 Oct;6(5):374-8. PMID: 25110542. **KQ1gE6b, KQ2gE6b, KQ1pE2a, KQ2pE2a, KQ3pE2a, KQ4pE2a, KQ5pE2a.**
7. Alvarado R, Jadresic E, Guajardo V, et al. First validation of a Spanish-translated version of the Edinburgh postnatal depression scale (EPDS) for use in pregnant women. A Chilean study. Arch Womens Ment Health 2014 Oct 11 PMID: 25300676. **KQ1gE6b, KQ2gE6b, KQ1pE5, KQ3pE5, KQ4pE7c, KQ5pE7c.**
8. Alwan S, Reefhuis J, Rasmussen SA, et al. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med 2007 Jun 28;356(26):2684-92. PMID: 17596602. **KQ1gE6b, KQ2gE6b, KQ1pE14, KQ2pE14, KQ3pE14, KQ4pE14, KQ5pE14.**
9. Alwan S, Reefhuis J, Botto LD, et al. Maternal use of bupropion and risk for congenital heart defects. Am J Obstet Gynecol 2010 Jul;203(1):52-6. PMID: 20417496. **KQ1gE6b, KQ2gE6b, KQ1pE14, KQ2pE14, KQ3pE14, KQ4pE14, KQ5pE14.**
10. Ammerman RT, Putnam FW, Altaye M, et al. Treatment of depressed mothers in home visiting: impact on psychological distress and social functioning. Child Abuse Negl 2013 Aug;37(8):544-54. PMID: 23623623. **KQ1gE6b, KQ2gE6b, KQ1pE7c, KQ2pE7c, KQ3pE7c, KQ5pE5.**
11. Ammerman RT, Putnam FW, Altaye M, et al. A clinical trial of in-home CBT for depressed mothers in home visitation. Behav Ther 2013 Sep;44(3):359-72. PMID: 23768664. **KQ1gE6b, KQ2gE6b, KQ1pE7c, KQ2pE7c, KQ3pE7c, KQ5pE5.**
12. Ammerman RT, Altaye M, Putnam FW, et al. Depression improvement and parenting in low-income mothers in home visiting. Arch Womens Ment Health 2014 Nov 5 PMID: 25369906. **KQ1gE6b, KQ2gE6b, KQ1pE7c, KQ2pE7c, KQ3pE7c, KQ5pE5.**
13. Ammerman RT, Peugh JL, Teeters AR, et al. Child maltreatment history and response to CBT treatment in depressed mothers participating in home visiting. J Interpers Violence 2014 Nov 13 PMID: 25395221. **KQ1gE6b, KQ2gE6b, KQ1pE7c, KQ2pE7c, KQ3pE7c, KQ5pE5.**
14. Ammerman RT, Putnam FW, Stevens J, et al. An open trial of in-home CBT for depressed mothers in home visitation. Matern Child Health J 2011;15(8):1333-41. PMID: 20936338. **KQ1gE6b, KQ2gE6b, KQ1pE7c, KQ2pE7c, KQ3pE7c, KQ4pE9a, KQ5pE9a.**
15. Andersen JT, Andersen NL, Horwitz H, et al. Exposure to selective serotonin reuptake inhibitors in early pregnancy and the risk of miscarriage. Obstet Gynecol 2014 Oct;124(4):655-61. PMID: 25198261. **KQ1gE6b, KQ2gE6b, KQ1pE8, KQ2pE8, KQ3pE8, KQ4pE8.**
16. Andrade C. Antidepressant use in pregnancy and risk of autism spectrum disorders: a critical examination of the evidence. J Clin Psychiatry 2013 Sep;74(9):940-1. PMID: 24107768. **KQ1gE6b, KQ2gE6b, KQ1pE7c, KQ2pE7c, KQ3pE7c, KQ4pE8, KQ5pE8.**
17. Andrade C. Antenatal exposure to selective serotonin reuptake inhibitors and duration of gestation. J Clin Psychiatry 2013 Jul;74(7):e633-e635. PMID: 23945457. **KQ1gE6b, KQ2gE6b, KQ1pE8, KQ2pE8, KQ3pE8, KQ4pE8, KQ5pE8.**
18. Andrade C. The safety of duloxetine during pregnancy and lactation. J Clin Psychiatry 2014 Dec;75(12):e1423-e1427. PMID: 25551238. **KQ1gE6b, KQ2gE6b, KQ1pE8, KQ2pE8, KQ3pE8, KQ4pE8, KQ5pE8.**
19. Andrade SE, McPhillips H, Loren D, et al. Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn. Pharmacoepidemiol Drug Saf 2009 Mar;18(3):246-52. PMID: 19148882. **KQ1gE6b, KQ2gE6b, KQ1pE14, KQ2pE14, KQ3pE14, KQ4pE14, KQ5pE14.**
20. Appleby L, Warner R, Whitton A, et al. A controlled study of fluoxetine and cognitive-behavioural counselling in the treatment of postnatal depression. BMJ 1997 Mar 29;314(7085):932-6. PMID: 9099116. **KQ1gE6b, KQ2gE6b, KQ1pE7c, KQ2pE7c, KQ3pE7c.**

21. Armstrong S, Small R. Screening for postnatal depression: not a simple task. Aust N Z J Public Health 2007 Feb;31(1):57-61. PMID: 17333610. **KQ1gE6b, KQ2gE6b, KQ1pE8, KQ2pE8, KQ3pE8, KQ4pE8, KQ5pE8.**

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406. Toh S, Mitchell AA, Louik C, et al. Selective serotonin reuptake inhibitor use and risk of gestational hypertension. Am J Psychiatry 2009 Mar;166(3):320-8. PMID: 19122006. **KQ1gE6b, KQ2gE6b, KQ1pE14, KQ2pE14, KQ3pE14, KQ4pE14, KQ5pE14.**

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Appendix D Table 1. Detailed Intervention Characteristics of Included Studies for Key Questions 1 and 3 (Pregnant and Postpartum Women)

Author, Year and Quality	Group	Intervention Name	DetailedDescription	Provider
Leung, 2011[104] Good	IG	Screening	EPDS used to identify pts w/ postnatal depression; those w/ scores ≥ 9/10 or suicidal ideation (positive answer to question 10) offered non-directive counseling by nurses or management by the community psychiatric team as appropriate. Nurses underwent 12-hour training course (3 hour lecture on postnatal depression and 9 hour workshop on non-directive counseling) in addition to basic professional and in-service training; also received ongoing support from doctors and community psychiatric team. Counseling lasted about 30-45 minutes, doctor not involved in study made final management recommendation according to protocol.	Nurse
	CG	Training in nondirective counseling	Nurses carried out usual clinical assessments; mothers deemed necessary to require further management were offered non-directive counseling or psychiatric referral. Nurses underwent 12-hour training course (3 hour lecture on postnatal depression and 9 hour workshop on non-directive counseling) in addition to basic professional and in-service training; also received ongoing support from doctors and community psychiatric team. Counseling lasted about 30-45 minutes, doctor not involved in study made final management recommendation according to protocol.	Nurse
Wickberg, 2005[106] Fair	IG	Screening results + brief depression training	Midwives received information about aim of study; also received a one-afternoon session about different aspects of depression (e.g., symptoms, aetiology and effects) and about the value of listening and support. All women took EPDS at gestational week 25 and week 36; those who scored ≥ 12 at week 25 were phoned to ask for permission to disclose score to midwife.	Midwife
	CG	Screening, no results to provider	Midwives received information about aim of study. All women took EPDS at gestational week 25 and week 36; no scores were disclosed to pts or midwives.	Midwife
Yawn, 2012[69] Fair	IG	Screening results + provider training & supports	All women screened w/ EPDS and PHQ-9, providers have routine access to screening test results. Training for multistep postpartum depression screening and diagnosis process, practices provided w/ a set of tools to facilitate diagnosis, followup and postpartum depression management including an immediate action protocol, outline for followup visits and nurse calls, medication information, self-help sheets, and partner's sheets.	Physician
	CG	Screening, no results to provider	All women screened w/ EPDS and PHQ-9, no routine access to screening test results. 30-minute presentation about postpartum depression. Practices continued to provide the same postpartum and mental health care or referall as before study inception; crossed over to intervention after 24 months.	Physician
MacArthur, 2002[105] Fair	IG	Screening + midwife training & supports	Care led by midwives w/ referral to GP as needed. Systematic screening at 4 week postpartum, midwives trained in postpartum depression care. Symptom checklist at first visit, day 10 and 28, and at discharge (10-12 weeks); EPDS for depression screening at day 28 and discharge. Care plans made and visits scheduled based on symptoms and EPDS results. 10 evidence-based guidelines, summarized in leaflets, were used for subsequent midwife management of physical and psychological disorders. All midwives also trained in general postnatal care, health and trial design. Continuing contact w/ midwives included monthly visit from a study midwife, daily telephone availability for consultations and monthly newsletters.	Midwife

Appendix D Table 1. Detailed Intervention Characteristics of Included Studies for Key Questions 1 and 3 (Pregnant and Postpartum Women)

Author, Year and Quality	Group	Intervention Name	DetailedDescription	Provider
	CG	Attention control for midwives	Midwives trained in postnatal care, health, and trial design, specifically studies of midwifery practice (attention control); written materials also provided. Continuing contact w/ midwives incuded monthly visit from a study midwife, daily telephone availability for consultations, and monthly newsletters. Community postnatal care usually consists w/ ~7 midwife home visits 10-14 days after birth (can continue to 28 days); and care from health visitors thereafter; some health visitors use the EPDS to screen for depression. GP routine home visit and final 6-8 week check.	Midwife
Morrell, 2009a (RM2322) Fair	IG1	Screening + intervention (combined)	Health visitors trained (manualized) to identify depressive symptoms using EPDS (face-to-face and/or postal) and to use clinical assessment skills to assess mother's mood including suicidal thoughts; trained to deliver psychologically informed sessions based on CBT or person-centered principles. At-risk women (EPDS scores ≥ 12; found to be moderately to severely depressed via interview) asked to state their preference for psychological sessions, SSRI or both. All other women offered usual care or psychological session if assessment indicates woman might benefit. EPDS assessments at 6 and 8 weeks postpartum, health visitor or GP informed if score ≥ 12.	Health visitor
	IG2	Screening + CBT	Health visitors trained in CBT and depression identification. CBT emphasized the identification of unhelpful patterns of behaviors, perceptions, or thoughts. These patterns were considered common and normal, and understanding of these patterns provided opportunities to make active change and test out new ways of thinking and behaving.	Health visitor
	IG3	Screening + person-centered counseling	Health visitors trained in person-centered approach to counseling and depression identification; health visitors provided opportunities to explore difficulties with another, who listened non-judgementally and reflected empathically, allowing the women to feel validated and facilitating their ability to manage their distress and find their own solutions.	Health visitor
	CG	Screening, no results to provider	Usual care; EPDS score not revealed	Health visitor
Glavin, 2010[103] Fair	IG	Screening + redesigned followup care	Home visit about 2 weeks postpartum w/ increased focus on maternal mental health (e.g., brochure); one supportive counseling session by public health nurse after EPDS completed at 6 weeks postpartum (20 min session w/ active listening and emphatic communication); supportive counseling for the depressed mothers (30 min session, individualized); openness about mental health issues at every visit at clinic; system for referral to further treatment in municipality. Nurses received 5 days of training about postpartum depression w/ monthly supervision by psychologists.	Public health nurse visitor
	CG	Usual Care	No training related to postpartum depression; standard care included home visit and followup appointments; no focused on mother's mental health	Public health nurse visitor

Abbreviations: CBT = cognitive behavioral therapy; CG = control group; EPDS = Edinburgh Postnatal Depression Scale; GP = general practitioner; IG = intervention group; PHQ = Patient Health Questionnaire; w/ = with.

Appendix D Table 2. Results From Included Studies for Key Question 1 (Pregnant and Postpartum Women): Depression

Author, Year and Quality	Subgroup	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
Depression Prevalence							
Glavin, 2010[103] Fair	All participants	EPDS ≥ 10, n (%)	1.5	IG	164 (9.1)	65 (4.3)	OR 0.4 (95% CI, 0.3 to 0.6), p=NR
				CG	64 (14.5)	42 (10.4)	
			4.5	IG	164 (9.1)	40 (3.6)	OR 0.5 (95% CI, 0.3 to 0.8), p=NR
				CG	64 (14.5)	32 (8.8)	
Leung, 2011[104] Good	All participants	EPDS score ≥ 10, n (%)	4	IG	NR	30 (13)	RR 0.59 (95% CI, 0.39 to 0.89), p=NR
				CG	NR	51 (22.1)	
			16	IG	NR	34 (17.4)	RR 1.10 (95% CI, 0.70 to 1.73), p=NR
				CG	NR	31 (13.4)	
MacArthur, 2002[105] Fair	All participants	EPDS score ≥ 13, n (%)	3	IG	NR	115 (14.4)	OR 0.47 (95% CI, 0.31 to 0.76), p=NR*
				CG	NR	149 (21.2)	
Morrell, 2009a[99] Fair	All participants	EPDS score ≥ 12, n (%)	5	IG1	404 (17.7)	205 (11.7)	IG1 vs. CG: OR 0.67 (95% CI, 0.52 to 0.86), p=0.002† IG2 vs. CG: OR 0.64 (95% CI, 0.46 to 0.89), p=0.0007† IG3 vs. CG: OR 0.70 (95% CI, 0.53 to 0.91), p=0.008†
				IG2	215 (18.7)	98 (11.6)	
				IG3	189 (16.8)	107 (11.9)	
				CG	191 (16.3)	150 (16.4)	
Wickberg, 2005[106] Fair	All participants	EPDS score ≥ 12, n (%)	2.75	IG	48 (15.1)	26 (9.5)	NR, p<0.0001
				CG	45 (12.8)	40 (11.6)	
Depressive Symptoms							
Glavin, 2010[103] Fair	All participants	EPDS score, median	1.5	IG	3.97 (95% CI, 0 to 25)	2.89 (95% CI, 0 to 23)	NR
				CG	5.09 (95% CI, 0 to 19)	4.01 (95% CI, 0 to 22)	
			4.5	IG	3.97 (95% CI, 0 to 25)	1.96 (95% CI, 0 to 24)	NR
				CG	5.09 (95% CI, 0 to 19)	4.05 (95% CI, 0 to 19)	

Appendix D Table 2. Results From Included Studies for Key Question 1 (Pregnant and Postpartum Women): Depression

Author, Year and Quality	Subgroup	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
Leung, 2011[104] Good	All participants	EPDS score, mean	4	IG	NR	5.14 (95% CI, 4.67 to 5.60)	NR, p<0.001
				CG	NR	6.50 (95% CI, 5.94 to 7.07)	
			16	IG	NR	5.77 (95% CI, 5.27 to 6.28)	NR, p=0.819
				CG	NR	5.85 (95% CI, 5.39 to 6.31)	
MacArthur, 2002[105] Fair	All participants	EPDS, mean (SD)	3	IG	NR	6.40	Mean Difference -2.68 (95% CI, -3.46 to -1.89), p=NR*
				CG	NR	8.06	
Morrell, 2009a[99] Fair	All participants	EPDS score, mean (SD)	5	IG1	6.6 (4.8)	5.5 (4.7)	IG1 vs. CG: Mean Difference -0.8 (95% CI, -1.2 to -0.4), p=0.000†
				IG2	NR	5.4	
				IG3	NR	5.5	
				CG	6.8 (5.0)	6.4 (5.2)	
	Depressed women at baseline (EPDS ≥ 12 at 6 weeks postpartum)	EPDS score, mean (SD)	5	IG1	15.1 (2.9)	9.2 (5.4)	IG1 vs. CG: Mean Difference -2.1 (95% CI, -3.3 to -0.9), p=0.001† IG2 vs. CG: Mean Difference -2.1 (95% CI, -3.4 to -0.8), p=0.004† IG3 vs. CG: Mean Difference -2.1 (95% CI, -3.4 to -0.8), p=0.002†
				IG2	NR	9.2 (5.3)	
				IG3	NR	9.2 (5.5)	
				CG	15.4 (3.2)	11.3 (5.8)	
Wickberg, 2005[106] Fair	All participants	EPDS score, mean	2.75	IG	6.41 (95% CI, 0 to 25)	5.39 (95% CI, 0 to 19)	NR, p<0.05
				CG	6.07 (95% CI, 0 to 21)	6.11 (95% CI, 0 to 22)	
Depression Remission							
Glavin, 2010[103] Fair	Depressed women at baseline (EPDS ≥ 10)	EPDS < 10, n (%)	1.5	IG	0 (0)	95 (74.2)	NR
				CG	0 (0)	32 (55.2)	
			4.5	IG	0 (0)	75 (78.1)	NR
				CG	0 (0)	29 (60.4)	

Appendix D Table 2. Results From Included Studies for Key Question 1 (Pregnant and Postpartum Women): Depression

Author, Year and Quality	Subgroup	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
Morrell, 2009a[99] Fair	Depressed women at baseline (EPDS ≥ 12 at 6 weeks postpartum)	EPDS score < 12, n (%)	5	IG1	0 (0)	179 (66.1)	IG1 vs. CG: OR 1.67 (95% CI, 1.05 to 2.63), p=0.028* IG2 vs. CG: OR 1.69 (95% CI, 0.98 to 2.94), p=0.061* IG3 vs. CG: OR 1.64 (95% CI, 0.97 to 2.78), p=0.064*
				IG2	0 (0)	94 (67.1)	
				IG3	0 (0)	85 (64.9)	
				CG	0 (0)	80 (54.4)	
Wickberg, 2005[106] Fair	Depressed women at baseline (EPDS ≥ 12 on either test)	EPDS ≤ 11, n (%)	2.75	IG	0 (0)	22 (52.4)	NR
				CG	0 (0)	8 (18.6)	
Depression Response							
Yawn, 2012[69] Fair	Depressed women at baseline (EPDS ≥ 10)	Improved PHQ-9 score, ≥ 5 point decrease, n (%)	6	IG	NR	NR	NR, p=0.07
				CG	NR	NR	
			12	IG	NR	98 (45)	OR 1.74 (95% CI, 1.05 to 2.86), p=NR
				CG	NR	60 (35)	

*Adjusted for other characteristics (age, parity, other adults in house, mode of delivery, Townsend quartiles, social support score, cluster size).
†Adjusted by 6-week EPDS score, lives alone, postnatal depression history, and life events.

Abbreviations: CG = control group; CI = confidence internval; EPDS = Edinburgh Postnatal Depression Scale; IG = intervention group; NR = not reported; OR = odds ratio; PHQ = Patient Health Questionnaire; vs = versus.

Appendix D Table 3. Results From Included Studies for Key Question 1 (Pregnant and Postpartum Women): Maternal Outcomes

Author, Year and Quality	Subgroup	Outcome	Timepoint (months)	Group	Results at Followup	Between Group Difference
Yawn, 2012[89] Fair	All participants	Completed suicides, n (%)	12	IG	0 (0)	NR
				CG	0 (0)	

Abbreviations: CG = control group; IG = intervention group; NR = not reported.

Appendix D Table 4. Results From Included Studies for Key Question 1 (Pregnant and Postpartum Women): Child and Infant Outcomes

Author, Year and Quality	Subgroup	Outcome	Timepoint (months)	Group	Results at Followup	Between Group Difference
Leung, 2011[104] Good	All participants	Body weight (kg), mean	4	IG	7.71 (95% CI, 7.60 to 7.82)	NR, p=0.504
				CG	7.66 (95% CI, 7.56 to 7.76)	
			16	IG	10.76 (95% CI, 10.63 to 10.90)	NR, p=0.563
				CG	10.72 (95% CI, 10.58 to 10.83)	
		Number of doctor visits, n (%)	4	IG	2.39 (95% CI, 2.07 to 2.70)	NR, p=0.039
				CG	1.97 (95% CI, 1.73 to 2.21)	
			16	IG	5.14 (95% CI, 4.57 to 5.71)	NR, p=0.625
				CG	4.97 (95% CI, 4.58 to 5.36)	
		Number of hospitalizations, n (%)	4	IG	0.37 (95% CI, 0.28 to 0.46)	NR, p=0.518
				CG	0.33 (95% CI, 0.23 to 0.42)	
			16	IG	0.42 (95% CI, 0.35 to 0.50)	NR, p=0.772
				CG	0.40 (95% CI, 0.31 to 0.50)	

Abbreviations: CG = control group; IG = intervention group; kg = kilogram(s); NR = not reported.

Appendix D Table 5. Results From Included Studies for Key Question 1 (Pregnant and Postpartum Women): Quality of Life

Author, Year and Quality	Subgroup	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
Leung, 2011[104] Good	All participants	Chinese Kansas marital satisfaction score, mean	4	IG	NR	16.94 (95% CI, 16.59 to 17.30)	NR, p=0.093
				CG	NR	16.47 (95% CI, 16.03 to 16.90)	
			16	IG	NR	16.35 (95% CI, 15.98 to 16.72)	NR, p=0.636
				CG	NR	16.22 (95% CI, 15.81 to 16.62)	
		GHQ score, mean	4	IG	NR	1.06 (95% CI, 0.83 to 1.30)	NR, p=0.084
				CG	NR	1.39 (95% CI, 1.10 to 1.67)	
			16	IG	NR	1.75 (95% CI, 1.39 to 2.11)	NR, p=0.727
				CG	NR	1.84 (95% CI, 1.45 to 2.24)	
		PSI total score, mean	4	IG	NR	80.89 (95% CI, 78.80 to 82.97)	NR, p=0.065
				CG	NR	83.67 (95% CI, 81.56 to 85.77)	
			16	IG	NR	87.13 (95% CI, 84.73 to 89.53)	NR, p=0.187
				CG	NR	89.33 (95% CI, 87.09 to 91.57)	
		PSI-difficult child score, mean	4	IG	NR	26.19 (95% CI, 25.37 to 27.01)	NR, p=0.397
				CG	NR	26.68 (95% CI, 25.88 to 27.48)	
			16	IG	NR	29.45 (95% CI, 28.52 to 30.37)	NR, p=0.654
				CG	NR	29.74 (95% CI, 28.84 to 30.64)	
		PSI-parent/child dysfunctional score, mean	4	IG	NR	24.77 (95% CI, 24.03 to 25.51)	NR, p=0.050
				CG	NR	25.85 (95% CI, 25.05 to 26.65)	
			16	IG	NR	26.60 (95% CI, 25.66 to 27.55)	NR, p=0.112
				CG	NR	27.65 (95% CI, 26.76 to 28.54)	
		PSI-parental distress score, mean	4	IG	NR	29.93 (95% CI, 29.03 to 30.84)	NR, p=0.063

Appendix D Table 5. Results From Included Studies for Key Question 1 (Pregnant and Postpartum Women): Quality of Life

Author, Year and Quality	Subgroup	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
				CG	NR	31.14 (95% CI, 30.24 to 32.03)	
			16	IG	NR	31.58 (95% CI, 30.61 to 32.54)	NR, p=0.426
				CG	NR	32.11 (95% CI, 31.22 to 32.99)	
MacArthur, 2002[105] Fair	All participants	SF-36, mental component score	3	IG	NR	50.50	Mean Difference 4.31 (95% CI, 2.50 to 6.12), p=NR*
				CG	NR	47.54	
		SF-36, physical component score	3	IG	NR	46.68	Mean Difference -0.80 (95% CI, -2.32 to 0.72), p=NR*
				CG	NR	47.84	
Morrell, 2009a[99] Fair	All participants	CORE-OM functioning, mean (SD)	5	IG1	NR	0.5 (0.6)	Mean Difference -0.1 (95% CI, -0.1 to -0.0), p=0.001†
				CG	NR	0.6 (0.7)	
		CORE-OM total score, mean (SD)	5	IG1	0.51 (0.49)	0.5 (0.5)	Mean Difference -0.1 (95% CI, -0.1 to -0.0), p=0.000†
				CG	0.55 (0.51)	0.5 (0.5)	
		PSI total stress, mean	5	IG1	NR	157.9 (15.3)	Mean Difference 2.3 (95% CI, 0.6 to 3.9), p=0.007†
				CG	NR	155.9 (16.9)	
		SF-12, mental component summary, mean (SD)	5	IG1	42.9 (9.3)	48.9 (9.5)	Mean Difference 1.4 (95% CI, 0.5 to 2.3), p=0.003†
				CG	42.7 (9.5)	47.6 (10.5)	
		SF-12, physical component summary, mean (SD)	5	IG1	51.4 (8.0)	54.7 (6.1)	Mean Difference 0.0 (95% CI, -0.4 to 0.5), p=0.871†
				CG	50.5 (8.7)	54.5 (6.8)	
		State anxiety (STAI), mean (SD)	5	IG1	NR	33.2 (10.9)	Mean Difference -1.3 (95% CI, -2.5 to -0.1), p=0.033†
				CG	NR	34.3 (11.7)	
		Trait anxiety (STAI), mean (SD)	5	IG1	NR	33.1 (9.6)	Mean Difference -1.1 (95% CI, -2.1 to -0.1), p=0.032†
				CG	NR	34.1 (10.3)	
	Depressed women at baseline (EPDS ≥ 12 at 6 weeks postpartum)	CORE-OM functioning, mean (SD)	5	IG1	NR	1.0 (0.8)	Mean Difference -0.3 (95% CI, -0.4 to -0.1), p=0.001†
				CG	NR	1.2 (0.8)	
		CORE-OM total score, mean (SD)	5	IG1	1.35 (0.49)	0.8 (0.6)	Mean Difference -0.2 (95% CI, -0.4 to -0.1), p=0.001†
				CG	1.40 (0.50)	1.1 (0.7)	
		PSI total stress, mean	5	IG1	NR	148.9 (17.0)	Mean Difference 9.3 (95% CI, 5.2 to 13.4), p=0.001†
				CG	NR	139.6 (20.4)	
		SF-12, mental component summary, mean (SD)	5	IG1	29.1 (8.0)	42.3 (10.8)	Mean Difference 5.2 (95% CI, 2.5 to 7.8), p=0.001†
				CG	29.4 (9.2)	37.8 (11.8)	
		SF-12, physical component summary, mean (SD)	5	IG1	50.1 (9.4)	53.0 (7.6)	Mean Difference -1.7 (95% CI, -3.6 to 0.1), p=0.069†
				CG	48.5 (10.9)	54.3 (9.0)	
		State anxiety (STAI), mean (SD)	5	IG1	NR	41.7 (11.8)	Mean Difference -3.9 (95% CI, -6.6 to -1.3), p=0.003†
				CG	NR	45.5 (12.5)	
		Trait anxiety (STAI), mean (SD)	5	IG1	NR	41.6 (10.4)	Mean Difference -3.7 (95% CI, -6.1 to -1.4), p=0.002†
				CG	NR	45.0 (10.9)	

Appendix D Table 5. Results From Included Studies for Key Question 1 (Pregnant and Postpartum Women): Quality of Life

Author, Year and Quality	Subgroup	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
Yawn, 2012[69] Fair	Depressed women at baseline (EPDS ≥ 10)	Elevated parenting stress, PSI score > 74, n (%)	12	IG	187 (81)	128 (72)	NR, p=0.82
				CG	196 (98)	117 (74)	
		Low partner satisfaction, DAS score ≤ 10%, n (%)	12	IG	3 (2)	2 (2)	NR, p=0.30
				CG	3 (2)	6 (5)	

*Adjusted by other characteristics (age, parity, other adults in house, mode of delivery, Townsend quartiles, social support score, cluster size)
†Adjusted by 6-week score, lives alone, postnatal depression history, and any life events

Abbreviations: CG = control group; CI = confidence interval; CORE-OM = Clinical Outcomes in Routine Evaluation Outcome Measure; DAS = Dyadic Adjustment Scale; EPDS = Edinburgh Postnatal Depression Scale; GHQ = General Health Questionnaire; IG = intervention group; NR = not reported; PSI = Parenting Stress Impacts; SD = standard deviation; SF = Short Form; STAI = State-Trait Anxiety Inventory.

Appendix D Table 6. Results From Included Studies for Key Question 1 (Pregnant and Postpartum Women): Health Care Use

Author, Year and Quality	Subgroup	Outcome	Timepoint (months)	Group	Results at Followup	Between Group Difference
Morrell, 2009a[99] Fair	All participants	Accident and Emergency attendances, mean	5	IG1	0.0	0.0
				CG	0.0	
		Antidepressant prescriptions, mean	5	IG1	0.0	Mean Difference -0.1 (95% CI, -0.1 to 0.0), p=NR
				CG	0.1	
	Depressed women at baseline (EPDS ≥ 12 at 6 weeks postpartum)	Accident and Emergency attendances, mean	5	IG1	0.0	0.0
				CG	0.0	
		Antidepressant prescriptions, mean	5	IG1	0.3	Mean Difference --0.2 (95% CI, -0.5 to 0.1), p=NR
				CG	0.5	
Yawn, 2012[69] Fair	Depressed women at baseline (EPDS ≥ 10)	Treatment, counseling, n (%)	12	IG	54 (20)	NR, p=0.02
				CG	20 (11)	
		Treatment, medication and counseling, n (%)	12	IG	176 (60)	NR, p<0.0001
				CG	70 (37)	
		Treatment, medication, n (%)	12	IG	169 (59)	NR, p<0.0001
				CG	67 (35)	

Abbreviations: CG = control group; IG = intervention group; EPDS = Edinburgh Postnatal Depresson Scale; NR = not reported.

