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Screening and Supplementation for Iron Deficiency and Iron Deficiency Anemia During Pregnancy: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation

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

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Structured Abstract

Background: Iron deficiency (ID) and iron deficiency anemia (IDA) during pregnancy may affect maternal health and infant birth outcomes. In 2015, the U.S. Preventive Services Task Force (USPSTF) determined the evidence was insufficient to assess the balance of benefits and harms of screening and preventive routine iron supplementation for IDA during pregnancy. For this update, the scope was expanded to include ID without anemia.

Purpose: To systematically update the prior USPSTF review on screening and supplementation for IDA in pregnancy with the addition of ID without anemia.

Data Sources: Ovid MEDLINE, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials from June 1, 2014 to May 24, 2023 for IDA, and since database inception for ID without anemia, and manually reviewed reference lists; with surveillance through November 24, 2023.

Study Selection: We included randomized controlled trials of iron supplementation and screening and related treatment on maternal and infant clinical outcomes, rates of IDA, ID, hematologic indices and ferritin levels, and harms.

Data Extraction: One investigator abstracted data and a second investigator checked data abstraction for accuracy. Two investigators independently assessed study quality using methods developed by the USPSTF.

Data Synthesis (Results): Seventeen trials of routine maternal iron supplementation reported intermediate and clinical outcomes for pregnant persons and infants. Prenatal iron supplementation resulted in no differences in maternal quality of life (1 trial), rates of gestational diabetes (2 trials), or rates of maternal hemorrhage (2 trials) compared with placebo. There was no effect of maternal iron supplementation on rates of hypertensive disorders of pregnancy (5 studies; N=13,610; 4.7% vs. 3.1% [pooled, weighted rates]; relative risk [RR], 1.24 [95% confidence interval (CI), 0.75 to 2.06]; I^2= 48%), cesarean delivery (8 trials; N=4,919; 42.8% vs. 41.5%; RR, 1.01 [95% CI 0.90 to 1.14]; I^2=42.7%), preterm birth (5 trials; N=16,827; 5.5% vs. 6.0%; RR, 0.92 [95% CI 0.81 to 1.04]; I^2=0%), infant low birth weight (6 trials; N=15,591; 2.7% vs. 2.9%; RR, 0.95; [95% CI 0.79 to 1.14]; I^2=0.0%), or infants small for gestational age (4 trials; N=5,386; 15.3% vs. 15.2%; RR, 0.94 [95% CI 0.67 to 1.31]; I^2=75.5%). Iron supplementation was associated with a decreased risk of maternal IDA at term (4 trials, N=2,230; 8.6% vs. 19.8%; RR, 0.40 [95% CI 0.26 to 0.61]; I^2=20.5%; absolute risk difference [ARD], -9.59% [95% CI, -16.20% to -2.98%]) and during the third trimester (3 trials; N=660; 9.1% vs. 13.8%; RR, 0.63; [95% CI 0.41 to 0.97]; I^2 =0%; ARD, -3.86% [95% CI, -7.74% to 0.02%]), and maternal ID at term (6 trials, N=2,361; 46% vs. 70%; RR, 0.47 [95% CI 0.33 to 0.67]; I^2=81.9%; ARD, -34.25% [95% CI, -46.49% to -22.01%]) and during the third trimester (4 trials; N=1,220; 40.3% vs. 57.1%; RR, 0.70 [95% CI 0.53 to 0.92]; I^2=77.4%; ARD, -16.95% [95% CI, -24.13% to -9.77%]) compared with placebo or no iron supplements. In analyses stratified by United Nations Human Development Index (HDI) country and iron dosage, findings were generally consistent with overall analyses. Reported harms of iron supplementation included transient

gastrointestinal side effects or non-adherence. There were no studies on the benefits or harms of screening for ID or IDA during pregnancy.

Limitations: Restriction to English language and exclusion of studies conducted in low or middle-income countries. Data from trials in countries with uncertain generalizability to U.S. populations were considered for some outcomes. Studies were methodologically heterogeneous and underpowered for key clinical outcomes.

Conclusions: Prenatal iron supplementation may improve maternal hematologic indices and reduce the incidence of ID and IDA during pregnancy, but evidence on maternal and infant health outcomes is limited or indicates no benefit. Routine iron supplementation is not associated with significant maternal harms. No studies addressed the benefits or harms of screening for ID or IDA during pregnancy. Research is needed to understand the association between changes in maternal iron status measures and health outcomes.

Table of Contents

Figures

Tables

Appendixes

Chapter 1. Introduction and Background

Purpose

This systematic review update will be used by the U.S. Preventive Services Task Force (USPSTF) to update its 2015 recommendation on screening for and prevention of iron deficiency anemia (IDA) via routine iron supplementation in pregnant persons.[1] In 2015, the USPSTF concluded that the current evidence was insufficient to assess the balance of benefits and harms of screening for IDA in pregnant persons to prevent adverse maternal health and birth outcomes ***(I statement)***.[1] This was due to the lack of studies evaluating the direct effects of routine screening in asymptomatic pregnant persons on maternal health or birth outcomes, inadequate evidence on the accuracy of screening tests in asymptomatic pregnant persons, and inadequate evidence to evaluate risk prediction tools to identify pregnant persons at increased risk for IDA. There was also inadequate evidence on the treatment of IDA in pregnant persons because none of the recent studies on treatment were generalizable to the general U.S. population. This was considered a critical gap in the evidence.[2]

In 2015, the USPSTF also concluded that the current evidence was insufficient to assess the balance of benefits and harms of routine preventive iron supplementation for pregnant persons to prevent adverse maternal health and birth outcomes ***(I statement)*** based on inadequate evidence on the effect of routine iron supplementation during pregnancy on maternal health or birth outcomes, such as maternal IDA, cesarean delivery, preterm delivery, infant mortality, or low birthweight. The USPSTF found adequate evidence that routine iron supplementation during pregnancy improved intermediate maternal hematologic indexes, such as serum ferritin and hemoglobin levels, and adequate evidence that routine iron supplementation during pregnancy had no effects on the length of gestation and infant Apgar scores at 1 and 5 minutes.

This report updates the 2015 USPSTF review.[3,4] Similar to the prior review, it synthesizes evidence on the benefits and harms of screening and preventive medications for ID and IDA in pregnant persons, and expands the scope by evaluating the effect on ID without anemia.

Condition Background

Condition Definition

Iron is required in the production of hemoglobin, an essential protein found in red blood cells that transports oxygen throughout the body from the respiratory organs. Over time, iron is stored in the body for use in hemoglobin production. ID occurs when the level of stored iron becomes depleted. IDA occurs when iron levels are sufficiently depleted to produce anemia, characterized by hypochromic and microcytic red blood cells.[5,6] Progression from ID alone (low iron stores) to IDA is a process that occurs in stages. When iron stores are depleted, IDA can develop with further iron losses.

The Centers for Disease Control and Prevention (CDC)[6] and the World Health Organization (WHO)[7] define IDA in pregnancy as ID (serum ferritin <12 µg/L) with a hemoglobin level of

less than 11.0 g/dL (or <110 g/L) and a hematocrit level of less than 33 percent.[8] ID without anemia can be diagnosed based on ferritin levels, a marker of iron stores, with varying cutoffs depending on the laboratory reference standard.[9] While the gold standard for documenting ID historically has been iron staining of a bone marrow aspirate smear, bone marrow correlations and international guidelines[8] support diagnosing ID using ferritin levels and considering an increase in the cutoff from 30 ng/mL to 50 ng/mL.[10,11]

Etiology and Natural History

Physiological anemia of pregnancy is observed in healthy pregnant persons and occurs as the result of greater expansion of plasma volume relative to the increase in hemoglobin mass and erythrocyte volume associated with pregnancy. This normal physiological change is responsible for a modest decrease in hemoglobin levels and is often referred to as dilutional anemia of pregnancy. Pregnancy-associated changes in plasma volume and red cell mass, normal differences in hemoglobin concentrations, and individual variation can also affect iron stores.

In the recent past, there have been race-based cutoffs for IDA, which are now recognized as a possible contributor to disparities in diagnosis, treatment, and outcomes.[12,13] Standardized cutoffs across all populations are recommended.[14,15] While there are disparities in reported prevalence of anemia during pregnancy based on race and ethnicity, the etiology of these differences is unclear (see Disparities section below). In light of these issues, using different cutoffs based on race or categorizing race or ethnicity as risk factors for anemia during pregnancy is not recommended.[16]

ID is the most common pathological cause of anemia in pregnancy. Total iron loss associated with pregnancy and lactation is about 1,000 mg. Iron is necessary for both fetal and placental development and to expand the maternal red cell mass. Iron is commonly prescribed as part of a prenatal multivitamin or as a separate supplement based on the assumption that iron stores during pregnancy are not often sufficient to support the physiologic demands of pregnancy.

Prevalence and Burden of Disease/Illness

During pregnancy there is a higher risk for ID compared with the nonpregnant state because of increased iron needs resulting from growth of the fetus and placenta, increased red cell mass, and the expansion of maternal blood volume, especially as the pregnancy progresses into the third trimester.[6,13,17-19] Analysis of National Health and Nutrition Examination Survey (NHANES) epidemiological data (n=1,171) from 1999 to 2006 found an overall prevalence of ID in pregnancy near 18 percent, with 5 percent of pregnant persons found to be anemic; prevalence of ID increased from 6.9 to 14.3 to 28.4 percent across the three trimesters.[19] From 2000 to 2004, reported rates of IDA in a population of low-income, pregnant women from the urban United States were 1.8 percent in the first trimester, 8.2 percent in the second trimester, and 27.4 percent in the third trimester.[18] Additional estimates of IDA in pregnant persons are not readily available but older data may underestimate the prevalence of ID due to lower ferritin cutoffs than currently accepted, therefore data is limited.

ID during pregnancy is associated with fatigue, reduced quality of life, and increased risk of postpartum depression[20,21] in pregnant persons, and higher risk of low birth weight and preterm birth.[22] Pregnant persons with IDA or ID may experience clinical symptoms of fatigue,

weakness, pallor, and in more severe cases, tachycardia or shortness of breath.[23] In countries where access to nutrition and healthcare is inadequate, severe maternal anemia during pregnancy has been associated with postpartum hemorrhage and higher risk of maternal death.[24,25]

Numerous older observational studies have shown various measures of iron status, including IDA, to be associated with serious negative infant outcomes, including low birthweight,[26-28] premature birth,[26-31] and perinatal death;[27] however, newer studies indicate that the association between iron status and negative outcomes for both pregnant persons and their infants is inconclusive and longer term data is needed.

Disparities

There are differences in prevalence of IDA according to population characteristics. NHANES data from 1999 to 2006 (n=1,171) found differences in the prevalence of IDA by race, with highest rates among non-Hispanic Black (30%) and Mexican American (24%) pregnant persons and lower rates among White pregnant persons (14%).[19] In one study, parity of two or more was associated with increased prevalence of ID (28%) compared with parity of zero (12%) or one (17%);[19] however, no associations were found in pregnant persons with lower educational levels or family income, associated with low socioeconomic status, which are mentioned as risk factors in other sources.[13,18] Rates of IDA may also differ by socioeconomic status. For example, a study of pregnant persons followed through 6 months postpartum found a higher prevalence of IDA in those with an income eligible for Federal aid, based on a poverty index ratio less than 130 percent, compared with pregnant persons with incomes above this threshold (10% vs. 2%, respectively).[32] Importantly, these differences do not address the contribution of nutritional status or other potential underlying contributors to these disparities such as food insecurity[33] or access to health care. IDA in pregnancy can persist into the postpartum period, with an estimated prevalence of 4 percent.[34] One study and one NHANES analysis found correlations between higher body mass index and decreased iron levels in pregnant persons.[35,36] Additional information on disparities is provided in Contextual Questions 1 and 2.

Risk Factors

The most commonly cited risk factors for IDA or ID in pregnancy include eating a diet low in iron-rich foods (e.g., vegan or vegetarian diet), having gastrointestinal issues that affect absorption, or having a short inter-pregnancy interval.[37] Tobacco use and living at high altitude may cause an increase in hematocrit and hemoglobin levels and impact interpretation of test results.[6]

Rationale for Screening/Screening Strategies

Screening asymptomatic pregnant persons for IDA may lead to earlier identification and therefore earlier treatment, which has the potential to prevent serious negative health outcomes. Strategies for screening can include either routine screening or targeted screening based on established risk factors, risk-assessment instruments, or diagnostic tests. Routine screening during pregnancy may occur when individuals first present for prenatal care and can occur during pregnancy depending on local practices.

In most clinical settings, the simplest and most cost-effective measurement of IDA is a complete blood count (CBC), which includes measurements of hemoglobin, hematocrit, mean corpuscular volume, and red blood cell distribution width (a measure of variability in red cell size); however, some data suggest the limited sensitivity of a CBC for IDA in pregnant populations.[38] Anemia alone (hemoglobin level <11.0 g/dL) is not an ideal screening parameter for IDA since it may not be the best indicator of iron levels and therefore other laboratory parameters such as total iron binding capacity (TIBC) or transferrin saturation may be measured.

Serum ferritin may be useful in screening for ID with or without anemia in pregnant persons,[39] however there is variation in thresholds used to define ID during pregnancy.[40] In one study of pregnant persons[9] serum ferritin was found to be a reliable indicator of reduced iron stores, with a sensitivity of 90 percent and specificity of 85 percent when used as a screening tool for ID. Ferritin is an acute phase reactant in the presence of adequate iron stores and can be elevated during inflammatory states, including liver disease, infection, and malignancy.[41] Changes in inflammatory measures have also been reported during pregnancy.[42] Serum ferritin may be of limited usefulness when concentrations decrease during late pregnancy, despite the presence of bone marrow iron.[40]

Interventions: Preventive Supplementation and Treatment

Preventive Supplementation

Primary prevention of ID during pregnancy consists of adequate dietary iron intake and routine iron supplementation.[43] This may include starting an oral low-dose (e.g., 30 mg/day) iron supplement at the beginning of pregnancy or integrating iron-rich foods and foods that enhance iron absorption. Prophylaxis for IDA in higher-risk populations may be accomplished with higher supplemental doses (e.g., 60 to 100 mg elemental iron per day).

Treatment

Treatment of ID in pregnancy is the same as that in nonpregnant, postpartum, premenopausal, and postmenopausal persons and begins with increased dietary intake of iron and oral iron supplementation. Pregnant persons with IDA are generally treated with additional oral iron supplements in combination with prenatal vitamins and dietary counseling. The dosage of elemental iron required to treat IDA in adults is 120 mg per day for 3 months. Therapy is continued for 3 months after the anemia is corrected to allow iron stores to become replenished. There are no standard recommendations for followup after initiating therapy for IDA; however, one suggested course is to perform a CBC every 3 months for 1 year.[44,45]

Iron is available orally as ferrous fumarate, ferrous sulfate, or ferrous gluconate and have higher bioavailability than ferrous citrate or sulfate.[46] Each iron salt provides different amounts of elemental iron (e.g., ferrous sulfate has 20% elemental iron per mg while ferrous fumarate has 33%). Variable formulations and dosing may affect the efficacy and tolerability profile of the product.

Adverse events are typically limited to gastrointestinal tract symptoms that limit the ability or willingness of patients to adhere to the regimen. It is estimated that 10 to 25 percent of patients

may report nausea, constipation, epigastric distress, and/or vomiting while taking oral iron, with symptom etiology considered directly related to the dose of elemental iron.[47] The absorption of iron is inhibited by some food including tea, foods high in calcium, and antacids, and is enhanced by a more acidic environment.[48] Therefore, experts usually recommend avoiding dosing with meals or within 2 hours of taking antacids and taking the dose with citrus fruits or ascorbic acid to maximize absorption. However, for patients who experience gastrointestinal adverse effects that affect adherence to the regimen, slowly increasing the dose over several days, reducing the amount of elemental iron taken per dose or daily, or taking the iron with food may improve symptoms. Urine and stool may be darker in color when taking iron, and liquid formulations can cause temporary gray staining of the teeth and gums. Iron can cause important interactions with several drugs.[49,50]

Indications for the use of parenteral iron are the same for pregnant persons as for nonpregnant persons, and has become more common for managing ID despite some concerns about adverse effects,[51-53] including allergic reactions and cost. Intravenous iron is generally used to replenish iron stores in selected patients who have not tolerated a trial of oral iron therapy, if oral iron does not effectively increase hemoglobin or ferritin levels,[8] or for those with severe ID.[54] Notably, there is no safety data for intravenous iron during the first trimester, but is considered safe and effective during the second and third trimesters.[55]

Current Clinical Practice

Rates of screening for IDA and iron supplementation in pregnant persons by clinicians are not well documented and may vary by clinical specialty or society practice standards. Screening may occur as part of routine prenatal care or to screen for anemia in pregnant persons to prepare for cesarean delivery or anticipated blood loss during a complicated delivery. Based on 1996 to 2006 NHANES epidemiological data (n=1,296), 77 percent of pregnant persons reported using a supplement within the previous 30 days and they most frequently used a multivitamin containing 48 mg of iron.[56] A summary of current screening and supplementation practices in U.S. populations is included in the Contextual Questions.

Recommendations of Other Groups

Recommendations of other groups are summarized in **Table 1**.

Screening

The American College of Obstetricians and Gynecologists (ACOG),[14] the U.S. Department of Veterans Affairs/Department of Defense (VA/DoD),[57] the CDC,[6] and the American Academy of Family Physicians (AAFP)[44] recommend that all pregnant persons be screened for anemia at some point during pregnancy. The VA/DoD recommends screening during the first prenatal visit. The National Academy of Medicine (NAM)[13] recommends screening for anemia in high-risk pregnant persons during each trimester and at 4 to 6 weeks postpartum. The Canadian Task Force on Preventive Health Care does not have a current recommendation for this topic.

Preventive Supplementation

While the CDC[6] and the WHO[58] recommend universal iron supplementation in pregnant persons, the VA/DoD states that there is insufficient evidence to recommend for or against universal supplementation.[57] The NAM,[13] ACOG,[14] and AAFP[44] recommend screening and treatment as necessary in lieu of routine supplementation. The Canadian Task Force on Preventive Health Care does not have a current recommendation for this topic.