Appendix D Table 7. Detailed Intervention Characteristics of Included Studies for Key Question 2 (Pregnant and Postpartum Women)

Author, Year and Quality	Index Test or Reference Standard	Name	Language	Description
English EPDS				
Yawn, 2012[69]	Index Test	EPDS	English	EPDS included in baseline survey packet
Fair	Reference Standard	PHQ-9 or physician evaluation	English	PHQ-9 included in baseline survey packet; a score ≥ 10 considered consistent of postpartum depression; if EPDS ≥ 10 but PHQ-9 was not elevated, clinical judgement used
Beck, 2001[108]	Index Test	EPDS	English	EDPS administered to women, in random order with the BDI and PDSS index tests.
Fair	Reference Standard	DSM-IV interview	English	DSM-IV diagnostic interview administered immediately following completion of the 3 index tests by a nurse psychotherapist
Tandon, 2012[118]	Index Test	EPDS	English	Cutoff of ≥ 16 for moderate depression, ≥ 24 for severe depression. Screening items read aloud.
Fair	Reference Standard	SCID-I/NP	English	Trained interviewer read questions aloud
Morrell, 2009a[99]	Index Test	EPDS	English	EPDS sent to women 6-weeks postnatally; English version
Fair	Reference Standard	SCAN interview	English	All women w/ EPDS score ≥ 9 and a random subset (proportion of women selected unspecified) of women w/ EPDS score <9 were interviewed using the Schedule for Clinical Assessment in Neuropsychiatry
Cox, 1996[100]	Index Test	EPDS	English	Women completed EPDS at baseline; those scoring 9 or above (n=96) and 1/3 of those scoring 0-8 (n=51) were selected for interview
Fair	Reference Standard	SPI	English	SPI semi-structured interview used to screen for major and minor depression using RDC; administered by one of two trained study investigators
Leverton, 2000[117]	Index Test	EPDS	English	EPDS administered at 6 weeks postnatal and again at 3 months post natal (in home)
Fair	Reference Standard	PSE	English	PSE administered in-home at 3 months postnatal by research psychiatrist; Bedford College classification applied to the PSE data
Harris, 1989[115]	Index Test	EPDS	English	EPDS completed in clinic; taken home and returned by post; cut-off of 13
Fair	Reference Standard	DSM-III interview	English	Assessed accordig to DSM-III criteria for major depression by an experienced psychiatrist followed by the Raskin 3 Area Scale for Depression and the MADRS; total interview took approximately 40 minutes
Non-English EPDS				
Chen, 2013[113]	Index Test	EPDS	Chinese	Completed between 1-22 weeks postpartum (median, 5 weeks); Chinese version
Fair	Reference Standard	Unstructured interview	Chinese	Screened privately in a room by oen of five trained case managers through an unstructured clinical interview; assessed for clinical depression based on DSM-IV-TR criteria
Lee, 2001[116]	Index Test	EPDS	Chinese	EPDS completed 6 weeks after confinement; Chinese version
Fair	Reference Standard	SCID-NP	Chinese	Semi-structured interview with the Chinese non-patient version of Structured Clinical Interview for DSM-III-R (SCID-NP) by one of the study investigators. Modified to make 6-week diagnoses instead of 1 month and to allow diagnosis of DSM-IV minor depressive disorder (2-week period of at least 2 but less than 5 depression sx' depressed mood or anhedonia being mandatory)

Appendix D Table 7. Detailed Intervention Characteristics of Included Studies for Key Question 2 (Pregnant and Postpartum Women)

Author, Year and Quality	Index Test or Reference Standard	Name	Language	Description
Guedeney, 1998[114] Fair	Index Test	EPDS	French	EPDS completed at baseline and 1 week later in woman's home; French version.
	Reference Standard	PSE-10	French	Semi-structured interview PSE conducted at BL and 1 week later in woman's home conducted by nurses; diagnosis of major depressive disorders and minor depressive disorders, definite and probable established according to RDC. Completed the PSE by the 3 items necessary to assess the RDC minor depressive disorder (tendency to self-pity, depressive facial expression and need of reassurance); scored fx and intensity of each sx according to usual PSE rating (0=absent, 1=at threshold, 2=moderate, 3=intense, 7=chronic, and 9=organic etiology). Only PSE items exploring depressive disorders according to the RDC reassessed at 1 week. Severity of depression assessed by CGI and VAS.
Adouard, 2005[107] Fair	Index Test	EPDS	French	EPDS administered at enrollment; French version
	Reference Standard	MINI	French	MINI administered after EDPS and HAD by psychiatrist, French version; DSM-IV criteria used for depression diagnosis and severity determined by CGI assessment
Toreki, 2013[120] Good	Index Test	EPDS	Hungarian	EPDS completed at antepartum check-up at 12 weeks gestation; Hungarian version
	Reference Standard	SCID	Hungarian	SCID interview completed at antepartum check-up at 12 weeks gestation; carried out by study investigator. DSM-IV criteria were adopted.
Toreki, 2014[121] Fair	Index Test	EPDS	Hungarian	EPDS completed 6-8 weeks after childbirth; Hungarian version
	Reference Standard	SCID	Hungarian	SCID completed 6-8 weeks after childbirth by principal investigator; diagnosis made using DSM-IV criteria
Carpiniello, 1997[112] Fair	Index Test	EPDS	Italian	Completed Italian EPDS at home 4-6 weeks postpartum
	Reference Standard	PSE	Italian	Clinical interviews by psychiatrists using Italian version of PSE for epidemiological studies at home 4-6 weeks postpartum; cases classified according to the PSE-index of Definition-Catego procedure with Level 5 considered the threshold level dividing cases from non-cases. Use N and R classes of Catego to identify depressive cases.
Benvenuti, 1999[109] Fair	Index Test	EPDS	Italian	EPDS administred at 8-12 weeks post partum; Italian version
	Reference Standard	MINI	Italian	MINI diagnostic interview conducted at 8-12 weeks postpartum following the EPDS; diagnosis made according to DSM-III-R criteria
Yamashita, 2000[122] Fair	Index Test	EPDS	Japanese	EPDS completed 5 days, 1 month and 3 months after delivery; translated for Japanese
	Reference Standard	SADS Diagnostic Interview	Japanese	SADS diagnostic interview conducted at 3 weeks and 3 months post-delivery; diagnosis based on Research Diagnostic Criteria
Bunevicius, 2009b[111]	Index Test	EPDS	Lithuanian	Symptoms of depression were evaluated using Lithuanian verions of EPDS with a cutoff score of 12 during 1st, 2nd, and 3rd trimesters of pregnancy; paper-pencil version

Appendix D Table 7. Detailed Intervention Characteristics of Included Studies for Key Question 2 (Pregnant and Postpartum Women)

Author, Year and Quality	Index Test or Reference Standard	Name	Language	Description
Fair	Reference Standard	SCID-NP	Lithuanian	Clinical diagnosis of depressive disorder was evaluated using Lituanian translation of a non-patient version of the semi-structured Structured Clinical Interview for DSM-III-R (SCID-NP) during 1st, 2nd, and 3rd trimesters of pregnancy; performed by a trained psychiatrist. This study used three modules of the SCID-NP: A for mood syndromes, D for mood disorders and I for adjustment disorders to evaluate MDD, dysthymia or adjustment disorder w/ depressed mood
Bunevicius, 2009a[110] Fair	Index Test	EPDS	Lithuanian	Symptoms of depression were evaluated using EPDS at 2 weeks postpartum; Lithuanian version, paper-pencil version, cut-off ≥ 12
	Reference Standard	CIDI-SF	Lithuanian	Clinical diagnoses of depressive disorders were established using the CIDI-SF, a structured cinical interview that ascertains the prescence of psychiatric disorders according to the DSM-IV; Lithuanian version
Garcia-Esteve, 2003[101] Fair	Index Test	EPDS	Spanish	EPDS completed at 6 weeks postpartum; Spanish version
	Reference Standard	SCID	Spanish	SCID diagnostic interview conducted at 6 weeks postpartum for DSM-II-R; the non-patient version was modified to diagnose minor depressive episode according to the DSM-IV criteria and also modified in the sleep (only include sleep disturbance not due to infant) and weight loss (substituted for appetite loss) questions. Interview carried out by study investigator
Alvarado, 2014[123] Fair	Index Test	EPDS	Spanish	EPDS; Spanish version
	Reference Standard	MINI	Spanish	The major depressive episode module fo the MINI short structured clinical interview enabled researches to diagnose psychiatric disorders according to the DSM-IV or ICD-10; interview conducted by trained psychologist.
Teng, 2005[119] Fair	Index Test	EPDS	Taiwanese	Women completed EPDS 6 weeks after giving birth; Taiwanese version
	Reference Standard	MINI	Taiwanese	Interviewed by psychiatric specialists 6 weeks after giving birth in person or by telephone; diagnosis establised by MINI and DSM-IV criteria w/ possible organic causes of depression ruled out before establishing diagnoses of depressive disorders

Abbreviations: BL = baseline; CGI = Clinical Global Impression; DSM = Diagnostic and Statistical Manual; EPDS = Edinburgh Postnatal Depressoin Scale; HADS = Hospital Anxiety and Depression Scale; MADRS = Montgomery Asberg Depression Rating Scale; MDD = major depressive disorder; MINI = Minim International Neuropsychiatric Interview; NP = nurse practitioner; PDSS = Postpartum Depression Screening Scale; PHQ = Patient Health Questionnaire; PSE = Present State Examination; RDC = Research Diagnostic Criteria; SADS = Schedule for Affective Disorders and Schizophrenia; SCAN = Schedules for Clinical Assessment in Neuropschiatry; SCID = Structured Clinical Interview for Disorders; SPI = Standardized Psychiatric Interview; VAS = Visual Analogue Scale.

Appendix D Table 8. Results of Included Studies for Key Question 2 (Pregnant and Postpartum Women): Diagnostic Accuracy

Author, Year and Quality	Subgroup	N Screened	Diagnosis	EPDS Cutoff	True Positives	False Positives	False Negatives	True Negatives	Sensitivity (%)*	Specificity (%)*	PPV (%)*	NPV (%)*
English EPDS												
Yawn, 2012[69] Fair	IG only (n=1353)	1353	MDD	≥ 10	194	128	77	954	NR	NR	NR	NR
Beck, 2001[108] Fair	All participants	150	MDD	≥ 13	14	1	4	131	78	99	93	96
			Any depression	≥ 9	27	15	19	89	59	86	64	82
Tandon, 2012[118] Fair	All participants	95	MDD	≥ 13	22	3	5	65	81.5	95.6	NR	NR
			Minor or major depression	≥ 11	24	6	3	62	88.9	91.2	NR	NR
				≥ 10	27	12	5	51	84.4	81.0	NR	NR
	Postpartum participants	63	MDD	≥ 11	17	3	3	40	85.0	93.0	NR	NR
			Minor or major depression	≥ 10	21	8	4	30	84.0	79.0	NR	NR
	Prenatal participants	32	MDD	≥ 10	6	4	1	21	85.7	84.0	NR	NR
Morrell, 2009a[99] Fair	All participants	860	Mild, moderate or severe depression	≥ 13	106	178	28	548	79.1	75.5	NR	NR
				≥ 12	116	239	18	487	86.6	67.1	32.7	NR
			Moderate or severe depression	≥ 13	46	238	8	568	85.2	70.5	37.3	NR
				≥ 12	50	305	4	501	92.6	62.2	NR	NR
Cox, 1996 (RM10552) Fair	Postnatal women	128	MDD	≥ 13	6	19	2	101	75	84	24	NR
				≥ 12	7	29	1	91	88	76	20	NR
				≥ 11	7	32	1	88	88	73	18	NR
				≥ 10	7	25	1	85	88	71	17	NR
				≥ 9	8	48	0	72	NR	NR	NR	NR
			Major or minor depression	≥ 13	13	12	8	95	62	89	52	NR
				≥ 12	16	20	5	87	76	81	44	NR
				≥ 11	16	23	5	84	76	79	41	NR
				≥ 10	17	25	4	82	81	77	41	NR
				≥ 9	19	37	2	70	NR	NR	NR	NR
	Postnatal women (extrapolated)	272	MDD	≥ 13	6	19	2	245	NR	NR	NR	NR
				≥ 12	7	29	1	235	NR	NR	NR	NR
				≥ 11	7	32	1	232	NR	NR	NR	NR
				≥ 10	7	35	1	229	NR	NR	NR	NR
				≥ 9	8	48	0	216	NR	NR	NR	NR
			Minor or major depression	≥ 13	13	12	14	233	NR	NR	NR	NR
				≥ 12	16	20	11	225	NR	NR	NR	NR
				≥ 11	16	23	11	222	NR	NR	NR	NR
				≥ 10	17	25	10	220	NR	NR	NR	NR
				≥ 9	19	37	8	208	NR	NR	NR	NR

Appendix D Table 8. Results of Included Studies for Key Question 2 (Pregnant and Postpartum Women): Diagnostic Accuracy

Author, Year and Quality	Subgroup	N Screened	Diagnosis	EPDS Cutoff	True Positives	False Positives	False Negatives	True Negatives	Sensitivity (%)*	Specificity (%)*	PPV (%)*	NPV (%)*
Leverton, 2000[117]	All participants	199	Case depression	≥ 13	2	19	1	177	NR	NR	NR	NR
				≥ 10	2	37	1	159	NR	NR	NR	NR
			Borderline or case depression	≥ 13	7	14	9	169	44	92	33	NR
Fair				≥ 10	11	28	5	155	69	85	28	NR
Harris, 1989[115]	All participants	126	MDD	≥ 13	21	7	1	97	95.0	93.0	NR	NR
				≥ 10	22	19	0	85	100	82	NR	NR
Fair												
Non-English EPDS												
Chen, 2013[113]	All participants	487	Any depression	≥ 14	26	12	4	445	86.7	NR	NR	NR
				≥ 13	26	15	4	442	86.7	96.7	NR	NR
Fair				≥ 12	27	22	3	435	90.0	NR	NR	NR
				≥ 11	27	33	3	424	90.0	NR	NR	NR
				≥ 10	27	43	3	414	90.0	NR	NR	NR
				≥ 9	27	63	3	394	90.0	NR	NR	NR
Lee, 2001[116]	All participants	145	Major or minor depression	≥ 10	14	18	3	110	82.0	86.0	44.0	97.0
Fair												
Guedeney, 1998[114]	All participants	87	Major or minor depression	≥ 12.5	27	1	18	41	60	97	97	69
				≥ 11.5	33	2	12	40	73	95	94	77
				≥ 10.5	36	3	9	39	80	92	91	81
Fair				≥ 9.5	38	9	7	33	84	78	80	82
Adouard, 2005[107]	All participants	60	MDD	≥ 12.5	11	8	4	37	73	82	NR	NR
				≥ 11.5	12	9	3	36	80	80	NR	NR
				≥ 10.5	12	12	3	33	80	73	NR	NR
Fair				≥ 9.5	13	13	2	32	87	71	NR	94
Toreki, 2013[120]	All participants	219	MDD	≥ 14	2	1	5	211	28.6	99.5	66.7	97.7
				≥ 13	2	3	5	209	28.6	98.6	40.0	97.7
				≥ 12	2	7	5	205	28.6	96.7	22.2	97.6
Good				≥ 11	3	11	4	201	42.9	94.8	21.4	98.0
				≥ 10	3	15	4	197	42.9	92.9	16.7	98.0
				≥ 9	5	18	2	194	71.4	91.5	21.7	99.0
			Any depression	≥ 14	3	0	19	197	13.6	100	100	91.2
				≥ 13	4	1	18	196	18.2	99.5	80.0	91.6
				≥ 12	6	3	16	194	27.3	98.5	66.7	92.4
				≥ 11	9	4	13	193	40.9	98.0	64.3	93.7
				≥ 10	11	7	11	190	50.0	96.5	61.1	94.5
				≥ 9	13	10	9	187	59.1	94.9	56.5	95.4

Appendix D Table 8. Results of Included Studies for Key Question 2 (Pregnant and Postpartum Women): Diagnostic Accuracy

Author, Year and Quality	Subgroup	N Screened	Diagnosis	EPDS Cutoff	True Positives	False Positives	False Negatives	True Negatives	Sensitivity (%)*	Specificity (%)*	PPV (%)*	NPV (%)*
Toreki, 2014[121] Fair	All participants	266	MDD	≥ 14	7	3	1	255	87.5	98.8	69.9	99.6
				≥ 13	8	6	0	252	100	97.7	57.1	100
				≥ 12	8	8	0	250	100	96.9	49.9	100
				≥ 11	8	13	0	245	100	95.0	38.0	100
				≥ 10	8	24	0	234	100	90.7	25.0	100
				≥ 9	8	45	0	213	100	82.6	15.1	100
			Any depression	≥ 14	10	0	34	222	22.7	100	100	86.7
				≥ 13	14	0	30	222	31.8	100	100	88.1
				≥ 12	15	1	29	221	34.1	99.6	93.7	88.4
				≥ 11	18	3	26	219	40.9	98.7	85.7	89.4
				≥ 10	24	8	20	214	54.5	96.4	75.0	91.5
				≥ 9	30	23	14	199	68.2	89.6	56.6	93.4
Carpiniello, 1997[112] Fair	All participants	61	Clinically depressed	≥ 14	4	0	5	52	44.0	100.0	100.0	91.0
				≥ 13	6	0	3	52	67.0	100.0	100.0	95.0
				≥ 12	7	1	2	51	78.0	98.0	88.0	96.0
				≥ 11	8	4	1	48	88.0	92.0	66.0	98.0
				≥ 10	9	9	0	43	100.0	83.0	50.0	100.0
Benvenuti, 1999[109] Fair	All participants	113	Any depression	≥ 13	10	1	8	94	55.6	98.9	90.9	NR
				≥ 12	10	2	8	93	55.6	97.9	83.3	NR
				≥ 11	11	5	7	90	61.1	94.7	68.8	NR
				≥ 10	15	10	3	85	83.3	89.5	60.0	NR
				≥ 9	17	12	1	83	94.4	87.4	58.6	NR
Yamashita, 2000[122] Fair	All participants	75	Major or minor depression	≥ 12	6	1	5	63	55	98	NR	NR
				≥ 10	8	1	3	63	73	98	NR	NR
				≥ 9	9	3	2	61	82	95	NR	NR
Bunevicius, 2009b[111] Fair	All participants (first trimester)	230	MDD	≥ 13	8	NR	4	NR	67	NR	NR	NR
				≥ 12	11	11	1	207	92	95	52	100
				≥ 11	11	NR	1	NR	92	NR	NR	NR
				≥ 10	11	NR	1	NR	92	NR	NR	NR
				≥ 9	12	NR	0	NR	100	NR	NR	NR
			Any depressive disorder	≥ 13	9	NR	5	NR	64	NR	NR	NR
				≥ 12	12	9	2	207	86	96	57	99
				≥ 11	12	NR	2	NR	86	NR	NR	NR
				≥ 10	12	NR	2	NR	86	NR	NR	NR
				≥ 9	13	NR	1	NR	93	NR	NR	NR
	All participants (second trimester)	230	MDD	≥ 13	3	NR	3	NR	50	NR	NR	NR
				≥ 12	4	NR	2	NR	67	NR	NR	NR
				≥ 10	6	NR	0	NR	100	NR	NR	NR
				≥ 11	6	18	0	206	100	92	25	100
				≥ 9	6	NR	0	NR	100	NR	NR	NR

Appendix D Table 8. Results of Included Studies for Key Question 2 (Pregnant and Postpartum Women): Diagnostic Accuracy

Author, Year and Quality	Subgroup	N Screened	Diagnosis	EPDS Cutoff	True Positives	False Positives	False Negatives	True Negatives	Sensitivity (%)*	Specificity (%)*	PPV (%)*	NPV (%)*
			Any depressive disorder	≥ 13	4	NR	4	NR	50	NR	NR	NR
				≥ 12	5	NR	3	NR	63	NR	NR	NR
				≥ 11	7	18	1	204	88	92	29	100
				≥ 10	7	NR	1	NR	88	NR	NR	NR
				≥ 9	7	NR	1	NR	88	NR	NR	NR
	All participants (third trimester)	230	MDD	≥ 13	5	NR	3	NR	63	NR	NR	NR
				≥ 12	5	NR	3	NR	63	NR	NR	NR
				≥ 11	7	18	1	204	88	92	29	100
				≥ 10	7	NR	1	NR	88	NR	NR	NR
				≥ 9	7	NR	1	NR	88	NR	NR	NR
			Any depressive disorder	≥ 13	4	NR	4	NR	50	NR	NR	NR
				≥ 12	4	NR	4	NR	50	NR	NR	NR
				≥ 11	6	16	2	206	80	93	33	99
				≥ 10	6	NR	2	NR	80	NR	NR	NR
				≥ 9	6	NR	2	NR	80	NR	NR	NR
Bunevicius, 2009a[110] Fair	All participants	94	Any depression	≥ 13	6	NR	7	NR	46	NR	NR	NR
				≥ 12	6	NR	7	NR	46	NR	NR	NR
				≥ 11	7	NR	6	NR	54	NR	NR	NR
				≥ 10	9	NR	4	NR	69	NR	NR	NR
				≥ 9	10	NR	3	NR	77	NR	NR	NR
				≥ 7	12	22	1	59	92	73	35	98
Garcia-Esteve, 2003[101] Fair	All participants (extrapolated)	1123	MDD	≥ 14	30	36	6	1051	83.3	96.7	49.0	99.4
				≥ 13	31	50	5	1037	86.1	95.4	45.5	99.5
				≥ 12	33	64	3	1023	91.7	94.1	33.7	99.7
				≥ 11	36	89	0	998	100	91.8	28.8	100
				≥ 10	36	122	0	965	100	88.8	22.8	100
				≥ 9	36	172	0	915	100	84.2	17.3	100
			Any depression	≥ 14	55	11	45	1012	55.0	98.9	83.3	95.7
				≥ 13	62	19	38	1004	62.0	98.1	76.5	96.4
				≥ 12	70	28	30	995	70.0	97.3	71.4	97.1
				≥ 11	79	46	21	977	79.0	95.5	63.2	97.9
				≥ 10	89	69	11	954	89.0	93.3	56.3	98.9
				≥ 9	100	108	0	915	100	89.4	48.1	100
	Selected participants w/ SCID interview	334	Any depression	≥ 9	100	108	0	126	NR	NR	NR	NR
Alvarado, 2014[123] Fair	All participants	111	MDD	≥ 13	29	5	9	68	76.3	93.2	85.3	88.3
				≥ 12	29	8	9	65	76.3	89.0	78.4	87.8
				≥ 11	31	8	7	65	81.6	89.0	79.5	90.3
				≥ 10	31	13	7	60	81.6	82.2	70.5	89.6
				≥ 9	32	20	6	53	84.2	72.6	61.5	89.8

Appendix D Table 8. Results of Included Studies for Key Question 2 (Pregnant and Postpartum Women): Diagnostic Accuracy

Author, Year and Quality	Subgroup	N Screened	Diagnosis	EPDS Cutoff	True Positives	False Positives	False Negatives	True Negatives	Sensitivity (%)*	Specificity (%)*	PPV (%)*	NPV (%)*
Teng, 2005[119] Fair	All participants	199	Any depressive disorder	≥ 13	19	27	1	152	96	85	46	99

*Study-reported diagnostic accuracy.

Abbreviations: EPDS = Edinburgh Postnatal Depression Scale; IG = intervention group; MDD = major depressive disorder; NPV = negative predictive value; NR = not reported; PPV = positive predictive value; SCID = Structured Clinical Interview for Disorders.

Appendix D Table 9. Detailed Interventions for Key Question 4 (Pregnant and Postpartum Women)

Author, Year and Quality	Group	Intervention	N Rand.	Provider	# of Sessions	Length of Sessions (hours)	Duration (months)	Estimated Hours of Contact	Detailed Description
CBT or Related Interventions									
McGregor, 2013[140] Fair	IG	CBT	21	Physician	6	0.167	1.5	1	Standard prenatal care and CBT sessions (initiated btwn 20th and 28th week gestation and occurred consecutively). First 2 sessions focused on education (antenatal depression and cognitive bx model) and bx activation. Next 3 sessions focused on education (interconnectedness btwn thoughts, feelings and bx) and cognitive restructuring; invited to complete thought records to examine negative thoughts and emotionally charged situations and apply alternative techniques. Final session reviewed previous sessions and continued implementation. Homework during first 5 sessions. Physicians given 2-hour training sessions by psychologist.
	CG	Usual Care	21	NA	NA	NA	NA	NA	Standard prenatal care
Milgrom, 2011b[142] Fair	IG1	CBT (combined)	45	Nurse or psychologist	6	NR	1.5	3	Analysis combining the two counseling groups
	IG2	CBT (Psychologist)	23	Psychologist	6 (mean, 4)	NR	1.5	3	Six sessions of manualized Overcoming Postnatal Depression Program by an experienced psychologist a a hospital psychology department as an adjunct to GP management. All women asked to scheduled at least 3 fortnightly checkups w/ GP.
	IG3	CBT (Nurse)	22	Nurse	6 (mean, 4.6)	NR	1.5	3	Six sessions of manualized Overcoming Postnatal Depression Program by trained nurse as an adjunct to GP management. Nurses trained in counseling-CBT intervention (assessment, goal setting, tx) by senior psychologist; sessions focused on psychoeducation, goal setting, problem solving, bx interventions, cognitive techniques; partner relationships, social support and mother-baby relationship. All women asked to scheduled at least 3 fortnightly checkups w/ GP.
	CG	Usual Care	23	NA	NA	NA	NA	NA	GP management. GP received brief, focused training, consisting of face-to-face sessions (45-60 min) w/ psychologist and printed training manual (screening, dx, risk assessment and management, engagement, biopsychosocial model of post-natal depression, medication during lactation, common pt concerns, referral and principles of tx). All women asked to scheduled at least 3 fortnightly checkups w/ GP.

Appendix D Table 9. Detailed Interventions for Key Question 4 (Pregnant and Postpartum Women)

Author, Year and Quality	Group	Intervention	N Rand.	Provider	# of Sessions	Length of Sessions (hours)	Duration (months)	Estimated Hours of Contact	Detailed Description
Cooper, 2003[128] Good	IG1	Any treatment (combined)	141	Trained therapists	10	NR	2.5	5	Analysis of the three interventions groups combined (CBT, psychotherapy and non-directive counseling)
	IG2	CBT	43	Trained therapists	10	NR	2.5	5	CBT primarily directed at problems identified by the mother in the management of her infant and observed problems in the quality of the mother-infant interaction; mother provided w/ advice about managing particular infant problems, helped to solve such problems systematically, encouraged to examine patterns of thinking about infant and self, and helped through modelling and reinforcement to alter aspects of her interactional style via a supportive therapeutic relationship
	IG3	Non-directive counseling	48	Trained therapists	10	NR	2.5	5	Non-directive counseling; women provided w/ the opportunity to air their feelings about any current concerns and concerns they might raise about their infant
	IG4	Psychodynamic	50	Trained therapists	10	NR	2.5	5	Psychodynamic theory using treatment techniques to understand the mother's representation of her infant and her relationship w/ her infant by exploring aspects of the mother's own early attachment history
	CG	Usual Care	52	NA	NA	NA	NA	NA	Normal care provided by GP and health visitor w/ no additional input from research team
Prendergast, 2001[146] Fair	IG	CBT	17	Trained early childhood nurses	6	1	1.5	6	Home-based CBT sessions by nurses who were trained by a psychiatrist, psychologist and senior psychiatry registrar in CBT method using small group tutorials, workbooks (contained psychoeducation, cognitive monitoring and thought challenging diaries and modules on anxiety management, assertiveness training, self-esteem and pleasant-event scheduling).
	CG	Ideal standard care	20	Early childhood nurses	6	0.33-1	1.5	4	Weekly clinic appointments for mothercraft (e.g., changing diapers) advice and non-specific emotional support; 20-60 minutes each

Appendix D Table 9. Detailed Interventions for Key Question 4 (Pregnant and Postpartum Women)

Author, Year and Quality	Group	Intervention	N Rand.	Provider	# of Sessions	Length of Sessions (hours)	Duration (months)	Estimated Hours of Contact	Detailed Description
Kozinzky, 2012[138] Good	IG	CBT - Related	119	Psychiatrists or health visitors	4	3	1	12	Four group meetings consisting of psychoeducation and psychotherapy for postpartum depression using group therapy, interpersonal psychotherapy and CBT. Patient education on pregnancy, labor and parenthood (session 1); postpartum depression screening and coping skills (session 2), recognizing distress and seeking help (session 3) and recapitulation and relaxation (session 4). Routine antepartum care (monthly visits by a trained health visitor who carries out a comprehensive health check; on five occasions, 4 times during pregnancy and once 6 weeks after delivery, gynecologist reviews pt).
	CG	Usual Care	205	Psychiatrists or health visitors	4	NR	1	4	Four group meetings where they received routine education on pregnancy, childbirth and baby care. Routine antepartum care (monthly visits by a trained health visitor who carries out a comprehensive health check; on five occasions, 4 times during pregnancy and once 6 weeks after delivery, gynecologist reviews pt).
Ammerman, 2013[124] Fair	IG	CBT - Related	47	Therapists, social workers/nurse (home visits)	16 (15 session + 1 optional booster session; mean 11.2 sessions)	1	4.75	15	Depression reduction using behavioral activation, identification of automatic thoughts and schemas, thought restructuring, and relapse prevention; adapted to setting, population and context and addressing the primary concerns of the mother. Treatment content focused on issues relevant to population (e.g., stress management, parenting challenges). Close collaboration w/ home visitors through written communication via web and telephone btwn therapist and home visitor w/ visitor attending the 15th session. CBT in addition to regular home visits emphasizing child health and development, nurturing mother-child relationship, maternal health and self-sufficiency, and linkage to community services following one of two models; permitted to receive depression treatment in the community.

Appendix D Table 9. Detailed Interventions for Key Question 4 (Pregnant and Postpartum Women)

Author, Year and Quality	Group	Intervention	N Rand.	Provider	# of Sessions	Length of Sessions (hours)	Duration (months)	Estimated Hours of Contact	Detailed Description
	CG	Standard home visiting	46	NA	NA	NA	NA	NA	Regular home visits by social worker or nurse emphasizing child health and development, nurturing mother-child relationship, maternal health and self-sufficiency, and linkage to community services following one of two models; permitted to receive depression treatment in the community.
Honey, 2002[133] Fair	IG	CBT - Related	23	Health visitors	8	2	2	16	Components: (1) educational information on post-natal depression, strategies for coping w/ difficult child-care situations and elicity social support; (2) CBT to tackle women's erroneous cognitions about motherhood and strategies for coping w/ anxiety; (3) teaching use of relaxation
	CG	Usual Care	22	NA	NA	NA	NA	NA	Routine primary care by health visitors
Milgrom, 2005[141] Fair	IG1	Any CBT (combined)	159	Therapists	12	1.5	3	18	All counseling interventions combined for analysis.
	IG2	CBT (Coping with Depression Course)	46	Therapists	12	1.5	3	18	Adapted Coping w/ Depression Course (Lewinsohn) and modified to fit unique needs of the mother by addition of partner sessions and modules on family of origin issue. For example, relaxation deferred in favor of earlier introduction of pleasant activities and time management; content also adapted to be less demanding in time and information processing. Components include psychoeducation, increasing pleasant events, assertiveness and self-esteem, realistic expectations of parenting, and cognitive restructuring.
	IG3	CBT Related - Group	47	Therapists	12	1.5	3	18	Counseling designed for depression and utilized supporting listening, history taking, problem clarification, goal formation, problem solving, partner sessions and group process.
	IG4	CBT Related - Individual	66	Therapists	12	1.5	3	18	Counseling designed for depression and utilized supporting listening, history taking, problem clarification, goal formation, problem solving, partner sessions and group process delivered on a one-to-one basis.
	CG	Usual Care	33	NA	NA	NA	NA	NA	Case-managed by their maternal and child health nurse and referred to other agencies/services as necessary.

Appendix D Table 9. Detailed Interventions for Key Question 4 (Pregnant and Postpartum Women)

Author, Year and Quality	Group	Intervention	N Rand.	Provider	# of Sessions	Length of Sessions (hours)	Duration (months)	Estimated Hours of Contact	Detailed Description
Wiklund, 2010[148] Fair	IG	CBT	33	Cognitive therapist	21	1	1.75	21	Cognitive-behavioral counseling focusing on the prevention and management of stress and low mood; functional analysis based on situation, behavior and consequences of pt's bx conducted. Pts encouraged to do home tasks (e.g., reading), daily breathing, and relaxation exercises, and thinking about positive things each week to help them accept what had happened during labor and to adapt to role as mothers.
	CG	Debriefing session	34	Midwife or obstetrician	1	NR	NR	0.25	Debriefing session w/ midwife or obstetrician
Other Behaviorally-based Interventions									
Holden, 1989[132] Fair	IG	Non-directive counseling	NR	Health visitors	8 (mean, 8.8)	≥ 0.5	2	4	Non-directive (Rogerian) counseling talking about feelings to an empathic and non-judgmental professional (i.e., health visitor) to have a more positive view on self and life conducted by trained health visitor; infant care discussed separately. Health visitors trained in listening, encouraging clients to make judgment-based decisions rather than giving advice; each health visitor given manual describing postnatal depression and counseling; attended 3 weekly 2-hour training group sessions; videotapes used to illustrate important of counseling and role-playing.
	CG	Usual Care	NR	NA	NA	NA	NA	NA	NR
Segre, 2014[149] Fair	IG	Non-directive counseling	41	Point of care provider	8	0.5-0.83	2	4.5	Listening visits either in home or OBGYN office included greeting participant, finding a private place to talked, reviewing previous visit, getting update about previous week, using key skills of reflective listening and problem solving, and summarizing to provide closure to sessions. Key therapeutic components include (a) empathetic listening to gain a full understanding of women's situation and (b) collaborative problemsolving to generate specific solutions. Also received usual home visiting or social services.

Appendix D Table 9. Detailed Interventions for Key Question 4 (Pregnant and Postpartum Women)

Author, Year and Quality	Group	Intervention	N Rand.	Provider	# of Sessions	Length of Sessions (hours)	Duration (months)	Estimated Hours of Contact	Detailed Description
	CG	Waitlist control	25	NA	NA	NA	NA	NA	Received usual social or prenatal/postpartum health care services such as linking family to appropriate health and child development services; educating clients about nutrition, newborn care, child development, and parenting; referring to community resources; providing the screening services. Participants offered intervention after 8 weeks.
Wickberg, 1996[147] Fair	IG	Non-directive counseling	20	Nurse	6	1	1.5	6	Counseling at home or clinic. Nurses received four half-day training sessions in non-directive counseling, approached based on assumption that talking to a non-judgmental and empathic professional will enable pt to have a more positive view of self and life; encourage pts to make decisions based on own judgment; encouraged to listening instead of giving advice; training included lectures, role-play and discussions.
	CG	Usual Care	21	NA	NA	NA	NA	NA	Ordinary routine care; no scheduled checkups but possibility of visiting the clinic whenever needed
Goodman, 2014[150] Fair	IG	Perinatal dyadic psychotherapy	21	Nurses	8	1	3	8	Individually-tailored Perinatal Dyadic Psychotherapy eight 1-hour sessions conducted in participants' home over 3 months by a trained nurse consisting of (a) supportive relationship-based mother-infant psychotherapeutic component, and (b) a developmentally-based infant-oriented component to enhance maternal sensitive responsiveness and promote positive mother-infant interactions. Areas of focus include (1) maternal emotional well-being, (2) infant behavior and development, (3) mother-infant relationship. First four visits were weekly, remaining four visits every other week.
	CG	Usual Care	21	Study coordinator	8	0.167	3	1.33	Telephone calls from study coordinator (eight calls; first four weekly then final four every other week) over three months for about 10 minutes each; focused on monitoring depression status through administration of the EPDS and on maintaining participant engagement in the study.
Heh, 2003[131] Fair	IG	Information support	35	Principal investigator	1	NA	NA	0.08	Printed 3-page booklet developed by principal investigator modified from previous leaflets sent by post
	CG	Usual Care	35	NA	NA	NA	NA	NA	Did not receive information booklet

Appendix D Table 9. Detailed Interventions for Key Question 4 (Pregnant and Postpartum Women)

Author, Year and Quality	Group	Intervention	N Rand.	Provider	# of Sessions	Length of Sessions (hours)	Duration (months)	Estimated Hours of Contact	Detailed Description
Horowitz, 2001[134] Fair	IG	Interaction coaching	NR	Advanced practice nurses	3	0.25	2.5	0.75	Interaction coaching for at-risk parents and their infants (ICAP) to strengthen the early dyadic relationship. Mother-infant face-to-face interaction observed for 5 minutes; six key elements of intervention applied (1) teaching mother to identify infant's behavioral cues and tailor response to infant's preferences, (2) guiding mother to align infant in vision line, (3) demonstrate ways to modulate use of pauses, imitation, sequences, and combinations of facial expressions, voice and touch, (4) encouraging practice of suggestions and trial/error learning, (5) reinforcing sensitive responsiveness whenever it occurred, and (6) praising success. Home visits at 4-8 weeks, 10-14 weeks, and 14-18 weeks postpartum. Also received standard postpartum primary care and also could receive additional psychiatric treatment for depression as needed.
	CG	Usual Care	NR	Advanced practice nurses	3	NR	2.5	0.75	Home visits at 4-8 weeks, 10-14 weeks, and 14-18 weeks postpartum; mother-infant face-to-face interaction observed for 5 minutes. Received standard postpartum primary care and also could receive additional psychiatric treatment for depression as needed.

Appendix D Table 9. Detailed Interventions for Key Question 4 (Pregnant and Postpartum Women)

Author, Year and Quality	Group	Intervention	N Rand.	Provider	# of Sessions	Length of Sessions (hours)	Duration (months)	Estimated Hours of Contact	Detailed Description
Stepped Care									
Gjerdingen, 2009[129] Fair	IG	Stepped care	19	Provider, care manager	NR, average 4.1 calls (range, 0-11)	NR, 20-30 min calls	9	1.7	Referral to primary care provider for initial treatment (antidepressant and/or psychotherapy referral); regular care manager telephone followup (20-30 minutes every 2 weeks); decision support for primary care providers (e.g., advice regarding specific antidepressants, additional treatment, or mental health referral); consultation or referral to a mental health specialist for complex cases (e.g., psychiatrists; therapists [psychotherapy, CBT, interpersonal therapy, other therapies]), and pt education provided through the primary physician, care manager (trained, registered nurse w/ mental health experience), and mailed postpartum depression brochure. Treatment continued until remission (PHQ-9 < 5) or pt passed the 9-month followup period. If at call or survey revealed suicide ideation, provider notified and plan of action developed. Providers given 1-hour training session and printed educational materials on postpartum depression.
	CG	Usual Care	20	NA	NA	NA	NA	NA	Informed of depression diagnosis and referred to their primary care provider who managed depression according to provider's usual practice. Providers given 1-hour training session and printed educational materials on postpartum depression.
Antidepressants									
Appleby, 1997[126] Fair	IG	Fluoxetine + CBT	43	Psychologist	1 or 6	1 hour (1st session), 30 min (subse-quent sessions)	2.75	1-3.5	Fluoxetine plus one or six CBT sessions. Each CBT session offered reassurance and practical advice on four areas: feelings of not coping, lack of enjoyable activities, lack of practical support, and caring for any older children; first session lasted one hour, additional sessions lasted 30 minutes
	CG	Placebo + CBT	44	Psychologist	1 or 6	1 hour (1st session), 30 min (subse-quent sessions)	2.75	1-3.5	Placebo plus one or six CBT sessions. Each CBT session offered reassurance and practical advice on four areas: feelings of not coping, lack of enjoyable activities, lack of practical support, and caring for any older children; first session lasted one hour, additional sessions lasted 30 minutes

Abbreviations: CBT = cognitive behavioral therapy; CG = control group; dx = diagnosis; GP = general practitioner; ICAP = Infant, Child, and Adolescent Psychiatry; IG = intervention group; min = minutes; NA = not applicable; NR = not reported; PHQ = Patient Health Questionnaire; pt(s) = participants; rand = randomized; tx = treatment; w/ = with.

Appendix D Table 10. Results From Included Studies for Key Question 4 (Pregnant and Postpartum Women): Depression

Category	Author, Year and Quality	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
Depression Remission	**CBT or Related Interventions**						
	McGregor, 2013[140] Fair	EPDS ≤ 12, n (%)	4	IG	NR	18 (85.7)	OR 1.0 (95% CI, 0.18 to 5.56), p=0.10
				CG	NR	18 (85.7)	
			6	IG	NR	18 (85.7)	OR 1.89 (95% CI, 0.39 to 9.09), p=0.43
				CG	NR	16 (76.2)	
		EPDS ≤ 9, n (%)	4	IG	0 (0)	16 (76.2)	OR 2.38 (95% CI, 0.64 to 9.09), p=0.19
				CG	0 (0)	12 (57.1)	
			6	IG	0 (0)	17 (80.9)	OR 3.85 (95% CI, 0.96 to 14.29), p=0.05
				CG	0 (0)	11 (52.4)	
	Cooper, 2003[128] Good	No SCID depression diagnosis, n (%)	4.5	IG1	0 (0)	82 (61)	IG1 vs. CG: RR 1.60 (95% CI, 1.14 to 1.98), p=0.01†
				IG2	0 (0)	24 (57)	IG2 vs. CG: RR 1.50 (95% CI, 0.92 to 1.98), p=0.09†
				IG3	0 (0)	26 (54)	IG3 vs. CG: RR 1.38 (95% CI, 0.82 to 1.89), p=0.14†
				IG4	0 (0)	32 (71)	IG4 vs. CG: RR 1.89 (95% CI, 1.33 to 2.23), p=0.002†
				CG	0 (0)	20 (40)	
			9	IG1	0 (0)	95 (73)	IG1 vs. CG: RR 1.09 (95% CI, 0.83 to 1.26), p=0.48†
				IG2	0 (0)	30 (75)	IG2 vs. CG: RR 1.12 (95% CI, 0.45 to 1.39), p=0.56†
				IG3	0 (0)	31 (66)	IG3 vs. CG: RR 0.99 (95% CI, 0.33 to 1.36), p=0.77†
				IG4	0 (0)	34 (79)	IG4 vs. CG: RR 1.15 (95% CI, 0.54 to 1.39), p=0.28†
				CG	0 (0)	33 (69)	
			18	IG1	NR	90 (70)	IG1 vs. CG: RR 0.87 (95% CI, 0.61 to 1.06), p=0.21†
				IG2	NR	30 (71)	IG2 vs. CG: RR 0.90 (95% CI, 0.31 to 1.18), p=0.26†
				IG3	NR	31 (69)	IG3 vs. CG: RR 0.87 (95% CI, 0.28 to 1.17), p=0.16†
				IG4	NR	29 (71)	IG4 vs. CG: RR 0.85 (95% CI, 0.25 to 1.17), p=0.20†
				CG	NR	39 (81)	
	Prendergast, 2001[146] Fair	EPDS < 10, n (%)	1.5	IG	0 (0)	14 (82)	NR
				CG	0 (0)	15 (77)	
			8	IG	0 (0)	14 (93)	NR
				CG	0 (0)	15 (82)	
	Kozinzky, 2012[138] Good	Leverton Questionnaire score < 11/12, n (%)	4.75	IG	0 (0)	80 (67.2)	NR
				CG	0 (0)	101 (49.3)	
	Ammerman, 2013[124] Fair	No SCID-I MDD diagnosis, n (%)	4.75	IG	0 (0)	35 (74.5)	OR 5.56, p<0.001
				CG	0 (0)	16 (34.8)	
			7.75	IG	0 (0)	39 (83.0)	OR 1.96, p<0.01
				CG	0 (0)	26 (56.5)	

Appendix D Table 10. Results From Included Studies for Key Question 4 (Pregnant and Postpartum Women): Depression

Category	Author, Year and Quality	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
	Honey, 2002[133] Fair	EPDS < 12, n (%)	2	IG	0 (0)	8 (35)	Chi-sqaure 0.30, p>0.01
				CG	0 (0)	6 (27)	
			8	IG	0 (0)	15 (65)	Chi-square 3.75, p≤0.05
				CG	0 (0)	8 (36)	
	Wiklund, 2010[148] Fair	EPDS ≤ 10, n (%)	2.75	IG	0 (0)	25 (75.8)	Chi-square 8.23, p=0.004
				CG	0 (0)	14 (41.2)	
	Other Behaviorally-based Interventions						
	Holden, 1989[132] Fair	No evidence of minor or major depression, n (%)	3.25	IG	0 (0)	18 (69)	% Difference 31.7 (95% CI, 5 to 58), p=0.03
				CG	0 (0)	9 (38)	
	Heh, 2003[131] Fair	EPDS score < 10, n (%)	1.5	IG	0 (0)	21 (60)	Chi-square 5.76 (1), p=0.02
				CG	0 (0)	11 (31.4)	
	Segre, 2014[149] Fair	EPDS, clinically significant improvement, n (%)	2	IG	NR	25 (64)	NR
				CG	NR	9 (43)	
		EPDS, mean (SD)	2	IG	17.18 (3.97)	10.33 (6.03)	Cohen's d 0.56 (95% CI, -0.03 to 1.2), p=0.064
				CG	15.10 (4.44)	11.14 (6.04)	
		HRSD, clinically significant improvement, n (%)	2	IG	NR	14 (36)	NR
				CG	NR	3 (14)	
		HRSD, deterioration, n (%)	2	IG	NR	0 (0)	NR
				CG	NR	1 (5)	
		HRSD, mean (SD)	2	IG	18.69 (6.52)	11.03 (7.30)	Cohen's d 0.72 (95% CI, 0.2 to 1.2), p=0.008
				CG	16.57 (6.56)	14.29 (8.19)	
		IDAS-GD, clinically significant improvement, n (%)	2	IG	NR	27 (69)	NR
				CG	NR	6 (29)	
		IDAS-GD, mean (SD)	2	IG	63.13 (12.77)	44.67 (15.14)	Cohen's d 0.62 (95% CI, 0.1 to 1.2), p=0.040
				CG	57.33 (13.79)	47.86 (16.42)	
	Goodman, 2014[150] Fair	Major depression, n (%)	3	IG	0 (0)	5 (100)	NR
				CG	0 (0)	1 (50)	
			6	IG	0 (0)	4 (80)	NR
				CG	0 (0)	2 (100)	

Appendix D Table 10. Results From Included Studies for Key Question 4 (Pregnant and Postpartum Women): Depression

Category	Author, Year and Quality	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
		Major or minor depression, n (%)	3	IG	0 (0)	6 (85.7)	NR
				CG	0 (0)	4 (66.7)	
			6	IG	0 (0)	6 (85.7)	OR 0.75 (95% CI, 0.22 to 2.44), p=0.80
				CG	0 (0)	6 (100)	
		Minor depression, n (%)	3	IG	0 (0)	1 (50)	NR
				CG	0 (0)	3 (75)	
			6	IG	0 (0)	2 (100)	NR
				CG	0 (0)	4 (100)	
	Stepped Care						
	Gjerdingen, 2009[129] Fair	PHQ-9 < 10, n (%)	9	IG	0 (0)	9 (56.3)	NR, p=0.475
				CG	0 (0)	13 (72.2)	
Depressive Symptoms	**CBT or Related Interventions**						
	McGregor, 2013[140] Fair	EPDS score, mean (SD)	4	IG	12.48 (2.84)	7.86 (5.15)	NR
				CG	12.38 (3.26)	9.62 (4.95)	
			6	IG	12.48 (2.84)	6.26 (4.84)	NR
				CG	12.38 (3.26)	8.62 (4.61)	
	Milgrom, 2011b[142] Fair	BDI-II score, mean (SD)	2	IG2	30.9 (10.7)	10.4 (9.5)*	IG1 vs. CG: NR, p=0.347
				IG3	25.5 (8.3)	6.7 (4.3)*	
				CG	27.9 (10.8)	11.0 (8.0)*	
	Cooper, 2003[128] Good	EPDS score, mean (SD)	4.5	IG1	13.3	9.4 (5.0)	IG1 vs. CG: Mean Difference -2.5 (95% CI, -3.9 to -1.0), p≤0.001† IG2 vs. CG: Mean Difference -2.7 (95% CI, -4.5 to -0.9), p=0.003† IG3 vs. CG: Mean Difference -2.1 (95% CI, -3.8 to -0.3), p=0.02† IG4 vs. CG: Mean Difference -2.6 (95% CI, -4.4 to -0.9), p=0.003†
				IG2	13.7	9.2 (4.8)	
				IG3	13.7	9.9 (5.9)	
				IG4	12.6	8.9 (4.2)	
				CG	12.4	11.3 (4.8)	
			9	IG1	13.3	9.3 (5.5)	IG1 vs. CG: Mean Difference -0.3 (95% CI, -2.0 to 1.3), p=0.70† IG2 vs. CG: Mean Difference -1.0 (95% CI, -4.4 to 2.4),
				IG2	13.7	8.6 (5.9)	
				IG3	13.7	9.6 (5.8)	
				IG4	12.6	9.5 (5.5)	

Appendix D Table 10. Results From Included Studies for Key Question 4 (Pregnant and Postpartum Women): Depression

Category	Author, Year and Quality	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
				CG	12.4	9.2 (5.4)	p=0.33† IG3 vs. CG: Mean Difference -0.2 (95% CI, -3.5 to 3.2), p=0.87† IG4 vs. CG: Mean Difference 0.2 (95% CI, -2.9 to 3.3), p=0.85†
			18	IG1	13.3	9.2 (5.5)	IG1 vs. CG: Mean Difference -0.1 (95% CI, -1.7 to 1.6), p=NR† IG2 vs. CG: Mean Difference 0.6 (95% CI, -3.9 to 2.8), p=NR† IG3 vs. CG: Mean Difference 0.3 (95% CI, -3.1 to 3.6), p=NR† IG4 vs. CG: Mean Difference 0.1 (95% CI, -3.3 to 3.5), p=NR†
				IG2	13.7	8.9 (5.4)	
				IG3	13.7	9.6 (5.2)	
				IG4	12.6	9.1 (5.6)	
				CG	12.4	8.9 (4.4)	
	Prendergast, 2001[146] Fair	EPDS score, mean (SD)	1.5	IG	15.9 (2.8)	8.1 (2.9)	NSD
				CG	13.7 (2.3)	6.5 (6.2)	
			8	IG	15.9 (2.8)	6.2 (4.2)	NSD
				CG	13.7 (2.3)	7.7 (3.9)	
		MADRS score, mean (SD)	1.5	IG	21.7 (3.6)	8.4 (5.3)	NSD
				CG	20.0 (5.0)	12.1 (8.3)	
	Ammerman, 2013[124] Fair	BDI-II, mean (SD)	4.75	IG	33.11 (9.90)	12.70 (15.44)	Mean Difference -13.81 (3.18), p<0.001
				CG	34.54 (10.04)	26.51 (13.49)	
			7.75	IG	33.11 (9.90)	12.31 (13.71)	Mean Difference -9.43 (3.26), p<0.01
				CG	34.54 (10.04)	21.74 (14.91)	
		EPDS, mean (SD)	4.75	IG	18.77 (3.96)	9.49 (7.35)	Mean Difference -5.77 (1.41), p<0.001
				CG	19.22 (4.07)	15.26 (5.47)	
			7.75	IG	18.77 (3.96)	8.59 (7.22)	Mean Difference -4.65 (1.76), p<0.05
				CG	19.22 (4.07)	13.24 (8.20)	
		HDRS, mean (SD)	4.75	IG	21.87 (4.37)	8.71 (7.86)	Mean Difference -6.34 (1.76), p<0.01
				CG	21.96 (4.40)	15.05 (8.24)	
			7.75	IG	21.87 (4.37)	7.28 (6.47)	Mean Difference -4.93 (1.70), p<0.01
				CG	21.96 (4.40)	12.21 (8.32)	
	Honey, 2002[133] Fair	EPDS score, mean (SD)	2	IG	19.35 (4.39)	14.87 (5.97)	OR 0.93 (95% CI, 0.28 to 3.06), p>0.1‡
				CG	17.95 (3.95)	16.95 (5.44)	
			8	IG	19.35 (4.39)	12.55 (4.62)	OR 1.11 (95% CI, 0.29 to 4.24), p>0.1‡
				CG	17.95 (3.95)	15.63 (7.28)	

Appendix D Table 10. Results From Included Studies for Key Question 4 (Pregnant and Postpartum Women): Depression

Category	Author, Year and Quality	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
	Wiklund, 2010[148] Fair	EPDS score, mean (SD)	2.75	IG	16.9 (3.90)	7.6	T-test 2.10, p=0.039
				CG	13.6 (1.93)	9.8	
	Other Behaviorally-based Interventions						
	Holden, 1989[132] Fair	EPDS score, median	3.25	IG	16.0	10.5	NR, p=0.01
				CG	15.5	12.0	
		Standardized psychiatric interview total score, median	3.25	IG	25.5	14.0	NR, p=0.01
				CG	24.0	23.0	
		Standardized psychiatric interview observed depression, median	3.25	IG	2.0	0.5	NR, p=0.01
				CG	2.0	2.0	
	Wickberg, 1996[147] Fair	MADRS score, mean	1.5	IG	19.6	10.9	Z-score -2.8, p=0.0058
				CG	17.1	14.7	
	Goodman, 2014[150] Fair	EPDS score, mean (SD)	3	IG	12.48 (3.39)	6.19 (3.64)	NR, p=NSD
				CG	12.14 (2.67)	6.35 (5.45)	
			6	IG	12.48 (3.39)	4.86 (3.35)	Coefficient -0.37 (95% CI, -2.27 to 1.54), p=0.71
				CG	12.14 (2.67)	6.05 (4.50)	
	Heh, 2003[131] Fair	EPDS score, mean (SD)	1.5	IG	16.5 (3.0)	10.8 (4.4)	NR, p=0.02
				CG	16.3 (2.7)	12.1 (3.0)	
	Horowitz, 2001[134] Fair	BDI-II score, mean (SD)	1.5	IG	15.5 (1.17)	10.99 (0.96)	NR
				CG	13.24 (0.92)	10.10 (0.84)	
			2.5	IG	15.5 (1.17)	10.27 (0.99)	F-test 0.36, p=0.67
				CG	13.24 (0.92)	9.51 (0.77)	
	Stepped Care						
	Gjerdingen, 2009[129] Fair	PHQ-9, mean (SD)	9	IG	10.5 (8.5)	9.0 (7.3)	NR, p=0.597
				CG	11.7 (7.2)	7.6 (6.5)	
		Self-reported depression symptoms after delivery, n (%)	9	IG	NR	16 (100)	NR, p=0.008
				CG	NR	11 (61.1)	

Appendix D Table 10. Results From Included Studies for Key Question 4 (Pregnant and Postpartum Women): Depression

Category	Author, Year and Quality	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
	Antidepressants						
	Appleby, 1997[126] Fair	EPDS scores, mean (95% CI)	3	IG	17.2 (95% CI, 16.2 to 18.2)	7.3 (95% CI, 5.5 to 9.6)	NR, p<0.05
				CG	16.9 (95% CI, 15.8 to 18.1)	9.9 (95% CI, 8.3 to 11.8)	
		Hamilton Depression Scale, mean (95% CI)	3	IG	14.2 (95% CI, 13.0 to 15.5)	4.7 (95% CI, 3.1 to 6.9)	NR, p<0.05
				CG	13.9 (95% CI, 12.5 to 15.4)	6.4 (95% CI, 4.9 to 8.4)	
		Revised clinical interview schedule scores, mean (95% CI)	3	IG	28.2 (95% CI, 26.4 to 30.1)	10.8 (95% CI 7.9 to 14.8)	NR, p<0.05
				CG	28.3 (95% CI, 26.6 to 30.1)	15.9 (95% CI 13.1 to 19.3)	

*Adjusted by baseline symptoms.
†Adjusted by mean centered BL EPDS score.
‡Adjusted by antidepressant use.

Abbreviations: BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CG = control group; CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale; HDRS = Hamilton Depression Rating Scale; IG = intervention group; MADRS = Montgomery Asberg Depression Rating Scale; MDD = major depressive disorder; OR = odds ratio; PHQ = Patient Health Questionnaire; RR = relative risk; SCID = Structured Clinical Interview for Disorders; SD = standard deviation; vs = versus.

Appendix D Table 11. Results From Included Studies for Key Question 4 (Pregnant and Postpartum Women): Child and Infant Outcomes

Author, Year and Quality	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
CBT or Related Interventions						
Cooper, 2003[128] Good	Adverse outcome, behaviour-management problems, n (%)	4.5	IG2	NR	13 (32)	IG2 vs. CG: RR 0.83 (95% CI, 0.37 to 1.50), p=0.60* IG3 vs. CG: RR 0.91 (95% CI, 0.42 to 1.58), p=0.77* IG4 vs. CG: RR 1.21 (95% CI, 0.62 to 1.87), p=0.52*
			IG3	NR	15 (35)	
			IG4	NR	19 (44)	
			CG	NR	13 (37)	
	Adverse outcome, infant attachment, n (%)	18	IG2	NR	22 (54)	IG2 vs. CG: RR 1.26 (95% CI, 0.78 to 1.70), p=0.30 IG3 vs. CG: RR 0.96 (95% CI, 0.54 to 1.46), p=0.89 IG4 vs. CG: RR 1.23 (95% CI, 0.76 to 1.68), p=0.86
			IG3	NR	16 (41)	
			IG4	NR	21 (52)	
			CG	NR	20 (43)	
	Adverse outcome, relationship problems, n (%)	4.5	IG2	NR	16 (39)	IG2 vs. CG: RR 0.46 (95% CI, 0.20 to 0.81), p=0.002* IG3 vs. CG: RR 0.63 (95% CI, 0.32 to 0.97), p=0.03* IG4 vs. CG: RR 0.57 (95% CI, 0.28 to 0.92), p=0.01*
			IG3	NR	23 (53)	
			IG4	NR	20 (47)	
			CG	NR	26 (74)	
	Behavioral Screening Questionnaire score, median (IQR)	18	IG2	NR	5 (4)	IG2 vs. CG: Chi-square 3.52 (1), p=0.06† IG3 vs. CG: Chi-square 12.19 (1), p=0.001† IG4 vs. CG: Chi-square 4.06 (1), p=0.03†
			IG3	NR	4 (3)	
			IG4	NR	4 (5)	
			CG	NR	6 (3)	
	Mental Development Index of Bayley scale, median (IQR)	18	IG2	NR	116 (24)	IG2 vs. CG: Median Difference 0 (95% CI, -7 to 7), p=NR IG3 vs. CG: Median Difference -2 (95% CI, -11 to 6), p=NR IG4 vs. CG: Median Difference 1 (95% CI, -6 to 7), p=NR
			IG3	NR	114 (32)	
			IG4	NR	118 (19)	
			CG	NR	116 (18)	
	Mother-infant interactions, maternal sensitivity, mean difference (95% CI)	4.5	IG2	NR	0.62 (95% CI, 0.35 to 0.90)	NR
			IG3	NR	0.88 (95% CI, 0.65 to 1.12)	
			IG4	NR	0.71 (95% CI, 0.47 to 0.97)	
			CG	NR	0.94 (95% CI, 0.71 to 1.16)	
	Reporting behaviour-management problems, n (%)	4.5	IG2	22 (54)	9 (41)	IG2 vs. CG: % Difference 3 (95% CI, -28 to 34), p=NR IG3 vs. CG: % Difference -3 (95% CI, -35 to 29), p=NR IG4 vs. CG: % Difference -24 (95% CI, -54 to 6), p=NR
			IG3	19 (47)	9 (47)	
			IG4	22 (55)	15 (68)	
			CG	18 (58)	8 (44)	
	Reporting relationship problems, n (%)	4.5	IG2	29 (71)	12 (41)	IG2 vs. CG: % Difference 42 (95% CI, -18 to 66), p=NR IG3 vs. CG: % Difference 11 (95% CI, -12 to 34), p=NR IG4 vs. CG: % Difference 33 (95% CI, 8 to 58), p=NR
			IG3	25 (63)	18 (72)	
			IG4	24 (60)	12 (50)	
			CG	23 (74)	19 (83)	

Appendix D Table 11. Results From Included Studies for Key Question 4 (Pregnant and Postpartum Women): Child and Infant Outcomes

Author, Year and Quality	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
Other Behaviorally-based Interventions						
Horowitz, 2001[134] Fair	Dyadic Mutuality Code score, mean (SD)	1.5	IG	8.83 (1.76)	9.73 (1.65)	T-test -3.15 (116), p=0.002
			CG	8.67 (1.64)	8.77 (1.72)	
		2.5	IG	8.83 (1.76)	9.55 (1.77)	T-test -2.22 (115), p=0.029
			CG	8.67 (1.64)	8.80 (1.86)	

*Adjusted by behavioural management problems prior to treatment.
†Adjusted by social adversity and maternal age.

Abbreviations: CBT = cognitive behavioral therapy; CG = control group; CI = confidence interval; IG = intervention group; IQR = interquartile range; NR = not reported; OR = odds ratio; RR = relative risk; SD = standard deviation; vs = versus.