Chapter 2. Methods

Key Questions and Analytic Frameworks

Using the methods developed by the USPSTF,[59] the USPSTF and the Agency for Healthcare Research and Quality (AHRQ) determined the scope and Key Questions for this update to the 2015 review.[3,4] Investigators created an analytic framework with the Key Questions and the patient populations, interventions, and outcomes for both routine preventive iron supplementation (**Figure 1**) and screening (**Figure 2**).

Key Questions for Routine Iron Supplementation During Pregnancy

Key Question 1. What are the benefits of routine iron supplementation during pregnancy on maternal and infant health outcomes?

Key Question 2. What are the harms of routine iron supplementation during pregnancy?

Key Question 3. In pregnant persons with iron deficiency, with or without anemia, what is the association between change in maternal iron status (including changes in ferritin or hemoglobin level) and improvement in newborn and peripartum outcomes in U.S.-relevant populations?

Key Questions for Screening for Iron Deficiency and Iron Deficiency Anemia During Pregnancy

Key Question 1. What are the benefits of screening for iron deficiency and iron deficiency anemia in asymptomatic pregnant persons on maternal and infant health outcomes?

Key Question 2. What are the harms of screening for iron deficiency and iron deficiency anemia in pregnant persons?

Key Question 3. What are the benefits of treatment of iron deficiency and iron deficiency anemia during pregnancy on maternal and infant health outcomes?

Key Question 4. What are the harms of iron treatment in pregnant persons?

Key Question 5. In pregnant persons with iron deficiency, with or without anemia, what is the association between change in maternal iron status (including changes in ferritin or hemoglobin level) and improvement in newborn and peripartum outcomes in U.S.-relevant populations?

Contextual Questions

In addition, three Contextual Questions were requested by the USPSTF to help inform the report. Contextual Questions are not reviewed using systematic review methodology.

Contextual Question 1. What are the current practices in identifying pregnant persons with ID and IDA? Do current practices of identification differ by race/ethnicity, diagnostic criteria, age,

socioeconomic status, cultural factors, educational attainment, insurance status, or health literacy?

Contextual Question 2. What are current practices for the use of iron supplementation during pregnancy? Do current practices differ by race/ethnicity, age, diagnostic criteria, socioeconomic status, cultural factors, educational attainment, insurance status, or health literacy of the pregnant person?

Contextual Question 3. How well do risk-assessment tools identify pregnant persons at increased risk for IDA?

Search Strategies

This report updates the previous report for the USPSTF,[3,4] which had searches through August 19, 2014. We searched Ovid MEDLINE®, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials from June 1, 2014 to May 24, 2023 for IDA; in addition, to cover the expanded scope of ID without anemia, additional searches began at database inception. Search strategies are available in **Appendix A1**. We also reviewed reference lists of relevant articles. Ongoing surveillance was conducted to identify major studies published since May 24, 2023 that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on November 24, 2023 and identified no studies affecting review conclusions.

Study Selection

All titles, abstracts, and studies identified through searches were independently reviewed by two members of the research team for eligibility against pre-defined inclusion/exclusion criteria organized by population, intervention, comparator, outcome, timing, study design (PICOTS) for both supplementation and screening frameworks (Appendix A2). Each full-text article was independently reviewed by two members of the research team for inclusion or exclusion on the basis of the eligibility criteria. Disagreements were resolved by discussion and consensus. All results were reviewed and tracked using DistillerSR and EndNote (Thomson Reuters, New York, NY). We excluded non-English–language articles and studies published only as conference abstracts. In accordance with the USPSTF Procedure Manual,[59] studies assessed as poor quality were excluded. The selection of literature is summarized in the literature flow diagram (Appendix A3). Appendix A4 lists included studies, and Appendix A5 lists excluded studies with reasons for exclusion.

Scope of Review

The population of interest was asymptomatic, pregnant adolescent and adults. We used nongendered terms (e.g., person, individual) to increase inclusivity, except where the data were specified as women or females for the purpose of accuracy. Among the nongendered terms, we used the term *pregnant person* to characterize the study population that includes pregnant women and other individuals capable of pregnancy, and acknowledge the current linguistic complexity and importance of centering inclusion.

Similar to the 2015 review,[3,4] this review addresses evidence using two distinct frameworks on the effectiveness of routine preventive iron supplementation during pregnancy, and separately, the effectiveness of screening for ID and IDA during pregnancy. For this update, the population was expanded to include populations with ID in addition to those with IDA. For the supplementation framework, the treated population includes those not known to have ID or IDA. For screening, the treated population is screen detected persons found to have ID or IDA. Studies of nonpregnant persons and patients with known nutritional deficiencies or symptoms of IDA were excluded.

For the supplementation framework, studies required a comparison between oral iron supplementation or iron-fortified foods and placebo or no supplementation. Specific timing for initiation of iron supplementation was not always clearly reported in the studies, therefore mean baseline gestational age at enrollment and/or gestational age specified in the eligibility criteria were sometimes used for estimating the timing of dose initiation. Due to the availability of good- and fair-quality randomized controlled trials (RCTs) of supplementation, observational studies were not included for the supplementation framework. Eligible maternal outcomes included clinical and health outcomes (e.g., mortality, health related quality of life, preeclampsia, postpartum hemorrhage, blood transfusion, postpartum depression, and cesarean delivery rates), as well as hematologic outcomes, including incidence of IDA or ID, and other hematologic indices and ferritin levels. Infant outcomes included clinical and health outcomes (e.g., perinatal mortality, respiratory distress, neonatal intensive care unit [NICU] admission, low birth weight, small for gestational age, and preterm delivery); infant hematologic indices and ferritin levels were also included. Adverse effects included clinical harms, harms leading to discontinuation, and accidental overdose. Timing of maternal outcomes were during pregnancy, at term, and post-partum; infant outcomes were limited to the first year of life.

An association question evaluating whether a change in iron status results in any changes in health outcomes was included in both the screening (Key Question 5) and supplementation (Key Question 3) frameworks. Studies eligible for this question were required to examine the association between a *change* in maternal ID or IDA as a result of treatment or supplementation and improved health outcomes.

For the screening framework, studies required a comparison between screening and no screening or treatment verses no treatment for pregnant adolescents or adults with screen-detected ID or IDA. Eligible interventions were routine blood tests (e.g., CBC) and oral or intravenous iron supplementation or iron-fortified foods. Eligible study designs for the screening framework included randomized controlled trials or controlled observational studies, and large uncontrolled observational studies on harms. The outcomes for the supplementation framework also apply to the screening framework, but also included harms more specific to screening such as overdiagnosis, anxiety, and labeling.

Studies from specialty settings and geographic areas in which the epidemiology and management of ID and IDA may differ substantially from U.S. primary/prenatal care settings were excluded. To inform generalizability to U.S. primary care settings, we categorized studies according to the country where it was conducted, utilizing the 2020 United Nations Human Development Index

(HDI) and limited inclusion to high or very high HDI.[60] Of note, China was reclassified from a medium to a high HDI rating in 2011.[61,62]

Two new contextual questions were added to examine issues of equity and health disparities related to current practices to identify persons with ID and IDA, and use of iron supplementation. One contextual question on the yield of repeat screening was not carried forward from the prior review, given the lack of evidence on effectiveness initial routine screening. Contextual questions were addressed through targeted literature searches to identify key articles to inform the USPSTF. For this update, language was revised to be more inclusive around sex and gender to consider all pregnant populations.

Data Abstraction and Quality Rating

For studies meeting inclusion criteria, we reviewed and updated data abstraction forms from the prior USPSTF review to summarize pertinent information from each study, including characteristics of study populations, interventions, comparators, outcomes, study designs, settings, and methods (Appendix B). One investigator conducted data abstraction, which was reviewed for completeness and accuracy by another team member. Abstractions from studies included in the prior report were reviewed for accuracy or updated.

Predefined criteria were used to assess the quality of individual controlled trials, systematic reviews, and observational studies by using criteria developed by the USPSTF[59] as appropriate (**Appendix A6**); studies were rated as "good," "fair," or "poor" per USPSTF criteria, depending on the seriousness of the methodological shortcomings. For each study, quality assessment was performed by two team members. Disagreements were resolved by consensus. Similar to the prior report, poor quality studies were excluded from the review due to the availability of good- and fair-quality studies.

Data Synthesis and Analysis

Meta-analyses were updated and new meta-analyses were conducted for outcomes and comparisons for which there were multiple studies comparable enough to provide a meaningful combined estimate. To determine whether meta-analysis could be meaningfully performed or updated, we considered the similarity between studies in design, patient population, interventions, outcomes, study quality, and setting, and relevance of the outcomes. We conducted meta-analyses to calculate risk ratios (RRs) and 95 percent confidence intervals (CIs) of the effects of routine iron supplementation on incidence of preterm delivery, low birth weight, small for gestational age, hypertensive disorders of pregnancy, cesarean delivery, IDA, ID, and anemia alone. The hematologic values were pooled separately at two time points, during the third trimester and at term. Postpartum time points varied widely and were less frequently reported so were not pooled. We did not pool isolated intermediate measures such as ferritin or hemoglobin because many studies also reported ID or IDA, which are more precise outcomes.

Due to anticipated statistical heterogeneity, meta-analyses to calculate RRs were conducted using the DerSimonian-Laird random effects models with Stata 14 software (StataCorp, Stata Statistical Software: Release 14, College Station, TX, 2015). Statistical heterogeneity was assessed using the I^2 statistic. Adjusted risk differences (ARDs) were calculated when RRs were

statistically significant. Stratified analyses were conducted to assess the sensitivity of results to variations across studies in characteristics including country HDI rating (defined as very high HDI versus medium/high HDI [medium noted due to China's change in rating]), and lower and higher supplementation dosing based on elemental iron doses (defined as ≥60 mg as high and <60 as low). We calculated p-values for the interaction of these characteristics and iron supplementation in effects on outcomes. Stratified analyses for ID, IDA, and anemia used the values reported at term. Due to inconsistent reporting of baseline anemia prevalence in the studies, we included baseline hemoglobin levels on forest plots. Stratified analyses are presented in **Table 2** and the **Appendix C Figures**.

Qualitative data was summarized in tables providing ranges, descriptive analysis, and interpretation of the results. Relative risks were calculated when not reported in studies and when available data was sufficient. Study applicability assessments were based on the country in which studies were performed (based on the HDI or other factors), patient demographic characteristics, iron supplementation or dosing regimens, and adherence.

For all Key Questions, the overall quality of evidence was determined using the approach described in the USPSTF Procedure Manual.[59] Evidence was rated "good," "fair," or "poor" based on the number, quality and size of studies, consistency of results between studies, and directness of evidence.[59] A summary of evidence table summarizes the overall quality of evidence for each Key Question.

USPSTF and AHRQ Involvement

The research team worked with USPSTF members to develop and refine the analytic frameworks, Key Questions, and scope for the final evidence synthesis. AHRQ staff provided oversight for the project, coordinated the systematic review, reviewed the draft report, and assisted in an external review of the draft evidence synthesis.

Expert Review and Public Comment

Key Informants provided input on the draft research plan to identify important target populations and inform the development of the scope and Key Questions. In addition, the draft research plan was posted on the USPSTF Web site for public comment from April 7, 2022, to May 4, 2022. In response to public comments, the USPSTF made minor edits to improve clarity, including revisions to the scope of the review to include ID in addition to IDA during pregnancy. The contextual questions were expanded to address disparities in the diagnosis and management of anemia and their effects on management decisions and health outcomes, in addition to addressing how practices for diagnosis or decisions for supplementation may differ in certain populations.

The draft report was reviewed by content experts and collaborative partners (**Appendix A7**). No additional studies for the Key Questions were suggested, and reviewers thought the studies included were appropriate. Reviewers recognized the limitations of the evidence base, including the variable dosing of iron supplements, duration of supplementation, and variability in baseline hemoglobin and ferritin levels. Some reviewers suggested additional references or minor

clarifications for the Introduction or Discussion sections that have been incorporated. The draft will also be posted for public comment and revised in response to comments before finalization.

Chapter 3. Results

A total of 5,788 new references from electronic database searches, manual searches of recently published studies, and prior report references were reviewed, and 376 full-text papers were evaluated for inclusion. We included 18 studies (reported in 28 publications[63-90]), including 17 RCTs and 1 observational study of association[67] for the supplementation framework. The same association study applied to Key Question 5 in the screening framework, but otherwise no studies evaluated the effectiveness of screening for ID or IDA. Twelve RCTs[63,64,66,68,69,74,76,77,81,83,88,89] were carried forward from the prior USPSTF report[4] addressing the supplementation framework; no association studies were included in the prior report. Five RCTs[70,72,80,85,86] and the association study[67] were newly added for this update. One of the supplementation trials only reported harms[70] and therefore was not included in Key Question 1. Included studies and quality ratings are described in **Appendix B**.

Routine Iron Supplementation During Pregnancy

Key Question 1. What Are the Benefits of Routine Iron Supplementation During Pregnancy on Maternal and Infant Health Outcomes?

Summary

Maternal Outcomes

- Routine iron supplementation during pregnancy was associated with a decreased risk of **maternal IDA** during the third trimester (3 trials; 9.1% vs. 13.8%; RR, 0.63 [95% CI, 0.41 to 0.97]; I^2 =0%; ARD, -3.9% [95% CI, -7.7% to 0.02%]) and at term (4 trials, 8.6% vs. 19.8%, RR, 0.40 [95% CI, 0.26 to 0.61]; I^2=20.5%; ARD, -9.59% [95% CI, -16.2% to -2.98%]), **maternal ID** during the third trimester (4 trials; 40.3% vs. 57.1%; RR, 0.70 [95% CI 0.53 to 0.92]; I^2=77.4%; ARD, -16.95% [95% CI, -24.13% to -9.8%]) and at term (6 trials, 46% vs. 70%; RR, 0.47; [95% CI, 0.33 to 0.67]; I^2=81.9%; ARD, -34.25% [95% CI, -46.49% to -22.01%]), and **anemia** during the third trimester (7 trials; 18.1% vs. 26.0%; RR, 0.71 [95% CI, 0.51 to 0.97]; I^2=64.2%; ARD, -7.97% [95% CI, -15.28% to -0.66%]), and at term (4 trials; 10.9% vs. 22.5%; RR, 0.43 [95% CI, 0.26 to 0.72]; I^2=43.7%; ARD, -11.73% [95% CI, -14.87% to -8.60%] compared with placebo or no iron supplements. There were no significant differences in estimates at term based on subgroup analyses by country or iron dose.
- There was no difference in the effect of routine iron supplementation and the risk of **hypertensive disorders of pregnancy** compared with placebo (5 trials; 4.7% vs.3.1% [pooled, weighted rates]; RR, 1.24 [95% CI, 0.75 to 2.06]; I^2= 48.0%)
- There was no difference in the effect of routine iron supplementation versus placebo on the risk of **cesarean delivery** (8 trials; 42.8% vs. 41.5%; RR, 1.01 [95% CI, 0.90 to

1.14]; I^2=42.7%); indications for cesarean delivery were not reported and estimates were imprecise.
- There were no differences between routine iron supplementation during pregnancy versus placebo in **quality of life** (1 trial), risk of gestational diabetes mellitus (2 trials), or risk of maternal hemorrhage (2 trials).

Infant Outcomes

- There were no differences between iron supplementation during pregnancy versus placebo in risk of **preterm birth** (5 trials; 5.5% vs. 6.0%; RR, 0.92 [95% CI, 0.81 to 1.04]; I^2= 0.0%), infants with **low birth weight** (6 trials; 2.7% vs. 2.9%; RR, 0.95 [95% CI, 0.79 to 1.14]; I^2= 0.0%), or infants **small for gestational age** (4 trials; 15.3% vs. 15.2%; RR, 0.94 [95% CI, 0.67 to 1.31]; I^2=75.5%).
- There were no differences between iron supplementation during pregnancy versus placebo in postpartum infant **hematologic indices** at 6 months or 1 year follow up (2 trials).

Evidence

Sixteen trials (in 26 publications) compared the effects of routine preventive iron supplementation versus no supplementation during pregnancy. Twelve trials (in 14 publications)[63,64,66,68,69,74,76-78,81,83,87-89] were carried forward from the prior review[4] (**Appendix B Table 1**). Four additional trials[65,71-73,75,80,82,84-86] and two new secondary publications[79,90] of older trials[74,77] were identified for this update. Some of the added studies for this update were published prior to the 2015 USPSTF review, but were identified during the expanded search because inclusion criteria were less restrictive regarding setting. Three studies were conducted in the United States,[66,76,83] three studies in China (rural),[72,85,86] four studies in Iran,[69,80,88,89] and the others were conducted in Hong Kong,[64] Australia,[74] or Europe.[63,68,77,81] Sample sizes of randomized study participants ranged from 52 to 12,513 participants, although only four studies had >1,000 participants. The three newly included studies conducted in rural China had the largest samples sizes (n=12,513,[72] 3,929,[85] and 2,371[86]). Most studies included pregnant persons at average risk for anemia and excluded pregnant persons with very low hematologic indices at baseline (below 8 to 11 g/dL), preexisting anemia, or related chronic conditions.[63,64,66,68,72,74,76,80,83,86,88,89] Baseline hemoglobin levels ranged from 11.9 to 14.3 g/dL. Several studies reported providing treatment beyond supplementation if hematologic indices dropped too low during the course of the study.[64,68,74,76,80,88,89] The majority of studies enrolled pregnant persons in their 20s, although two studies also included adolescents.[76,83] One Australian study[74] reported 95 percent participants identified as White race and ethnicity; one U.S. study from Ohio reported 56 to 57 percent White, 24 to 25 percent Black, and 16 to 17 percent Hispanic race and ethnicity,[66] and another U.S. study from North Carolina reported 31 to 37 percent White and 58 to 65 percent Black race and ethnicity.[83] These two studies were limited to those eligible for or participating in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) services. Race and ethnicity and socioeconomic statuswere not reported in the third U.S.-based study that was set in private group practice in Wisconsin.[76] In other studies, participants largely represented the country of origin or race and ethnicity was not reported. No studies stratified results according to population characteristics.