Appendix D Table 12. Results From Included Studies for Key Question 4 (Pregnant and Postpartum Women): Quality of Life and Functioning

Author, Year and Quality	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
CBT or Related Interventions						
McGregor, 2013[140] Fair	STAI-State score, mean (SD)	4	IG	45.38 (9.31)	37.62 (11.08)	NR
			CG	45.29 (11.52)	42.0 (12.62)	
		6	IG	45.38 (9.31)	31.62 (11.38)	NR
			CG	45.29 (11.52)	35.52 (10.43)	
Milgrom, 2011b[142] Fair	DASS 21 SF Anxiety Scale, mean	2	IG2	7.9	4.1	NSD
			IG3	9.5	3.0	
			CG	8.0	4.0	
Ammerman, 2013[124] Fair	Global Assessment of Functioning Scale, mean (SD)	4.75	IG	55.51 (6.29)	72.22 (13.88)	Mean Difference 8.99 (2.85), p<0.01
			CG	56.11 (6.44)	63.23 (12.18)	
		7.75	IG	55.51 (6.29)	73.41 (13.48)	Mean Difference 8.02 (3.02), p<0.05
			CG	56.11 (6.44)	65.39 (12.39)	
	Brief Symptom Inventory-Global Severity, mean (SD)	4.75	IG	74.3 (5.2)	60.8 (12.2)	T-test: 3.47, p<0.001
			CG	74.4 (5.7)	69.4 (10.0)	
		7.75	IG	74.3 (5.2)	57.6 (16.5)	T-test: 3.22, p<0.001
			CG	74.4 (5.7)	67.8 (10.7)	
	Interpersonal Support Evaluation List total score, mean (SD)	4.75	IG	55.8 (21.4)	75.8 (22.9)	T-test: 1.75, p=0.084
			CG	60.4 (21.8)	66.5 (25.5)	
		7.75	IG	55.8 (21.4)	83.6 (21.4)	T-test: 2.84, p<0.01
			CG	60.4 (21.8)	68.1 (26.4)	
	ASQ-SE, mean (SD)	4.75	IG	0.06 (0.57)	-0.08 (0.56)	Cohen's d: 0.13, p=NS*
			CG	0.20 (0.64)	-0.01 (0.53)	
		7.75	IG	0.06 (0.57)	0.01 (0.71)	Cohen's d: -0.09, p=NS *
			CG	0.20 (0.64)	-0.04 (0.42)	
	HOME total score, mean (SD)	4.75	IG	31.36 (5.75)	34.58 (5.73)	Cohen's d: -0.44, p=0.053 *
			CG	31.32 (6.41)	31.88 (6.61)	
		7.75	IG	31.36 (5.75)	34.45 (5.88)	Cohen's d: -0.16, p=NS *
			CG	31.32 (6.41)	33.59 (4.87)	
	PSI-SF, mean (SD)	4.75	IG	83.49 (18.93)	73.34 (23.65)	Cohen's d: 0.29, p=NS *
			CG	87.31 (20.07)	79.56 (18.47)	
		7.75	IG	83.49 (18.93)	64.58 (31.00)	Cohen's d: 0.39, p=NS *
			CG	87.31 (20.07)	75.92 (27.27)	
Other Behaviorally-based Interventions						
Segre, 2014[149] Fair	WSAS, clinically significant improvement, n (%)	2	IG	NR	19 (49)	NR
			CG	NR	8 (38)	
	WSAS, mean (SD)	2	IG	23.44 (9.03)	15.56 (10.95)	Cohen's d 0.13 (95% CI, -0.4 to 0.6), p=0.625
			CG	20.19 (11.17)	13.67 (10.98)	
	Q-LES-Q, clinically significant improvement, n (%)	2	IG	NR	22 (56)	NR
			CG	NR	3 (14)	
	Q-LES-Q, mean (SD)	2	IG	33.46 (8.38)	42.49 (11.57)	Cohen's d 0.60 (95% CI, 0.2 to 1.03), p=0.015
			CG	38.62 (10.77)	41.52 (10.48)	

Appendix D Table 12. Results From Included Studies for Key Question 4 (Pregnant and Postpartum Women): Quality of Life and Functioning

Author, Year and Quality	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
Goodman, 2014[150] Fair	CIB-dyadic reciprocity, mean (SD)	3	IG	NA (NA)	3.46 (0.68)	NR
			CG	NA (NA)	3.60 (0.83)	
		6	IG	NA (NA)	3.72 (0.97)	Coefficient -0.09 (95% CI, -0.51 to 0.34), p=0.70
			CG	NA (NA)	3.73 (0.91)	
	CIB-infant involvement, mean (SD)	3	IG	NA (NA)	3.20 (0.69)	NR
			CG	NA (NA)	3.34 (0.78)	
		6	IG	NA (NA)	3.79 (0.52)	Coefficient 0.01 (95% CI, -0.29 to 0.31), p=0.95
			CG	NA (NA)	3.66 (0.48)	
	CIB-maternal sensitivity, mean (SD)	3	IG	NA (NA)	3.69 (0.59)	NR
			CG	NA (NA)	3.95 (0.55)	
		6	IG	NA (NA)	3.73 (0.84)	Coefficient -0.21 (95% CI, -0.56 to 0.15), p=0.25
			CG	NA (NA)	3.88 (0.66)	
	PSI-SF, mean (SD)	3	IG	NA (NA)	73.67 (18.61)	NR
			CG	NA (NA)	64.30 (15.35)	
		6	IG	NA (NA)	69.43 (15.46)	Coefficient 7.51 (95% CI, -1.45 to 16.47), p=0.10
			CG	NA (NA)	63.81 (13.44)	
	MRSI, mean (SD)	3	IG	3.52 (0.56)	4.05 (0.34)	NR, NSD
			CG	3.79 (0.36)	4.16 (0.34)	
		6	IG	3.52 (0.56)	4.17 (0.36)	Coefficient -0.17 (95% CI, -0.37 to 0.35), p=0.11
			CG	3.79 (0.36)	4.26 (0.36)	
	STAI state anxiety, mean (SD)	3	IG	43.62 (9.47)	35.29 (9.03)	NR, NSD
			CG	36.00 (10.39)	31.40 (9.65)	
		6	IG	43.62 (9.47)	33.43 (7.49)	Coefficient 5.05 (95% CI, 0.50 to 9.60), p=0.03
			CG	36.00 (10.39)	29.76 (8.24)	
	Any anxiety disorder diagnosis, n (%)	3	IG	9 (42.9)	5 (23.8)	NR
			CG	7 (33.3)	3 (14.3)	
		6	IG	9 (42.9)	2 (9.5)	OR 1.97 (95% CI, 0.62 to 5.13), p=0.34
			CG	7 (33.3)	0 (0)	
Stepped Care						
Gjerdingen, 2009[129] Fair	Hours of missed work over past week, mean (SD)	9	IG	NR	4.0 (5.7)	NR, p=0.296
			CG	NR	1.5 (2.1)	
	Impact of health problems on work productivity, mean (SD)	9	IG	NR	1.0 (1.4)	NR, p=0.604
			CG	NR	2.0 (2.4)	
	Impact of problems on regular activities, mean (SD)	9	IG	NR	3.9 (3.1)	NR, p=0.562
			CG	NR	2.4 (2.8)	
	SF-36 general health, mean (SD)	9	IG	2.9 (0.9)	2.8 (1.0)	NR, p=0.851
			CG	3.2 (0.8)	2.8 (0.6)	
	SF-36 mental health, mean (SD)	9	IG	18.1 (6.3)	18.8 (5.9)	NR, p=0.356
			CG	18.0 (5.8)	20.7 (5.4)	

*Adjusted using a false discovery rate.

Appendix D Table 12. Results From Included Studies for Key Question 4 (Pregnant and Postpartum Women): Quality of Life and Functioning

Abbreviations: ASQ-SE = Ages and Stages Questionaire: Social Emotional; CG = control group; DASS = Depression Anxiety Stress Scales; HOME = Home Observation for Measurement of the Environment; IG = intervention group; NR = not reported; NSD = no significant difference; PSI-SF = Parenting Stress Index Short Form; Q-LES-Q = Quality of Life, Enjoyment and Satisfaction Questionnaire; SD = standard deviation; SF = Short Form; STAI = State-Trait Anxiety Inventory; WSAS = Work and Social Life Adjustment Scale.

Appendix D Table 13. Results From Included Studies for Key Question 4 (Pregnant and Postpartum Women): Health Care Use

Author, Year and Quality	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
CBT or Related						
McGregor, 2013[140]	Medication for stress, anxiety or sleep, n (%)	6	IG	NR	1 (4.8)	NSD
			CG	NR	3 (14.3)	
Fair	Psychiatric services, n (%)	6	IG	NR	2 (9.5)	NSD
			CG	NR	4 (19.0)	
Stepped Care						
Gjerdingen, 2009[129]	Number of baby's clinic/urgent care visits, mean (SD)	9	IG	0.1 (0.5)	0.1 (0.3)	NR, p=0.407
			CG	0 (0)	0.6 (1.9)	
Fair	Number of mom's clinic/urgent care visits, mean (SD)	9	IG	0.3 (0.7)	0.2 (0.8)	NR, p=0.972
			CG	0.6 (2.0)	0.2 (0.04)	
	Received antidepressants, n (%)	9	IG	NR	15 (93.8)	NR, p=0.019
			CG	NR	10 (55.6)	
	Received counseling, n (%)	9	IG	NR	7 (43.8)	NR, p=1.00
			CG	NR	5 (27.8)	
	Received treatment (antidepressants or psychotherapy), n (%)	9	IG	NR	15 (93.8)	NR, p=0.019
			CG	NR	10 (55.6)	

Abbreviations: CBT = cognitive behavioral therapy; CG = control group; IG = intervention group; NR = not reported; NSD = no significant difference; SD = standard deviation.

Appendix D Table 14. Major Inclusion Criteria and Data Source Descriptions for Key Question 5 (Pregnant Women)

Author, Year and Quality	N	Major Incusion Criteria	Data Sources
Palmsten, 2013a[144] Good	85,326	Live-born infant, maternal depression (inpatient or outpatient diagnosis).	Linked Medicaid enrollment information to inpatient and outpatient procedures and diagnoses and to outpatient pharmacy dispensing data to identify women with delivery-related diagnoses. Live-born infants were linked to these women by state and Medicaid ID numbers.
Palmsten, 2013b[143] Good	102,722	Pregnant women aged 12-55 years with a pregnancy ending in a live birth, Medicaid enrollment from 5 months before delivery until after delivery, diagnoses for mood (including bipolar) or anxiety disorders between 1 and 5 months before delivery	Linked Medicaid enrollment information to inpatient and outpatient procedures and diagnoses and to outpatient pharmacy dispensing data. Live-born infants were linked to these women by state and Medicaid ID numbers.
Lupattelli, 2014[139] Fair	57,279	Pregnant women who had both a record in the Medical Birth Registry and had answered MoBa questionnaires #1, 3 and 4; live births only.	Linked MoBa data with the birth registry and examined AD use and bleeding outcomes. Exposure and outcomes based on self-report.
Andersen, 2014[125] Good	1,279,840	Registered pregnancies from 1997-2010.	Linked data on pregnancies, births/birth outcomes, and prescription medication use for all registered pregnancies from 1997 to 2010.
Kjaersgaard, 2013[137] Good	1,005,319	Clinically recognized pregnancies in Denmark with an estimated conception and an observed pregnancy outcome in the period Feb 1, 1997 to Dec 31, 2008. Spontaneous abortion had to occur at less than 22 weeks gestation.	Linked administrative health registries for documented abortions, AD exposure (redeemed prescriptions), maternal psychiatric illness, and Statistics Denmark (for socio-demographic details).
Hayes, 2012[130] Good	228,876	Women aged 15-44 years with singleton pregnancies who were enrolled in the Tennessee Medicaid Program from 1995 to 2007 with 180 days continuous enrollment before their LMP through 90 days after delivery.	Linked data from Medicaid database and birth certificates.
Jensen, 2013a[136] Good	673,853	Singleton deliveries with a gestational age of at least 22 weeks during the period 1996-2006.	Linked national register data for all pregnancies with the national psychiatric register, the Medicinal Product Statistics Register (a nationwide prescription database), and Statistic Denmark (national sociodemographic data).
Ban, 2014[127] Good	349,127	Live singleton births from 1990 to 2009 among women aged 14-45 years.	Nationally representative database validated for pharmacoepidemiology studies.
Polen, 2013[145] Fair	27,045	Cases include live births, still births (at least 20 weeks gestation) and elective terminations diagnosed with one of more than 30 selected major birth defects from 1997 to 2007. Controls include live born infants without birth defects from same source population and time period as case infants.	10 state-level surveillance systems, with cases confirmed by clinical geneticist. Exposure ascertained by interview between 6w prior to delivery date and 24m after delivery.
Yazdy, 2014[151] Fair	2,624	Cases: Infants less than 1 year of age w/a diagnosis of talipes equinovarus ("clubfoot"). Controls: Infants with no major malformations or foot problems drawn from same birth population as cases.	Birth defect registries in Massachusetts, New York, and North Carolina from 2006-2011

Appendix D Table 14. Major Inclusion Criteria and Data Source Descriptions for Key Question 5 (Pregnant Women)

Author, Year and Quality	N	Major Incusion Criteria	Data Sources
Louik, 2014[152] Good	16,524	Cases (n=7,913): Infants with malformation, with primary focus on VSD, left outflow tract defects, coarctation of the aorta, and hypoplastic left heart syndrome. Controls (n=8,611): Nonmalformed infants matched to cases by age w/in 2 months.	Birth Defects Study (BDS) data from centers in Boston, Philadelphia, Toronto (through 2003), San Diego (since 2000), parts of New York state (since 2004), and the entire state of Massachusetts (since 1998) using hospital admission and discharge lists from 1992-2010 for identification of malformed subjects, as well as birth-defect registries in Massachusetts and New York.
Huybrechts, 2014[135] Good	931,259	All completed pregnancies from 2000 to 2007 in women and adolescents aged 12 to 55 years who were exclusively covered by Medicaid from 3 months before LMP through 1 months after delivery.	Linked data for mother and infants from Medicaid Analytic eXtract for 46 U.S. States and Washington, D.C. from 2000 through 2007. Four states (Montana, Connecticut, Michigan, Arizona) excluded for missing or difficult-to-link data.

Abbreviations: AD = antidepressants; ICD = International Classification of Disease; LMP = last menstrual period; MoBa = Norwegian Mother and Child Cohort Study; SSRI = selective serotonin reuptake inhibitors; w/ = with.

Appendix D Table 15. Results From Included Studies for Key Question 5 (Pregnant Women): Harms

Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
Maternal outcomes						
Palmsten, 2013a[144] Good	Pre-eclampsia, n (%)	SSRI	Exposed	19000	1033 (5)	OR 1.03 (95% CI, 0.95 to 1.12), p=NR‡‡
			Nonexposed	59219	3215 (5)	
		SSRI (by dose)	High (>midpoint of usual dose range)	2726	171 (6.3)	High (> midpoint of usual dose range) vs. Nonexposed: RR 1.10 (95% CI, 0.95 to 1.28), p=NR‡‡ Medium (≤ midpoint of usual dose range) vs. Nonexposed: RR 1.00 (95% CI, 0.91 to 1.09), p=NR‡‡ Low (< lowest usual dose) vs. Nonexposed: RR 0.95 (95% CI, 0.84 to 1.08), p=NR‡‡
			Medium (≤midpoint of usual dose range)	11361	614 (5.4)	
			Low (<lowest usual dose)	4913	248 (5.1)	
			Nonexposed	59219	3215 (5.4)	
		SSRI (by duration)	Long (>90 days)	4586	267 (5.8)	Long (> 90 days) vs. Nonexposed: RR 1.05 (95% CI, 0.93 to 1.19), p=NR‡‡ Medium (31-90 days) vs. Nonexposed: RR 0.98 (95% CI, 0.89 to 1.09), p=NR‡‡ Short (≤ 30 days) vs. Nonexposed: RR 0.99 (95% CI, 0.89 to 1.10), p=NR‡‡
			Medium (31-90 days)	7782	416 (5.4)	
			Short (≤30 days)	6632	350 (5.3)	
			Nonexposed	59219	3215 (5.4)	
		Buproprion	Exposed	2622	153 (6)	RR 1.06 (95% CI, 0.91 to 1.25), p=NR‡‡
			Nonexposed	59219	3215 (5)	
		Buproprion (by dose)	High or Medium (≥midpoint of usual dose range)	424	24 (5.7)	High or Medium (≥ midpoint of usual dose range) vs. Nonexposed: RR 1.01 (95% CI, 0.68 to 1.50), p=NR‡‡ Low (< lowest usual dose) vs. Nonexposed: RR 1.07 (95% CI, 0.90 to 1.28), p=NR‡‡
			Low (<lowest usual dose)	2198	129 (5.9)	
			Nonexposed	59219	3215 (5.4)	
		Buproprion (by duration)	Long (>90 days)	423	26 (6.2)	Long (> 90 days) vs. Nonexposed: RR 1.05 (95% CI, 0.72 to 1.52), p=NR‡‡ Medium (31-90 days) vs. Nonexposed: RR 1.01 (95% CI, 0.78 to 1.31), p=NR‡‡ Short (≤ 30 days) vs. Nonexposed: RR 1.12 (95% CI, 0.89 to 1.40), p=NR‡‡
			Medium (31-90 days)	987	56 (5.7)	
			Short (≤30 days)	1212	71 (5.9)	
			Nonexposed	59219	3215 (5.4)	
		Citalopram	Exposed	1680	91 (5)	RR 1.01 (95% CI, 0.82 to 1.23), p=NR‡‡
			Nonexposed	59219	3215 (5)	
		Duloxetine	Exposed	NR	NR (7)	RR 0.89 (95% CI, 0.43 to 1.83), p=NR‡‡
			Nonexposed	59219	3215 (5)	
		Escitalopram	Exposed	1936	125 (6)	RR 1.14 (95% CI, 0.96 to 1.36), p=NR‡‡
			Nonexposed	59219	3215 (5)	
		Fluoxetine	Exposed	5650	299 (5)	RR 0.97 (95% CI, 0.87 to 1.09), p=NR‡‡
			Nonexposed	59219	3215 (5)	

Appendix D Table 15. Results From Included Studies for Key Question 5 (Pregnant Women): Harms

Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
		Mirtazapine	Exposed	253	14 (6)	RR 0.81 (95% CI, 0.50 to 1.34), p=NR‡‡
			Nonexposed	59219	3215 (5)	
		Paroxetine	Exposed	3517	183 (5)	RR 0.99 (95% CI, 0.86 to 1.15), p=NR‡‡
			Nonexposed	59219	3215 (5)	
		Sertraline	Exposed	7143	398 (6)	RR 1.03 (95% CI, 0.93 to 1.14), p=NR‡‡
			Nonexposed	59219	3215 (5)	
		SNRI	Exposed	1216	107 (9)	OR 1.52 (95% CI, 1.17 to 1.98), p=NR‡‡
			Nonexposed	59219	3215 (5)	
		SNRI (by dose)	High (>midpoint of usual dose range)	NR	NR (11.9)	High (> midpoint of usual dose range) vs. Nonexposed: RR 1.98 (95% CI, 1.08 to 3.64), p=NR‡‡
			Low (<lowest usual dose)	239	15 (6.3)	
			Medium (≤midpoint of usual dose range)	910	84 (9.2)	Medium (≤ midpoint of usual dose range) vs. Nonexposed: RR 1.63 (95% CI, 1.32 to 2.00), p=NR‡‡
			Nonexposed	59219	3215 (5.4)	Low (< lowest usual dose) vs. Nonexposed: RR 1.01 (95% CI, 0.63 to 1.64), p=NR‡‡
		SNRI (by duration)	Long (> 90 days)	507	48 (9.5)	Long (> 90 days) vs. Nonexposed: RR 1.64 (95% CI, 1.25 to 2.16), p=NR‡‡
			Medium (31-90 days)	407	41 (10.1)	
			Short (≤ 30 days)	302	18 (6.0)	Medium (31-90 days) vs. Nonexposed: RR 1.75 (95% CI, 1.31 to 2.34), p=NR‡‡
			Nonexposed	59219	3215 (5.4)	Short (≤ 30 days) vs. Nonexposed: RR 1.01 (95% CI, 0.64 to 1.57), p=NR‡‡
		Trazadone	Exposed	339	14 (4)	RR 0.63 (95% CI, 0.38 to 1.05), p=NR‡‡
			Nonexposed	59219	3215 (5)	
		Venlafaxine	Exposed	1113	100 (9)	RR 1.57 (95% CI, 1.29 to 1.91), p=NR‡‡
			Nonexposed	59219	3215 (5)	
Palmsten, 2013b[143] Good	Postpartum hemorrhage, n (%)	All anti-depressants	Current exposure	16029	620 (3.9)	Current exposure vs. Nonexposed: RR 1.44 (95% CI, 1.32 to 1.58), p=NR§§
			Recent exposure	7577	247 (3.3)	
			Past exposure	13350	357 (2.7)	Recent exposure vs. Nonexposed: RR 1.21 (95% CI, 1.06 to 1.38), p=NR§§
			Nonexposed	69044	1896 (2.8)	Past exposure vs. Nonexposed: RR 0.98 (95% CI, 0.88 to 1.10), p=NS§§
		SSRI + venlafaxine	Depressed - Current exposure	8917	357 (4.0)	Depressed - Current exposure vs. Depressed - No exposure: RR 1.46 (95% CI, 1.29 to 1.65), p=NR§§
			Depressed - Recent exposure	4344	153 (3.5)	Depressed - Recent exposure vs. Depressed - No exposure: RR 1.28 (95% CI, 1.08 to 1.52), p=NR§§
			Depressed - Past exposure	7432	190 (2.6)	
			Depressed - No exposure	36457	1008 (2.8)	

Appendix D Table 15. Results From Included Studies for Key Question 5 (Pregnant Women): Harms

Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
			Exposed	10203	415 (4.1)	Depressed - Past exposure vs. Depressed - No exposure: RR 0.92 (95% CI, 0.79 to 1.08), p=NR§§ Exposed vs. Nonexposed: OR 1.52 (95% CI, 1.35 to 1.71), p=NR§§
			Nonexposed	53348	1479 (2.8)	
		SSRI + venlafaxine (by dose)	High dose	1597	66 (4.1)	High dose vs. Nonexposed: RR 1.55 (95% CI, 1.21 to 1.97), p=NR§§ Medium dose vs. Nonexposed: RR 1.51 (95% CI, 1.34 to 1.70), p=NR§§ Low dose vs. Nonexposed: RR 1.29 (95% CI, 1.07 to 1.55), p=NR§§
			Low dose	3236	113 (3.5)	
			Medium dose	7877	324 (4.1)	
			Nonexposed	69044	1896 (2.8)	
		SSRI + venlafaxine monotherapy	Current exposure	12710	503 (4.0)	Current exposure vs. Nonexposed: RR 1.47 (95% CI, 1.33 to 1.62), p=NR§§ Recent exposure vs. Nonexposed: RR 1.19 (95% CI, 1.03 to 1.38), p=NR§§ Past exposure vs. Nonexposed: RR 0.93 (95% CI, 0.82 to 1.06), p=NR§§
			Recent exposure	6096	196 (3.2)	
			Past exposure	10416	264 (2.5)	
			Nonexposed	69044	1896 (2.8)	
		SSRI	Current exposure	11516	440 (3.8)	Current exposure vs. Nonexposed: RR 1.42 (95% CI, 1.27 to 1.57), p=NR§§ Recent exposure vs. Nonexposed: RR 1.21 (95% CI, 1.04 to 1.40), p=NR§§ Past exposure vs. Nonexposed: RR 0.93 (95% CI, 0.81 to 1.06), p=NR§§
			Recent exposure	5706	186 (3.3)	
			Past exposure	9675	244 (2.5)	
			Nonexposed	69044	1896 (2.8)	
		Buproprion	Current exposure	1162	42 (3.6)	Current exposure vs. Nonexposed: RR 1.32 (95% CI, 0.98 to 1.79), p=NR§§ Recent exposure vs. Nonexposed: RR 1.17 (95% CI, 0.77 to 1.79), p=NR§§ Past exposure vs. Nonexposed: RR 1.32 (95% CI, 1.02 to 1.69), p=NR§§
			Recent exposure	660	21 (3.2)	
			Past exposure	1712	61 (3.6)	
			Nonexposed	69044	1896 (2.8)	
		Buproprion monotherapy	Current exposure	1114	40 (3.6)	Current exposure vs. Nonexposed: RR 1.32 (95% CI, 0.97 to 1.80), p=NR§§
			Recent exposure	649	21 (3.2)	
			Past exposure	1666	60 (3.6)	

Appendix D Table 15. Results From Included Studies for Key Question 5 (Pregnant Women): Harms

Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
			Nonexposed	69044	1896 (2.8)	Recent exposure vs. Nonexposed: RR 1.20 (95% CI, 0.79 to 1.83), p=NR§§ Past exposure vs. Nonexposed: RR 1.33 (95% CI, 1.03 to 1.71), p=NR§§
		Citalopram	Current exposure	891	36 (4.0)	Current exposure vs. Nonexposed: RR 1.48 (95% CI, 1.07 to 2.04), p=NR§§ Recent exposure vs. Nonexposed: RR 0.70 (95% CI, 0.37 to 1.34), p=NR§§ Past exposure vs. Nonexposed: RR 0.76 (95% CI, 0.47 to 1.23), p=NR§§
			Recent exposure	462	NR	
			Past exposure	830	17 (2.1)	
			Nonexposed	69044	1896 (2.8)	
		Escitalopram	Current exposure	1022	43 (4.2)	Current exposure vs. Nonexposed: RR 1.56 (95% CI, 1.16 to 2.09), p=NR§§ Recent exposure vs. Nonexposed: RR 1.01 (95% CI, 0.61 to 1.70), p=NR§§ Past exposure vs. Nonexposed: RR 0.96 (95% CI, 0.64 to 1.42), p=NR§§
			Recent exposure	520	14 (2.7)	
			Past exposure	940	24 (2.6)	
			Nonexposed	69044	1896 (2.8)	
		Fluoxetine	Current exposure	3322	137 (4.1)	Current exposure vs. Nonexposed: RR 1.51 (95% CI, 1.27 to 1.79), p=NR§§ Recent exposure vs. Nonexposed: RR 1.14 (95% CI, 0.86 to 1.50), p=NR§§ Past exposure vs. Nonexposed: RR 0.93 (95% CI, 0.75 to 1.17), p=NR§§
			Recent exposure	1628	50 (3.1)	
			Past exposure	3075	78 (2.5)	
			Nonexposed	69044	1896 (2.8)	
		Mirtazapine	Current exposure	129	NR	Current exposure vs. Nonexposed: RR 0.87 (95% CI, 0.29 to 2.66), p=NR§§ Recent exposure vs. Nonexposed: RR NR (95% CI, NR to NR), p=NR§§ Past exposure vs. Nonexposed: RR 1.07 (95% CI, 0.40 to 2.82), p=NR§§
			Recent exposure	57	0 (0)	
			Past exposure	135	NR	
			Nonexposed	69044	1896 (2.8)	
		Atypical anti-depressants	Depressed - Current exposure	1012	42 (4.2)	Depressed - Current exposure vs. Depressed - No exposure: RR 1.52 (95% CI, 1.12 to 2.06), p=NR§§ Depressed - Recent exposure vs. Depressed - No exposure: RR 1.08 (95% CI, 0.68 to 1.70), p=NR§§
			Depressed - Recent exposure	616	18 (2.9)	
			Depressed - Past exposure	1460	51 (3.5)	

Appendix D Table 15. Results From Included Studies for Key Question 5 (Pregnant Women): Harms

Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
			Depressed - No exposure	36457	1008 (2.8)	Depressed - Past exposure vs. Depressed - No exposure: RR 1.26 (95% CI, 0.95 to 1.67), p=NR§§
			Exposed	1162	45 (3.9)	
			Nonexposed	52192	1475 (2.8)	Exposed vs. Nonexposed: OR 1.39 (95% CI, 1.03 to 1.89), p=NR§§
		Paroxetine	Current exposure	2055	77 (3.8)	Current exposure vs. Nonexposed: RR 1.36 (95% CI, 1.09 to 1.71), p=NR§§
			Recent exposure	962	40 (4.2)	
			Past exposure	1617	49 (3.0)	
			Nonexposed	69044	1896 (2.8)	Recent exposure vs. Nonexposed: RR 1.52 (95% CI, 1.12 to 2.07), p=NR§§ Past exposure vs. Nonexposed: RR 1.13 (95% CI, 0.85 to 1.49), p=NR§§
		Sertraline	Current exposure	4526	162 (3.6)	Current exposure vs. Nonexposed: RR 1.31 (95% CI, 1.12 to 1.54), p=NR§§
			Recent exposure	2266	78 (3.4)	
			Past exposure	3812	85 (2.2)	
			Nonexposed	69044	1896 (2.8)	Recent exposure vs. Nonexposed: RR 1.27 (95% CI, 1.01 to 1.59), p=NR§§ Past exposure vs. Nonexposed: RR 0.82 (95% CI, 0.66 to 1.01), p=NR§§
		SNRI monotherapy	Current exposure	702	35 (5.0)	Current exposure vs. Nonexposed: RR 1.90 (95% CI, 1.37 to 2.63), p=NR§§
			Recent exposure	217	NR	
			Past exposure	423	12 (2.8)	
			Nonexposed	69044	1896 (2.8)	Recent exposure vs. Nonexposed: RR 1.21 (95% CI, 0.58 to 2.54), p=NR§§ Past exposure vs. Nonexposed: RR 1.05 (95% CI, 0.60 to 1.83), p=NR§§
		Trazadone	Current exposure	139	NR	Current exposure vs. Nonexposed: RR 1.85 (95% CI, 0.90 to 3.80), p=NR§§
			Recent exposure	73	NR	
			Past exposure	226	NR	
			Nonexposed	69044	1896 (2.8)	Recent exposure vs. Nonexposed: RR 2.01 (95% CI, 0.77 to 5.24), p=NR§§ Past exposure vs. Nonexposed: RR 0.61 (95% CI, 0.23 to 1.67), p=NR§§
		Venlafaxine	Current exposure	763	46 (6.0)	Current exposure vs. Nonexposed: RR 2.24 (95% CI, 1.69 to 2.97), p=NR§§
			Recent exposure	237	NR	
			Past exposure	458	12 (2.6)	

Appendix D Table 15. Results From Included Studies for Key Question 5 (Pregnant Women): Harms

Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
			Nonexposed	69044	1896 (2.8)	Recent exposure vs. Nonexposed: RR 1.10 (95% CI, 0.53 to 2.30), p=NR§§ Past exposure vs. Nonexposed: RR 0.98 (95% CI, 0.56 to 1.70), p=NR§§
Lupattelli, 2014[139] Fair	Postpartum hemorrhage, n (%)	SSRIs/SNRIs	Exposed (week 30 to birth)	122	18 (14.6)	Exposed (week 30 to birth) vs. Nonexposed (week 30 to birth): OR 0.97 (95% CI, 0.57 to 1.65), p=NR††
			Nonexposed (week 30 to birth)	55862	8009 (14.3)	
	Vaginal bleeding, any type during early pregnancy, n (%)	SSRIs/SNRIs	Depressed- nonexposed	1282	293 (22.9)	Depressed- nonexposed vs. Not depressed- nonexposed: OR 1.22 (95% CI, 1.06 to 1.39), p=NR†† Exposed (first trimester) vs. Nonexposed (first trimester): OR 0.91 (95% CI, 0.72 to 1.16), p=NS††
			Exposed (1st trimester)	427	90 (21.1)	
			Nonexposed (1st trimester)	55533	11066 (19.9)	
			Not depressed-nonexposed	55411	11037 (19.9)	
	Vaginal bleeding, any type during mid-pregnancy, n (%)	SSRIs/SNRIs	Depressed- nonexposed	1282	158 (12.3)	Depressed- nonexposed vs. Not depressed- nonexposed: OR 1.28 (95% CI, 1.07 to 1.55), p=NR†† Exposed (second trimester) vs. Nonexposed (second trimester): OR 0.81 (95% CI, 0.5 to 1.31), p=NS††
			Exposed (2nd trimester)	222	22 (9.9)	
			Nonexposed (2nd trimester)	55750	5212 (9.3)	
			Not depressed-nonexposed	55411	5176 (9.3)	
Andersen, 2014[125] Good	Miscarriage, n (%)	SSRIs	Exposed	22884	2883 (12.6)	Exposed vs. Nonexposed: HR 1.27 (95% CI, 1.22 to 1.33), p=NR¶ Exposed vs. Previous exposure: p=0.47¶ Exposed (low dose) vs. Exposed (high dose): HR 1.00 (95% CI, 0.91 to 1.09), p=NS¶ Previous exposure vs. Nonexposed: HR 1.24 (95% CI, 1.18 to 1.30), p=NR¶
			Exposed (high dose)	NR	NR	
			Exposed (low dose)	NR	NR	
			Previous exposure	14016	1936 (13.8)	
			Nonexposed	1256956	139210 (11.1)	
		Citalopram	Exposed	9927	NR	Exposed vs. Nonexposed: HR 1.29 (95% CI, 1.21 to 1.37), p=NR¶ Exposed vs. Previous exposure: p=0.94¶ Exposed (low dose) vs. Exposed (high dose): HR 1.08 (95% CI, 0.94 to 1.23), p=NS¶ Previous exposure vs. Nonexposed: HR 1.26 (95% CI, 1.17 to 1.35), p=NR¶
			Exposed (high dose)	NR	NR	
			Exposed (low dose)	NR	NR	
			Previous exposure	6857	NR	
			Nonexposed	1256956	NR	
		Escitalopram	Exposed	2377	NR	Exposed vs. Previous exposure: p=0.13¶
			Exposed (high dose)	NR	NR	

Appendix D Table 15. Results From Included Studies for Key Question 5 (Pregnant Women): Harms

Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
			Exposed (low dose)	NR	NR	Exposed vs. Nonexposed: HR 1.25 (95% CI, 1.09 to 1.42), p=NR¶ Exposed (low dose) vs. Exposed (high dose): HR 0.99 (95% CI, 0.76 to 1.31), p=NR¶ Previous exposure vs. Nonexposed: HR 1.33 (95% CI, 1.17 to 1.51), p=NR¶
			Previous exposure	1839	NR	
			Nonexposed	1256956	NR	
		Fluoxetine	Exposed	4111	NR	Exposed vs. Nonexposed: HR 1.10 (95% CI, 1.01 to 1.21), p=NR¶ Exposed vs. Previous exposure: p=0.69¶ Exposed (low dose) vs. Exposed (high dose): HR 0.83 (95% CI, 0.68 to 1.02), p=NS¶ Previous exposure vs. Nonexposed: HR 1.17 (95% CI, 1.03 to 1.33), p=NR¶
			Exposed (high dose)	NR	NR	
			Exposed (low dose)	NR	NR	
			Previous exposure	1738	NR	
			Nonexposed	1256956	NR	
		Paroxetine	Exposed	2739	NR	Exposed vs. Nonexposed: HR 1.27 (95% CI, 1.14 to 1.42), p=NR¶ Exposed vs. Previous exposure: p=0.59¶ Exposed (low dose) vs. Exposed (high dose): HR 1.03 (95% CI, 0.8 to 1.32), p=NS¶ Previous exposure vs. Nonexposed: HR 1.20 (95% CI, 1.05 to 1.37), p=NR¶
			Exposed (high dose)	NR	NR	
			Exposed (low dose)	NR	NR	
			Previous exposure	1469	NR	
			Nonexposed	1256956	NR	
		Sertraline	Exposed	4453	NR	Exposed vs. Nonexposed: HR 1.45 (95% CI, 1.33 to 1.58), p=NR¶ Exposed vs. Previous exposure: p=0.13¶ Exposed (low dose) vs. Exposed (high dose): HR 0.95 (95% CI, 0.79 to 1.14), p=NS¶ Previous exposure vs. Nonexposed: HR 1.20 (95% CI, 1.08 to 1.34), p=NR¶
			Exposed (high dose)	NR	NR	
			Exposed (low dose)	NR	NR	
			Previous exposure	2755	NR	
			Nonexposed	1256956	NR	
Kjaersgaard, 2013[137] Good	Spontaneous abortion, n (%)	Any anti-depressant	Depressed- exposed	1674	210 (12.5)	Depressed- exposed vs. Depressed- nonexposed: RR 1.00 (95% CI, 0.80 to 1.24), p=NR** Not depressed- exposed vs. Not depressed- nonexposed:
			Depressed- nonexposed	820	105 (12.8)	
			Exposed	15463	2637 (17.1)	
			Nonexposed	819246	110482 (13.5)	

Appendix D Table 15. Results From Included Studies for Key Question 5 (Pregnant Women): Harms

Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
			Not depressed- exposed	13789	2427 (17.6)	RR 1.17 (95% CI, 1.13 to 1.22), p=NR**
			Not depressed- nonexposed	818426	110377 (13.5)	Exposed vs. Nonexposed: RR 1.14 (95% CI, 1.10 to 1.18), p=NR**
		Citalopram	Depressed- exposed	NR	NR	RR 1.11 (95% CI, 0.79 to 1.55), p=NS
			Depressed- nonexposed	NR	NR	
		Duloxetine	Depressed- exposed	NR	NR	RR 3.12 (95% CI, 1.55 to 6.31), p=NR
			Depressed - nonexposed	NR	NR	
		Escitalopram	Depressed- exposed	NR	NR	RR 0.94 (95% CI, 0.49 to 1.94), p=NS
			Depressed- nonexposed	NR	NR	
		Fluoxetine	Depressed- exposed	NR	NR	RR 0.63 (95% CI, 0.38 to 1.06), p=NS
			Depressed - nonexposed	NR	NR	
		Mirtazapine	Depressed- exposed	NR	NR	RR 2.23 (95% CI, 1.34 to 3.7), p=NR
			Depressed - nonexposed	NR	NR	
		Paroxetine	Depressed- exposed	NR	NR	RR 0.70 (95% CI, 0.29 to 1.65), p=NS
			Depressed - nonexposed	NR	NR	
		Sertraline	Depressed- exposed	NR	NR	RR 0.84 (95% CI, 0.55 to 1.27), p=NS
			Depressed - nonexposed	NR	NR	
		SSRI	Depressed- exposed	NR	NR	RR 0.8 (95% CI, 0.62 to 1.03), p=NS
			Depressed - nonexposed	NR	NR	
		Venlafaxine	Depressed- exposed	NR	NR	RR 1.8 (95% CI, 1.19 to 2.72), p=NR
			Depressed – nonexposed	NR	NR	
Infant Outcomes						
Hayes, 2012[130] Good	Gestational age, mean (SD)	Any anti-depressant	Depressed- ≥3 prescriptions	6196	269.7 (16.2)	*Pre-term labor:* Depressed- ≥ 3 prescriptions vs. Depressed- no prescription: OR 1.04 (95% CI, 0.98 to 1.11), p=NR‖ ‖ Depressed – 1-2 prescription vs. Depressed- no prescription: OR 2.55 (95% CI, 2.40 to 2.71)‖ ‖
			Depressed- 1-2 prescriptions	10700	270.6 (16.3)	
			Depressed- no prescription	16907	270.5 (16.5)	
			Not depressed- nonexposed	195079	270.8 (17.7)	
		Second trimester exposure	Depressed - 1 prescription	NR	NR	Depressed- ≥ 3 prescriptions vs. Women with no prescriptions during indicated trimester: Mean Difference -6.6 (95% CI, -4.6 to -8.6), p<0.0001† Depressed - 2 prescriptions vs. Women with no prescriptions during indicated trimester: Mean Difference -5.8 (95% CI, -3.9 to -7.8), p<0.0001† Depressed - 1 prescription vs. Women with no prescriptions during indicated trimester: Mean Difference -2.6 (95% CI, -1.3 to -3.9), p<0.0001†
			Depressed - 2 prescriptions	NR	NR	
			Depressed- ≥3 prescriptions	NR	NR	
			Women with no prescriptions during indicated trimester	NR	NR	

Appendix D Table 15. Results From Included Studies for Key Question 5 (Pregnant Women): Harms

Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
		Third trimester exposure	All women with no prescriptions	NR	NR	Depressed- ≥ 3 prescriptions vs. Women with no prescriptions during indicated trimester: Mean Difference 6.4 (95% CI, 5.5 to 7.3), p=NR†
			Depressed - 1 prescription	NR	NR	
			Depressed - 2 prescriptions	NR	NR	Depressed - 2 prescriptions vs. Women with no prescriptions during indicated trimester: Mean Difference 1.8 (95% CI, 0.9 to 2.7), p=NR†
			Depressed- ≥3 prescriptions	NR	NR	
			Women with no prescriptions during indicated trimester	NR	NR	Depressed - 1 prescription vs. Women with no prescriptions during indicated trimester: Mean Difference 0.9 (95% CI, 0.3 to 1.6), p=NR†
Hayes, 2012[130] Good	Preterm birth, born 32-37 weeks, n (%)	Any anti-depressant	Depressed- ≥3 prescriptions	6196	787 (12.7)	*Gestational age 32-36 weeks (calculated):* Depressed- ≥ 3 prescriptions vs. Depressed- no prescription: OR 1.12 (95% CI, 1.03 to 1.23), p=NR‖ ‖
			Depressed- 1-2 prescriptions	10700	1231 (11.5)	
			Depressed- no prescription	16907	1939 (11.5)	Depressed – 1-2 prescription vs. Depressed- no prescription: OR 1.91 (95% CI, 1.77 to 2.07)‖ ‖
			Not depressed- nonexposed	195079	21524 (11.1)	*Gestational age < 32 weeks (calculated):* Depressed- ≥ 3 prescriptions vs. Depressed- no prescription: OR 0.95 (95% CI, 0.77 to 1.17), p=NR‖ ‖
						Depressed – 1-2 prescription vs. Depressed- no prescription: OR 1.54 (95% CI, 1.29 to 1.85)‖ ‖
Jensen, 2013a[136] Good	Small for gestational age, number	Any anti-depressant	Depressed- exposed	166	NR	Depressed- exposed (pre- and during pregnancy) vs. Not depressed- nonexposed: HR 1.42 (95% CI, 1.2 to 1.68), p=NR§
			Depressed- exposed (pre- and during pregnancy)	1134	NR	
			Depressed- nonexposed	1926	NR	Depressed- nonexposed vs. Not depressed- nonexposed: HR 1.04 (95% CI, 0.92 to 1.20), p=NS§
			Depressed- nonexposed (pre- or during pregnancy)	740	NR	
			Exposed	8511	NR	Depressed- nonexposed (pre- or during pregnancy) vs. Not depressed- nonexposed: HR 0.91 (95% CI, 0.72 to 1.16), p=NS§
			Exposed- SSRI	NR	NR	
			Not depressed- nonexposed	638116	NR	Exposed- SSRI vs. Not depressed- nonexposed: HR 1.22 (95% CI, 1.13 to 1.32), p=NR§
						Exposed vs. Not depressed- nonexposed: HR 1.19 (95% CI, 1.11 to 1.28), p=NR§
						Depressed- exposed vs. Not depressed- nonexposed: HR 1.44 (95% CI, 0.89 to 2.31), p=NS§

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Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
		First trimester exposure	Exposed	NR	NR	HR 1.07 (95% CI, 0.98 to 1.16), p=NR§
			Not depressed-nonexposed	NR	NR	
		Second trimester exposure	Exposed	NR	NR	HR 1.15 (95% CI, 0.97 to 1.35), p=NR§
			Not depressed-nonexposed	NR	NR	
		Third trimester exposure	Exposed	NR	NR	HR 1.18 (95% CI, 1.00 to 1.40), p=NR§
			Not depressed-nonexposed	NR	NR	
Hayes, 2012[130] Good	Neonatal convulsions, n (%)	Any anti-depressant	Depressed- ≥ 3 prescriptions	6196	41 (0.66)	Depressed- ≥ 3 prescriptions vs. Depressed- no prescription: OR 2.39 (95% CI, 1.57 to 3.64), p=NR‖ ‖ Depressed – 1-2 prescription vs. Depressed- no prescription: OR 1.04 (95% CI, 0.66 to 1.64)‖ ‖
			Depressed- 1-2 prescriptions	10700	31 (0.29)	
			Depressed- no prescription	16901	47 (0.28)	
			Not depressed-nonexposed	195079	429 (0.22)	
		Second trimester exposure	Depressed - 1 prescription	NR	NR	Depressed- ≥ 3 prescriptions vs. Women with no prescriptions during indicated trimester: OR 1.12 (95% CI, 0.50 to 2.44), p=NR† Depressed - 2 prescriptions vs. Women with no prescriptions during indicated trimester: OR 1.59 (95% CI, 0.79 to 3.24), p=NR† Depressed - 1 prescription vs. Women with no prescriptions during indicated trimester: OR 0.85 (95% CI, 0.47 to 1.76), p=NR†
			Depressed - 2 prescriptions	NR	NR	
			Depressed- ≥3 prescriptions	NR	NR	
			Women with no prescriptions during indicated trimester	NR	NR	
		Third trimester exposure	Depressed - 1 prescription	NR	NR	Depressed- ≥ 3 prescriptions vs. Women with no prescriptions during indicated trimester: OR 4.9 (95% CI, 2.6 to 9.5), p=NR† Depressed - 2 prescriptions vs. Women with no prescriptions during indicated trimester: OR 2.8 (95% CI, 1.4 to 5.5), p=NR† Depressed - 1 prescription vs. Women with no prescriptions during indicated trimester: OR 1.4 (95% CI, 0.7 to 2.8), p=NR†
			Depressed - 2 prescriptions	NR	NR	
			Depressed- ≥3 prescriptions	NR	NR	
			Women with no prescriptions during indicated trimester	NR	NR	
Hayes, 2012[130] Good	Respiratory distress, n (%)	Any anti-depressant	Depressed- ≥3 prescriptions	6196	333 (5.4)	Depressed- ≥ 3 prescriptions vs. Depressed- no prescription: OR 1.18 (95% CI, 1.04 to 1.35), p=NR‖ ‖ Depressed – 1-2 prescription vs. Depressed- no
			Depressed- 1-2 prescriptions	10700	516 (4.8)	

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Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
			Depressed- no prescription	16907	774 (4.6)	prescription: OR 1.06 (95% CI, 0.94 to 1.18)‖ ‖
			Not depressed-nonexposed	195079	8358 (4.3)	
		Second trimester exposure	Depressed - 1 prescription	NR	NR	Depressed- ≥ 3 prescriptions vs. Women with no prescriptions during indicated trimester: OR 1.6 (95% CI, 1.2 to 2.0), p=NR†
			Depressed - 2 prescriptions	NR	NR	
			Depressed- ≥ 3 prescriptions	NR	NR	Depressed - 2 prescriptions vs. Women with no prescriptions during indicated trimester: OR 1.4 (95% CI, 1.1 to 1.8), p=NR†
			Women with no prescriptions during indicated trimester	NR	NR	Depressed - 1 prescription vs. Women with no prescriptions during indicated trimester: OR 1.1 (95% CI, 0.9 to 1.3), p=NR†
		Third trimester exposure	Depressed - 1 prescription	NR	NR	Depressed- ≥ 3 prescriptions vs. Women with no prescriptions during indicated trimester: OR 0.6 (95% CI, 0.5 to 0.8), p=NR†
			Depressed - 2 prescriptions	NR	NR	
			Depressed- ≥3 prescriptions	NR	NR	Depressed - 2 prescriptions vs. Women with no prescriptions during indicated trimester: OR 0.8 (95% CI, 0.6 to 1.0), p=NR†
			Women with no prescriptions during indicated trimester	NR	NR	Depressed - 1 prescription vs. Women with no prescriptions during indicated trimester: OR 0.9 (95% CI, 0.7 to 1.1), p=NR†
Polen, 2013[145] Fair	Anencephaly, n (%)	Venlafaxine	Cases-Exposed	91	4 (4.4)	Cases vs. Controls: OR 6.3 (95% CI, 1.5 to 20.2), p=NR‖
			Cases-Exposed (2003-2007)	69	4 (5.8)	Cases (2003-2007) vs. Controls (2003-2007): OR 6.5 (95% CI, 1.5 to 21.7), p=NR
			Cases-Nonexposed	26954	407 (1.5)	
			Cases-Nonexposed (2003-2007)	13462	206 (1.5)	
			Controls-Exposed	91	14 (15.4)	
			Controls-Exposed (2003-2007)	69	4 (5.8)	
			Controls-Nonexposed	26954	7988 (29.6)	
			Controls-Nonexposed (2003-2007)	13462	206 (1.5)	
	Cleft palate (alone), n (%)	Venlafaxine	Cases-Exposed	91	7 (7.7)	Cases vs. Controls: OR 3.3 (95% CI, 1.1 to 8.8), p=NR‖
			Cases-Exposed (2003-2007)	69	5 (7.2)	Cases (2003-2007) vs. Controls (2003-2007): OR 3.1 (95% CI, 0.9 to 9.6), p=NR
			Cases-Nonexposed	26954	1116 (4.1)	

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Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
			Cases-Nonexposed (2003-2007)	13462	517 (3.8)	
			Controls-Exposed	91	14 (15.4)	
			Controls-Exposed (2003-2007)	69	4 (5.8)	
			Controls-Nonexposed	26954	7988 (29.6)	
			Controls-Nonexposed (2003-2007)	13462	206 (1.5)	
	Gastroschisis, n (%)	Venlafaxine	Cases-Exposed	91	6 (6.7)	Cases vs. Controls: OR 5.7 (95% CI, 1.8 to 15.9), p=NR Cases (2003-2007) vs. Controls (2003-2007): OR 3.3 (95% CI, 0.9 to 10.2), p=NR
			Cases-Exposed (2003-2007)	69	5 (7.2)	
			Cases-Nonexposed	26954	905 (9.9)	
			Cases-Nonexposed (2003-2007)	13462	503 (3.7)	
			Controls-Exposed	91	14 (15.4)	
			Controls-Exposed (2003-2007)	69	4 (5.8)	
			Controls-Nonexposed	26954	7988 (29.6)	
			Controls-Nonexposed (2003-2007)	13462	206 (1.5)	
Ban, 2014[127] Good	Major congenital anomaly -all combined, n (per 10,000)	SSRIs alone	Depressed- exposed	7683	204 (266)	Depressed- exposed vs. Not depressed- nonexposed: OR 1.01 (95% CI, 0.88 to 1.17), p=NS* Depressed- exposed vs. Depressed- nonexposed: OR 0.93 (95% CI, 0.78 to 1.11), p=NS* Depressed- nonexposed vs. Not depressed- nonexposed: OR 1.07 (95% CI, 0.96 to 1.18), p=NS*
			Depressed- nonexposed	13432	380 (283)	
			Not depressed-nonexposed	325294	8731 (268)	
		Citalopram	Depressed- exposed	1946	NR (267)	Depressed- exposed vs. Depressed- nonexposed: OR 0.97 (95% CI, 0.71 to 1.31), p=NS* Depressed- exposed vs. Not depressed- nonexposed: OR 1.06 (95% CI, 0.80 to 1.40), p=NS*
			Depressed- nonexposed	13432	380 (283)	
			Not depressed-nonexposed	325294	8731 (268)	
		Escitalopram	Depressed- exposed	333	NR (210)	Depressed- exposed vs. Not depressed- nonexposed: OR 0.85 (95% CI, 0.4 to 1.81), p=NS* Depressed- exposed vs. Depressed- nonexposed: OR 0.77 (95% CI, 0.36 to 1.66), p=NS*
			Depressed- nonexposed	13432	380 (283)	
			Not depressed-nonexposed	325294	8731 (268)	
		Fluoxetine	Depressed- exposed	3189	NR (241)	Depressed- exposed vs. Depressed- nonexposed: OR 0.85 (95% CI, 0.66 to 1.09), p=NS*
			Depressed- nonexposed	13432	380 (283)	

Appendix D Table 15. Results From Included Studies for Key Question 5 (Pregnant Women): Harms

Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
			Not depressed-nonexposed	325294	8731 (268)	Depressed- exposed vs. Not depressed- nonexposed: OR 0.91 (95% CI, 0.73 to 1.15), p=NS*
		Paroxetine	Depressed- exposed	1200	NR (300)	Depressed- exposed vs. Not depressed- nonexposed: OR 1.08 (95% CI, 0.77 to 1.50), p=NS*
			Depressed- nonexposed	13432	380 (283)	
			Not depressed-nonexposed	325294	8731 (268)	Depressed- exposed vs. Depressed- nonexposed: OR 1.01 (95% CI, 0.71 to 1.44), p=NS*
		Sertraline	Depressed- exposed	757	NR (330)	Depressed- exposed vs. Depressed- nonexposed: OR 1.17 (95% CI, 0.78 to 1.77), p=NS*
			Depressed- nonexposed	13432	380 (283)	
			Not depressed-nonexposed	325294	8731 (268)	Depressed- exposed vs. Not depressed- nonexposed: OR 1.27 (95% CI, 0.85 to 1.89), p=NS*
	Specific heart anomalies-atrial septal defect, n (per 10,000)	SSRIs alone	Depressed- exposed	7683	NR (18)	Depressed- nonexposed vs. Not depressed- nonexposed: OR 0.85 (95% CI, 0.48 to 1.51), p=NS*
			Depressed- nonexposed	13432	NR (9)	
			Not depressed-nonexposed	325294	NR (10)	Depressed- exposed vs. Not depressed- nonexposed: OR 1.68 (95% CI, 0.98 to 2.91), p=NS*
	Specific heart anomalies-other, n (per 10,000)	SSRIs alone	Depressed- exposed	7683	NR (44)	Depressed- nonexposed vs. Not depressed- nonexposed: OR 1.20 (95% CI, 0.90 to 1.58), p=NS*
			Depressed- nonexposed	13432	NR (40)	
			Not depressed-nonexposed	325294	NR (33)	Depressed- exposed vs. Not depressed- nonexposed: OR 1.27 (95% CI, 0.90 to 1.80), p=NS*
	Specific heart anomalies-right ventricular outflow tract defect, n (per 10,000)	SSRIs alone	Depressed- exposed	7683	NR (8)	Depressed- nonexposed vs. Not depressed- nonexposed: OR 1.58 (95% CI, 0.73 to 3.4), p=NS*
			Depressed- nonexposed	13432	NR (5)	
			Not depressed-nonexposed	325294	NR (3)	Depressed- exposed vs. Not depressed- nonexposed: OR 2.22 (95% CI, 0.98 to 5.03), p=NS*
	Specific heart anomalies-septal defect, n (per 10,000)	SSRIs alone	Depressed- exposed	7683	NR (43)	Depressed- nonexposed vs. Not depressed- nonexposed: OR 1.09 (95% CI, 0.86 to 1.39), p=NS*
			Depressed- nonexposed	13432	NR (51)	
			Not depressed-nonexposed	325294	NR (47)	Depressed- exposed vs. Not depressed- nonexposed: OR 0.89 (95% CI, 0.63 to 1.27), p=NS*
	Specific heart anomalies-ventricular septal defect, n (per 10,000)	SSRIs alone	Depressed- exposed	7683	NR (21)	Depressed- exposed vs. Not depressed- nonexposed: OR 1.09 (95% CI, 0.81 to 1.45), p=NS*
			Depressed- nonexposed	13432	NR (36)	
			Not depressed-nonexposed	325294	NR (33)	Depressed- exposed vs. Not depressed- nonexposed: OR 0.63 (95% CI, 0.38 to 1.03), p=NS*
	Specific heart anomalies-	SSRIs alone	Depressed- exposed	7683	NR (1)	Depressed- nonexposed vs. Not depressed- nonexposed: OR 1.59 (95% CI, 0.36 to 7.16), p=NS*
			Depressed- nonexposed	13432	NR (1)	

Appendix D Table 15. Results From Included Studies for Key Question 5 (Pregnant Women): Harms

Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
	left ventricular outflow tract defect, n (per 10,000)		Not depressed- nonexposed	325294	NR (1)	Depressed- exposed vs. Not depressed- nonexposed: OR 1.5 (95% CI, 0.2 to 11.24), p=NS*
	Cardiac malform-ations, n (per 10,000)	SSRIs alone	Depressed- exposed	7683	68 (89)	Depressed- exposed vs. Depressed- nonexposed: OR 1.04 (95% CI, 0.76 to 1.41), p=NS* Depressed- exposed vs. Not depressed- nonexposed: OR 1.14 (95% CI, 0.89 to 1.45), p=NS* Depressed- nonexposed vs. Not depressed- nonexposed: OR 1.10 (95% CI, 0.91 to 1.33), p=NS*
			Depressed- nonexposed	13432	112 (83)	
			Not depressed- nonexposed	325294	2444 (75)	
		Citalopram	Depressed- exposed	1946	NR (87)	Depressed- exposed vs. Depressed- nonexposed: OR 1.02 (95% CI, 0.61 to 1.70), p=NS* Depressed- nonexposed vs. Not depressed- nonexposed: OR 1.13 (95% CI, 0.70 to 1.82), p=NS*
			Depressed- nonexposed	13432	112 (83)	
			Not depressed- nonexposed	325294	2444 (75)	
		Escitalopram	Depressed- exposed	333	NR (90)	Depressed- exposed vs. Depressed- nonexposed: OR 1.09 (95% CI, 0.34 to 3.50), p=NS* Depressed- nonexposed vs. Not depressed- nonexposed: OR 1.15 (95% CI, 0.36 to 3.65), p=NS*
			Depressed- nonexposed	13432	112 (83)	
			Not depressed- nonexposed	325294	2444 (75)	
		Fluoxetine	Depressed- exposed	3189	NR (66)	Depressed- exposed vs. Depressed- nonexposed: OR 0.79 (95% CI, 0.49 to 1.26), p=NS* Depressed- nonexposed vs. Not depressed- nonexposed: OR 0.84 (95% CI, 0.55 to 1.30), p=NS*
			Depressed- nonexposed	13432	112 (83)	
			Not depressed- nonexposed	325294	2444 (75)	
		Paroxetine	Depressed- exposed	1200	NR (142)	Depressed- exposed vs. Depressed- nonexposed: OR 1.67 (95% CI, 1.00 to 2.80), p=0.051* Depressed- nonexposed vs. Not depressed- nonexposed: OR 1.78 (95% CI, 1.09 to 2.88), p=0.02*
			Depressed- nonexposed	13432	112 (83)	
			Not depressed- nonexposed	325294	2444 (75)	
		Sertraline	Depressed- exposed	757	NR (119)	Depressed- exposed vs. Depressed- nonexposed: OR 1.39 (95% CI, 0.70 to 2.74), p=NS* Depressed- nonexposed vs. Not depressed- nonexposed: OR 1.52 (95% CI, 0.78 to 2.96), p=NS*
			Depressed- nonexposed	13432	112 (83)	
			Not depressed- nonexposed	325294	2444 (75)	
Polen, 2013[145] Fair	Atrial septal defect, type 2 or not otherwise	Venlafaxine	Cases-Exposed	91	11 (12.1)	Cases vs. Controls: OR 3.1 (95% CI, 1.3 to 7.4), p=NR‖ Cases (2003-2007) vs. Controls (2003-2007): OR 1.7 (95% CI, 0.5 to 4.8), p=NS
			Cases-Exposed (2003-2007)	69	6 (8.7)	
			Cases-Nonexposed	26954	2170 (8.1)	

Appendix D Table 15. Results From Included Studies for Key Question 5 (Pregnant Women): Harms

Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
	specified, n (%)		Cases-Nonexposed (2003-2007)	13462	1215 (9.0)	
			Controls-Exposed	91	14 (15.4)	
			Controls-Exposed (2003-2007)	69	4 (5.8)	
			Controls-Nonexposed	26954	7988 (29.6)	
			Controls-Nonexposed (2003-2007)	13462	206 (1.5)	
	Coarctation of the aorta, n (%)	Venlafaxine	Cases-Exposed	91	6 (6.0)	Cases vs. Controls: OR 4.1 (95% CI, 1.3 to 11.5), p=NR Cases (2003-2007) vs. Controls (2003-2007): OR 3.2 (95% CI, 0.7 to 10.5), p=NS
			Cases-Exposed (2003-2007)	69	4 (5.8)	
			Cases-Nonexposed	26954	762 (2.8)	
			Cases-Nonexposed (2003-2007)	13462	423 (3.1)	
			Controls-Exposed	91	14 (15.4)	
			Controls-Exposed (2003-2007)	69	4 (5.8)	
			Controls-Nonexposed	26954	7988 (29.6)	
			Controls-Nonexposed (2003-2007)	13462	206 (1.5)	
	Conotruncal heart defects, n (%)	Venlafaxine	Cases-Exposed	91	6 (6.6)	Cases vs. Controls: OR 1.9 (95% CI, 0.6 to 5.3), p=NS Cases (2003-2007) vs. Controls (2003-2007): OR 1.2 (95% CI, 0.2 to 4.5), p=NS
			Cases-Exposed (2003-2007)	69	3 (4.3)	
			Cases-Nonexposed	26954	1748 (6.5)	
			Cases-Nonexposed (2003-2007)	13462	823 (6.1)	
			Controls-Exposed	91	14 (15.4)	
			Controls-Exposed (2003-2007)	69	4 (5.8)	
			Controls-Nonexposed	26954	7988 (29.6)	
			Controls-Nonexposed (2003-2007)	13462	206 (1.5)	
	Hypoplastic left heart syndrome, n (%)	Venlafaxine	Cases-Exposed	91	2 (2.2)	NR
			Cases-Exposed (2003-2007)	69	2 (2.9)	
			Cases-Nonexposed	26954	423 (1.6)	
			Cases-Nonexposed (2003-2007)	13462	218 (1.6)	
			Controls-Exposed	91	14 (15.4)	
			Controls-Exposed (2003-2007)	69	4 (5.8)	
			Controls-Nonexposed	26954	7988 (29.6)	

Appendix D Table 15. Results From Included Studies for Key Question 5 (Pregnant Women): Harms

Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
			Controls-Nonexposed (2003-2007)	13462	206 (1.5)	
	Left ventricular outflow tract obstruction defects, n (%)	Venlafaxine	Cases-Exposed	91	9 (9.9)	Cases vs. Controls: OR 3.3 (95% CI, 1.2 to 8.2), p=NR‖ Cases (2003-2007) vs. Controls (2003-2007): OR 3.0 (95% CI, 1.0 to 8.3), p=NR
			Cases-Exposed (2003-2007)	69	7 (10.1)	
			Cases-Nonexposed	26954	1435 (5.3)	
			Cases-Nonexposed (2003-2007)	13462	783 (5.8)	
			Controls-Exposed	91	14 (15.4)	
			Controls-Exposed (2003-2007)	69	4 (5.8)	
			Controls-Nonexposed	26954	7988 (29.6)	
			Controls-Nonexposed (2003-2007)	13462	206 (1.5)	
	Peri-membranous ventricular septal defect, n (%)	Venlafaxine	Cases-Exposed	91	6 (6.6)	Cases vs. Controls: OR 2.4 (95% CI, 0.8 to 6.7), p=NS‖ Cases (2003-2007) vs. Controls (2003-2007): OR 2.0 (95% CI, 0.5 to 6.8), p=NS
			Cases-Exposed (2003-2007)	69	4 (5.8)	
			Cases-Nonexposed	26954	1404 (5.2)	
			Cases-Nonexposed (2003-2007)	13462	655 (4.9)	
			Controls-Exposed	91	14 (15.4)	
			Controls-Exposed (2003-2007)	69	4 (5.8)	
			Controls-Nonexposed	26954	7988 (29.6)	
			Controls-Nonexposed (2003-2007)	13462	206 (1.5)	
	Pulmonary valve stenosis, n (%)	Venlafaxine	Cases-Exposed	91	5 (5.5)	Cases vs. Nonexposed: OR 2.7 (95% CI, 0.8 to 7.9), p=NS‖ Cases (2003-2007) vs. Nonexposed (2003-2007): OR 1.9 (95% CI, 0.3 to 6.9), p=NS
			Cases-Exposed (2003-2007)	69	3 (4.3)	
			Cases-Nonexposed	26954	980 (3.6)	
			Cases-Nonexposed (2003-2007)	13462	540 (4.0)	
			Controls-Exposed	91	14 (15.4)	
			Controls-Exposed (2003-2007)	69	4 (5.8)	
			Controls-Nonexposed	26954	7988 (29.6)	
			Controls-Nonexposed (2003-2007)	13462	206 (1.5)	
	Right ventricular outflow tract obstruction	Venlafaxine	Cases-Exposed	91	5 (5.5)	Cases vs. Controls: OR 2.3 (95% CI, 0.6 to 6.6), p=NS‖ Cases (2003-2007) vs. Controls (2003-2007): OR 1.5 (95% CI, 0.3 to 5.6), p=NS
			Cases-Exposed (2003-2007)	69	3 (4.3)	
			Cases-Nonexposed	26954	1245 (4.6)	

Appendix D Table 15. Results From Included Studies for Key Question 5 (Pregnant Women): Harms

Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
	defects, n (%)		Cases-Nonexposed (2003-2007)	13462	666 (4.9)	
			Controls-Exposed	91	14 (15.4)	
			Controls-Exposed (2003-2007)	69	4 (5.8)	
			Controls-Nonexposed	26954	7988 (29.6)	
			Controls-Nonexposed (2003-2007)	13462	206 (1.5)	
	Septal heart defects, n (%)	Venlafaxine	Cases-Exposed	91	18 (19.8)	Cases vs. Controls: OR 3.0 (95% CI, 1.4 to 6.4), p=NR‖ Cases (2003-2007) vs. Controls (2003-2007): OR 2.1 (95% CI, 0.8 to 5.1), p=NS
			Cases-Exposed (2003-2007)	69	11 (15.9)	
			Cases-Nonexposed	26954	3603 (13.4)	
			Cases-Nonexposed (2003-2007)	13462	1784 (13.3)	
			Controls-Exposed	91	14 (15.4)	
			Controls-Exposed (2003-2007)	69	4 (5.8)	
			Controls-Nonexposed	26954	7988 (29.6)	
			Controls-Nonexposed (2003-2007)	13462	206 (1.5)	
	Ventricular septal defect-atrial septal defect association, n (%)	Venlafaxine	Cases-Exposed	91	3 (3.3)	Cases vs. Controls: OR 3.1 (95% CI, 0.6 to 11.3), p=NS‖
			Cases-Exposed (2003-2007)	69	1 (1.4)	
			Cases-Nonexposed	26954	573 (2.1)	
			Cases-Nonexposed (2003-2007)	13462	307 (2.3)	
			Controls-Exposed	91	14 (15.4)	
			Controls-Exposed (2003-2007)	69	4 (5.8)	
			Controls-Nonexposed	26954	7988 (29.6)	
			Controls-Nonexposed (2003-2007)	13462	206 (1.5)	
Yazdy, 2014[151]	Clubfoot, n (%)	SSRI	Cases- Depressed, Exposed >30 days	622	33 (5)	Cases- Depressed, Exposed > 30 days vs. Controls- Depressed, Exposed > 30 days: OR 1.8 (95% CI, 1.1 to 2.8), p=NR***
			Cases- Not Depressed, Nonexposed	622	477 (77)	
			Controls- Depressed, Exposed >30 days	2002	58 (3)	
			Controls- Not Depressed, Nonexposed	2002	1650 (82)	
		Escitalopram	Cases- Depressed, Exposed >30 days	622	9 (1)	Cases- Depressed, Exposed > 30 days vs. Controls- Depressed, Exposed > 30 days: OR 2.9 (95% CI, 1.1 to

Appendix D Table 15. Results From Included Studies for Key Question 5 (Pregnant Women): Harms

Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
			Cases- Not Depressed, Nonexposed	622	477 (77)	7.2), p=NR***
			Controls- Depressed, Exposed > 30 days	2002	11 (1)	
			Controls- Not Depressed, Nonexposed	2002	1650 (82)	
		Fluoxetine	Cases- Depressed, Exposed > 30 days	622	13 (2)	Cases- Depressed, Exposed > 30 days vs. Controls- Depressed, Exposed > 30 days: OR 1.6 (95% CI, 0.8 to 3.2), p=NR***
			Cases- Not Depressed, Nonexposed	622	477 (77)	
			Controls- Depressed, Exposed > 30 days	2002	26 (1)	
			Controls- Not Depressed, Nonexposed	2002	1650 (82)	
Louik, 2014[152] Good	Atrial septal defects, n (%)	SSRI	Cases- exposed	1135	42 (3.7)	Cases vs. Controls: OR 1.3 (95% CI, 0.9 to 1.8), p=NR¶¶
			Cases- nonexposed	1135	NR	
			Controls- exposed	8611	290 (3.4)	
			Controls- nonexposed	8611	8241 (95.7)	
	Atrioventricular canal defects, n (%)	SSRI	Cases- exposed	514	19 (3.7)	Cases vs. Controls: OR 1.3 (95% CI, 0.8 to 2.0), p=NR¶¶
			Cases- nonexposed	514	NR	
			Controls- exposed	8611	290 (3.4)	
			Controls- nonexposed	8611	8241 (95.7)	
	Coarcation of aorta, n (%)	SSRI	Cases- exposed	471	22 (4.7)	Cases vs. Controls: OR 1.8 (95% CI, 1.2 to 2.9), p=NR¶¶
			Cases- nonexposed	471	442 (93.8)	
			Controls- exposed	8611	290 (3.4)	
			Controls- nonexposed	8611	8241 (95.7)	
	Conotruncal / major arch anomalies, n (%)	SSRI	Cases- exposed	1418	61 (4.3)	Cases vs. Controls: OR 1.6 (95% CI, 1.2 to 2.1), p=NR¶¶
			Cases- nonexposed	1418	NR	
			Controls- exposed	8611	290 (3.4)	
			Controls- nonexposed	8611	8241 (95.7)	
	Left-sided defects, n (%)	SSRI	Cases- exposed	1220	48 (3.9)	Cases vs. Controls: OR 1.4 (95% CI, 1.0 to 1.9), p=NR¶¶
			Cases- nonexposed	1220	1159 (95.0)	
			Controls- exposed	8611	290 (3.4)	
			Controls- nonexposed	8611	8241 (95.7)	
	Right-sided defects, n (%)	SSRI	Cases- exposed	1022	47 (4.6)	Cases vs. Controls: OR 1.7 (95% CI, 1.2 to 2.3), p=NR¶¶
			Cases- nonexposed	1022	NR	
			Controls- exposed	8611	290 (3.4)	
			Controls- nonexposed	8611	8241 (95.7)	
	Ventricular septal defects, n (%)	SSRI	Cases- exposed	2704	102 (3.8)	Cases vs. Controls: OR 1.3 (95% CI, 1.0 to 1.6), p=NR¶¶
			Cases- nonexposed	2704	2571 (95.1)	
			Controls- exposed	8611	290 (3.4)	

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Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
			Controls- nonexposed	8611	8241 (95.7)	
	Ventricular septal defects, n (%)	Buproprion	Cases- exposed	2704	23 (0.9)	Cases vs. Controls: OR 1.6 (95% CI, 1.0 to 2.8), p=NR¶¶
			Cases- nonexposed	2704	2571 (95.1)	
			Controls- exposed	8611	39 (0.5)	
			Controls- nonexposed	8611	8241 (95.7)	
Huybrechts, 2014[135] Good	Any cardiac malformations, number	Buproprion	Depressed- exposed	6698	57	OR 0.95 (95% CI, 0.71 to 1.26), p=NS‡
			Depressed- nonexposed	180563	1497	
		Fluoxetine	Depressed- exposed	8676	84	OR 1.10 (95% CI, 0.87 to 1.40), p=NS‡
			Depressed- nonexposed	180563	1497	
		Paroxetine	Depressed- exposed	8756	71	OR 0.93 (95% CI, 0.72 to 1.19), p=NS‡
			Depressed- nonexposed	180563	1497	
		Sertraline	Depressed- exposed	11045	106	OR 1.06 (95% CI, 0.86 to 1.32), p=NS‡
			Depressed- nonexposed	180563	1497	
		SNRI	Depressed- exposed	5999	69	OR 1.20 (95% CI, 0.91 to 1.56), p=NS‡
			Depressed- nonexposed	180563	1497	
		SSRI	Depressed- exposed	36783	341	OR 1.08 (95% CI, 0.94 to 1.23), p=NS‡
			Depressed- nonexposed	180563	1497	
	Other cardiac defect, number	Buproprion	Depressed- exposed	6687	37	OR 1.26 (95% CI, 0.88 to 1.81), p=NS‡
			Depressed- nonexposed	180563	743	
		Fluoxetine	Depressed- exposed	8655	45	OR 1.22 (95% CI, 0.88 to 1.69), p=NS‡
			Depressed- nonexposed	180563	743	
		Paroxetine	Depressed- exposed	8751	40	OR 1.08 (95% CI, 0.77 to 1.52), p=NS‡
			Depressed- nonexposed	180563	743	
		Sertraline	Depressed- exposed	11069	57	OR 1.19 (95% CI, 0.89 to 1.59), p=NS‡
			Depressed- nonexposed	180563	743	
		SNRI	Depressed- exposed	6001	37	OR 1.36 (95% CI, 0.94 to 1.97), p=NS‡
			Depressed- nonexposed	180563	743	
		SSRI	Depressed- exposed	36783	189	OR 1.21 (95% CI, 1.00 to 1.45), p=NR‡
			Depressed- nonexposed	180563	743	
	Right ventricular outflow tract obstruction, number	Buproprion	Depressed- exposed	6696	<11	OR 1.07 (95% CI, 0.55 to 2.08), p=NS‡
			Depressed- nonexposed	180563	246	
		Fluoxetine	Depressed- exposed	8676	12	OR 0.87 (95% CI, 0.47 to 1.63), p=NS‡
			Depressed- nonexposed	180563	246	
		Paroxetine	Depressed- exposed	8760	13	OR 1.03 (95% CI, 0.57 to 1.85), p=NS‡
			Depressed- nonexposed	180563	246	
		Sertraline	Depressed- exposed	11064	17	OR 1.08 (95% CI, 0.64 to 1.82), p=NS‡
			Depressed- nonexposed	180563	246	
		SNRI	Depressed- exposed	36783	53	OR 0.99 (95% CI, 0.70 to 1.38), p=NS‡
			Depressed- nonexposed	180563	246	
		SSRI	Depressed- exposed	36783	53	OR 0.99 (95% CI, 0.7 to 1.38), p=NS‡
			Depressed- nonexposed	180563	246	

Appendix D Table 15. Results From Included Studies for Key Question 5 (Pregnant Women): Harms

Author, Year and Quality	Outcome	Subgroup or Specific Drug Exposure	Exposure Group	n	Results	Between Group Difference
	Ventricular septal defect, number	Buproprion	Depressed- exposed	6696	26	OR 0.86 (95% CI, 0.57 to 1.31), p=NS‡
			Depressed- nonexposed	180563	751	
		Fluoxetine	Depressed- exposed	8676	41	OR 1.04 (95% CI, 0.74 to 1.46), p=NS‡
			Depressed- nonexposed	180563	751	
		Paroxetine	Depressed- exposed	36783	155	OR 0.99 (95% CI, 0.81 to 1.21), p=NS‡
			Depressed- nonexposed	180563	751	
		Sertraline	Depressed- exposed	11065	50	OR 0.98 (95% CI, 0.72 to 1.34), p=NS‡
			Depressed- nonexposed	180563	751	
		SNRI	Depressed- exposed	5993	34	OR 1.18 (95% CI, 0.80 to 1.73), p=NS‡
			Depressed- nonexposed	180563	751	
		SSRI	Depressed- exposed	36783	189	OR 1.21 (95% CI, 1.00 to 1.45), p=NR‡
			Depressed- nonexposed	180563	743	

*Adjusted by maternal age at end of pregnancy, year of childbirth, Townsend deprivation quintile, maternal smoking history, body mass index before pregnancy, maternal diabetes, hypertension, asthma, and epilepsy in the year pre-conception or during pregnancy.
†Adjusted by maternal age, smoking during pregnancy, maternal race, education, comorbidity, adequacy of prenatal care, maternal parity, infant sex, year of delivery, depression diagnosis before last menstrual period, anxiety disorder, substance abuse, filling prescription before last menstrual period, psych med polytherapy, co-existing psych diagnoses.
‡Adjusted by sociodemographics, multiple gestation, chronic maternal illnesses, use of antidiabetic and antihypertension medications, depression severity, other mental health disorders, sleep disorders, smoking, pain-related diagnoses, premenstrual tension syndrome, chronic fatigue syndrome.
§Adjusted by maternal age, smoking, social status, calendar year, sex of newborn, and use of antiepileptics, antipsychotics and other meds.
‖Adjusted by age and race/ethnicity.
¶Adjusted by year of outcome or censoring, maternal age, educational length, income, and number of previous miscarriages.
**Adjusted by maternal age, cohabitation, education, and history of severe mental disorders and drug abuse.
††Adjusted by maternal age, body mass index, parity, educational level, smoking, placenta previa, coagulation defects, abortion history, placental abruption, and depressive symptoms.
‡‡Adjusted by pre-eclampsia risk factor adjustment and number of outpatient depression diagnoses, number of inpatient depression diagnoses, mental disorder complicating pregnancy, pain-related diagnosis, sleep disorder, anticonvulsant dispensing, benzodiazepine dispensing, number of baseline prescription drugs, and number of baseline outpatient visits.
§§Adjusted by delivery year, age, race, multiple pregnancy, diabetes, coagulopathy, number of outpatient mood/anxiety disorder diagnoses, number of inpatient mood/anxiety disorder diagnoses, psychotic disorder, other mental health disorder, pain indication, sleep disorder, anticonvulsant dispensing, benzodiazepine dispensing, aspirin dispensing, heparin dispensing, low molecular weight heparin dispensing, warfarin dispensing, and number of outpatient visits and days in hospital during baseline.
‖‖Calculated crude OR.
¶¶Adjusted by study center and last menstrual period.
***Adjusted by maternal smoking, alcohol use, and BMI.

Abbreviations:CI = confidence interval; HR = hazard ratio; NR = not reported; NS = not significant; NSD = no significant difference; OR = odds ratio; RR = relative risk; SNRI = selective norepinephrine reuptake inhibitor; SRI = serotnonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Appendix D Table 16. Detailed Interventions for Key Question 1 (General and Older Adults)

Author, Year and Quality	Group	Intervention Name	DetailedDescription	Provider
General Adults				
Williams, 1999[154] Fair	IG1	Case-finding (Combined)	Case-finding interventions (single question and 20-item CES-D instrument) were similar, therefore, groups combined	Physician
	IG2	Case-finding (20-item)	CES-D validated questionnaire w/ 20-items that focuses on depressive symptoms in the last week; scores ≥ 16 identify people w/ probable depression; self-administered unless pt could not read or requested it be read to them	Physician
	IG3	Case-finding (1 item)	Single question: "Have you felt depressed or sad much of the time in the past year?"; self-administered unless pt could not read or requested it be read to them	Physician
	CG	Usual Care	No case-finding	Physician
Bergus, 2005[72] Fair	IG	Screening results to provider	Providers asked to review patient's PHQ-9; providers educated about PHQ-9 but were not otherwise influenced to change their practices	Medical provider
	CG	Usual Care	Providers not informed of PHQ-9 results	Medical provider
Jarjoura, 2004[157] Fair	IG	Screening results + treatment protocol	Screening nurse gave residents screening results and provided treatment protocol outline asking them to: (1) explore sx with the pt to affirm screen results; (2) attempt to rule out physical conditions, medications, or other primary psychiatric dx that could explain the results; and (3) do the following if a depression diagnosis was appropriate: (a) educate pt about depression, (b) give pt materials, (c) encourage behavioral treatment at partner agency, (d) discuss antidepressants and decide if appropriate, (e) schedule appt in 4 wks, and (f) ensure pts sees nurse for referral info/help. Nurse arranged behav tx appointment if desired, or instructions to make an appointment. Nurse faxed pt information to behavioral tx provider. All residents were trained to follow AHRQ depression tx guidelines. Meds provided for free.	Resident physicians
	CG	Usual Care	Nurses screened pts, but did not inform residents of results. Pts screening positive told by nurse that they may have a problem with depression and that tx is effective for depression. Pts could discuss depression w/ provider during subsequent visit. All residents were trained to follow AHRQ depression tx guidelines. Meds provided for free.	Resident physicians
Rost, 2001[73] Good	IG	Screening results + provider training & supports	Physicans and nurses in intervention sites participated in a series of 4 1.5 hours conference calls. Calls reviewed study protocol, went over guideline for detection and evaluation of depression in primary care, and provided training on pharmacological therapy and referral to mental health specialists. One nurse in each site also completed an 8-hour training session plus 1 phone call to: 1) review current clinical issues in detection and management of major depression in PC settings; 2) used manual and videotapes to train nurses in treatment protocol, and 3) use role playing and written test to ensure nurses mastery of material. Admin staff training in study protocol, including 2-stage depression screening. Once the intervention began, physicians in enhanced care practices were informed of their enrolled positive screening resutls, and told to evaluate the depression diagnosis, give the patient a copy of the AHCPR's Patient Guide to Depression, and ask the patient to return in 1 week to meet with the nurse and see the physician again. At the 1-week visit, the nurse assessed the nine criteria for major depression, evaluated the patient's treatment preferences (drugs, CBT, watchful waiting) and identified barriers to care. Nurses provided physicians with a description of the patients' symptoms and treatment preferences for their review before seeing the patient on that same day. Phone and in-person followup took place for the next 5-8 weeks. Nurses prepared monthly patient summaries for providers	Physician, nurse
	CG	Usual Care	CG physicians were not informed which patients were participating in the study, nor did CG nurses meet on a regular basis with depressed patients.	Physician, nurse

Appendix D Table 16. Detailed Interventions for Key Question 1 (General and Older Adults)

Author, Year and Quality	Group	Intervention Name	DetailedDescription	Provider
Wells, 2000[155] Fair	IG1	Screening results, provider training & support (combined)	QI-Med Support and QI-CBT groups analyzed together	Psychotherapists, nurse specialists, physicians
	IG2	Screening results, provider training & support, CBT	In both IGs, practices provided in-kind resources; training provided to PCP, nursing supervisor, and MH specialist to implement the interventions, including a 2-day workshop to review depression treatment and principals of collaborative care. Trained 'leaders' distributed clinician manuals, initiated monthly lectures, and provided academic detailing prior to pt recruitment. Monthly team mtgs held where leaders provided audit+feedback on the clinic or clinician level. Nurses also received 1-day workshop on how to condcut brief clinical assessments, patient education, and behavioral activiation based on study manual/video. Monthly phone calls held btw leaders and study team to review study progress.Other materials provided to sites (slides, pocket cards, videos, study charts, etc.). IG provided list of enrolled patients. QI-Therapy- PCC used nurse asst to formulate treatment plan with patient and referred, as appropriate, to CBT-available in English and Spanish. Study-trained psychotherapists provided individual and group CBT for a reduce co-pay ($0-10); patients could access other therapy for the usual co-pyaments ($20-35). Brief (4-session) CBT recommended for patients with minor depression. Medication treatment from regular PCP was available if preferred by patient, but nurse specialists did not provide monthly medication management followup.	Psychotherapists, nurse specialists, physicians
	IG3	Screening results, provider training & support, medication support	In both IGs, practices provided in-kind resources; training provided to PCP, nursing supervisor, and MH specialist to implement the interventions, including a 2-day workshop to review depression treatment and principals of collaborative care. Trained 'leaders' distributed clinician manuals, initiated monthly lectures, and provided academic detailing prior to pt recruitment. Monthly team mtgs held where leaders provided audit+feedback on the clinic or clinician level. Nurses also received 1-day workshop on how to condcut brief clinical assessments, patient education, and behavioral activiation based on study manual/video. Monthly phone calls held btw leaders and study team to review study progress.Other materials provided to sites (slides, pocket cards, videos, study charts, etc.). IG provided list of enrolled patients. In QI-Meds, nurse specialist peformed initial patient assessment, PCP used that assessment to formulate a treatment plan with the patient. Nurses supported med adherence through monthly visits or calls. QI-Meds patients able to access counseling via usual options with usual co-pay.	Nurse specialists, physicians
	CG	Usual Care	UC practices received a mailed copy of the Agency for Healthcare Policy Research practice guidelines. Usual care patients were told they could inform their provider that they screened for depression, but the study did not notify the clinic. Usual care practice includes options for medication and behavioral treatment through normal PC channels, but no extra efforts to manage depression in UC.	Physicians
Older Adults				
van der Weele, 2012[158] Good	IG	Screening results + referral for stepped care	PCPs instructed to inform screen-positive pts about their result and motivate them for referral to Community Mental Health Clinic for a stepped care intervention which included: 1) individual counseling about treatment needs and motivation of the patient during 1 or 2 home visits by a community psychiatric nurse; 2) coping with depression course; 3) referral back to GP to discuss further treatment. The Coping with Depression course was based on CBT and consists of 10 weekly group meetings with 2 course instructors and 6-10 participants. If patients could not attend, they were offered the course in-home.	General practitioner, mental health professional

Appendix D Table 16. Detailed Interventions for Key Question 1 (General and Older Adults)

Author, Year and Quality	Group	Intervention Name	DetailedDescription	Provider
	CG	Usual Care	GPs in control practices were not informed about screen-positive pts in their practice before the end of the study, except in case of severe depression symptoms MADRS score >30 pts and/or suicidal ideation. Patients in control practices were not individually informed about being screen-positive and treatment allocation.	General practitioner
Whooley, 2000[156] Fair	IG	Screening results + provider training + psychoed course	1 hour education session for all PCPs on depression assessment and management skills. PCPs notified of participant's GDS score on the day of their visit to the clinic and given an instruction sheet indicating the range of scores associated with depression. For scores >=11, referral to psychiatry recommended. Patients, and families invited to attend 6 weekly group education sessions, followed by a booster session 4-6 months later. Sessions covered nature and course of depression, physical and emotional manifestations, relation to other medical conditions, treatment alternatives, medications and side effects, coping mechanisms, and preventive strategies.	Primary care physician, psychiatric nurse
	CG	Usual Care + provider education	1 hour education session for all PCPs on depression assessment and management skills. PCPs not notified of their patients' GDS scores or advised of the availability of a patient education program. GDS scores for patients with appts in control clinics were not calculated until the time of the followup interview.	Primary care physicians
Bijl, 2003[159] Fair	IG	Screening results + provider training	4 hour training session covering screeing, diagnosis, and treatment of depression. GPs instructed to provide education, information, drug therapy, and supportive contact to patient. Based on Dutch depession guideline (van Marwijk, 1994). GPs completed diagnostic interview using PRIME-MD when notified patient had screened positive on GDS. Patient enrolled and treated if GP assigned MDD diagnosis.	General practitoners
	CG	Usual Care	Treatment of depression in the usual care group depended on whether the GP recognized the patient as being depressed and was not restricted in any way.	General practitioners
Callahan, 1994[153] Fair	IG	Screening results + provider support	PC providers received the following feedback: a letter specific to the individual patient with HAM-D score and interpretation, previous HAM-D scores (if applicable), a list of currently prescribed medications that have been associated with depression, a reminder that psychiatric consultation is available, an educational flyer on depression, an algorithm for initiating/managing antidepressant treatment of patients. Three additional appointments were scheduled for each patient over 3-month period, where PCP determined if a patient would benefit from therapy. General recommendations included 1) Record diagnosis of depression 2) Discontinue medications that might be causing depression, and substitute drug (if possible) 3) review education flyer and give it to patient at each visit, if appropriate 4) consider antidpressant initiation, using treatment algorithm. 5) After the 3 visits PCPs asked to complete brief questionnaire concerning their clinical decision-making for each patient.	Physicians
	CG	Usual Care	PCPs received no feedack of depression scores or treatment suggestions, and there were no additional appointments scheduled with PCP.	Physicians

Abbreviations: AHCPR/AHRQ = Agency for Healthcare Research and Quality/Agency for Healthcare Policy Research; asst = assistant; CBT = cognitive behavioral therapy; CES-D = Center for Epidemiologic Studies Depression; CG = control group; dx = diagnosis; GDS = Geriatric Depression Scale; GP = general practitioner; HAM-D = Hamilton Rating Scale for Depression; IG = intervention group; MADRS = Montgomery Asberg Depression Rating Scale; MDD = major depressive disorder; med = medication; mtg = meeting; PCP = primary care physician; PHQ = Patient Health Questionnaire; PRIME-MD = Primary Care Evaluation of Mental Disorders; pt(s) = patient(s); QI = quality improvmenet; sx = symptoms; tx = treatment; UC = usual care; w/ =with; wk(s) = week(s).