The timing of supplementation varied from the first prenatal visit up to 20 weeks gestation and continued until delivery; mean gestational age at enrollment ranged from 11 to 16 weeks, but was not always reported. In two of the U.S. studies, all participants in the placebo group were reassigned to supplementation at 26 to 29 weeks gestation. As such, we only analyzed results relevant to that time period.[66,83] Outcomes were measured during the third trimester, at delivery, or included followup into the postpartum period (1 day to 6 months postpartum); one study included health-related quality of life followup up to 4 years.[90] Supplement dosing ranged from 20 to 200 mg of elemental iron daily. Intervention groups in the majority of studies received 30 to 60 mg of elemental iron daily; and two smaller studies used higher doses of either 120 mg[63] or 200 mg.[81] Non-adherence, usually based on pill counts or a similar measure, ranged from 4.5 to 68 percent and were mostly similar between groups in the 10 studies reporting adherence;[64,66,68,72,74,76,81,83,85,86] however, adherence data was not available for all included participants.

Twelve studies were rated fair quality[63,64,66,68,69,76,77,80,81,83,85,86] and four studies were rated good quality[72,74,88,89] (**Appendix B Table 2**). Methodologic limitations of fair-quality studies included unclear randomization and allocation concealment methods; unclear masking of outcome assessors; high or unclear loss to followup or differential loss to followup; and inadequate randomization methods. As described in the methods, poor-quality studies were excluded from the review.

Maternal Clinical Outcomes

Quality of Life

One good-quality trial conducted in Australia (n=430) included in the prior report reported no differences in a standardized, clinical quality of life measurement, the Short-Form 36 (SF-36).[74,90] Scores were measured at 36 weeks of gestation, 6 weeks postpartum, 6 months and 4 years postpartum, and compared those taking 20 mg iron supplementation starting at 20 weeks gestation versus placebo on the form's eight health concepts of physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and general mental health (**Table 3**).

Hypertensive Disorders of Pregnancy

Five (three fair- and two good-quality) trials (N=14,468) reported an inconsistent effect of iron supplementation on risk of hypertensive disorders of pregnancy (**Table 3**).[63,69,72,80,89] Three were included in the prior report. Studies were conducted in high and very high HDI countries with supplemental dosing from 30 mg to 120 mg elemental iron initiated at 13 to 20 weeks gestation. Hypertensive disorders were described as pregnancy induced hypertension in three studies[69,72,80] and were poorly defined in two studies.[63,89] Iron supplementation was not associated with a statistically significant change in the risk of hypertensive disorders compared with placebo (5 studies; 4.7% vs. 3.1% [pooled, weighted rates]; RR, 1.24 [95% CI, 0.75 to 2.06]; I^2= 48%; **Figure 3**[63,69,72,80,89]), and the estimate was imprecise. While some statistical heterogeneity was present, no individual study reported a statistically significant effect. Stratified analysis by HDI country and dose resulted in similar findings (**Appendix C Figures 1 and 2; Table 2**). In the

trial that reported preeclampsia, there was also no difference between supplementation versus placebo on this outcome (3.9% vs. 2.7%; RR, 1.45 [95% CI, 0.67 to 3.16]).

Gestational Diabetes

Two fair-quality trials (N=2,124) reported no differences between iron supplementation versus placebo in risk of gestational diabetes (**Table 3**).[64,80] One trial from Hong Kong, also included in the prior report (n=1,164), found no difference in risk of gestational diabetes between 60 mg iron supplementation beginning at less than 16 weeks versus placebo (based on oral glucose tolerance tests at 28 and 36 weeks) (9.9% vs. 10%; odds ratio [OR], 1.04 [95% CI, 0.7 to 1.53]).[64] A second trial[80] conducted in Iran (n=960) was newly added and also reported no differences between in risk of gestational diabetes for 30 mg iron supplementation beginning in the first trimester versus placebo (criteria not reported; 0.5% vs. 0.8%, RR, 0.61 [95% CI 0.10 to 3.60]).

Cesarean Delivery

Cesarean delivery was reported in eight trials (five fair- and three good-quality; N=6,160, **Table 3**)[63,64,74,76,80,86,88,89] comparing groups of pregnant persons receiving 20 mg to 120 mg iron supplementation beginning in the first or second trimester versus no supplementation. Iron supplementation was not associated with a statistically significant difference versus placebo in risk of cesarean delivery (8 studies; 42.8% vs. 41.5%; RR, 1.01 [95% CI, 0.90 to 1.14]; I^2=42.7%, **Figure 4**). Stratified analysis by HDI country and dose resulted in similar findings (**Appendix C Figures 3 and 4; Table 2**). Clinical indications for cesarean were not reported in any study. Five studies were included in the prior review. One large, (n=1,164) fair-quality trial conducted in Hong Kong found a statistically significant reduction in the rate of cesarean delivery for pregnant persons receiving 60 mg elemental iron daily versus placebo (25.2% vs. 33.1%; OR, 0.58 [95% CI, 0.37 to 0.89]).[64] However, seven trials conducted in Australia (n=430), the United States (n=144), Ireland (n=97), Iran (n=727; n=782; n=244), and rural China (n=2,371) demonstrated no effect on cesarean rates for pregnant persons receiving 20 to 60 mg elemental iron supplementation versus placebo.[63,74,76,80,86,88,89] Two studies from Iran and rural China had unusually high rates of cesarean delivery in the supplementation versus placebo groups, respectively (51.2% vs. 45.8%[80] and 70.1% vs. 66.0%[86]), but the differences between groups were not statistically significant.

Hemorrhage

Two studies (N=341), both in the prior report, reported no difference in rates of maternal hemorrhage, though rates of this outcome were low (**Table 3**).[63,88] A fair-quality study from Ireland (n=97) comparing 120 mg supplemental iron to placebo starting at the end of the first trimester reported no differences in antepartum hemorrhage (5.7% vs. 4.5%; RR, 1.25 [95% CI, 0.22 to 7.12]).[63] A good-quality study from Iran (n=244) comparing 50 mg elemental iron to placebo starting at 20 weeks gestation also reported no differences in risk of postpartum hemorrhage (1.8% vs. 1.7%; RR, 1.05 [95% CI, 0.15 to 7.35].[88]

Maternal Hematologic Outcomes

Sixteen good- or fair-quality trials reported maternal intermediate outcomes including hematologic parameters or incidence of ID or IDA (**Tables 4–6**).[63-66,68,69,71-89]

Iron Deficiency Anemia

Seven trials (N=4,045) reported incidence of IDA, defined as hemoglobin <11.0 g/dL and serum ferritin of <12 or <20 µg/L. The proportion of patients with IDA during the third trimester (**Table 4**), at delivery (**Table 5**), or postpartum (**Table 6**)[66,69,74,76,78,83,86] ranged from 0 to 12.7 percent in groups receiving supplementation and from 0 to 29 percent in groups receiving placebo.

Third Trimester

Three trials, also included in the prior report, found daily iron supplementation associated with reduced risk of IDA during the third trimester compared with placebo (3 trials; 9.1% vs. 13.8%; RR, 0.63; [95% CI, 0.41 to 0.97]; I^2 =0%; ARD, -3.86% [95% CI, -7.74% to 0.02%])[66,69,83] (**Figure 5**). Doses ranged from 30 to 60 mg elemental iron daily starting at <20 weeks gestation.

Term

Four trials found daily iron supplementation associated with reduced risk of IDA at term compared with placebo (4 trials; 8.6% vs. 19.8%; RR, 0.40 [95% CI, 0.26 to 0.61]; I^2 =20.5%; ARD, -9.59% [95% CI, -16.20% to -2.98%], **Figure 5**).[74,76,78,86] Stratified analysis by HDI country and dose resulted in similar findings (**Appendix C Figures 5 and 6; Table 2**). Three trials were included in the prior report. Doses ranged from 20 to 66 mg elemental iron starting in between 12 to 20 weeks gestation. The study from Iran was not included in the pooled analysis due to no events reported for this outcome in either group.

Postpartum

One good-quality study from Australia, also included in the prior report (n=383), found no difference in rates of IDA at 6 months postpartum for 20 mg iron supplementation started during the second trimester versus placebo (2.6% vs. 1.7%; RR, 1.55 [95% CI, 0.38 to 6.40]).[74]

Iron Deficiency

Nine trials (N=16,556) reported incidence of ID, defined as serum ferritin <12 to <20 µg/L (**Tables 4–6**).[66,68,69,72,74,77,81,83,86] Seven studies were included in the prior report. Dosing ranged from 20 to 200 mg elemental iron starting in the first or second trimester. Rates of ID varied widely across studies: overall ranges were 0 to 57 percent for those in the supplementation group and 24 to 85 percent in the placebo group.

Third Trimester

Four trials (three fair-quality, one good-quality) found 30 to 60 mg iron supplementation started in the first trimester associated with decreased risk of ID in the third trimester versus placebo (4 trials; 40.3% vs. 57.1%; RR, 0.70 [95% CI, 0.53 to 0.92]; I^2 =77.4%; ARD, -16.95% [95% CI, -24.13% to -9.77%], **Figure 6**).[66,69,72,83] Statistical heterogeneity was high for the pooled estimate, but the direction of effect was consistent across studies. Estimates in all studies favored iron supplementation and were statistically significant in three studies, with heterogeneity only in the magnitude of benefit for the pooled estimate. Three studies were included in the prior review, two of which were U.S. trials that included pregnant persons at higher risk for ID based on both study populations representing WIC participants.

Term

Six trials (five fair- and one good-quality; N=3,339) reported ID at term associated with 20 to 200 mg iron supplementation started in the first or second trimester, versus placebo. Five studies were included in the prior report. Iron supplementation was associated with a reduced risk of ID versus placebo (6 trials; RR, 0.47 [95% CI 0.33 to 0.67]; I^2=81.9%; ARD -34.25% [95% CI -46.49% to -22.01%], **Figure 6**).[68,69,74,77,81,86] Statistical heterogeneity was also high, but the direction of effect was consistent. Each study showed a statistically significant reduction in risk associated with iron supplementation (RR 0.03 to 0.74); sample size and precision varied widely (range N=52 to 2,371). Stratified analysis by HDI country (**Appendix C Figure 7**) and dose (**Appendix C Figure 8**) resulted in similar findings, with one exception; there were no differences in stratified analyses for the effects of supplementation versus placebo in medium to high HDI countries (RR, 0.57 [95% CI, 0.29 to 1.13]; I^2=69.5% (**Table 2**).

Postpartum

Two trials also included in the prior report evaluated risk of postpartum ID.[68,74] One trial from Australia reported 20 mg iron supplementation starting in the second trimester was associated with lower risk of ID at 6 months postpartum versus placebo (16% vs. 29%; RR, 0.57, [95% CI, 0.38 to 0.84]).[74] A trial from Norway comparing 27 mg iron to placebo starting at 20 weeks gestation found significantly lower rates of ID for supplemented pregnant persons at both 6 to 10 weeks postpartum (18% vs. 52%; RR, 0.34 [95% CI, 0.17 to 0.69] and 24 weeks postpartum (10% vs. 51%; RR, 0.20 [95% CI, 0.08 to 0.50]).[68]

Anemia

Nine trials (N=20,330) reported incidence of anemia, defined as hemoglobin less than 10.0 or 11.0 g/dL in the third trimester and at term, and as hemoglobin less than 12.0 or 12.1 g/dL for postpartum anemia 4 weeks to 6 months (two postpartum studies with timing of 1 day to 1 week, defined anemia as less than 10.0 or 11.0 g/dL).[66,68,72,74,77,81,83,85,86] (**Tables 4–6**). Six studies were included in the prior report.[66,68,74,77,81,83] Supplement dosing ranged from 30 to 200 mg, started during the first or second trimester. The proportion of participants with anemia ranged from zero to 45 percent for those randomized to supplementation and from 4.5 to 61 percent for placebo.

Third Trimester

Seven trials (N=18,266) reported inconsistent results for effects of iron supplementation during pregnancy and risk of anemia during the third trimester.[66,72,74,77,81,83,85] Five were included in the prior report.[66,74,77,81,83] Doses ranged from 20 to 200 mg elemental iron starting in the first or second trimester. Iron supplementation was associated with a statistically significant decreased risk of anemia versus placebo (7 studies; 18.1% vs. 26.0%; RR, 0.71 [95% CI, 0.51 to 0.97]; I^2=64.2%; ARD, -7.97% [95% CI, -15.28% to -0.66%]; **Figure 7**); statistical heterogeneity was high. Two fair-quality trials (n=275 and 867) conducted in U.S. pregnant persons at higher risk for ID found no statistically significant difference in risk of anemia between iron supplementation versus no iron.[66,83]

Term

Four trials (one good- and three fair-quality; N=3,101) found 20 to 200 mg iron supplementation beginning in the first or second trimester associated with lower risk of anemia at term versus no iron[74,77,81,86] (4 trials; 10.9% vs. 22.5%; RR, 0.43 [95% CI, 0.26 to 0.72]; I^2=43.7%; ARD, -11.73% [95% CI, -14.87% to -8.60%]).[74,77,81,86] Stratified analysis by HDI country (**Appendix C Figure 9**) and dose (**Appendix C Figure 10**) resulted in similar findings.

Postpartum

Five trials (two good- and three fair-quality) reported somewhat inconsistent effects of iron supplementation during pregnancy on postpartum anemia, though results favored supplementation in all trials except for one.[68,72,74,78,86] Due to variability in the timing of when anemia was measured, rates of postpartum anemia were not pooled; however, results did not vary according to when anemia was assessed. A good-quality trial from Australia (n=430) found no difference between 20 mg elemental iron supplementation starting in the second trimester versus placebo in risk of anemia at 6 months postpartum, though the estimate was imprecise and favored supplementation (3.7% vs. 4.5%; RR, 0.82, 95% CI, 0.30 to 2.21).[74] However, a good-quality trial from China (n=12,513) found supplementation and placebo associated with similar risk of anemia at 4 to 6 weeks postpartum (26.8% vs. 27.2%; OR, 0.98, [95% CI, 0.93 to 1.05]).[72] Three fair-quality trials (N=2,709)[68,77,86] reported results that favored supplementation, though only one trial from China reported a statistically significant difference in rates of anemia measured one day postpartum (RR, 0.71 [95% CI, 0.66 to 0.78], rates not reported).[86]

Hemoglobin

Fifteen trials (four good- and 11 fair-quality; N=20,069) of iron supplementation during pregnancy versus placebo (or another supplement with versus without iron), reported hemoglobin levels at either the third trimester, delivery, or up to 6 months postpartum.[63,64,66,69,72,74,76,78,80,81,83,85,86,88,89] Across trials, hemoglobin levels ranged from 11.0 to 13.9 g/dL for those randomized to iron supplementation and from 10.5 to 13.4 g/dL for those randomized to control (**Tables 4–6**).

Third Trimester

Three trials (two good quality and one fair quality, N=1,277) conducted in Australia, Iran, and Ireland found iron supplementation (20, 50, or 120 mg elemental iron daily) associated with higher third trimester hemoglobin levels versus placebo.[63,74,89] Differences in hemoglobin levels ranged from 0.4 to 1.2 g/dL; in one of the trials,[63] the difference was not statistically significant when adjusted for smoking (p=0.25). Two trials from China (one good quality [n=12,513][72,75] and one fair quality [n=3,929][85]) reported no differences in hemoglobin level between iron and folate supplementation versus folate alone. The good-quality trial from China reported a very small (<0.1 g/dL) but statistically significant increase in hemoglobin at 24 to 28 weeks associated with supplemental iron (n=11,809; MD, 0.04 g/dL [95% CI, 0.01 to 0.07]), but no difference at 28 to 32 weeks in a subset of patients (n=562; 12.44 vs. 12.45 g/dL; p>0.05; venous blood). The fair-quality study found the addition of iron supplementation associated with higher hemoglobin at 28 to 32 weeks (11.01 vs. 10.53 g/dL; MD, 0.50 [95% CI, 0.20 to 0.80]). Two fair-quality trials of higher-risk pregnant persons both conducted in the United States (n=275 and 867) found no difference in hemoglobin levels between groups (11.7 g/dL with iron vs. 11.6 g/dL with placebo, p=0.499[66] and 11.4 vs. 11.4 g/dL, p=0.81 for prenatal supplements with vs. without iron[83]).

Term

Ten trials (N=5,858) reported hemoglobin levels at term.[63,64,69,74,76,77,80,81,86,88] The trials were conducted in Australia (one trial), Hong Kong (one trial), China (one trial), Iran (three trials), Europe (three trials), and the United States (one trial, n=144); sample sizes ranged from 45 to 2,371. Participants received 20 to 200 mg elemental iron daily beginning in the first or second trimester. Hemoglobin levels were higher with iron supplementation in all 10 trials, with differences ranging from 0.2 to 1.7 g/dL; differences were statistically significant in eight trials.[63,64,74,76,77,80,86,88]

Postpartum

Three trials (N=13,191) reported mixed results for the association between prenatal iron supplementation versus no iron and postpartum hemoglobin levels. A fair-quality trial from Denmark (n=248) found 66 mg elemental iron supplementation beginning during the second trimester associated with a small increase in hemoglobin level at 8 weeks post-partum versus placebo (13.4 vs. 12.9 g/dL, p<0.001).[77] However, two good-quality trials from China (n=11,544) and Australia (n=430) found no differences in postpartum hemoglobin levels with 20 to 30 mg supplemental iron versus no iron starting in the first or second trimester (12.38 vs. 12.36 g/dL; MD, 0.02 [95% CI, -0.01 to 0.05] at 4 to 6 weeks postpartum[72,82] and 13.5 vs. 13.4 g/dL; MD, 0.16 [95% CI, -0.01 to 0.33] at 6 months postpartum,[74] respectively).

Serum Ferritin

Thirteen trials (N=19,075) reported serum ferritin levels at either the third trimester, delivery, or up to 6 months postpartum (**Tables 4-6**).[63,64,66,69,72,74,76,78,80,81,83,86,88] Serum ferritin at these time points ranged from 7.4 to 34 µg/L in the supplementation group and from 6.0 to 26 µg/L in the placebo group.