Appendix D Table 17. Results From Included Studies for Key Question 1 (General and Older Adults): Depression

Category	Author, Year and Quality	Subgroup	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
Depression Prevalence	**General Adults**							
	Williams, 1999[154] Fair	All participants	Depression, n (%)	3	IG1	NR	56 (37)	NR, p=0.19
					CG	NR	30 (46)	
Depression Remission	Williams, 1999[154] Fair	All participants	≤1 DSM-III-R symptom, n (%)	3	IG1	NR	32 (48)	% Difference 21 (95% CI, 1 to 41), p=0.03†
					CG	NR	8 (27)	
	Bergus, 2005[72] Fair	All participants	% PHQ-9 < 5, n (%)	2	IG	0 (0)	13 (54)	NR, p=0.22
					CG	0 (0)	10 (37)	
				6	IG	0 (0)	12 (52)	NR, p=0.35
					CG	0 (0)	10 (38)	
		Depressed at baseline (PHQ-9 ≥10)	% PHQ-9 <5, n (%)	2	IG	0 (0)	5 (36)	NSD
					CG	0 (0)	6 (38)	
				6	IG	0 (0)	8 (54)	NSD
					CG	0 (0)	5 (31)	
	Rost, 2001[73] Good	New Treatment Episode	CESD <16, n (%)	6	IG	0 (0)	30 (31)	NR
					CG	0 (0)	21 (23)	
				12	IG	0 (0)	40 (47)	NR
					CG	0 (0)	24 (28)	
				24	IG	0 (0)	51 (74)	Mean Difference 33 (95% CI, 7 to 46), p=NR
					CG	0 (0)	30 (41)	
	Wells, 2000[155] Fair	All participants	CES-D <20, n (%)	6	IG1	NR	343 (44.6)	NR, p=0.005§
					CG	NR	137 (35.6)	
				12	IG1	NR	342 (45.5)	NR, p=0.04§
					CG	NR	144 (38.6)	
			CIDI 2-item negative, n (%)	6	IG1	NR	463 (60.1)	IG1 vs. CG: NR, p=0.001§
					IG2	NR	263 (59)	
					IG3	NR	230 (59)	IG2 vs. CG: NR, p<0.05‖
					CG	NR	193 (50.1)	IG3 vs. CG: NR, p<0.05‖
				12	IG1	NR	439 (58.4)	IG1 vs. CG: NR, p=0.005§
					IG2	NR	263 (59)	
					IG3	NR	226 (58)	IG2 vs. CG: NR, p<0.05‖
					CG	NR	183 (48.8)	IG3 vs. CG: NR, p<0.05‖
				24	IG1	NR	482 (57.7)	IG2 vs. CG: NSD‖
					IG2	NR	268 (60)	
					IG3	NR	214 (55)	IG3 vs. CG: NSD‖
					CG	NR	235 (57)	
				57	IG1	NR	428 (63.0)	IG2 vs. CG: NR, p=0.05‖
					IG2	NR	228 (63.8)	
					IG3	NR	200 (62.1)	IG3 vs. CG: NR, p=0.08‖
					CG	NR	176 (56.4)	

Appendix D Table 17. Results From Included Studies for Key Question 1 (General and Older Adults): Depression

Category	Author, Year and Quality	Subgroup	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
			Full CIDI, n (%)	24	IG2	NR	285 (69)	IG2 vs. CG: NSD‖
					IG3	NR	218 (61)	
					CG	NR	255 (66)	IG3 vs. CG: NSD‖
		AA+Latino	CIDI 2-item negative, n (%)	57	IG1	NR	133 (60.5)	IG2 vs. CG: NR, p=0.01*
					IG2	NR	84 (64.4)	
					IG3	NR	49 (54.6)	IG3 vs. CG: NR, p=0.13*
					CG	NR	46 (44.2)	
		Whites	CIDI 2-item negative, n (%)	57	IG1	NR	274 (66.8)	IG2 vs. CG: NR, p=0.74*
					IG2	NR	131 (65.6)	
					IG3	NR	143 (68.1)	IG3 vs. CG: NR, p=0.34*
					CG	NR	122 (64)	
	Older Adults							
	Whooley, 2000[156]	All participants	GDS <6, n (%)	24	IG	0 (0)	56 (58)	OR 1.43 (95% CI, 0.8 to 2.5), p=0.3¶
					CG	0 (0)	55 (50)	
	Fair	Depressed at baseline (GDS ≥11)	GDS <6, n (%)	24	IG	0 (0)	5 (38)	OR 1.25 (95% CI, 0.3 to 5.0), p=0.8
					CG	0 (0)	7 (33)	
	Bijl, 2003[159]	All participants	PRIME-MD recovered, n (%)	12	IG	0 (0)	25 (43.1)	% Difference -4.7 (95% CI, -22.5 to 13.1), p=0.60
	Fair				CG	0 (0)	32 (47.8)	
	Callahan, 1994[153]	All participants	HAM-D ≤10, n (%)	6	IG	0 (0)	10 (13)	NR
	Fair				CG	0 (0)	7 (12)	
Depression Response	**General Adults**							
	Bergus, 2005[72]	All participants	50% decrease in PHQ-9, n (%)	2	IG	0 (0)	16 (67)	NSD
					CG	0 (0)	13 (48)	
	Fair			6	IG	0 (0)	12 (52)	NSD
					CG	0 (0)	13 (48)	
		Depressed at baseline (PHQ-9 ≥10)	50% decrease in PHQ-9, n (%)	2	IG	0 (0)	9 (64)	NSD
					CG	0 (0)	10 (60)	
				6	IG	0 (0)	10 (69)	NSD
					CG	0 (0)	9 (54)	
	Jarjoura, 2004[157]	All participants	10-pt reduction in BDI-II, n (%)	12	IG	0 (0)	11 (32)	NR
	Fair				CG	0 (0)	5 (17)	
	Older Adults							
	van der Weele, 2012[158]	All participants	≥50% decrease in MADRS score, n (%)	6	IG	0 (0)	17 (15.9)	NR, p=0.24
					CG	0 (0)	23 (22.3)	
				12	IG	0 (0)	21 (20.8)	NR, p=0.049

Appendix D Table 17. Results From Included Studies for Key Question 1 (General and Older Adults): Depression

Category	Author, Year and Quality	Subgroup	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
	Good				CG	0 (0)	31 (33.3)	
		75-79 years	≥50% decrease in MADRS score, n (%)	6	IG	0 (0)	7 (14.9)	NR, p=0.68
					CG	0 (0)	9 (18)	
				12	IG	0 (0)	13 (28.3)	NR, p=0.13
					CG	0 (0)	20 (43.5)	
		80+ years	≥50% decrease in MADRS score, n (%)	6	IG	0 (0)	10 (16.7)	NR, p=0.21
					CG	0 (0)	14 (26.4)	
				12	IG	0 (0)	8 (14.5)	NR, p=0.25
					CG	0 (0)	11 (23.4)	
	Bijl, 2003[159] Fair	All participants	MADRS 50% reduction, n (%)	2	IG	NR	21 (31)	NR, p<0.05
					CG	NR	12 (16)	
				6	IG	NR	25 (42)	NSD
					CG	NR	17 (26)	
				12	IG	NR	26 (46)	NSD
					CG	NR	26 (39)	
Depressive Symptoms	**General Adults**							
	Williams, 1999 (RM2042) Fair	All participants	DSM-III-R symptoms counts, mean change from baseline (SD)	3	IG1	NR	1.6	NR, p=0.21†
					CG	NR	1.5	
	Bergus, 2005 (RM2302) Fair	All participants	PHQ-9 score, mean	2	IG	12.0	6.3	NR
					CG	12.7	6.9	
				6	IG	12.0	6.3	NR, p=0.45
					CG	12.7	7.5	
		Depressed at baseline (PHQ-9 ≥10)	PHQ-9 score, mean	2	IG	16.1	8.1	NSD
					CG	15.4	6.9	
				6	IG	16.1	6.8	NSD
					CG	15.4	7.2	
	Jarjoura, 2004[157] Fair	All participants	BDI-II score, mean	6	IG	28 (2)	NR	Mean difference in change -7.6 (95% CI, -15.0 to -0.44), p=NR
					CG	23 (2)	NR	
				12	IG	28 (2)	NR	Mean difference in change -4.9 (), p=0.05
					CG	23 (2)	NR	
	Rost, 2001[73] Good	New Treatment Episode-AD	CESD score, mean	6	IG	57.9	31.5	Mean Difference 16.2 (95% CI, 4.5 to 27.9), p=0.007
					CG	53.6	43.4	
		New Treatment Episode	CESD score, mean	6	IG	55.1	33.4	Mean Difference 8.2 (95% CI, 0.2 to 16.1), p=0.04
					CG	52.7	39.2	
		New Treatment Episode-No AD	CESD score, mean	6	IG	50.8	35.5	Mean Difference -1.1, p=NSD
					CG	52.1	35.7	

Appendix D Table 17. Results From Included Studies for Key Question 1 (General and Older Adults): Depression

Category	Author, Year and Quality	Subgroup	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
		Recently Treated	CESD score, mean	6	IG	56.9	42.4	Mean Difference 3.5, p=NSD
					CG	57.4	46.4	
	Older Adults							
	van der Weele, 2012[158] Good	All participants	MADRS score, median	6	IG	12 (95% CI, 8 to 18)	12 (95% CI, 7 to 16)	Mean difference in change 1.4, p=0.056
					CG	14 (95% CI, 11 to 17)	11 (95% CI, 6 to 15)	
				12	IG	12 (95% CI, 8 to 18)	10 (95% CI, 6 to 14)	NR, p=0.088
					CG	14 (95% CI, 11 to 17)	10 (95% CI, 5 to 13)	
		75-79 years	MADRS score, median	6	IG	12 (95% CI, 8 to 18)	12 (95% CI, 7 to 16)	Mean difference in 1.6, p-0.12
					CG	14 (95% CI, 10 to 18)	10 (95% CI, 7 to 14)	
				12	IG	12 (95% CI, 8 to 18)	9 (95% CI, 5 to 13)	NR, p=0.78
					CG	14 (95% CI, 10 to 18)	9 (95% CI, 4 to 12)	
		80+ years	MADRS score, median	6	IG	12 (95% CI, 8 to 18)	13 (95% CI, 8 to 17)	Mean difference in 1.2, p=0.25
					CG	13 (95% CI, 11 to 17)	11 (95% CI, 6 to 15)	
				12	IG	12 (95% CI, 8 to 18)	10 (95% CI, 7 to 15)	NR, p=0.055
					CG	13 (95% CI, 11 to 17)	10 (95% CI, 6 to 14)	
	Whooley, 2000[156] Fair	All participants	Change in GDS, mean change from baseline (SE)	24	IG	8.2 (2.1)	-1.8 (0.4)	Mean Difference 0.3 (95% CI, -0.7 to 1.4), p=0.41‡
					CG	8.4 (2.4)	-2.2 (0.4)	
		Depressed	Change in GDS,	24	IG	NR	-1.6 (0.4)	NR, p=0.7‡

Appendix D Table 17. Results From Included Studies for Key Question 1 (General and Older Adults): Depression

Category	Author, Year and Quality	Subgroup	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
		at baseline (GDS 6-10)	mean change from baseline (SE)		CG	NR	-1.8 (0.4)	
		Depressed at baseline (GDS ≥11)	Change in GDS, mean change from baseline (SE)	24	IG	NR	-5.6 (1.2)	OR 1.25 (95% CI, 0.29 to 5), p=0.15‡
					CG	NR	-3.4 (0.9)	
	Bijl, 2003[159] Fair	All participants	GDS-15, mean	2	IG	7.3	5.5	NSD
					CG	7.6	5.8	
				6	IG	7.3	4.7	NSD
					CG	7.6	5.2	
				12	IG	7.3	4.7	NSD
					CG	7.6	4.7	
			MADRS, mean change from baseline (SD)	12	IG	19.3 (8.7)	-7.8 (9.0)	Mean Difference -0.6 (95% CI, -3.8 to 2.6), p=0.70
					CG	18.7 (7.7)	-7.2 (9.0)	
			MADRS, mean (SE)	2	IG	21.66 (2.86)	19.56 (3.32)	NR
					CG	20.94 (2.48)	19.58 (3.49)	
				6	IG	21.66 (2.86)	9.23 (2.84)	NR, p<0.05
					CG	20.94 (2.48)	11.45 (2.52)	
				12	IG	21.66 (2.86)	10.80 (2.85)	NR
					CG	20.94 (2.48)	10.09 (2.50)	
			PRIME-MD, mean (SE)	6	IG	6.10 (0.8)	2.80 (1.04)	NSD
					CG	6.33 (1.01)	3.99 (1.22)	
				12	IG	6.10 (0.80)	3.23 (1.04)	NSD
					CG	6.33 (1.01)	3.74 (1.21)	
	Callahan, 1994[153] Fair	All participants	HAM-D score, mean	6	IG	22	17.8	NSD
					CG	21.8	16.9	
				9	IG	22	15.9	NSD
					CG	21.8	14.8	

*Adjusted for baseline health status, sociodemographics, randomization blocks.
†Adjusted for baseline depression severity.
‡Adjusted for income, fair/poor health, marital status.
§Adjusted for probability of enrollment, attrition, wave response, clusters, HRQOL, probability of enrollment, attrition wave response.
‖Adjusted for age, sex, education, wealth, ethnicity, marital status, count of chronic medical conditions, depression diagnostic status at baseline, presence of comorbid anxiety disorder, clusters.
¶Adjusted for clinic, baseline variables with significant differences between group groups at p=0.10.

Appendix D Table 17. Results From Included Studies for Key Question 1 (General and Older Adults): Depression

Abbreviations: BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies Depression; CG = control group; CI = confidence interval; CIDI = Composite International Diagnostic Interview; DSM = Diagnostic and Statistical Manual; GDS = Geriatric Depression Scale; HAM-D = Hamilton Rating Scale for Depression; IG = intervention group; MADRS = Montgomery Asberg Depression Rating Scale; NR = not reported; NSD = no significant difference; OR = odds ratio; PHQ = Patient Health Questionnaire; PRIME-MD = Primary Care Evaluation of Mental Disorders; SD = standard deviation; SE = standard error.

Appendix D Table 18. Results From Included Studies for Key Question 1 (General and Older Adults): Quality of Life and Functioning

Author, Year and Quality	Subgroup	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
General Adults							
Jarjoura, 2004[157] Fair	All participants	SF-36 total score, mean	6	IG	NR	NR	Mean Difference -7.6 (95% CI, -15 to -0.44), p=NR
				CG	NR	NR	
			12	IG	NR	NR	Mean Difference -6.5 (95% CI, -14 to 1.2), p=NR
				CG	NR	NR	
Rost, 2001[73] Good	New treatment episode	SF-36 emotional, mean	6	IG	35	65	NR
				CG	38	58	
			12	IG	35	69	NR
				CG	38	57	
			24	IG	35	73	Mean Difference 24 (3.13), p=0.002
				CG	38	49	
		SF-36 physical, mean	6	IG	50	56	NR
				CG	50	51	
			12	IG	50	60	NR
				CG	50	51	
			24	IG	50	63	Mean Difference 17 (2.8), p=0.005
				CG	50	46	
Wells, 2000[155] Fair	All participants	MCS-12 score, mean (95% CI)	6	IG1	35.6 (0.41)	41.6 (0.47)	IG1 vs. CG: NR, p=0.009*
				IG2	35.3	41.9	
				IG3	35.3	40.9	IG2 vs. CG: NR, p<0.05†
				CG	36.1 (0.52)	39.8 (0.57)	
			12	IG1	35.6 (0.41)	40.9 (0.48)	IG1 vs. CG: NR, p=0.04*
				IG2	35.3	42.2	
				IG3	35.3	40.9	IG2 vs. CG: NR, p<0.05†
				CG	36.1 (0.52)	39.3 (0.62)	
			24	IG2	35.3	42.7	IG2 vs. CG: NR, p<0.05
				IG3	35.3	40.8	
				CG	35.3	40.6	IG3 vs. CG: NSD
			57	IG2	34.6 (10.0)	44.3 (95% CI, 42.5 to 46.0)	IG2 vs. CG: NR, p=0.14
				IG3	35.6 (10.7)	43.9 (95% CI, 42.5 to 45.3)	
				CG	36.9 (11.4)	42.6 (95% CI, 40.9 to 44.3)	IG3 vs. CG: NR, p=0.21
		PCS-12 score, mean (95% CI)	6	IG1	45.2 (0.41)	43.9 (0.45)	NR, p=0.72
				CG	44.6 (0.53)	43.7 (0.52)	
			12	IG1	45.2 (0.41)	44.1 (0.43)	NR, p=0.38
				CG	44.6 (0.53)	44.6 (0.50)	
	African American and Latino	MCS-12 score, mean (95% CI)	57	IG2	NR	44.5 (95% CI, 41.6 to 47.5)	IG2 vs. CG: NR, p=0.03
				IG3	NR	41.6 (95% CI, 39.5 to 43.8)	
				CG	NR	40.0 (95% CI, 37.2 to 42.8)	IG3 vs. CG: NR, p=0.35
	White	MCS-12 score, mean (95% CI)	57	IG2	NR	44.6 (95% CI, 42.9 to 46.3)	IG2 vs. CG: NR, p=0.92
				IG3	NR	45.4 (95% CI, 43.5 to 47.3)	
				CG	NR	44.5 (95% CI, 42.9 to 46.1)	IG3 vs. CG: NR, p=0.45

Appendix D Table 18. Results From Included Studies for Key Question 1 (General and Older Adults): Quality of Life and Functioning

Author, Year and Quality	Subgroup	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
Older Adults							
Bijl, 2003[159] Fair	All participants	EuroQoL, mean	6	IG	62.0	64.9	NSD
				CG	62.3	65.9	
			12	IG	62.0	62.4	NSD
				CG	62.3	62.9	
		SF-36 MCS, mean	2	IG	47.0	54.4	NSD
				CG	50.2	54.6	
			6	IG	47.0	58.4	NSD
				CG	50.2	57.6	
			12	IG	47.0	59.2	NSD
				CG	50.2	60.6	
		SF-36 PCS, mean	2	IG	60.5	60.7	NSD
				CG	61.2	63.5	
			6	IG	60.5	61.4	NSD
				CG	61.2	63.1	
			12	IG	60.5	60.7	NSD
				CG	61.2	63.6	
Callahan, 1994[153] Fair	All participants	SIP score, mean (SD)	6	IG	33	29.4	NSD
				CG	29.9	25.0	
			9	IG	33	27.5 (NR)	NSD
				CG	29.9	23.9	

*Adjusted for probability of enrollment, attrition, wave response, clusters.
†Adjusted for age, sex, education, wealth, ethnicity, marital status, count of chronic medical conditions, depression diagnostic status at BL, presence of comorbid anxiety disorder, clusters.

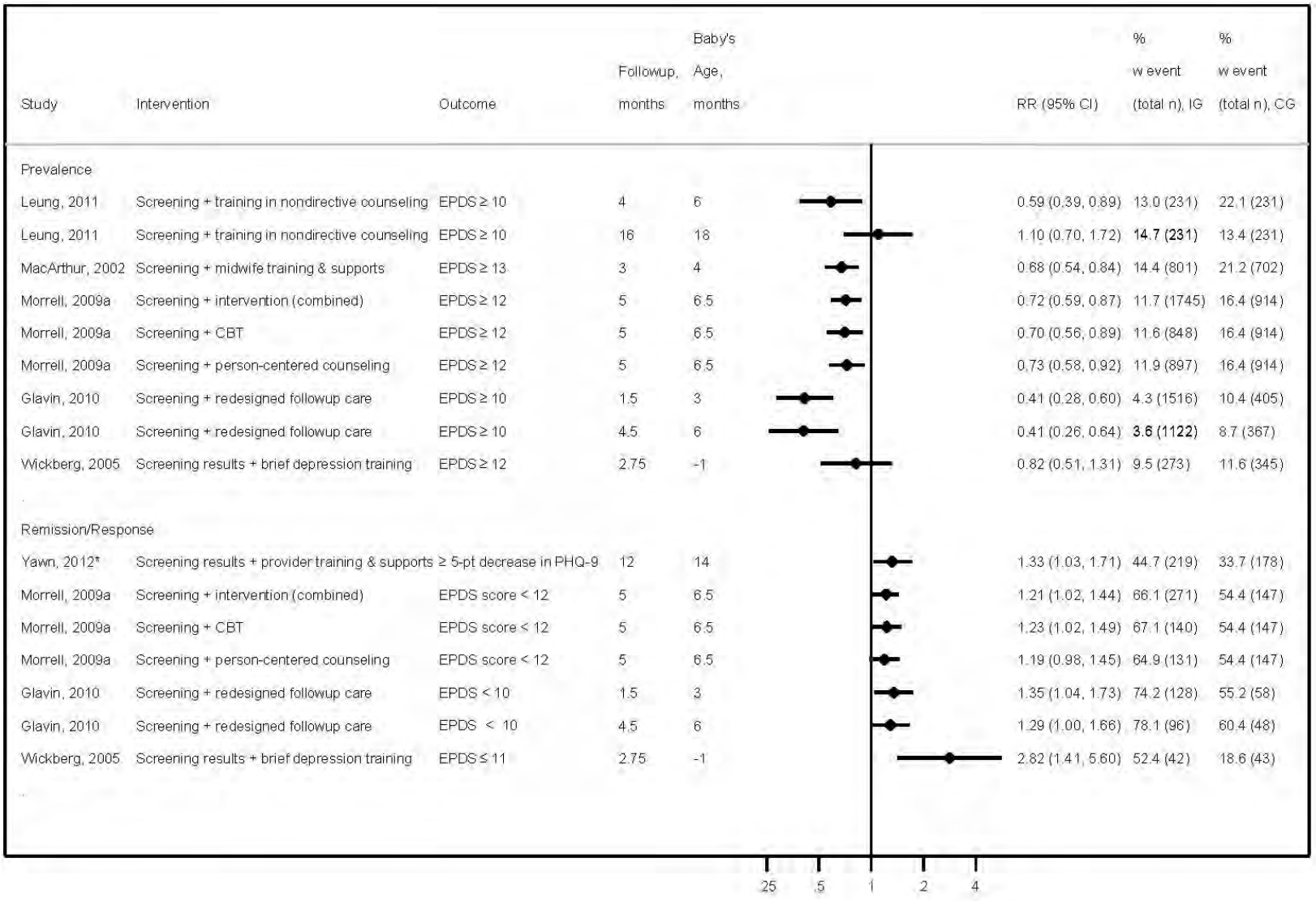
Abbreviations: CG = control group; CI = confidence interval; EuroQoL = European Quality of Life; IG = intervention group; MCS = mental component score; NR = not reported; NSD = no significant difference; PCS = physical component score; SD = standard deviation; SF = Short Form; SIP = Sickness Impact Profile; vs = versus.

Appendix D Table 19. Results From Included Studies for Key Question 1 (General and Older Adults): Process Outcomes

Author, Year and Quality	Subgroup	Outcome	Timepoint (months)	Group	Baseline	Results at Followup	Between Group Difference
General Adults							
Williams, 1999[154] Fair	All participants	Diagnosis recognized by physician, n (%)	3	IG1	NR	30 (39)	% Difference 10 (95% CI, -23 to 43), p=NR
				CG	NR	11 (29)	
		New diagnosis of depression, n (%)	3	IG1	NR	10 (13)	% Difference 10 (95% CI, 1 to 19), p=NR
				CG	NR	1 (3)	
Bergus, 2005[72] Fair	All participants	% advised counseling, n (%)	2	IG	0 (0)	5 (22)	NR, p=0.32
				CG	0 (0)	3 (12)	
		% newly prescribed antidepressants or advised counseling, n (%)	2	IG	0 (0)	11 (49)	NR, p=0.36
				CG	0 (0)	9 (33)	
		% newly prescribed antidepressants, n (%)	2	IG	0 (0)	10 (42)	NR, p=0.34
				CG	0 (0)	8 (30)	
	Depressed at baseline (PHQ-9 ≥10)	% advised counseling, n (%)	2	IG	0 (0)	4 (29)	NR, p=0.59
				CG	0 (0)	3 (20)	
		% newly prescribed antidepressants or advised counseling, n (%)	2	IG	0 (0)	7 (50)	NR, p=1.00
				CG	0 (0)	8 (50)	
		% newly prescribed antidepressants, n (%)	2	IG	0 (0)	6 (43)	NR, p=0.96
				CG	0 (0)	7 (44)	
Jarjoura, 2004[157] Fair	All participants	Treated w/ antidepressants or counseling, n (%)	12	IG	0 (0)	23 (70)	NR
				CG	0 (0)	4 (15)	
Wells, 2000[155] Fair	All participants	Any appropriate antidepressant medications, n (%)	6	IG1	219 (27.6)	268 (34.7)	NR, p=0.001
				CG	106 (27.0)	79 (20.9)	
			12	IG1	219 (27.6)	233 (31.0)	NR, p=0.01
				CG	106 (27.0)	89 (24.0)	
		Any specialty counseling, n (%)	6	IG1	235 (29.5)	294 (38.2)	NR, p<0.001
				CG	105 (26.9)	99 (25.6)	
			12	IG1	235 (29.5)	205 (27.3)	NR, p=0.03
				CG	105 (26.9)	78 (20.9)	
		Overall appropriate care, n (%)	6	IG1	351 (44.2)	393 (50.9)	NR, p<0.001
				CG	166 (42.5)	151 (39.7)	
			12	IG1	351 (44.2)	426 (59.2)	NR, p=0.006
				CG	166 (42.5)	153 (50.1)	
Older Adults							
Whooley, 2000[156] Fair	All participants	Prescriptions for antidepressants, n (%)	24	IG	0 (0)	59 (36)	OR 0.8 (95% CI, 0.5 to 1.2), p=0.30
				CG	0 (0)	72 (43)	
	Depressed at baseline (GDS ≥11)	Prescriptions for antidepressants, n (%)	24	IG	0 (0)	12 (50)	OR 1.1 (95% CI, 0.4 to 3.1), p=0.80
				CG	0 (0)	17 (47)	
Callahan, 1994[153] Fair	All participants	Started an antidepressant, n (%)	6	IG	0 (0)	26 (26)	NR, p=0.01
				CG	0 (0)	6 (8)	

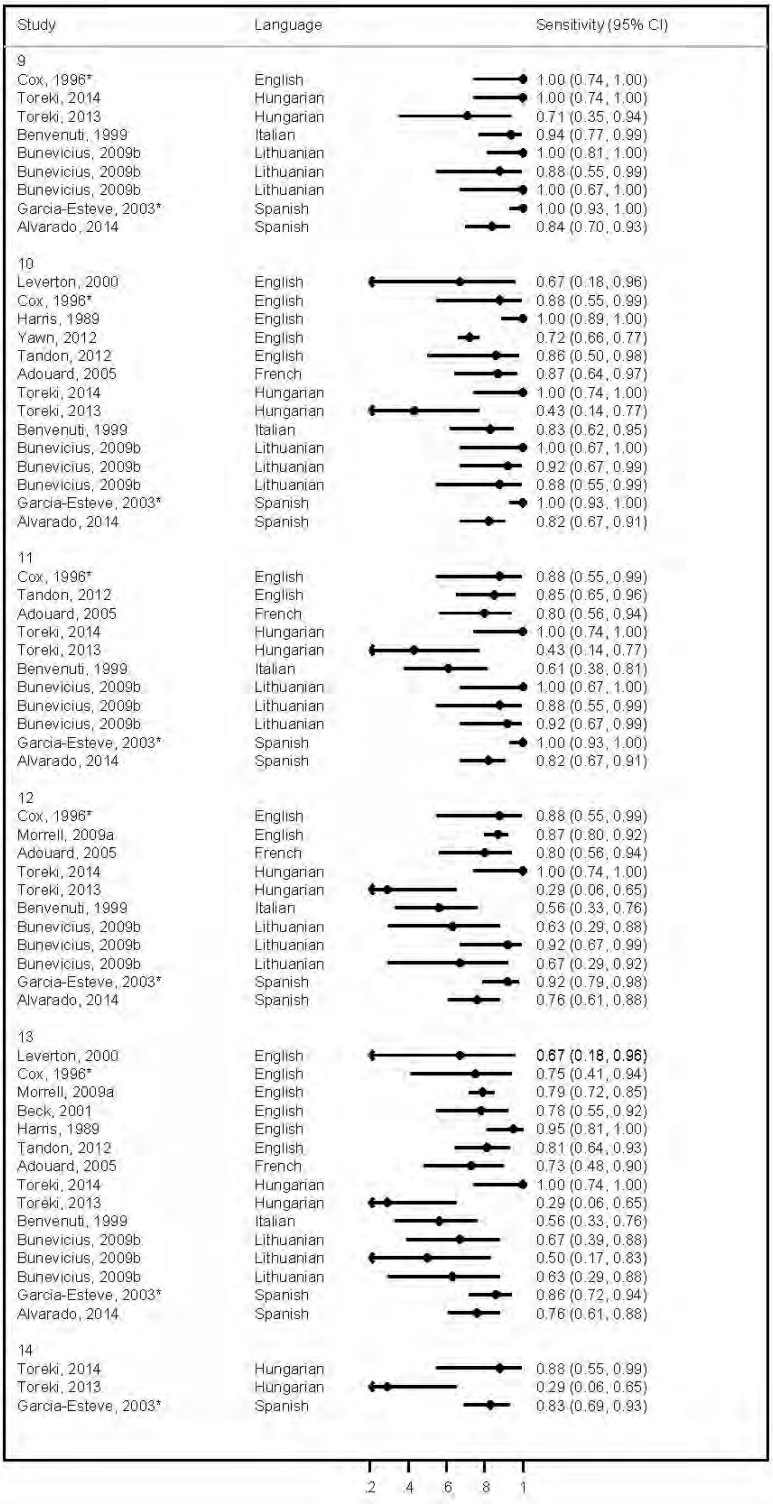
Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; NR = not reported; OR = odds ratio; w/ = with.

Appendix D Figure 1. Forest Plot of Depression Prevalance and Remission/Response in Pregnant and Postpartum Women (Key Question 1)



Abbreviations: CBT = cognitive behavioral therapy; CG = control group; CI = confidence interval; EPDS = Edinburgh Postnatal Depression Scale; IG = intervention group; RR = relative risk.

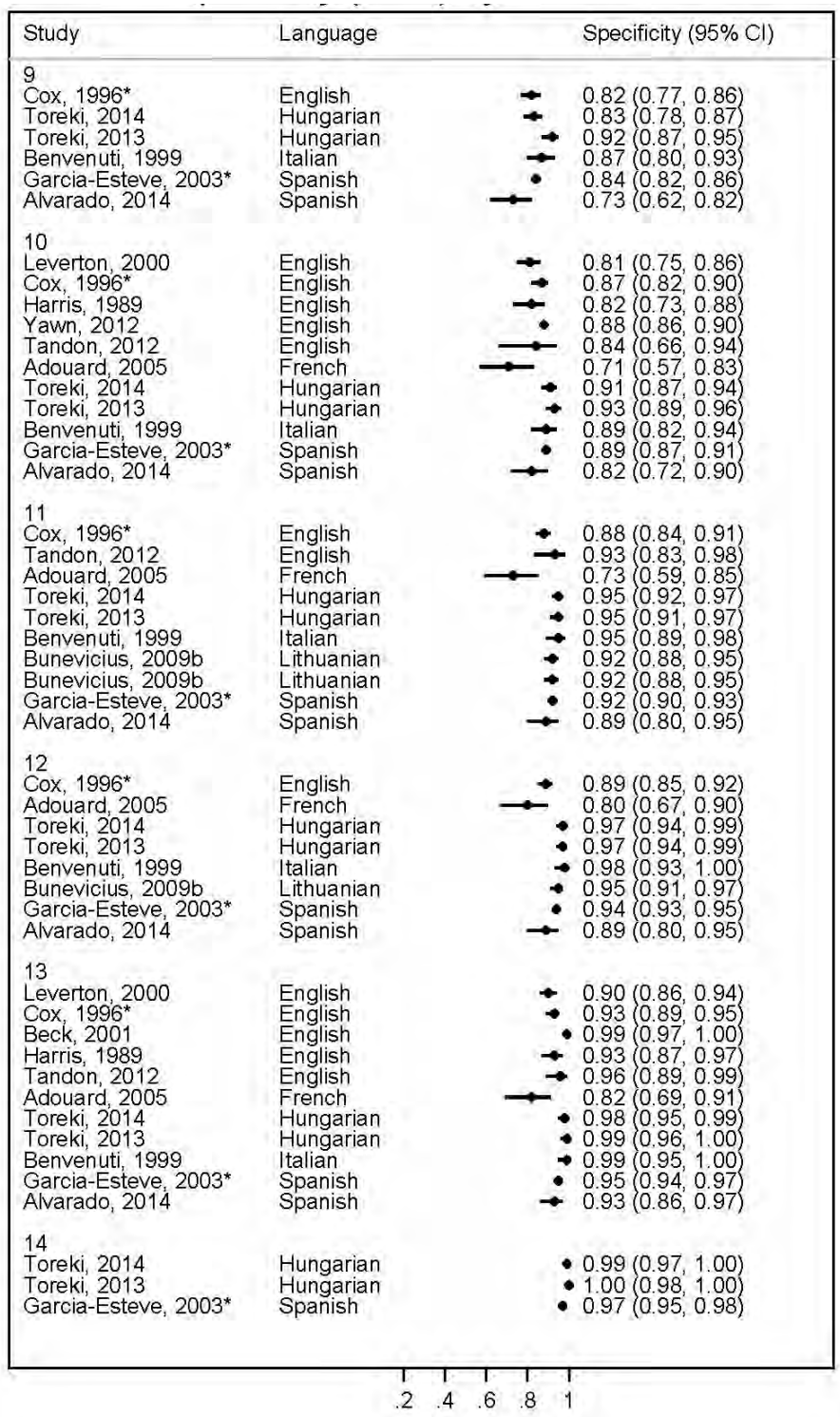
Appendix D Figure 2. Sensitivity of the EPDS for Identifying Major Depressive Disorder in Key Question 2, by Cutoff (Pregnant and Postpartum Women)



Data are extrapolated from partial verification.