Third Trimester

Four trials (N=13,752) reported inconsistent effects of iron supplementation on third trimester ferritin levels.[63,66,72,83] Two fair-quality trials (N=1,142) of pregnant persons at higher risk for ID conducted in the United States found no difference between 30 mg iron supplementation starting in the first trimester versus placebo measured by third trimester serum ferritin levels (7.4 vs. 7.4 µg/L; p=0.985[66] and 22.0 vs. 20.3 µg/L; p=0.48[83]). However, a fair-quality trial conducted in Ireland of 120 mg elemental iron daily and a good-quality trial conducted in China of 30 mg daily iron supplementation starting in the first trimester reported increased third trimester ferritin levels versus no iron (32.6 vs. 12.8 µg/L; p=0.04 and 16.7 vs. 11.3 µg/L; p<0.05).[72,75]

Term

Nine trials (two good- and seven fair-quality; N=5,761[64,69,74,76,77,80,81,86,88]) reported effects of iron supplementation versus no iron supplementation on ferritin levels at term. The trials were conducted in Hong Kong (one trial), Australia (one trial), Europe (two trials), the United States (one trial), Iran (three trials), and China (one trial), and found 20 to 200 mg elemental iron supplementation beginning in the first or second trimester associated with increased serum ferritin levels at delivery. The difference favoring iron supplementation ranged from 4.2 to 18 µg/L and was statistically significant in the eight trials that reported a statistical comparison.

Postpartum

A good-quality trial from Australia (n=430) found 20 mg elemental iron daily beginning in the second trimester associated with higher serum ferritin levels versus placebo at 6 months postpartum (34 vs. 26 µg/L; MD, 7.9 [95% CI, 3.5 to 12.3][74]).

Infant Clinical Outcomes

Eleven trials (three good quality [72,74,89] and eight fair quality[63,64,69,76,78,80,81,85]) reported infant birth outcomes including infant mortality, preterm delivery, small size for gestational age, and low birth weight (**Table 7**). Similar to the prior report, there were no differences between iron supplemented groups versus placebo for infant outcomes.

Infant Mortality

Six trials (three good- and three fair quality; N=17,863) evaluated effects of prenatal iron supplements on infant mortality with inconsistent results.[63,72,74,76,89] Five were included in the prior report. Prenatal iron supplement dosing ranged from 20 mg to 120 mg beginning in the first or second trimester. Infant mortality rates were not a prespecified outcome in any study and event rates were generally low. Four trials were of nonanemic pregnant persons; the fifth trial (conducted in rural China[85]) did not describe baseline hematologic indices. The largest (n=12,513), good quality trial from rural China[72] reported no difference between iron supplementation versus placebo in infant mortality during the first year of life (7.42 vs. 7.62 cases per 1,000; RR, 0.97 [95% CI, 0.64 to 1.48]). However, a post-hoc analysis from a smaller, fair-quality trial (n=3,929) conducted in rural China found iron supplementation associated with decreased risk of neonatal mortality among live born infants within 28 days of delivery versus

controls in a post-hoc analysis (1.1% vs. 2.0%; RR, 0.53 [95% CI, 0.29 to 0.97][85]). Another good-quality trial from Iran (n=750) reported no difference in perinatal mortality between the supplementation and placebo groups (0.8% vs. 1.7%; RR, 0.48 [95% CI, 0.12 to 1.91]), but estimates were imprecise and based on a total of 9 events.[89] Three other trials conducted in Australia (n=430), Ireland (n=97), and the United States (n=144) reported no or one infant death.[63,74,76]

Preterm Birth

Five trials (four fair quality and one good quality; N=18,714) conducted in Hong Kong, rural China, and Iran reported the association between supplemental iron versus placebo and risk of preterm birth, defined as delivery <37 weeks.[64,69,72,80,85] Two studies were included in the prior report.[59,64] Supplemental dosing ranged from 30 to 60 mg beginning in the first or second trimester. Prenatal iron supplementation was not associated with a reduced risk of preterm delivery versus placebo (5 trials; 5.5% vs. 6.0%; RR, 0.92 [95% CI, 0.81 to 1.04]; I^2=0%; **Figure 8**). Stratified analysis by HDI country and dose resulted in similar findings (**Appendix C Figures 11 and 12; Table 2**).

Small for Gestational Age

Four trials (three fair quality and one good quality; N=6,803) conducted in Hong Kong, rural China, and Iran reported inconsistent findings for effects of prenatal iron supplementation on risk of infants small for gestational age[64,85,89] or with intrauterine growth restriction.[80] Both outcomes were defined as <10th percentile of birth weight for gestational age. Iron supplementation dosing ranged from 30 to 60 mg of elemental iron and was initiated between 13 to 20 weeks. There was no association between iron supplementation and small for gestational age infants (15.3% vs. 15.2%; RR, 0.94 [95% CI, 0.67 to 1.31]; I^2=75.5%, **Figure 9**); statistical heterogeneity was high. One trial from Hong Kong found 60 mg iron supplementation versus placebo associated with decreased risk of having an SGA infant (3.6% vs. 7.5%, RR 0.48, [95% CI 0.26 to 0.87]);[64] the three trials from lower-HDI countries showed mixed results. Otherwise, stratified analysis by HDI country and dose resulted in similar findings (**Appendix C Figures 13 and 14; Table 2**).

Low Birth Weight

Six trials (3 fair quality and 3 good quality; N=17,261) conducted in the United States, Iran, Ireland, rural China, and Australia reported the association between iron supplementation and risk of having an infant born with low birth weight, primarily defined as <2500 g.[63,69,72,74,76,85] Iron supplementation dosing ranged from 20 to 120 mg and was initiated between 12 and 20 weeks of gestation. Iron supplementation was not associated with decreased risk of infant low birth weight versus placebo (6 trials; 2.7% vs. 2.9%; RR, 0.95; [95% CI, 0.79 to 1.14] I^2=0.0%; **Figure 10**). Stratified analysis by HDI country and dose resulted in similar findings (**Appendix C Figures 15 and 16; Table 2**).

Infant Hematologic Outcomes

Two good-quality trials[72,74] (N=12,943) reported postpartum infant hematologic outcomes. One trial conducted in rural China (n=12,513)[72] reported infant hemoglobin (mean range 12.17 to

12.22 g/dL) and anemia (5.0% to 6.9%) outcomes at 6 months and 1 year, and a smaller Australian-based trial (n=430)[74] reported infant hemoglobin (11.9 to 12.1 g/dL), ferritin (30.8 to 32.5 ug/L), iron deficiency (4% to 6%), and iron deficiency anemia (0%) outcomes at 6 months (**Appendix B Table 1**). No differences were found between groups at these time points for any of the indices.

Key Question 2. What Are the Harms of Routine Iron Supplementation During Pregnancy?

Summary

- No serious adverse events associated with iron supplementation were reported.
- 12 trials (11 included in KQ1) assessed harms of routine iron supplementation during pregnancy; five trials were newly added. Consistent with the prior review, none of the harms were serious or associated with long term clinical outcomes, and there were mostly no significant differences between groups. Most reported harms included transient gastrointestinal treatment effects such as nausea, constipation, and diarrhea and some studies reported non-adherence rates.
- One large study in rural China reported a statistically significant difference in gastrointestinal symptoms between the supplementation group and controls (RR, 1.59 [95% CI, 1.28 to 1.97]); the other two studies newly identified for this update reported no differences.
- No infant harms were reported in any trial.

Evidence

Eleven trials[64,66,68,72,74,76,80,81,83,85,86] included for Key Question 1 and one additional trial (n=179)[70] conducted in Iran (total N=22,716) addressed harms; five trials[70,72,80,85,86] were added for this update (**Table 8; Appendix B Tables 1 and 2**).

Serious Adverse Events

No trials reported any serious adverse events from iron supplementation.

Discontinuation Due to Adverse Events

While evidence was lacking on discontinuation of supplements due to adverse effects, adherence or non-adherence was reported and was used as a proxy measure for the harm of discontinuation. Ten studies reported rates of non-adherence. Non-adherence was lower with iron supplementation in adults compared with placebo, but did not reach statistical significance in adolescents compared to placebo in one small (n=111) U.S. trial (2.2% vs. 16.1%; p=0.036, and 4.5% vs. 12.6%; p=0.320, respectively[76]). Nine other trials found no difference in non-adherence to supplementation versus placebo,[64,66,68,72,74,81,83,85,86] with ranges from 2 to 68 percent; however most studies reported that adherence/non-adherence data was not available for all included participants.

Maternal Gastrointestinal Effects

Six trials[70,72,74,76,85,86] (N=19,566) reported the association between iron supplementation during pregnancy and risk gastrointestinal symptoms such as nausea, vomiting, constipation, or diarrhea. Iron supplementation doses ranged from 20 to 60 mg elemental iron. One large (n=12,513) trial conducted in rural China added for this update found 30 mg elemental iron supplementation beginning in the second trimester associated with increased risk of gastrointestinal symptoms versus placebo (3.6% vs. 2.3%; RR, 1.59 [95% CI, 1.28 to 1.97]).[72] However, consistent with findings from the two trials from Australia[74] and the United States[76] that were carried forward from the prior report, two newly identified studies from rural China[85,86] and one newly identified study from Iran[70] reported no statistically significant differences in rates of various, minor gastrointestinal adverse effects between supplementation and placebo groups.

Infant Harms

Infant harms were not reported in any study.

Key Question 3. In Pregnant Persons With Iron Deficiency, With or Without Anemia, What Is the Association Between Change in Maternal Iron Status (Including Changes in Ferritin or Hemoglobin Level) and Improvement in Newborn and Peripartum Outcomes in U.S.-Relevant Populations?

Summary

- No studies in the prior review compared the association in pregnant persons with ID with or without anemia and a change in maternal iron status and clinical outcomes.
- One observational study (n=20,690) conducted in the United States identified for this update found having a response to iron therapy associated with reduced risk of preeclampsia and preterm delivery compared with those with untreated anemia or not responding to treatment, but did not compare outcomes of responders versus specifically non-responders.

Evidence

The prior review did not include this question for the supplementation framework and did not identify any studies for the screening framework. One fair quality observational study conducted in the United States that was added for this update compared the association between response to iron supplementation in pregnant persons with ID (with or without anemia) and risk of preeclampsia and preterm delivery (**Appendix B Tables 3 and 4**).[67] Patients in a perinatal database were classified as anemic (n=7,416), based on a hemoglobin level less than 11 g/dL for a third trimester delivery or 10.5 g/dL in the second trimester, or a nonanemic reference group (n=13,274). Patients with anemia were further categorized by treatment group (treated or untreated anemic, n=3,402), and among those treated, response to treatment (refractory anemic,

n=1,319; or successfully treated n=2,695). Those who were considered successfully treated or who had a response to treatment were defined as those presenting to labor and delivery with normal hemoglobin who reported taking iron supplementation. The dosing, timing and duration of treatment or iron supplementation was not reported. Most participants were 18 to 35 years of age at delivery (76% to 82%), and Hispanic (43% to 63%) or African American (9% to 24%) race or ethnicity.

Successful response to treatment was associated with reduced risk of preterm birth (adjusted OR, 0.59 [95% CI, 0.47 to 0.72]) and preeclampsia (adjusted OR, 0.75 [95% CI, 0.6 to 0.91]) versus nonanemic persons. Refractory or untreated anemia was also associated with increased risk of preterm birth and preeclampsia (adjusted OR, 1.44 [95% CI, 1.16 to 1.76] and adjusted OR, 1.45 [95% CI, 1.26 to 1.67], respectively) versus no anemia. There were no differences between groups in composite neonatal morbidity. This study has very limited utility for assessing the association between response to iron therapy and improvement in health outcomes because it did not compare outcomes in responders versus non-responders (separate from untreated patients). In addition, the study classified participants using iron supplementation as anemic, which could have resulted in misclassification; lack of information on dose, timing, or duration of treatment; and lack of reporting on methods of outcome assessment.

Screening for Iron Deficiency and Iron Deficiency Anemia During Pregnancy

Key Question 1. What Are the Benefits of Screening for Iron Deficiency and Iron Deficiency Anemia in Asymptomatic Pregnant Persons on Maternal and Infant Health Outcomes?

No randomized trial or observational study compared clinical outcomes between pregnant persons screened and not screened for ID or IDA.

Key Question 2. What Are the Harms of Screening for Iron Deficiency and Iron Deficiency Anemia in Pregnant Persons?

No randomized trial or observational study compared harms between pregnant persons screened and not screened for ID or IDA.

Key Question 3. What Are the Benefits of Treatment of Iron Deficiency and Iron Deficiency Anemia During Pregnancy on Maternal and Infant Health Outcomes?

No randomized trial or observational study meeting inclusion criteria compared clinical outcomes between pregnant persons treated versus not treated for ID or IDA.

Key Question 4. What Are the Harms of Iron Treatment in Pregnant Persons?

No randomized good or fair quality trial or observational study meeting inclusion criteria compared harms of treatment for pregnant persons for ID or IDA.

Key Question 5. In Pregnant Persons With Iron Deficiency, With or Without Anemia, What Is the Association Between Change in Maternal Iron Status (Including Changes in Ferritin or Hemoglobin Level) and Improvement in Newborn and Peripartum Outcomes in U.S.-Relevant Populations?

See Key Question 3 in the Iron Supplementation framework.

Contextual Questions

Contextual Question 1. What Are the Current Practices in Identifying Pregnant Persons With Iron Deficiency and Iron Deficiency Anemia? Do Current Practices of Identification Differ by Race or Ethnicity, Diagnostic Criteria, Age, Socioeconomic Status, Cultural Factors, Educational Attainment, Insurance Status, or Health Literacy of the Pregnant Person?

A surveillance report from the CDC reported rates of anemia and testing among pregnant participants in WIC from 2008 to 2018.[91] Across 90 WIC agencies across the U.S, rates of anemia increased from 10.1 to 11.4 percent between 2008 and 2018. Among those tested, overall anemia prevalence (>20%) was higher among non-Hispanic Black persons compared with other racial or ethnic groups (7% to 12%) and among persons assessed during the third trimester versus the first or second trimester; for all three trimesters, rates of anemia were highest in Black persons. In 2018, 52.8 percent of all pregnant persons enrolled in WIC received hemoglobin testing during the first trimester of pregnancy, 36.8 percent during the second trimester, and 10.4 percent during the third trimester. Compared with national data, the prevalence of anemia was higher in WIC participants during this time period, although rates varied by state, race, and ethnicity.

A cross-sectional study from New Mexico[92] reviewed laboratory data from 2018 and 2019 to determine anemia prevalence in a pregnant population (n=985). CBC testing was completed in 91 percent of the sample population during the first trimester, and 53.6 percent during the third trimester; 52.8 percent had testing in both the first and second trimesters, 48.8 percent had testing in both the first and third trimester, and 22.7 percent had testing in all three trimesters. Of the 252 persons identified with anemia, 20.6 percent had iron studies ordered, and 79.4 percent did not. For those with an anemia workup, 0.3 percent had an iron panel, 11.5 percent had an iron lab alone, and 12.8 percent had a ferritin alone, whereas 3.8 percent had a reticulocyte panel, a complete blood count, and an iron study panel, suggesting generally low rates of full diagnostic testing for anemia.

A large, cross-sectional study from the United States (n=268,594)[93] examined racial and ethnic disparities in the use of selected prenatal services among Medicaid recipients in 4 states. Non-Hispanic Black participants represented 19 to 49 percent of pregnant Medicaid recipients; Hispanic persons accounted for 23 to 50 percent of participants in three states, though comprised only 2.6 percent in the fourth state (Georgia). In all states, less than 2 percent of participants identified as Asian/Pacific Islander. Compared with non-Hispanic White pregnant populations, those identifying as non-Hispanic Black, Hispanic, and Asian/Pacific Islander were significantly less likely (raw ORs 0.51 to 0.92) to receive a complete blood cell count in 3 of 4 states surveyed. However, in Georgia, non-Hispanic Black pregnant persons were 1.26 times (95% CI 1.20 to 1.32) more likely to receive a complete blood cell count than non-Hispanic White

pregnant persons.[94] Among pregnancies with a laboratory result for hemoglobin and hemocrit, 99.9 percent also had mean corpuscular volume measured on the same day.

A cross-sectional study from the United States examined the feasibility of surveillance of anemia, iron deficiency, and IDA among first-trimester pregnancies in a private health system using electronic health records from 2005 to 2016.[94] Among the 41,991 pregnancies, 92.7 percent (n=38,925) had a laboratory result for hemoglobin or hematocrit in the electronic health record within the first 14 weeks of pregnancy. The total number of hemoglobin/hematocrit tests per pregnancy in the first trimester ranged from 1 to 20 and characteristics of those screened for anemia differed from those who were not screened. Anemia screening tended to be lower among women who were younger (18–24 years of age) or older (≥35 years of age), were Non-Hispanic Black, covered by Medicaid, or had obesity. Screening was lowest among pregnant women missing data on smoking, parity, or multiple gestation status; most (>97%) women missing at least one of these variables had a pregnancy that did not end with a live birth (data not shown). Among pregnancies not screened, a higher proportion ended in the first trimester (37.1%) compared with pregnancies screened for anemia (8.5%; $p<0.0001$). In this study, overall anemia prevalence was reported as low (2.7% among those screened), but >5 times higher among Non-Hispanic Black women compared with Non-Hispanic White women. This data is consistent with earlier data from NHANES.[19,95]

Contextual Question 2. What Are Current Practices for the Use of Iron Supplementation During Pregnancy? Do Current Practices Differ by Race or Ethnicity, Age, Diagnostic Criteria, Socioeconomic Status, Cultural Factors, Educational Attainment, Insurance Status, or Health Literacy of the Pregnant Person?

Recommendations for iron supplementation during pregnancy vary by professional organization (**Table 1**), which may impact current practices. Observational studies on current iron supplementation practices had limitations such as not addressing population characteristics of interest for this contextual question or utilizing older data sets.

A large (n=160,482), cross-sectional study of a pregnant Medicaid population[93] examined racial and ethnic disparities in the use of prescriptions for multivitamin and iron supplements in four states. The study found that non-Hispanic Black pregnant persons were significantly more likely to have filled prescriptions for iron supplements in three states (adjusted ORs 1.48 to 1.77), as were Hispanic pregnant persons in two of the three states (adjusted ORs 1.11 and 1.19) than non-Hispanic White persons. However, non-Hispanic Black and Hispanic pregnant persons were significantly less likely to have filled multiple vitamin prescriptions compared with non-Hispanic White pregnant persons in two of the three states (adjusted ORs 0.69 to 0.91), and Asian/Pacific Islander pregnant persons were less likely in one of the three states (adjusted OR 0.80).

A U.S.-based cross-sectional study of 1,045 pregnant persons[33] used NHANES survey data from 1999 to 2010 to compare those with food security (n=881) to those with food insecurity (n=164),

as defined by the U.S. food security survey module, and the use of iron supplements and ID. Compared with the food-secure group, population characteristics of those in the food-insecure group included a higher percentage of Mexican American and other Hispanic individuals, lower poverty income ratio, and less health insurance coverage compared with the food-secure comparison group. Mean iron intake did not differ between groups, but mean supplemental iron intake was 10 mg/day lower (p=0.02) and there was an increased risk of ID based on ferritin values (<12.0 µg/L), transferrin (>4.4 mg/L), or total body iron (<0 mg/kg), among those with food insecurity versus the food-secure group (adjusted OR, 2.90 [95% CI 1.29 to 6.51]).

A U.S.-based longitudinal birth cohort study[96] compared nutritional intake and supplement use from the years 2000 to 2001 during pregnancy among 474 immigrants born in Mexico (n=425) versus Mexican-American persons born in the United States (n=49), and according to number of years lived in the United States. All participants had access to free prenatal vitamins, and approximately 90 percent were taking supplements by their second trimester. No differences were seen between the groups in vitamin supplement use before or during pregnancy.

Contextual Question 3. How Well Do Risk-Assessment Tools Identify Pregnant Persons at Increased Risk for Iron Deficiency Anemia?

There is limited evidence available on the accuracy of risk prediction tools to identify pregnant persons at increased risk for IDA. Three studies provided some information regarding prediction rules for ID in pregnancy, including one study from the prior report.[97]

A feasibility study[98] from Germany (n=200) used a questionnaire to evaluate whether risk of ID can be predicted by diet history and self-reported iron intake and iron losses (e.g., history of blood donation, menstrual history, surgery, history of ID). Participants were enrolled during their first or second trimester. Blood samples showed that 6 percent of study participants had anemia but 39 to 47 percent of participants were iron deficient without anemia, based on transferrin saturation. Incidence of ID increased with gestational age (from 41.3% at less than 20 weeks to 66.7% over 20 weeks gestation). In the first analysis, predictors of ID included gestational age greater than 21 weeks, and pre-pregnancy menstrual blood flow 6 days or longer and use of a high absorption tampon. Details about the final prediction rule or its diagnostic accuracy were not reported.

A prospective cohort study[99] (n=1,527) from Israel followed pregnant persons undergoing vaginal delivery >36 weeks to determine a prediction rule for anemia at delivery. Risk factors for anemia at delivery were identified by conducting a secondary analysis of a prospective cohort study database. The study found that the optimal hemoglobin cutoff between 24 and 30 gestational weeks for predicting anemia at delivery using the area under the receiver operating characteristic (AUROC) curve was a hemoglobin <10.5 g/dL. Risk factors for anemia at delivery included hemoglobin at 24 to 30 weeks and infrequent iron supplement intake. Further analysis demonstrated a hemoglobin cut-off at 24 to 30 weeks less than 10.6 g/dL had a sensitivity of 75 percent and a specificity of 74 percent to predict anemia at delivery. While anemia was considered most likely due to ID, no specific testing was done to determine iron status.

A third cohort study[97] (n=141) conducted in the United States in a population of primarily Black, urban, pregnant persons in all three trimesters of pregnancy, tested whether red blood cell indices could be used to develop a clinical prediction rule to identify patients at increased risk for IDA based on screening (ferritin <10 ng/dL). The final model used either a hemoglobin <9.7 g/dL or red cell distribution width >15 in persons under 20 weeks of gestation and had a specificity of 96 percent for ID. The study found that a risk score of ≥2 (on a 4-item scoring system that included an interaction term) was the best predictor of IDA, correctly identifying 74 percent of persons with IDA. However, although specificity was high (88%), sensitivity was poor (45%), resulting in a non-informative positive likelihood ratio (1.1). Discrimination was also modest, with the AUROC curve of 0.66 (95% CI, 0.6 to 0.7). Limitations of this study include evaluation of only urban, Black persons who met criteria for anemia, potentially reducing generalizability of findings.

Chapter 4. Discussion

Summary of Review Findings

This report synthesizes evidence on the effects of iron supplementation and screening for ID and IDA during pregnancy. The evidence reviewed in this update is summarized for routine supplementation in **Table 9** and for screening in **Table 10**.

Evidence added for this review was consistent with findings from the previous USPSTF review[4] that found that iron supplementation may be effective for improving maternal hematologic indices and decreasing risk of IDA during pregnancy and at delivery, with no clear effects on improvement in maternal or infant clinical outcomes. The expanded scope to assess the impact of iron supplementation or screening on ID alone did not impact results. Five RCTs[70,72,80,85,86] were newly added for this update. The three newly included studies conducted in rural China had the largest sample sizes (n=12,513[72], 3,929[85], and 2,371[86]) and represented populations from countries with lower HDI (high versus very high). With the addition of these trials, results remained consistent with findings from the prior review.

Sixteen trials of iron supplementation versus placebo or no supplementation evaluated clinical outcomes for pregnant individuals and their infants. Limited evidence from one study indicated no differences in maternal quality of life up to 4 years postpartum for iron supplementation during pregnancy compared with placebo. There were also no clear effects of prenatal iron supplementation on maternal clinical outcomes including hypertensive disorders of pregnancy, gestational diabetes, or cesarean delivery; though results were somewhat inconsistent for cesarean delivery, with one fair-quality, large trial finding supplementation associated with reduced risk of cesarean delivery but eight finding no difference. Results for cesarean delivery are difficult to interpret because trials did not report indications for cesarean, which may occur for a variety of reasons, including elective, with variability in practice. In addition, cesarean delivery has not been causally associated with ID or IDA, though is examined in the studies. Some observational studies[100-102] not included for this review have examined supplement use versus no use and effects on gestational diabetes and suggest iron supplementation may increase the risk of gestational diabetes, but results are susceptible to residual confounding.

Iron supplementation was not associated with rates of preterm delivery, low birth weight infants, or infants small for gestational age. There was insufficient evidence to assess the effect of prenatal iron supplementation on infant mortality due to inconsistency and low event rates in most trials. One trial reporting a decreased risk of infant mortality was conducted in China and favored supplementation. Infant mortality incidence in the U.S trial were too low to determine the direction of effect. Findings regarding infant outcomes were limited by relatively small numbers of trials (e.g., 6 trials reporting preterm delivery, 3 trials reporting small for gestational age, and 6 trials for low birth weight) and insufficient power in some trials to evaluate these outcomes.

Sixteen good- or fair-quality trials[63,64,66-69,72,76,78,81,83,85,86,88,89] were consistent with the prior USPSTF review in finding an association between maternal iron supplements versus placebo or

no iron supplements and improvement in hematologic parameters or incidence of IDA, but the clinical significance of the findings remains unclear. Assessment and reporting of harms were limited, but no serious adverse effects were reported. Although one trial reported an increased risk of gastrointestinal side effects, other trials did not find increased risk with iron supplementation compared with placebo and the direction of these effects was inconsistent.

As in the prior USPSTF review no trial evaluated outcomes of screening versus no screening for IDA in pregnant persons; there were also no trials of screening for ID. One study added to this review provided insufficient evidence to evaluate the association between a change in maternal iron status and clinical outcomes and had serious methodological limitations.

In other reviews, data are mixed on the association between routine maternal iron supplementation and infant outcomes. An older literature review found that maternal anemia diagnosed at entry to prenatal care associated with an increased risk for preterm delivery, but anemia diagnosed during the third trimester was not associated with these negative outcomes.[103] Studies have evaluated the effect of treatment for IDA, including Cochrane reviews of up to 49 trials conducted in mostly developing countries, that compared daily oral iron versus intermittent oral iron supplementation or assessed iron treatment during pregnancy and found overall methodologically poor evidence showing no effect of supplementation or treatment on infant outcomes, including low birth weight, delayed development, preterm birth, infection, and postpartum hemorrhage.[104-107] In the 2015 USPSTF review,[4] trial and controlled observational study evidence from countries similar to the United States demonstrated inconsistent effects of routine supplementation, screening, and screening-related treatment on maternal and infant outcomes. Most studies included in this review focused on pregnant persons at average risk for anemia and excluded pregnant persons with very low hematologic indices at baseline or preexisting anemia or related chronic conditions. Therefore results of this review may not apply to countries with lower baseline hematologic indices or higher incidence of severe anemia.

Limitations

We excluded non-English language articles, which could result in language bias, though we did not identify any non-English language studies that would have met inclusion criteria. We could not formally assess for publication bias with graphical or statistical methods because of small numbers of studies, and differences in study design, populations, and outcomes assessed. We included some trials from countries that may not be directly generalizable to the United States due to differences in nutritional status, resources, infrastructure, and other factors (Hong Kong, rural China, Iran); however they all were rated as at least high on the HDI.[60] In addition, stratified analyses did not indicate subgroup differences based on HDI category. Findings may not be applicable in countries where nutritional resources and healthcare systems are different from U.S. settings.[24,25]

Due to anticipated statistical heterogeneity in pooled analyses with regard to setting, rates of ID or IDA, supplementation dose, and timing, we used the DerSimonian and Laird random-effects model to pool studies, which may result in narrow confidence intervals when heterogeneity is present, particularly when the number of studies is small.[108] To evaluate statistical heterogeneity, we performed subgroup analysis to assess the sensitivity of results to variations across study

characteristics, including country HDI rating and low and high supplementation dosing based on elemental iron doses. We calculated p-values for the interaction of these characteristics and results did not indicate statistically significant subgroup effects based on these characteristics (**Table 2**). However, the utility of stratified analyses was limited by relatively small numbers of trials.

Emerging Issues/Next Steps

Screening and routine preventive supplementation of asymptomatic pregnant persons is common, though data on the reported incidence of IDA is limited. Observational studies report some differences in rates of screening and supplementation in key groups such as WIC recipients and by race or ethnicity. However, the influence of conflicting guidelines, variable clinical practices, changing cutoffs for diagnosis, and access to health care services may affect the accuracy of reported rates. Studies that evaluate the impact of social determinants of health, race or ethnicity, diagnostic criteria, age, cultural factors, or health literacy would help inform strategies to reduce disparities in diagnosis of ID or IDA and provision of iron (as treatment for ID or IDA, or as a supplement). New research in prenatal screening and iron supplementation appears to be very limited, likely due to current clinical recommendations and that this area may not be perceived as high priority. Nonetheless, studies addressing effects of treating ID or IDA or routine iron supplementation on maternal or neonatal outcomes could better inform the utility of routine screening or supplementation.

Relevance for Priority Populations

We did not identify any studies that evaluated how outcomes of supplementation varied for priority populations, including those based on race or ethnicity. However, two of the included iron supplementation trials conducted in the United States primarily included those eligible for WIC[66,83] or composed of a largely (>50%) Black population.[83] Both of these trials ended the placebo phase of the trial at 28 weeks gestation, after which all participants in the study received routine iron supplementation, therefore limiting applicability to supplementation that persists through term. These studies were carried forward from the prior review and had findings consistent with other studies identified for this review.

Future Research

Research is needed to clarify long-term effects of iron supplementation during pregnancy on maternal and infant health outcomes. Trials should use standardized definitions for hypertensive disorders of pregnancy and anemia and report outcomes for emergency cesarean delivery separately, including those with complications, including indications for procedures. Few studies addressed postpartum outcomes, which varied widely and were less frequently reported. In the absence of more definitive data on the effects of supplementation or treatment for ID or IDA on health outcomes, research on the association between improvements maternal hematologic outcomes following prenatal iron supplementation and health outcomes would be useful to understand the clinical implications of the positive effects of supplementation on hematological outcomes. Additional trials with sufficient sample sizes and duration of followup would

strengthen the evidence base informing infant and maternal benefits and harms of iron supplementation during pregnancy.

Conclusions

Prenatal iron supplementation may improve maternal hematologic indices and reduce the incidence of ID and IDA during pregnancy, but evidence on maternal and infant health outcomes is limited or indicates no benefit. Routine iron supplementation is not associated with significant maternal harms. No studies addressed the benefits or harms of screening for ID or IDA during pregnancy. Research is needed to understand the association between changes in maternal iron status measures and health outcomes.

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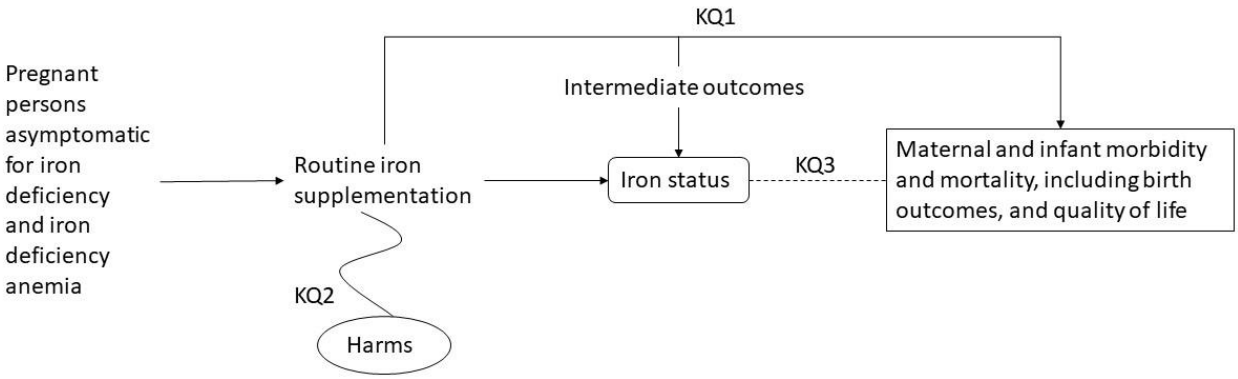
Figure 1. Analytic Framework and Key Questions for Routine Iron Supplementation During Pregnancy



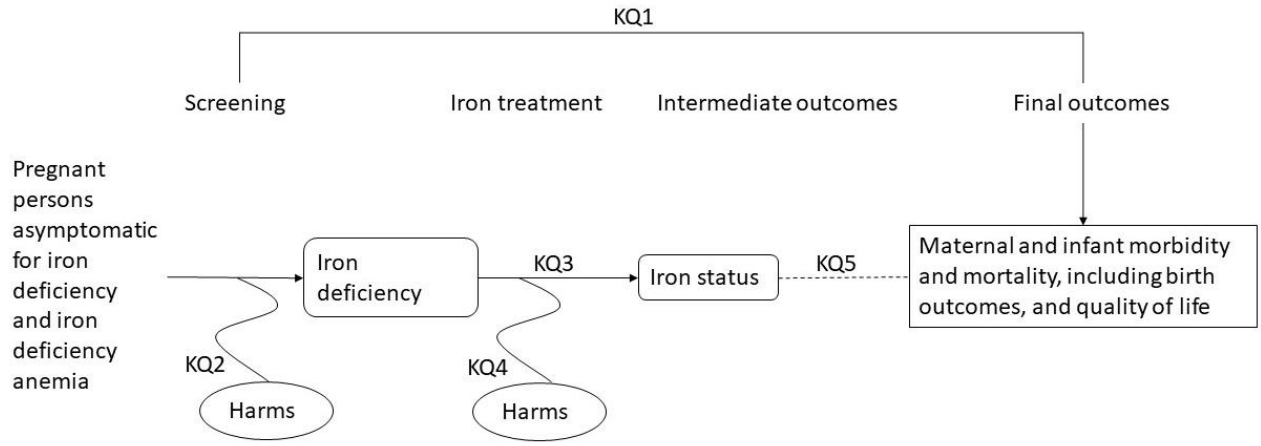
KQ 1. What are the benefits of routine iron supplementation during pregnancy on maternal and infant health outcomes?

KQ 2. What are the harms of routine iron supplementation during pregnancy?

KQ 3. In pregnant persons with iron deficiency, with or without anemia, what is the association between change in maternal iron status (including changes in ferritin or hemoglobin level) and improvement in newborn and peripartum outcomes in U.S.-relevant populations?

Abbreviation: KQ=Key Question.

Figure 2. Analytic Framework and Key Questions for Screening for Iron Deficiency and Iron Deficiency Anemia During Pregnancy



KQ 1. What are the benefits of screening for iron deficiency and iron deficiency anemia in asymptomatic pregnant persons on maternal and infant health outcomes?

KQ 2. What are the harms of screening for iron deficiency and iron deficiency anemia in pregnant persons?

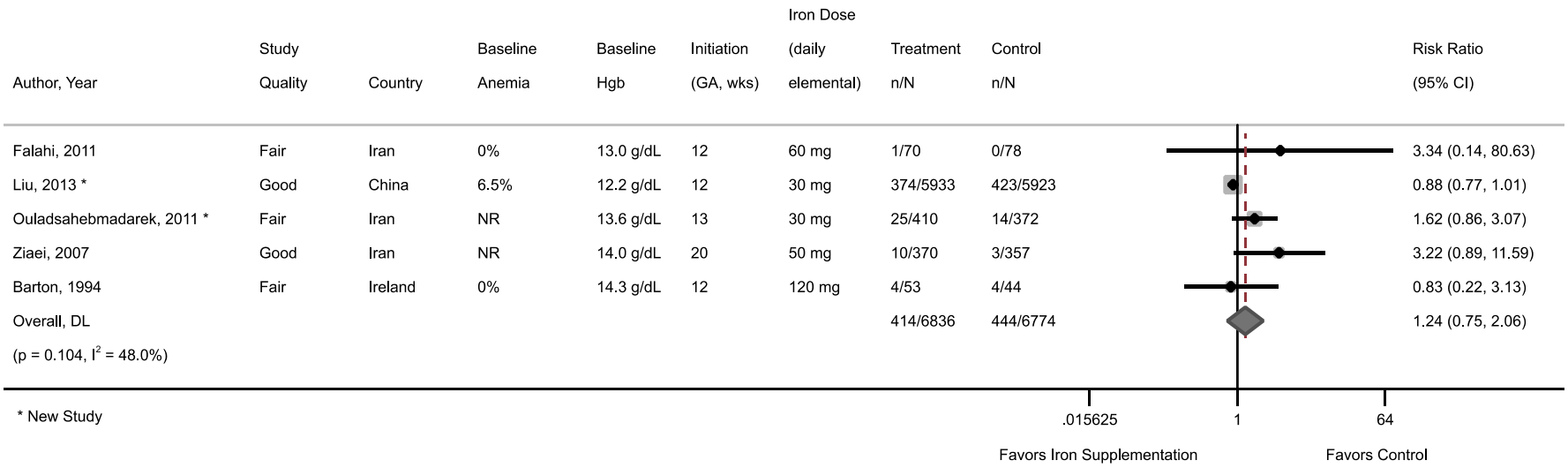
KQ 3. What are the benefits of treatment of iron deficiency and iron deficiency anemia during pregnancy on maternal and infant health outcomes?