Abbreviation: CI = confidence interval.

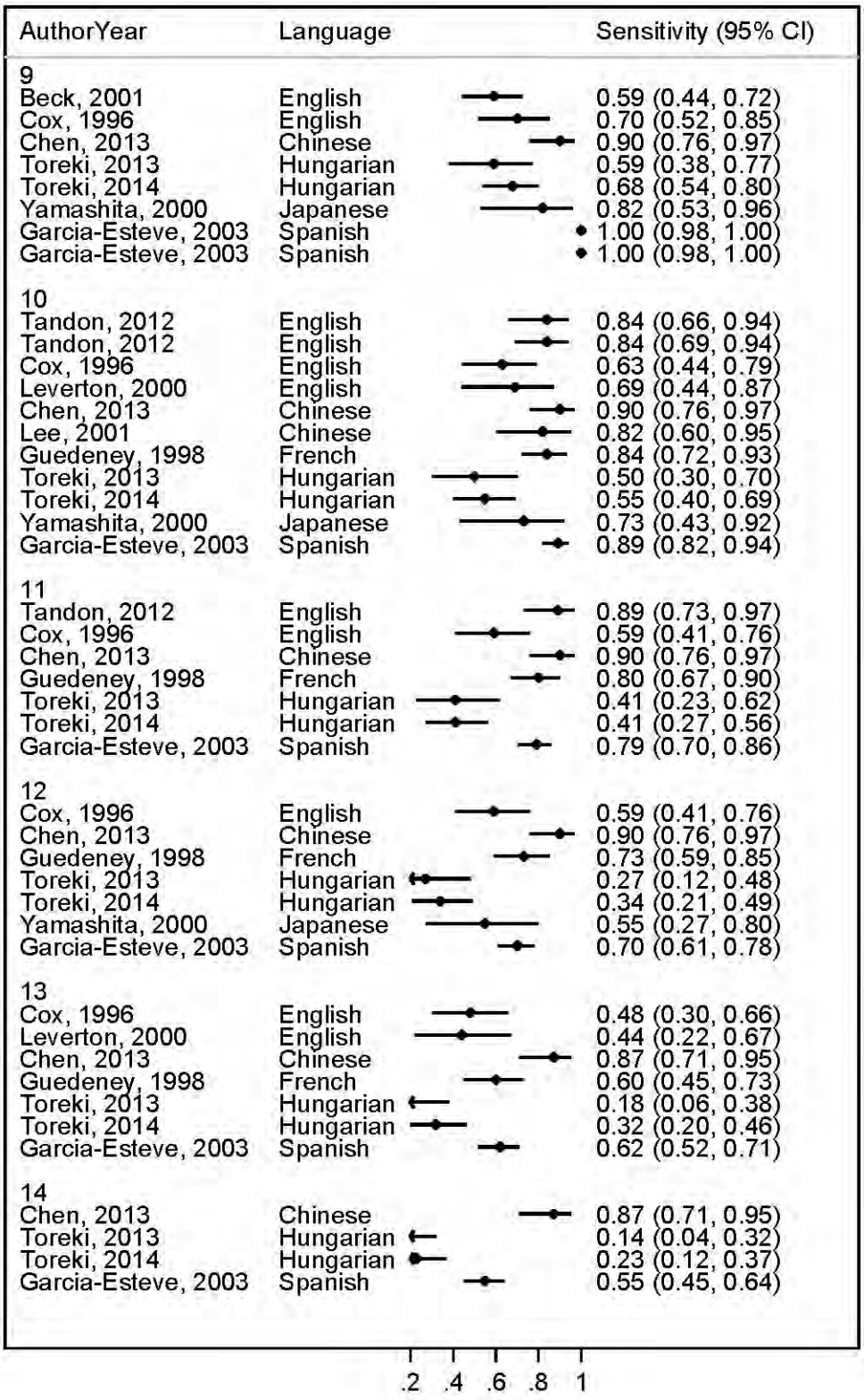
Appendix D Figure 3. Specificity of the EPDS for Identifying Major Depressive Disorder in Key Question 2, by Cutoff (Pregnant and Postpartum Women)



*Data are extrapolated from partial verification.

Abbreviation: CI = confidence interval.

Appendix D Figure 4. Sensitivity of the EPDS for Identifying Minor or Major Depressive Disorder in Key Question 2, by Cutoff (Pregnant and Postpartum Women)



Abbreviation: CI = confidence interval.

Appendix E. Benefits of Depression Treatment in General and Older Adults With Screen-Detected Depression

We identified 18 randomized controlled trial or cluster controlled trials, published between 1983 and 2013 which examined the effectiveness of behavioral and/or pharmacologic treatments for depression in adults (k=13) and older adults (k=5) whose depression was identified through screening in primary care settings. Five trials were conducted in the United States,[200-204] eleven in Europe,[205-214,216] one in Australia, [217] and one in Asia.[215] Follow up periods ranged from six weeks[215] to 24 months.[156,204] All but one study[217] reported percentage of female participants, which varied from 53 to 89 percent. Mean age in studies of general adults ranged from 38 to 53 years; for studies of older adults, mean age ranged from 66 to 74 years. Most of the trials excluded participants who were currently receiving treatment or recently treated for depression.

Several different types of behavioral interventions were utilized including traditional psychological approaches (e.g., brief psychotherapy, interpersonal therapy, CBT, problem-solving treatment), provider training and/or patient psychoeducation, as well as one study that investigated a computer-tailored intervention which involved individualized feedback and a work-book for home study. Several studies utilized a stepped care and/or collaborative care treatment approach that typically involved multiple treatment components such as provider training, patient education and self-management of depression, antidepressant medication, care management, and referral for specialized mental health treatment if needed. Interventions were typically offered by mental health providers (psychiatrists, psychologists, therapists, or counselors), physicians, or nurses. Several of the collaborative care studies utilized a care manager to coordinate treatment. The number of sessions varied considerably (range 3 to 16 sessions) across studies. Interventions were primarily conducted in individual format, although a few studies conducted sessions in group format, online, or by telephone. One of the RCTs[202] included an antidepressant treatment arm and five of the stepped/collaborative care studies[204,207,209,210,214] included antidepressants as a component of treatment.

We found seven trials of collaborative care or other system-level approaches,[201,204,209-211,214,218] and five of these showed beneficial results after 6 or more months, including both trials that were limited to older adults.[204,214] For example, the PROSPECT study found greater declines in suicidal ideation, earlier treatment response, and higher depression remission rates at 24-month followup.[204] These findings are consistent with a recent Community Guide systematic review and meta-analysis of 32 individual studies, which concluded that collaborative care treatments are more beneficial than usual care treatments in terms of multiple depression outcomes, including reduction of depression symptoms, adherence to prescribed treatment, response to treatment, remission or recovery, quality of life or functional status, and satisfaction with treatment.[83]

Eleven trials tested behavioral interventions in the general or older adult populations,[200,202,203,205,206,208,212,216,217,219,220] and results were mixed. Some studies noted that participants with more severe depression symptoms at baseline showed greater treatment effects[200,212] and that treatment effects tended to diminish over longer followup periods.[209,214] One trial studied the effect of an antidepressant in a screened population, and reported a beneficial effect after 8 months of treatment.[202]

A systematic evidence review by Arroll and colleagues[271] of 14 RCTs investigated the effectiveness of TCA and SSRIs antidepressants in primary care (although not necessarily screened in primary care settings). Important to note, studies with a majority (> 50%) of participants over age 65 were

excluded from this review. This review concluded that both TCAs and SSRIs were superior to placebo with relative risks of 1.24 (95% CI, 1.11 to 1.38) and 1.28 (95% CI, 1.15 to 1.43), respectively. Adverse effects were more common with TCAs, although discontinuation rates due to adverse effects were similar for both classes of antidepressant medications.

Overall, the literature supports the effectiveness of both behavioral and pharmacological treatment of depression in adults and older adults who are screened in primary care settings, particularly in the short-term and with patients with more severe depression symptoms at baseline. Stepped care, collaborative care, and more intensive behavioral treatments seem particularly promising.

Appendix E Table 1. Depression Treatment in General and Older Adults With Screen-Detected Depression

Study Country	Design	Setting	Screening Criteria	Intervention Groups (N Rand)	# Sessions	Session Format	Treatment Provider	% Female	Mean Age (years)	% Current/ Recent Treatment	Follow-up (m)	Brief Summary of Results
General Adults												
Brodaty, 1983[217] Australia	RCT	Family practice clinics	GHQ-30 ≥5, symptoms for 6 months	Brief psycho-therapy (n=18) Family practitioner therapy (n=18) UC (n=20)	5-8	Individual	Psychiatrist, family practitioner	NR	NR	NR	12	NSD between groups on Factor 1 (symptoms and social disability) or Factor 2 (physical disability)
Schulberg, 1996[202] United States	RCT	Primary care health centers (academic-affiliated)	MDD + HAM-D >13	IPT (n=93) Nortriptyline (n=91) UC (n=92)	16	Individual	Psychiatrists, psychologists	83	38	NR	8	Severity of depressive symptoms reduced more rapidly and more effectively in drug and IPT groups compared to UC. 70% of pts in treatment groups were recovered at 8 months vs. 20% in the UC group.
King, 2002[216] United Kingdom	RCT	General practice clinics	HADS ≥11	Brief CBT (n=137) UC (n=135)	4	Individual	General practitioner	70	NR	NR	3, 6	NSD between groups on BDI scores at 6 months
Simpson, 2003[205] United Kingdom	RCT	General practice clinics	BDI 14-40, depressed for 6 months	Psycho-dynamic counseling (n=73) UC (n=72)	6-12	Individual	Counselors	NR	18-70	0	6, 12	NSD between the two groups on any of the measures at 6 or 12 months.
Lang, 2006[203] United States	RCT	Primary care clinics (mix of screening, provider referral, self-referral)	MDD, dysthymia, anxiety; BSI-18 T score ≥63 on one or more scales	Brief psycho-therapy (n=32) UC (n=30)	4	Individual	Therapists	53	47	0 therapy/ 55 psycho-tropics	6	8-point decrease at 3 months and 3-point decrease at 6 months in IG. 2 point and 3 point decreases, respectively, in CG on BSI Depression Scale

Appendix E Table 1. Depression Treatment in General and Older Adults With Screen-Detected Depression

Study Country	Design	Setting	Screening Criteria	Intervention Groups (N Rand)	# Sessions	Session Format	Treatment Provider	% Female	Mean Age (years)	% Current/ Recent Treatment	Follow-up (m)	Brief Summary of Results
Schreuders, 2007[206] Netherlands	RCT	General practice clinics	Depress-ion or anxiety, GHQ-12 ≥3	PST (n=88) UC (n=87)	6	Individual	Nurses	71	53	0	3	NSD between groups at followup on HADS.
Levesque, 2011[200] United States	RCT	Primary care clinics	PHQ >5	Computer-tailored intervention (individualized feedback, workbook) (n=174) UC (n=176)	NA	Online	NA	66	18-88	0	9	IG experienced significantly greater improvements in depression; trend toward improved physical functioning but NS. Pts w/ moderate to severe depression at baseline showed greatest improvement.
Casañas, 2012[208] Spain	RCT	Primary care centers	MDD, mild to moderate (BDI ≥10 and <30)	Psycho-education (n=119) UC (n=112)	12	Group	Nurses	89	53	56% taking anti-depressant; 54% taking anxiolytics	3, 6, 9	Intervention superior to UC in terms of reduction of depression symptoms at all followup time points for pts w/ depression at baseline. Significant differences at 3-month followup only for pts w/ moderate symptoms at baseline.
Seekles, 2011[207] Netherlands	RCT	Primary care practices	MDD, dysthymia, minor depress-ion, or anxiety disorder, HADS >12	Stepped care (watchful waiting, guided self-help, PST, pharma-cotherapy and/or referral) (n=60) UC (n=60)	NA	Individual	Care managers	65	50	0	2,4,6	Symptoms of depression and anxiety decreased significantly over time for both groups. However, there was NSD between groups.

Appendix E Table 1. Depression Treatment in General and Older Adults With Screen-Detected Depression

Study Country	Design	Setting	Screening Criteria	Intervention Groups (N Rand)	# Sessions	Session Format	Treatment Provider	% Female	Mean Age (years)	% Current/ Recent Treatment	Follow-up (m)	Brief Summary of Results
Kilbourne, 2013[201] United States	RCT	Primary care (1 site) and mental health specialty clinics (3 sites)	MDD or bipolar disorder, screening checklist by physician	Life Goals Collaborative Care (self-management group + monthly care management contact) (n=29) UC (n=31)	5-11	Group and individual	Care manager	73	46	NR	3,6	IG was associated w/ greater likelihood of depression symptom remising at 6 months, 50% reduction in PHQ-9 score, and improved well-being.
Berghöfer, 2012[209] Germany	C-RCT	Primary care practices	PHQ>4 + MDD + "high utilizer patient"	Collaborative care (sertraline and doxepin, case management, provider training, patient info brochure) (n=19) UC (n=44)	NA	Individual	Physician, case manager	73	50	0	6, 12	NSD between groups in terms of physician rated improvement (HAM-D). Intervention superior to treatment at 6 months according to patient self-ratings (B-PHQ) of treatment response and depression severity. No longer significant at 12 months.
Huijbregts, 2013[210] Netherlands	C-RCT	Primary care centers	PHQ ≥10	Collaborative care (anti-depressant, self-help manual, PST, referral to specialized care) (n=101) UC (n=49)	NA	Individual	Care manager, physician	70	49	NR	3, 6, 9, 12	IG superior to UC in achieving treatment response at 3 months and 9 months. NSD at 6 and 12 months. NNT to achieve response in one additional pt were low (2-3).

Appendix E Table 1. Depression Treatment in General and Older Adults With Screen-Detected Depression

Study Country	Design	Setting	Screening Criteria	Intervention Groups (N Rand)	# Sessions	Session Format	Treatment Provider	% Female	Mean Age (years)	% Current/ Recent Treatment	Follow-up (m)	Brief Summary of Results
Menchetti, 2013[211] Italy	C-RCT	Primary care practices	PHQ	Collaborative care/stepped care (provider training, stepped care protocol, depression management toolkit, psychiatric consultation) (n=128) UC (n=99)	NA	Individual	Physician, psychiatric consultant	76	52	0	3, 6, 12	Trend toward more positive results in IG, but not significant.
Guide to Community Preventive Services (2010)[83]	SR (k=32)	Primary Care	Varied	Collaborative care	NA	Individual	Varied	NA	NA	NA	NA	Compared to usual care, results indicate that effects due to collaborative care were favorable and statistically significant for multiple depression outcomes including improvement in depression symptoms, remission or recovery, and response to treatment.
Arroll, 2009[271] (Cochrane) United Kingdom	SR (k= 14)	"Primary Care"	HAM-D	TCAs or SSRIs	NA	NA	NA	NA	NA	NA	NA	Both TCAs and SSRIs effective at for depression. AEs more common w/ TCAs. Studies w/ the majority of pts > 65 years were excluded from review.

Appendix E Table 1. Depression Treatment in General and Older Adults With Screen-Detected Depression

Study Country	Design	Setting	Screening Criteria	Intervention Groups (N Rand)	# Sessions	Session Format	Treatment Provider	% Female	Mean Age (years)	% Current/ Recent Treatment	Follow-up (m)	Brief Summary of Results
Older Adults												
Van Schaik, 2006[212] Netherlands	RCT	General practice clinics	GDS-15 >5 + MDD	IPT (n=69) UC (74)	10	Individual	Psychologist, psychiatric nurses	69	68	0	2, 6	MADRS ≥10; post-hoc analysis revealed IPT superior to UC for moderately to severely depressed, but not mildly depressed pts.
Serfaty, 2009[213] United Kingdom	RCT	General Practice Research Network	GDS ≥5	CBT (n=70) Talking control (n=67) UC (n=67)	Up to 12	Individual	Trained CBT therapists	79	74	0 (CBT or ECT)	10	CBT superior to UC and talking control in improvements in BDI-II scores at followup.
Lam, 2010[215] Hong Kong	RCT	Govern-ment funded general outpatient clinics	HADS	Brief PST (n=149) Placebo (video) (n=150)	3	Individual	Primary care provider	59	72	0	1.5, 3, 6, 12	NSD between groups (both groups improved).
Van Marwijk, 2008[214] Netherlands	C-RCT	General practice clinics	GDS ≥ 5	Primary care management (pt education, paroxetine, supportive counseling) (n=70) UC (n=75)	8	Individual	Primary care provider	57	66	0	6,12	IG superior to UC in recovery and symptom reduction at 6 month followup (MADRS scores), but not at 12 months. NSD in PRIME-MD scores at any time point.
Alexopoulos 2009[204] PROSPECT Study United States	C-RCT	Primary care practices	MDD or minor depression + HAM-D ≥10	Collaborative care (citalopram, case management, IPT, home visits, referrals) (n=320) UC (n=279)	NA	Individual	Physician, care manager	72	NR	NR	24	IG pts 2.2 greater decline in suicidal ideation, earlier treatment response, higher remission rates.

Abbreviations: AE(s) = adverse effect(s); BDI = Beck Depression Inventory; BSI = Beck Scale for Suicide Ideation; CBT = cognitive behavioral therapy; GHQ = General Health Questionnaire; GDS = Geriatric Depression Scale; HADS = Hospital Anxiety and Depression Scale; HAM-D = Hamilton Rating Scale for Depression; IG = intervention group; IPT = interpersonal therapy; MDD = major depressive disorder; NA = not applicable; NNT = number needed to treat; NR = not reported; NS = not significant; NSD = no significant difference; PHQ = Patient Health Questionnaire; PRIME-MD = Primary Care Evaluation of Mental Disorders;

Appendix E Table 1. Depression Treatment in General and Older Adults With Screen-Detected Depression

PST = problem-solving therapy; pt(s) = participant(s); RCT = randomized controlled trial; SR = systematic review; TCA = tricyclic antidepressants; UC = usual care; vs = versus' w/ = with.

Appendix F. Screening Accuracy of the Patient Health Questionnaire and the Geriatric Depression Scale

We identified limited evidence within our body of included studies that utilized either the PHQ[72] or GDS[156,158,159] for depression screening; none of which assessed the accuracy of these instruments in comparison to reference standard diagnostic interviews.

The PHQ-9, as well as the briefer PHQ-2 and PHQ-8 versions, are commonly used and easy to administer.[222] The PHQ-9 is a nine-item, three-page, self-administered version of the PRIME-MD, which has been previously validated.[272] The exclusive focus of the PHQ-9 is on the nine diagnostic criteria for DSM-IV depressive disorders, thus it does not capture symptoms like loneliness and anxiety. The PHQ-9 score ranges from 0 to 27 and cut-points of 5, 10, 15, and 20 represent the thresholds for mild, moderate, moderately severe, and severe depression, respectively.[273]

A previous meta-analysis of the PHQ-9 by Manea and colleauges included 18 validation studies, including 7,180 participants, conducted in a range of clinical settings.[221] The majority of included studies used the English version PHQ (k=10), and included studies were required to use a standardized diagnostic interview to make a diagnosis and have a sample size ≥ 250. There was significant between-study heterogeneity, for which the only predictive source was the reported blind application of a diagnostic gold standard. The authors concluded that the PHQ-9 had acceptable diagnostic properties for detecting major depressive disorder for cut-off scores between 8 and 11, with a pooled specificity from 0.83 (95% CI, 0.69 to 0.92) for a cut-off score of 8, to 0.89 (95% CI, 0.79 to 0.94) for a cut-off score of 11. Corresponding pooled sensitivity estimates ranged from 0.82 (95% CI, 0.66 to 0.92) for a cut-off score of 8, to 0.89 (95% CI, 0.75 to 0.96) for a cut-off score of 11. There were no significant differences in the diagnostic properties of the PHQ-9 for cut-off scores between 8 and 11. A cut-off score of 11 appeared to have the optimal trade-off between sensitivity and specificity, however the authors acknowledged this may vary according to clinical setting. The diagnostic OR was lower in hospital settings (diagnostic OR, 25.43 [95% CI, 11.35 to 57.00]) than in primary care settings (diagnostic OR, 65.26 [95% CI, 9.17 to 464.47]).

A more recent review of the PHQ questionnaires is underway by Thombs and colleagues,[222] using an individual patient data (IPD) meta-analysis approach. Although not yet complete, a manuscript describing the methods for this review included a criticism of the meta-analysis conducted by Manea and colleagues[221] described above, suggesting that the results were limited by selective reporting from the included studies. Other stated concerns were related to the inclusion of patients already being treated for depression.[222,274] This concern was acknowledged by Manea and colleagues as a limitation to the meta-analysis.[221]

The GDS was originally developed as a 30-item (GDS-30) self-administered depression screening instrument specifically developed for the elderly, however the authors of the original GDS did not provide threshold cut-offs for depression diagnoses.[275] Questions use a simple yes/no format, and are designed to assess the severity of depression in older adults, with recognition that other depression scales used in the general population may not be adequate for older adults. Due to concerns that the length of the GDS may contribute to fatigue or concentration and attention span difficulties, shorter versions have been developed, including the GDS (15, 10, 8, 5, and 4 items). The survey can be self-administered or interviewer-administered, however one study evaluating the influence of administration method on scores from GDS-15 found that when participants self-administered, scores were 0.7 points higher when self-administered, and 23 percent left items unanswered.[59]

Appendix F. Screening Accuracy of the Patient Health Questionnaire and the Geriatric Depression Scale

One review of the GDS-15 and GDS-30, published in 2010, included a meta-analysis of 17 studies conducted in primary care settings.[223] The principle inclusion criteria were studies that compared the diagnostic validity of the GDS to that of the semi-structured psychiatric interview for diagnosing late-life (aged 55 years or older) depression. Studies evaluating the GDS-15 (k=7) used cut-offs ranging from 3 to 7, resulting in an adjusted sensitivity of 81.3 percent (95% CI, 77.2 to 85.2) and a specificity of 78.4 percent (95% CI, 71.2 to 84.8). Studies evaluating the GDS-30 (k=10) used cut-offs ranging from 7 to 11, resulting in an adjusted sensitivity of 77.4% (95% CI, 66.3 to 86.8) and a specificity of 65.4 percent (95% CI, 44.2 to 83.8). In order to more fully examine the clinical utility of the GDS, the authors also evaluated general practitioners' ability to detect depression without a screening tool. Using data from six studies, the authors' reported a pooled sensitivity of 56.3 percent (95% CI, 40.0 to 72.0) and specificity of 73.6 percent (95% CI, 71.7 to 75.5). The authors concluded that the GDS-30 had modest diagnostic success, modest clinical utility, and limited benefit beyond the GP's unassisted clinical skills. The GDS-15, however, was believed to have adequate diagnostic value with significantly greater accuracy than the GDS-30 and, thus, good clinical utility. Furthermore, use of the GDS-15 by GP's has the potential to increase unassisted case detection by 8 percent.

Another systematic review of the GDS-15 and GDS-30, published in 2006, described the screening accuracy of the GDS, as well as a comparison of the validity indices of the GDS to other commonly used screening instruments.[276] The review included 42 studies, including 6,314 participants, conducted in a range of clinical settings. In most studies (76%), the GDS was administered in the English language. All included studies compared GDS screening results with external case criterion, or gold standard, which could be a non-specified clinical psychiatric interview. Interviewers were known to be blinded in 26 out of 42 (62%) of included studies. Among studies using the GDS-30 (k=33), most used a cut-off of 10 or 11 (k=21), and among studies using the GDS-15 (k=21), most used a cut-off of 5 or 6 (k=13). Depression prevalence rates ranged from 6 to 51.5 percent. For the GDS-30, the mean sensitivity was 0.753 (range, 0.340 to 1.000), and the mean specificity was 0.770 (range, 0.629 to 0.964). For the GDS-15, the mean sensitivity was 0.805 (range, 0.600 to 0.940), and the mean specificity was 0.750 (range, 0.570 to 0.870). When compared to the CES-D instrument, the GDS showed similar criterion validity.

More recently, efforts to develop a new 10-item version of the GDS (termed GDS-R) in the Spanish language were reported as successful in retaining the diagnostic performance of the GDS-30, while increasing the sensitivity and predictive values relative to other shortened versions.[275] Using an optimal cut-off score of 5, the GDS-R resulted in 100 percent sensitivity (95% CI, 66.2 to 100), and 97.9 percent specificity (95% CI, 93.7 to 99.7). In comparison, other shortened versions of the GDS (GDS-5, GDS-10, GDS-15) report sensitivities ranging from 66.7 to100 percent and specificities from 78.1 to 87.5 percent.

Appendix G. Ongoing Studies

Relevant Key Question	Study Country	Aim	Participants (number of participants)	Intervention	Comparator	Relevant Outcomes	Status
Depression treatment in pregnant and postpartum women (KQ 4 & 5)	Integrated Maternal Psychosocial Assessment to Care Trial (IMPACT)[277] Canada	Evaluate an integrated process of online psychosocial assessment, referral, and CBT for pregnant women	Pregnant women aged ≥16 years (n=54)	Integrated process of online psychosocial assessment, referral, and CBT	Usual prenatal care (no formal screening or specialized care)	Self-reported prenatal depression	Estimated completion date, February 2015
	PRegnancy Outcomes after a Maternity Intervention for Stressful EmotionS (PROMISES)[278] Netherlands	Assess the effects of CBT in pregnant women with anxiety or depression symptoms	Pregnant women with at least moderate levels of anxiety or depression at the end of their first trimester (n=300)	CBT, 10-14 individual sessions during pregnancy and after delivery	Usual care	Depressive symptoms (EPDS)	Results to be published in 2015
	Dennis, 2012[279] Canada	Evaluate the effect of telephone-based IPT in the treatment of postpartum depression	Postpartum women self-identified as depressed or referred by health professional based on EPDS score >12 (n=240)	Telephone-based IPT, 12 weekly 50-60 minute sessions	Usual care	Depression diagnosis and symptomatology	Completed, only protocol published
	Flanagan, 2011[280] United States	Evaluate a multi-media, computer-based, skills-training psychotherapy treatment	Mothers experiencing postpartum depression (n=122)	Multi-media, computer-based, skills-training psychotherapy treatment, *Mommy Emotion and Psychological Training Experience*	Treatment as usual	Depression, quality of life	Published meeting abstract only
	Katz & Joseph, 2009 (DC-HOPE)[281,282] United States	Evaluate the effectiveness of brief behavioral treatment of depression in prenatal care settings	Low-income pregnant African-American women (n=373)	CBT, 10 sessions	Usual care	Depression symptoms	Completed, publication with relevant outcomes not yet published

Appendix G. Ongoing Studies

Relevant Key Question	Study Country	Aim	Participants (number of participants)	Intervention	Comparator	Relevant Outcomes	Status
	Kammerer, 2014[283] United Kingdom	Evaluate the efficacy of an internet-based CBT in women suffering from depression in pregnancy	Pregnant women aged 18-40 years with depressive symptoms (EPDS score 12-22) (n=120)	Online CBT, 10 40-minute sessions beginning during pregnancy and continuing after delivery	Usual care	Change in EPDS scores	Estimated completion, January 2016
	Lenze, 2014[284] United States	Test the feasibility, acceptability, and effectiveness of IPT dyad	Pregnant women aged ≥18 years with an EPDS score ≥13 and depression diagnosis (n=40)	Dyadic IPT	Enhanced usual care	Change in EPDS scores	Estimated completion date, October 2015
	Monk, 2011[285] United States	Evaluate effectiveness of group IPT for prevention of postpartum depression in depressed pregnant women	Pregnant women aged 18-40 years with an EPDS score ≥10 (n=116)	Group IPT, 12 weekly sessions	Usual care	Postpartum depression	Completed, no relevant publications
	O'Mahen, 2013 (The Netmums Project)[286] United Kingdom	Evaluate an internet-based behavioral activation treatment	Women screened positive for depression (n=1,261)	Postnatal electronic behavioral activation	Treatment as usual	Depression symtpoms, quality of life	Published meeting abstract only
	Postmontier, 2013[287] United States	Evaluate feasibility, acceptability and safety of nurse midwife counseling telephone-administered interpersonal psychotherapy	Women with postpartum depression (n=100)	Telephone-administered interpersonal psychotherapy, 8 sessions	Wait list / treatment as usual	Depression symtpoms, quality of life	Published meeting abstract only
	Wisner, 2013[288] United States	Evaluate the effectiveness of a telephone-based screening and care management program in treating depression in postpartum women	Postpartum women aged ≥18 years with an EPDS score ≥10 (n=628)	Telephone calls from depression care manager encouraging women to seek appropriate depression care	Usual care	Depressive symptoms	Completed, no relevant publications

Appendix G. Ongoing Studies

Relevant Key Question	Study Country	Aim	Participants (number of participants)	Intervention	Comparator	Relevant Outcomes	Status
Screening for depression in general and/or older adults (KQ 1 & 2)	Sadavoy, 2007[289] Canada	Evaluate the acceptability of a mental health screening program	Chinese older adults aged 55-85 years	Received results of depression screening	Did not receive results of depression screening	Healthcare utilization	Unknown
	Thombs, 2014[222] Canada	Determine whether USPSTF depression screening guideline is supported by evidence	Adults	Depression screening tool with a defined cut-off score to make decisions regarding further assessment or treatment of depression	NR	Depression symptom outcomes	Published

Abbreviations: CBT = cognitive behavioral therapy; EPDS = Edinburgh Postnatal Depression Scale; IPT = interpersonal therapy.