KQ 4. What are the harms of iron treatment in pregnant persons?

KQ 5. In pregnant persons with iron deficiency, with or without anemia, what is the association between change in maternal iron status (including changes in ferritin or hemoglobin level) and improvement in newborn and peripartum outcomes in U.S.-relevant populations?

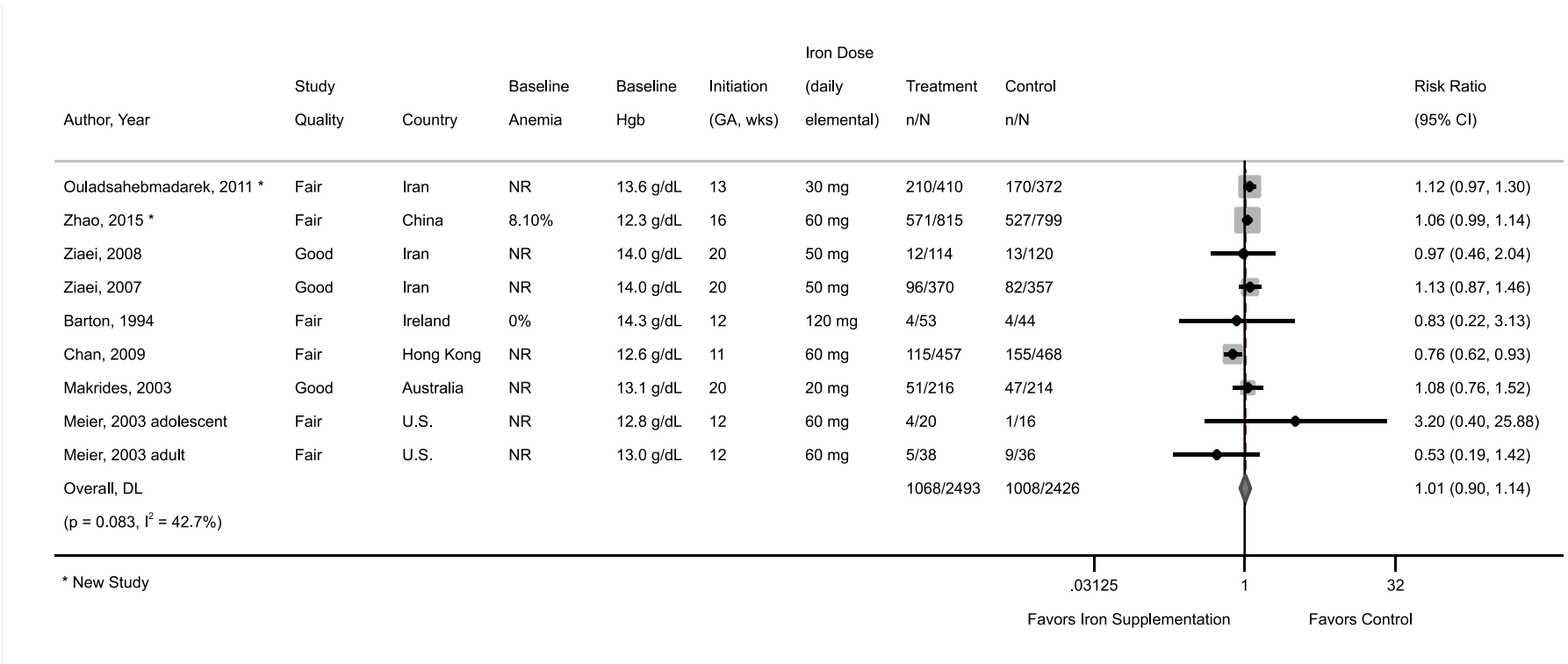
Abbreviation: KQ=Key Question.

Figure 3. Meta-Analysis: Hypertensive Disorders of Pregnancy



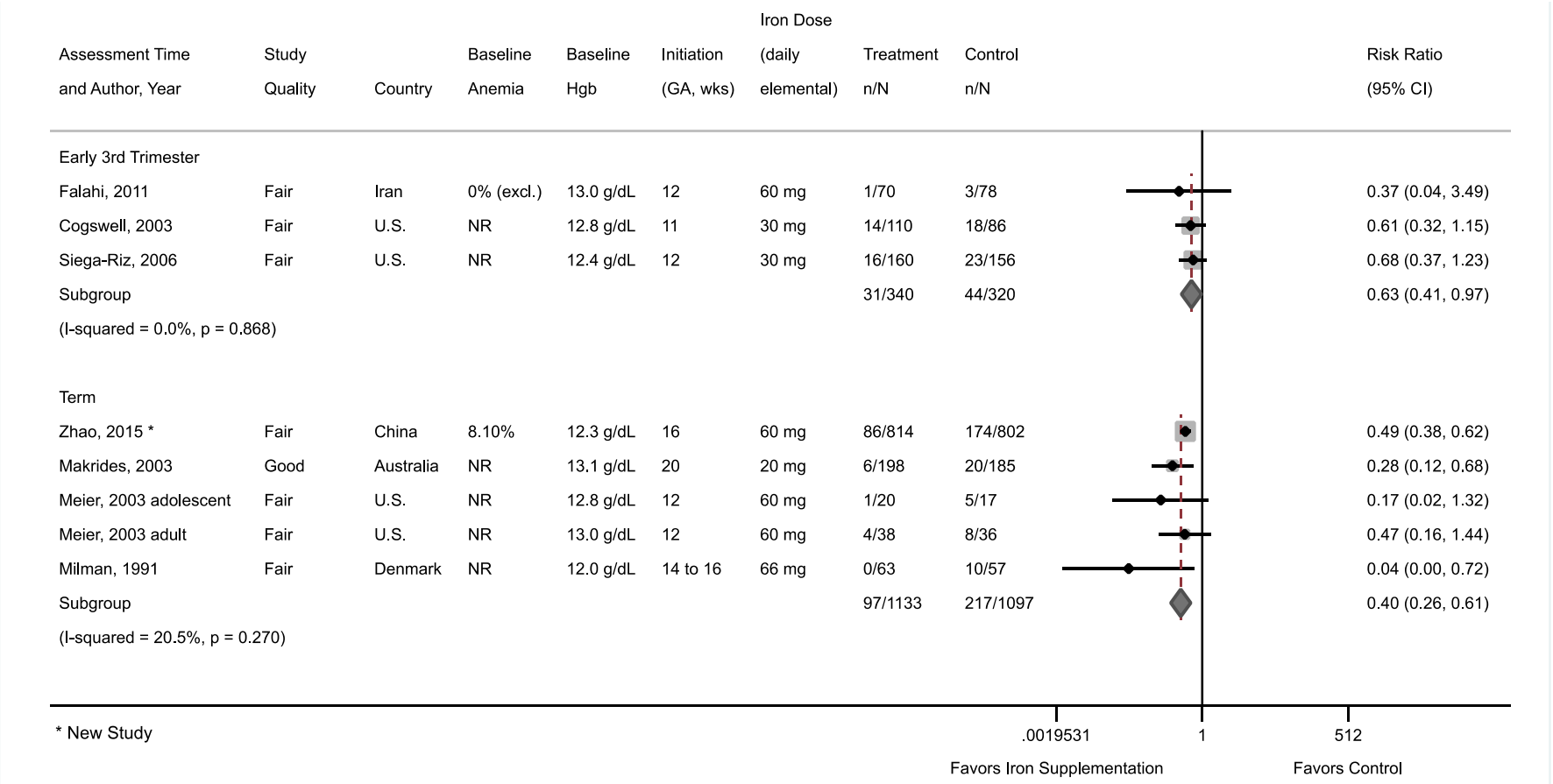
Abbreviations: CI=confidence interval; DL=DerSimonian Laird; GA, wks=gestational age, weeks; Hgb=hemoglobin; NR=not reported.

Figure 4. Meta-Analysis: Cesarean Delivery



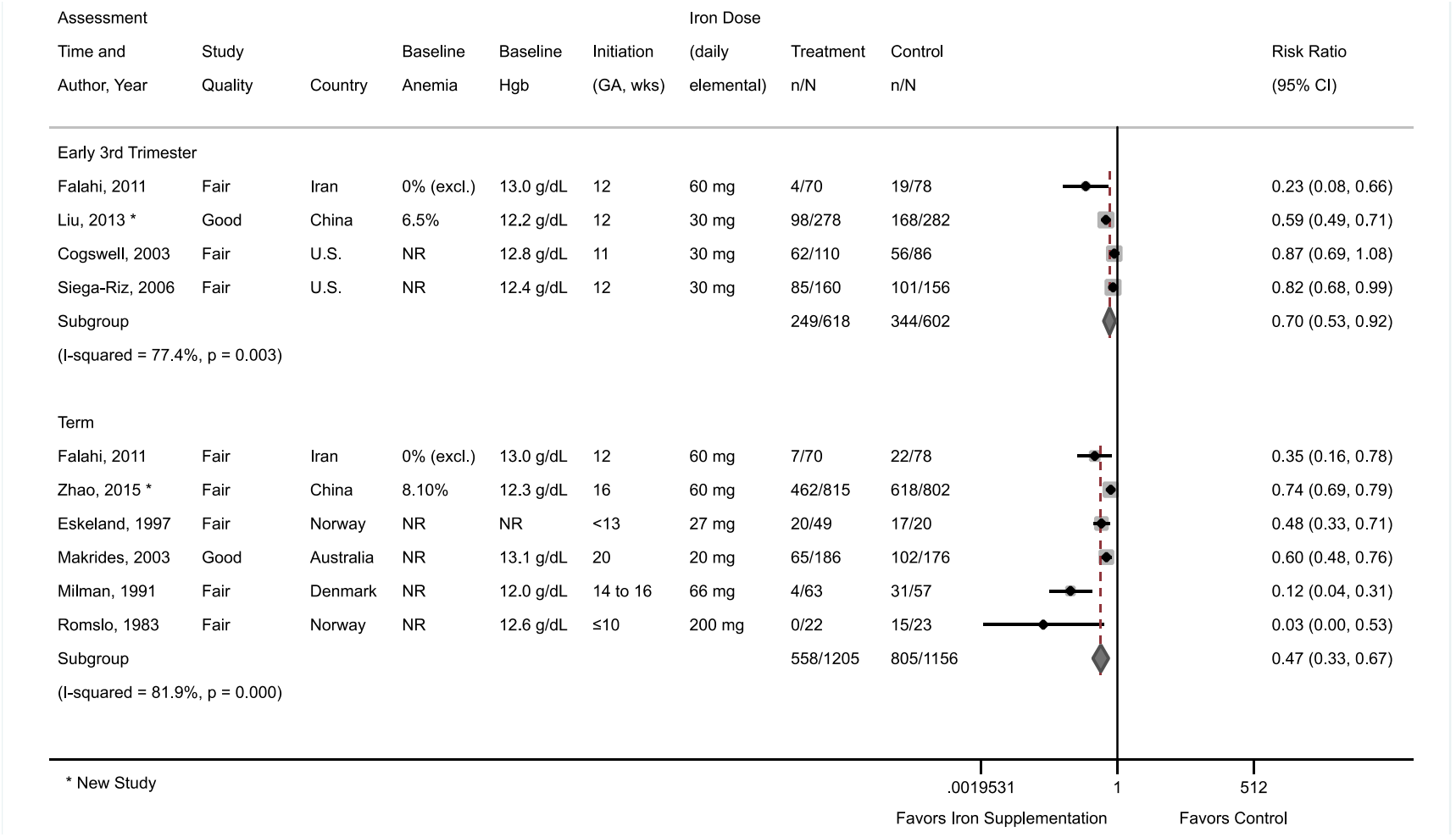
Abbreviations: CI=confidence interval; DL=DerSimonian Laird; GA, wks=gestational age, weeks; Hgb=hemoglobin; NR=not reported.

Figure 5. Meta-Analysis: Iron Deficiency Anemia During Third Trimester and at Term



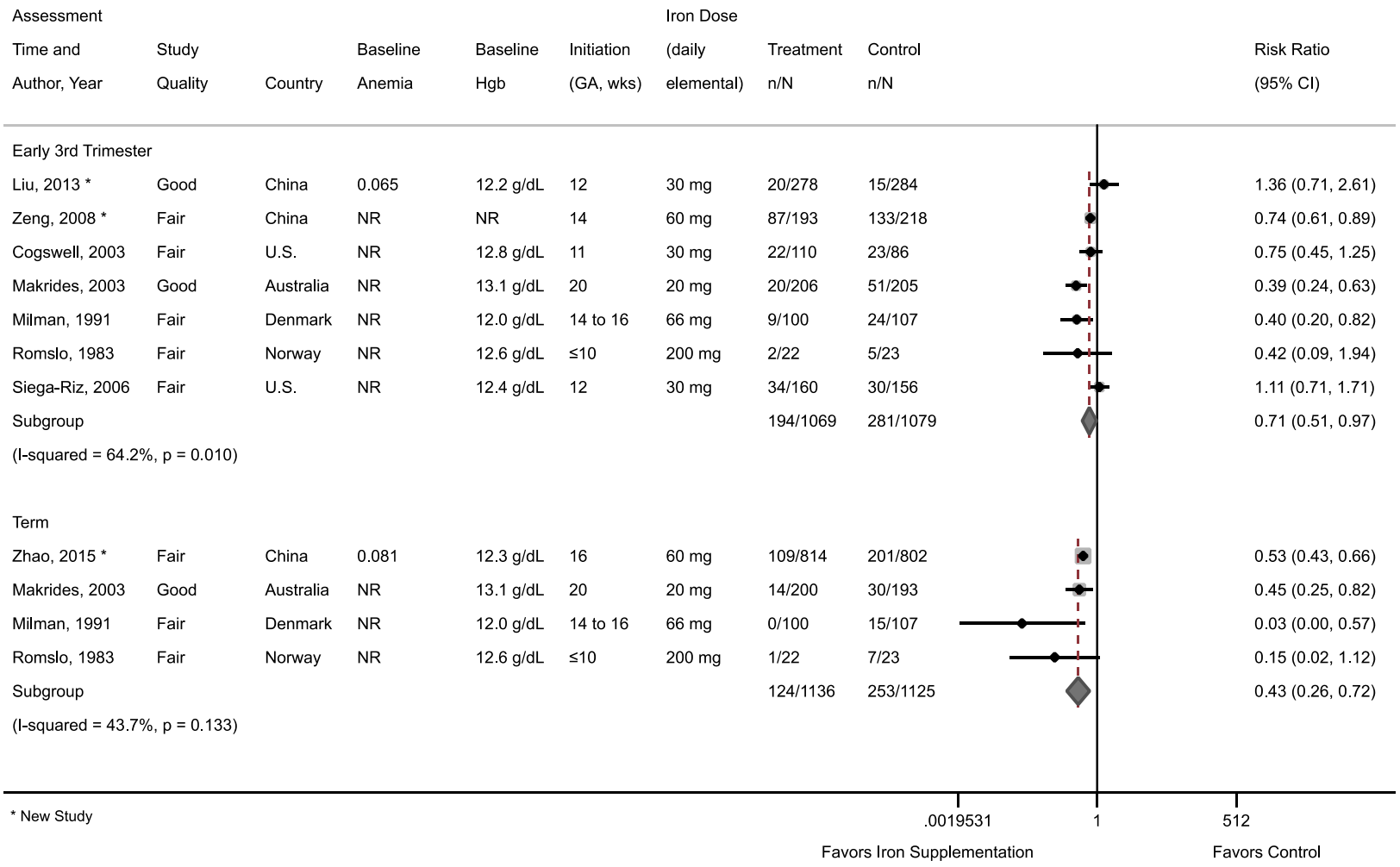
Abbreviations: CI=confidence interval; GA, wks=gestational age, weeks; Hgb=hemoglobin; NR=not reported.

Figure 6. Meta-Analysis: Iron Deficiency During Third Trimester and at Term



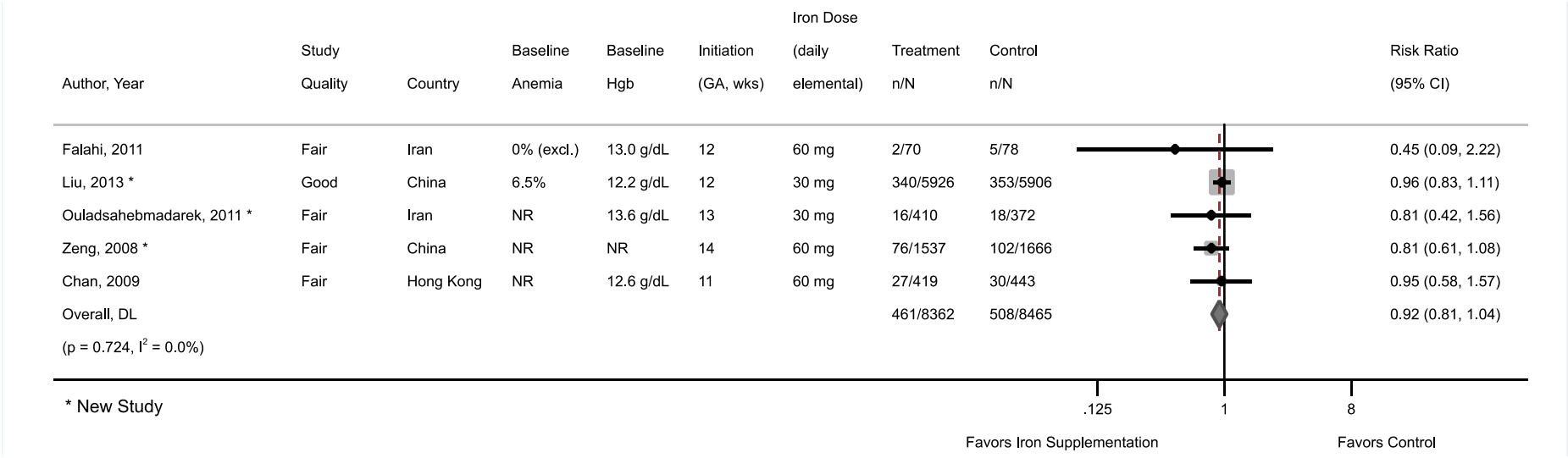
Abbreviations: CI=confidence interval; GA, wks=gestational age, weeks; Hgb=hemoglobin; NR=not reported.

Figure 7. Meta-Analysis: Anemia During Third Trimester and at Term



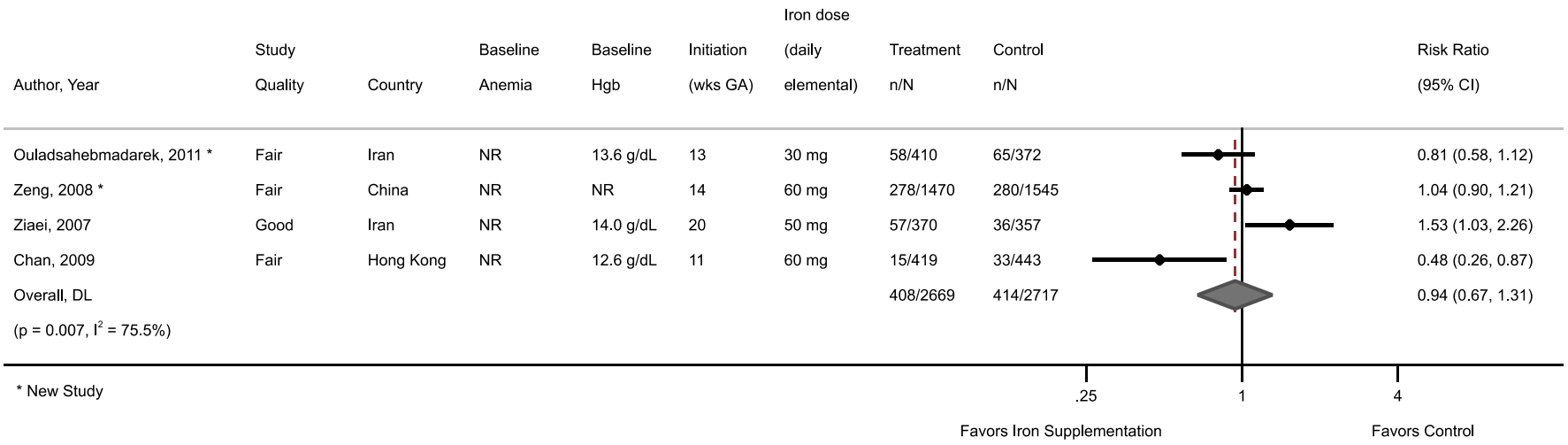
Abbreviations: CI=confidence interval; GA, wks=gestational age, weeks; Hgb=hemoglobin; NR=not reported.

Figure 8. Meta-Analysis: Preterm Birth



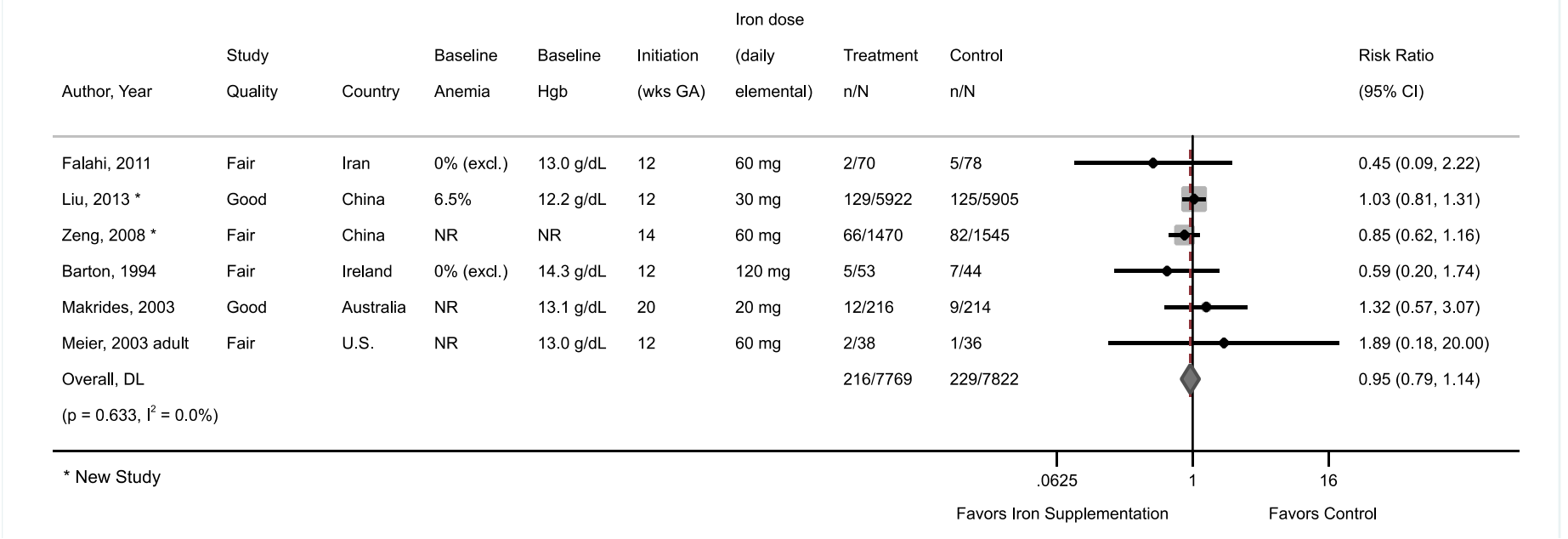
Abbreviations: CI=confidence interval; DL=DerSimonian Laird; GA, wks=gestational age, weeks; Hgb=hemoglobin; NR=not reported.

Figure 9. Meta-Analysis: Small for Gestational Age



Abbreviations: CI=confidence interval; DL=DerSimonian Laird; GA, wks=gestational age, weeks; Hgb=hemoglobin; NR=not reported.

Figure 10. Meta-Analysis: Low Birth Weight



Abbreviations: CI=confidence interval; DL=DerSimonian Laird; GA, wks=gestational age, weeks; Hgb=hemoglobin; NR=not reported.

Table 1. Recommendations of Other Groups

Organization, year	Recommendations
American Academy of Family Physicians (AAFP), 2013[44]	All pregnant women should be screened for iron deficiency anemia. Supplemental iron may be given initially, followed by further workup if the patient is not responsive to therapy. In pregnant patients, poor compliance or intolerance should be considered, and parenteral iron may produce a better response.
American College of Obstetricians and Gynecologists (ACOG), 2021[14]	All pregnant women should be screened for anemia with a complete blood count in the first trimester and again at 24 to 28 weeks of gestation. Patients who meet criteria for anemia based on hematocrit levels less than 33% in the first and third trimesters and less than 32% in the second trimester should be evaluated to determine the cause. Those with iron deficiency anemia should be treated with supplemental iron, in addition to prenatal vitamins.
Centers for Disease Control and Prevention (CDC), 1998[6]	All pregnant women, at their first prenatal visit, begin taking an oral, low dose (30 mg/day) supplement of iron and be screened for iron deficiency anemia.
National Institute for Health and Care Excellence (NICE), 2000[109]	Offer pregnant women screening for anemia at the initial appointment and again at 28 weeks. If iron deficiency is identified, then treatment should be considered, but iron supplementation should not be offered routinely to all pregnant women.
National Academy of Medicine (NAM), 1993[13]	All pregnant women should be screened for iron deficiency anemia at the first prenatal visit and at least once during each subsequent trimester. Nutrition education about diet during pregnancy should be provided at every prenatal visit. When the hemoglobin level is between 9.0 and 10.9 g/dL and the serum ferritin concentration is between 12 and 20 µg/L or the hemoglobin level is 11.0 g/dL or greater and the serum ferritin concentration is 20 µg/L or less, 30 mg of supplemental iron should be provided on a daily basis. The clinician should prescribe 60-120 mg of supplemental iron per day when the hemoglobin level is between 9.0 and 10.9 g/dL and the serum ferritin concentration is less than 12 µg/L.
Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis, 2018[110]	Screen pregnant women for anemia during their first visit and at 28 weeks. Offer women in areas of low prevalence for anemia in pregnancy but who may be at increased risk of developing anemia iron supplementation (30-60 mg/day) to prevent the onset of anemia.
Department of Veterans Affairs/Department of Defense (VA/DoD), 2018[58]	Screen pregnant women for anemia in the first trimester.
World Health Organization (WHO), 2016[58]	Recommend daily oral iron and folic acid supplementation with 30 mg to 60 mg of elemental iron and 400 µg (0.4 mg) folic acid for pregnant women. Recommend intermittent oral iron and folic acid supplementation with 120 mg of elemental iron and 2800 µg (2.8 mg) folic acid once if daily iron is not acceptable due to side-effects, and in populations with an anemia prevalence among pregnant women of less than 20%.

Table 2. Summary of Meta-Analyses

Outcome Subgroup	Subgroup Definition	No. of trials (Total N)	RR (95% CI) and ARD if significant[a]	I^2
Maternal Iron Deficiency, at Term All Trials	NA	6 (2,361)	**0.47 (0.33 to 0.67)** **ARD -34 (-46% to -22%)**	81.9%
Maternal Iron Deficiency, at Term Country *(p=0.597 for interaction)*	U.S. or other applicable countries (very high HDI)	4 (596)	**0.35 (0.18 to 0.65)** **ARD -44% (-63% to -25%)**	79.3%
	Rural China, Iran (medium to high HDI)	2 (1,765)	0.57 (0.29 to 1.13)	69.5%
Maternal Iron Deficiency, at Term Dose *(p=0.577 for interaction)*	Low (<60 mg iron)	2 (431)	**0.57 (0.46 to 0.69)** **ARD -32% (-52% to -11%)**	0.0%
	High (≥60 mg iron)	4 (1,930)	**0.26 (0.09 to 0.77)** **ARD -36% (-54% to -18%)**	86.0%
Maternal Iron Deficiency, 3rd trimester All Trials	NA	4 (1,220)	**0.70 (0.53 to 0.92)** **ARD -17% (-24% to -10%)**	77.4%
Maternal Iron Deficiency Anemia, at Term All Trials	NA	4 (2,230)	**0.40 (0.26 to 0.61)** **ARD -10% (-16% to -3%)**	20.5%
Maternal Iron Deficiency Anemia, at Term Country *(p=0.361 for interaction)*	U.S. or other applicable countries (very high HDI)	3 (614)	**0.29 (0.15 to 0.55)** **ARD -12% (-19% to -6%)**	0.0%
	Rural China (medium to high HDI)	1 (1,616)	**0.49 (0.38 to 0.62)** **ARD -5% (-16% to 5%)**	NA
Maternal Iron Deficiency Anemia, at Term Dose *(p=0.371 for interaction*	Low (<60 mg iron)	1 (383)	**0.28 (0.12 to 0.68)** **ARD -8% (-13% to -3%)**	NA
	High (≥60 mg iron)	3 (1,847)	**0.42 (0.24 to 0.71)** **ARD -11% (-19% to -2%)**	21.0%
Maternal Iron Deficiency Anemia, 3rd Trimester All Trials	NA	3 (660)	**0.63 (0.41 to 0.97)** **ARD -4% (-8% to 0.02%)**	0.0%
Maternal Anemia, at Term All Trials	NA	4 (2,261)	**0.43 (0.26 to 0.72)** **ARD -12% (-15% to -9%)**	43.7%
Maternal Anemia, at Term Country *(p=0.605 for interaction)*	U.S. or other applicable countries (very high HDI)	3 (645)	**0.22 (0.06 to 0.84)** **ARD -12% (-19% to -6%)**	49.3%
	Rural China (medium to high HDI)	1 (1,616)	**0.53 (0.43 to 0.66)** **ARD -12% (-15% to -8%)**	NA
Maternal Anemia, at Term Dose *(p=0.953 for interaction)*	Low (<60 mg iron)	1 (393)	**0.45 (0.25 to 0.82)** **ARD -9% (-15% to -2%)**	NA
	High (≥60 mg iron)	3 (1,868)	0.22 (0.05 to 1.02)	61.1%
Maternal Anemia, 3rd Trimester All Trials	NA	7 (2,148)	**0.71 (0.51 to 0.97)** **ARD -8% (-15% to -0.66%)**	64.2%

Table 2. Summary of Meta-Analyses

Outcome Subgroup	Subgroup Definition	No. of trials (Total N)	RR (95% CI) and ARD if significant[a]	I^2
Maternal Hypertensive Disorders of Pregnancy All Trials	NA	5 (13,610)	1.24 (0.75 to 2.06)	48.0%
Maternal Hypertensive Disorders of Pregnancy Country *(p=0.640 for interaction)*	Ireland (very high HDI)	1 (97)	0.83 (0.22 to 3.13)	NA
	Rural China, Iran (medium to high HDI)	4 (13,513)	1.38 (0.74 to 2.56)	60.9%
Maternal Hypertensive Disorders of Pregnancy Dose *(p=0.640 for interaction)*	Low (<60 mg iron)	3 (13,365)	1.35 (0.70 to 2.61)	71.6%
	High (≥60 mg iron)	2 (245)	1.02 (0.30 to 3.47)	0.0%
Maternal Cesarean Delivery All Trials	NA	8 (4,919)	1.01 (0.90 to 1.14)	42.7%
Maternal Cesarean Delivery Country *(p=0.025 for interaction)*	U.S. or other applicable countries (very high HDI)	4 (1,562)	0.85 (0.66 to 1.11)	23.8%
	Rural China, Iran (medium to high HDI)	4 (3,357)	1.07 (1.01 to 1.14)	0.0%
Maternal Cesarean Delivery Dose *(p=0.235 for interaction)*	Low (<60 mg iron)	4 (2,173)	1.11 (0.99 to 1.25)	0.0%
	High (≥60 mg iron)	4 (2,746)	0.89 (0.67 to 1.20)	67.6%
Infant Preterm Birth All Trials	NA	5 (16,827)	0.92 (0.81 to 1.04)	0.0%
Infant Preterm Birth Country *(p=0.882 for interaction)*	Hong Kong (very high HDI)	1 (862)	0.95 (0.58 to 1.57)	NA
	Rural China, Iran (medium to high HDI)	4 (15,965)	0.92 (0.81 to 1.04)	0.0%
Infant Preterm Birth Dose *(p=0.409 for interaction)*	Low (<60 mg iron)	2 (12,614)	0.95 (0.83 to 1.10)	0.0%
	High (≥60 mg iron)	3 (4,213)	0.83 (0.65 to 1.06)	0.0%
Infant Low Birth Weight All Trials	NA	6 (15,591)	0.95 (0.79 to 1.14)	0.0%
Infant Low Birth Weight Country *(p=0.831 for interaction)*	U.S. or other applicable countries (very high HDI)	3 (601)	1.02 (0.54 to 1.94)	0.0%
	Rural China, Iran (medium to high HDI)	3 (14,990)	0.95 (0.78 to 1.15)	0.0%
Infant Low Birth Weight Dose *(p=0.262 for interaction)*	Low (<60 mg iron)	2 (12,257)	1.05 (0.83 to 1.33)	0.0%
	High (≥60 mg iron)	4 (3,334)	0.82 (0.61 to 1.10)	0.0%
Infant Small for Gestational Age All Trials	NA	4 (5,386)	0.94 (0.67 to 1.31)	75.5%
Infant Small for Gestational Age Country *(p=0.214 for interaction)*	U.S. or other applicable countries (very high HDI)	1 (862)	**0.48 (0.26 to 0.87)**	NA
	Rural China, Iran (medium to high HDI)	3 (4,524)	1.07 (0.80 to 1.41)	66.6%

Table 2. Summary of Meta-Analyses

Outcome Subgroup	Subgroup Definition	No. of trials (Total N)	RR (95% CI) and ARD if significant[a]	I^2
Infant Small for Gestational Age	Low (<60 mg iron)	2 (1,509)	1.10 (0.59 to 2.05)	83.3%
Dose *(p=0.526 for interaction)*	High (≥60 mg iron)	2 (3,877)	0.75 (0.35 to 1.59)	83.7%

Abbreviations: ARD=absolute risk difference; CI=confidence interval; HDI=Human Development Index; NA=not applicable; RR=relative risk.

[a] Bold estimates indicate a statistically significant difference.

Table 3. Effect of Maternal Iron Supplementation vs. Placebo on Maternal Health and Clinical Outcomes

Study, year *Quality*	Country N randomized	Iron supplement dose and formulation, initiation	Quality of life	Cesarean delivery	Gestational diabetes	Hypertensive disorders of pregnancy	Hemorrhage
Barton 1994[63] *Fair*	Ireland N=97	120 mg elemental iron daily starting at end of first trimester	-	7.5% (4/53) vs. 9.1% (4/44), RR 0.83 (95% CI 0.22 to 3.13)	-	Hypertensive disorder: 7.5% (4/53) vs. 9.0% (4/44), RR 0.83 (95% CI 0.22 to 3.13)	Antepartum hemorrhage: 5.7% (3/53) vs. 4.5% (2/44), RR 1.25 (95% CI 0.22 to 7.12)
Chan 2009[64] *Fair*	Hong Kong N=1,164	60 mg elemental iron daily starting at <16 weeks gestation	-	25.2% (115/457) vs. 33.1% (155/468), **RR 0.76 (95% CI 0.62 to 0.93)**	At 28 weeks: 9.9% (56/565) vs. 10% (60/599), OR 1.04, 95% CI 0.7 to 1.53, RR 0.99 (95% CI 0.70 to 1.40) Cumulative at 36 weeks: 13% (72/565) vs. 13% (77/599), RR 0.99 (95% CI 0.73 to 1.34)	-	-
Falahi 2011[69] *Fair*	Iran N=148	60 mg elemental iron daily starting at <20 weeks gestation	-	-	-	Pregnancy-induced hypertension: 1.4% (1/70) vs. 0% (0/78), RR 3.34 (95% CI 0.14 to 80.64)	-
Liu 2013[72] *Good*	China (rural) N=12,513	30 mg elemental iron daily starting at <20 weeks gestation	-	-	-	Pregnancy-induced hypertension: 6.3% (374/5933) vs. 7.1% (423/5923), OR 0.88 (95% CI 0.76 to 1.01), RR 0.88 (95% CI 0.77 to 1.01)	-
Makrides 2003[74,90] *Good*	Australia N=430	20 mg elemental iron daily starting at 20 weeks gestation	SF-36: no significant differences in any of the 8 health concepts at 36 weeks of gestation, 6 weeks, 6 months, or 4 years postpartum	23.6% (51/216) vs 22.0% (47/214), RR 1.08 (95% CI 0.76 to 1.52)	-	-	

Table 3. Effect of Maternal Iron Supplementation vs. Placebo on Maternal Health and Clinical Outcomes

Study, year *Quality*	Country N randomized	Iron supplement dose and formulation, initiation	Quality of life	Cesarean delivery	Gestational diabetes	Hypertensive disorders of pregnancy	Hemorrhage
Meier 2003[76] *Fair*	U.S. N=144	60 mg elemental iron daily starting at 1st prenatal visit	-	Adolescents: 20% (4/20) vs. 6.2% (1/16), RR 3.20 (95% CI 0.40 to 25.88) Adults: 14.3% (5/38) vs. 25% (9/36), RR 0.53 (95% CI 0.20 to 1.42) Combined: 16% vs. 19%, p=NS	-	-	-
Ouladsaheb madarek, 2011[80] *Fair*	Iran N=960	30 mg elemental iron daily starting at 13 weeks gestation	-	51.2% (210/410) vs. 45.7% (170/372), RR 1.12 (95% CI 0.97 to 1.30)	0.5% (2/410) vs. 0.8% (3/372), RR of 0.61 (95% CI 0.10 to 3.60)	Pregnancy-induced hypertension: 6.7% (25/410) vs. 3.4% (14/372), RR 1.62 (95% CI 0.86 to 3.07) Preeclampsia: 3.9% (16/410) vs. 2.7% (10/372), RR 1.45 (95% CI 0.67 to 3.16)	-
Zhao 2015[86] *Fair*	China (rural) N=2,371	60 mg elemental iron daily starting at enrollment	-	70.1% (571/815) vs. 66.0% (527/799), RR 1.06 (95% CI 0.9933 to 1.14)	-	-	-
Ziaei 2007[89] *Good*	Iran N=750	50 mg elemental iron daily starting at 20 weeks gestation	-	25.9% (96/370) vs. 23% (82/357), RR 1.13 (95% CI 0.87 to 1.46)	-	Hypertensive disorder: 2.7% (10/370) vs. 0.8% (3/357), RR 3.22 (95% CI 0.89 to 11.59)	-
Ziaei 2008[88] *Good*	Iran N=244	50 mg elemental iron daily starting at 20 weeks gestation	-	10.5% (12/114) vs. 10.8% (13/120), RR 0.97 (95% CI 0.46 to 2.04)	-	-	Postpartum hemorrhage: 1.8% (2/114) vs. 1.7% (2/120), RR 1.05 (95% CI 0.15 to 7.35)

Abbreviations: NS, not significant; OR, odds ratio; RR, relative risk; SES, socioeconomic status.
Bolded values show a statistically significant difference.

Table 4. Effect of Maternal Iron Supplementation vs. Placebo on Maternal Hematologic Outcomes: 3rd Trimester

Study, year *Quality*	Timing of measure-ment	Country N randomized	Iron supplement dose, formulation, initiation	Hemoglobin, mean	Serum ferritin, mean	Iron deficiency[a] %	Anemia[b] %	Iron deficiency anemia[c] %
Barton 1994[63] *Fair*	3rd trimester, 36 weeks	Ireland N=97	120 mg elemental iron daily starting at end of first trimester	13.5 vs. 12.6 g/dL, **p=0.043** (adjusted for smoking p=0.25)	32.6 vs. 12.8 µg/L, **p=0.04**	-	"No patients were withdrawn from the study due to anemia"	-
Cogswell 2003[66] *Fair*	3rd trimester, 28 weeks	U.S. N=275	30 mg elemental iron daily starting at <20 weeks gestation	11.7 vs. 11.6 g/dL, p=0.499	7.4 vs. 7.4 µg/L, p=0.985	56.4% (62/110) vs 65.1% (56/86), RR 0.87 (95% CI 0.69 to 1.08)	19.8% vs 26.7%, p=0.251	12.7% (14/110) vs 20.9% (18/86), RR 0.61 (95% CI 0.32 to 1.15)
Falahi 2011[69] *Fair*	3rd trimester, 28 weeks	Iran N=148	60 mg elemental iron daily starting at <20 weeks gestation	-	-	5.7% (4/70) vs. 24.4% (19/78), **RR 0.23 (95% CI 0.08 to 0.66)**	-	1.4% (1/70) vs 3.8% (3/78), **RR 0.37 (95% CI 0.04 to 3.49)**
Liu 2013[72] *Good*	3rd trimester, 24 to 28 weeks	China (rural) N=12,513	30 mg elemental iron daily starting at <20 weeks gestation	12.2 vs. 12.2 g/dL, **MD 0.04 (95% CI 0.01 to 0.07)**	-	-	5.5% (327/5913) vs. 7.7% (452/5896), **RR 0.72 (95% CI 0.63 to 0.83)**	-
Liu 2013[72] *Good*	3rd trimester, 28 to 32 weeks	China (rural) N=12,513	30 mg elemental iron daily starting at <20 weeks gestation	12.4 vs. 12.5 g/dL, p>0.05	16.7 vs. 11.3 µg/L, **p<0.05**	35.3% (98/278) vs. 59.6% (168/282), **RR 0.59 (95% CI 0.49 to 0.71)**	7.2% vs. 5.3%, p>0.05	-
Makrides 2003[74] *Good*	3rd trimester, 28 weeks	Australia N=430	20 mg elemental iron daily starting at 20 weeks gestation	12.0 vs. 11.6 g/dL, **MD 0.34 (95% CI 0.17 to 0.53)**	-	-	9.7% (20/206) vs. 24.9% (51/205), **RR 0.39 (95% CI 0.24 to 0.63)**	-
Milman, 1991[77] *Fair*	3rd trimester, 27 to 30 weeks	Denmark N=207	66 mg elemental iron daily starting at 14 to 16 weeks gestation	-	-	-	9.0% vs. 22.4% **RR 0.40 (95% CI 0.20 to 0.82)**	-
Romslo, 1983[81] *Fair*	3rd trimester, 28 to 32 weeks	Norway N=45	200 mg elemental iron starting at ≤10 weeks gestation	-	-	-	9.1% vs. 21.7% RR 0.42 (95% CI 0.09 to 1.94)	-
Siega-Riz 2006[83] *Fair*	3rd trimester, 26-29 weeks	U.S. N=429	30 mg elemental iron daily starting at <20 weeks gestation	11.4 vs. 11.4 g/dL, p=0.81	22.0 vs. 20.3 µg/L, p=0.48	53% (85/160) vs. 65% (101/156), **RR 0.82 (95% CI 0.68 to 0.99)**[a]	21% (34/160) vs. 19% (30/156), RR 1.11 (95% CI 0.71 to 1.71)	10% (16/160) vs. 15% (23/156), RR 0.68 (95% CI 0.37 to 1.23)[b]
Zeng 2008[85] *Fair*	3rd trimester, 28 to 32 weeks	China (rural) N=3,929 (n=411 for this outcome)	60 mg elemental iron daily starting at 14 weeks gestation	11.0 vs. 10.5 g/dL, **MD 0.50 (95% CI 0.20 to 0.80)**	-	-	45.1% (87/193) vs. 61.0% (133/218), **RR 0.74 (95% CI 0.61 to 0.91)**	-

Table 4. Effect of Maternal Iron Supplementation vs. Placebo on Maternal Hematologic Outcomes: 3rd Trimester

Study, year *Quality*	Timing of measure-ment	Country N randomized	Iron supplement dose, formulation, initiation	Hemoglobin, mean	Serum ferritin, mean	Iron deficiency[a] %	Anemia[b] %	Iron deficiency anemia[c] %
Ziaei 2007[89] *Good*	3rd trimester, timing NR	Iran N=750	50 mg elemental iron daily starting at 20 weeks gestation	13.8 vs 12.6 g/dL, **p<0.001**	-	-		-

Abbreviations: Hb, hemoglobin; MCV, mean corpuscular volume; MD, mean difference; NS, not significant; RCT, randomized controlled trial; RR, relative risk; SES, socioeconomic status; SF, serum ferritin; US, United States.

[a]Iron deficiency defined as serum ferritin <12 µg/L.

[b]Anemia defined as hemoglobin <11.0 g/dL.

[c]Iron deficiency anemia defined as hemoglobin <11.0 g/dL and serum ferritin <12 µg/L).

Note that definitions used in some studies varied slightly from the above definitions.

Bolded values show a statistically significant difference.

Table 5. Effect of Maternal Iron Supplementation vs. Placebo on Maternal Hematologic Outcomes: Term

Study, year *Quality*	Country N randomized	Iron supplement dose, formulation, initiation	Hemoglobin, mean	Serum ferritin, mean	Iron deficiency[a] %	Anemia[b] %	Iron deficiency anemia[c] %
Barton 1994[63] *Fair*	Ireland N=97	120 mg elemental iron daily starting at end of first trimester	13.7 vs. 12.0 g/dL, **p<0.001**	-	-	"No patients were withdrawn from the study due to anemia"	-
Chan 2009[64] *Fair*	Hong Kong N=1,164	60 mg elemental iron daily starting at <16 weeks gestation	12.2 vs. 11.8 g/dL**, p<0.001**	30.0 vs. 24.9 µg/L, **p<0.003**	-	-	-
Eskeland 1997[68] *Fair* 38 weeks to term	Norway N=90	27 mg elemental iron daily starting at 20 weeks gestation	-	-	41% (20/49) (both iron arms) vs. 85% (17/20), **RR 0.48 (95% CI 0.33 to 0.71)**	-	0% (both iron arms) vs. 14% (4 cases)
Falahi 2011[69] *Fair*	Iran N=148	60 mg elemental iron daily starting at <20 weeks gestation	12.3 vs. 12.1 g/dL, p=NS	28.1 vs. 22.1 µg/L, p=NS	10.0% (7/70) vs. 28.2% (22/78), **RR 0.35 (95% CI 0.16 to 0.78)**	-	0% vs 0%, p=NS
Makrides 2003[74] *Good*	Australia N=430	20 mg elemental iron daily starting at 20 weeks gestation	12.7 vs. 12.0 g/dL, **MD 0.69 (0.44 to 0.93)**	21 vs. 14 µg/L, **MD 7.1 (4.0 to 10.2)**	35% (65/186) vs. 58% (102/176) **RR 0.60 (0.48 to 0.76)**	7% vs 16% **RR 0.45 (0.25 to 0.82)**	3% (6/198) vs. 11% (20/185), **RR 0.28 (0.12 to 0.68)**
Meier 2003[76] *Fair*	U.S. N=144	60 mg elemental iron daily starting at 1st prenatal visit	Adolescents: 12.2 vs. 11.5 g/dL, **p=0.024** Adults: 12.1 vs. 11.7 g/dL, p=0.135	Adolescents: 12.0 vs. 6.2 µg/L, **p=0.010** Adults: 12.9 vs. 7.6 µg/L, **p=0.027**	-	-	Adolescents 5% (1/20) vs 29% (5/17), RR 0.17 (95% CI 0.02 to 1.32) Adults 10.5% (4/38) vs 22.2% (8/36), RR 0.47 (95% CI 0.16 to 1.44)
Milman 1994, Milman 1991[77,78] *Fair*	Denmark N=248	66 mg elemental iron daily starting at 14-16 weeks gestation	12.7 vs. 11.6 g/dL, **p<0.0001**	22 vs. 14 µg/L, **p<0.0001**	6.3% (4/63) vs. 54.4% (31/57), **RR 0.12 (95% CI 0.04 to 0.31)**	0% vs. 14.3% **RR 0.03 (0.00 to 0.57)**	0% (0/63) vs. 17.5% (10/57), **RR 0.04 (95% CI 0.00 to 0.72)**
Ouladsahebmadarek, 2011[80] *Fair*	Iran N=960	30 mg elemental iron daily starting at 13 weeks gestation	13.5 vs. 12.5 g/dL, **p=0.03**	26.91 vs. 9.26 µg/dL, **p=0.048**	-	-	-

Table 5. Effect of Maternal Iron Supplementation vs. Placebo on Maternal Hematologic Outcomes: Term

Study, year *Quality*	Country N randomized	Iron supplement dose, formulation, initiation	Hemoglobin, mean	Serum ferritin, mean	Iron deficiency[a] %	Anemia[b] %	Iron deficiency anemia[c] %
Romslo 1983[81] *Fair*	Norway N=52	200 mg elemental iron daily starting within 10 weeks gestation	12.6 vs. 11.3 g/dL, p-value NR	24.0 vs. 6.0 µg/L, p-value NR	0% (0/22) vs. 65.2% (15/23), **RR 0.03 (95% CI 0.00 to 0.53)**	4.5% vs. 30.4% RR 0.15 (0.02 to 1.12)	-
Zhao 2015[86] *Fair*	China (rural) N=2,371	60 mg elemental iron daily starting at enrollment	12.2 vs. 11.7 g/dL, **p<0.001**	15.3 vs. 11.1 µg/L, **p<0.001**	56.8% (462/815) vs. 77.1% (618/802), **RR: 0.74 (95% CI 0.69 to 0.79)**	13.4% (109/814) vs. 25.1% (201/802), **RR 0.53 (95% CI 0.43 to 0.66)**	10.6% (86/814) vs. 21.7% (174/802), **RR 0.49 (95% CI 0.38 to 0.62)**
Ziaei 2008[88] *Good*	Iran N=244	50 mg elemental iron daily starting at 20 weeks gestation	13.9 vs. 12.8 g/dL, **p<0.0001**	26.2 vs. 19.1 µg/L, **p<0.0001**	-	-	-

Abbreviations: Hb, hemoglobin; MCV, mean corpuscular volume; NS, not significant; RCT, randomized controlled trial; RR, relative risk; SES, socioeconomic status; SF, serum ferritin; US, United States.

[a]Iron deficiency defined as serum ferritin <12 µg/L.

[b]Anemia defined as hemoglobin <11.0 g/dL.

[c]Iron deficiency anemia defined as hemoglobin <11.0 g/dL and serum ferritin <12 µg/L).

Note that definitions used in some studies varied slightly from the above definitions.

Bolded values show a statistically significant difference.

Table 6. Effect of Maternal Iron Supplementation vs. Placebo on Maternal Hematologic Outcomes: Postpartum

Study, year *Quality*	Timing of measure-ment	Country N randomized	Iron supplement dose, formulation, initiation	Hemoglobin, mean	Serum ferritin, mean	Iron deficiency[a] %	Anemia[b] %	Iron deficiency anemia[c] %
Eskeland 1997[68] *Fair*	Post-partum, 1 week	Norway N=90	27 mg elemental iron daily starting at 20 weeks gestation	-	-	-	11.5% vs. 20.7%, p=0.25	-
Eskeland 1997[68] *Fair*	Post-partum, 6-10 weeks	Norway N=90	27 mg elemental iron daily starting at 20 weeks gestation	-	-	18% (9/51) (both iron arms) vs. 52% (12/23), **RR 0.34 (95% CI 0.17 to 0.69)**[c]	-	-
Eskeland 1997[68] *Fair*	Post-partum, 24 weeks	Norway N=90	27 mg elemental iron daily starting at 20 weeks gestation	-	-	10% (5/48) (both iron arms) vs. vs 51% (12/23), **RR 0.20 (95% CI 0.08 to 0.50)**[c]	-	-
Liu 2013[72] *Good*	Post-partum, 4-6 weeks	China (rural) N=12,513	30 mg elemental iron daily starting at <20 weeks gestation	12.4 vs. 12.4 g/dL, MD 0.02 (95% CI -0.01 to 0.05)	-	-	26.8% (1547/5779) vs. 27.2% (1568/5765), OR 0.98 (95% CI 0.93 to 1.05)	-
Makrides 2003[74] *Good*	Post-partum, 6 months	Australia N=430	20 mg elemental iron daily starting at 20 weeks gestation	13.5 vs. 13.4 g/dL, MD 0.16 (-0.01 to 0.33)	34 vs. 26 µg/L, **MD 7.9 (3.5 to 12.3)**	16% vs. 29%, **RR 0.57 (0.38 to 0.84)**	3.7% vs 4.5%, RR 0.82 (0.30 to 2.21)	2.6% vs 1.7%, RR 1.55 (0.38 to 6.40)
Milman 1994[78] *Fair*	Post-partum, 8 weeks	Denmark N=248	66 mg elemental iron daily starting at 14-16 weeks gestation	13.4 vs. 12.9 g/dL, **p<0.001** Hb <12.1 g/dL, 3.2% vs. 21.1%	Ferritin ≤20 µg/L: 16.1% vs. 40.4%	-	3.2% vs. 21.1%	-
Zhao 2015[86] *Fair*	Post-partum,1 day	China (rural) N=2,371	60 mg elemental iron daily starting at enrollment	-	-	-	RR 0.71 (95% CI 0.66 to 0.78)	-

Abbreviations: Hb, hemoglobin; MCV, mean corpuscular volume; NS, not significant; RCT, randomized controlled trial; RR, relative risk; SES, socioeconomic status; SF, serum ferritin; US, United States.

[a]Iron deficiency defined as serum ferritin <12 µg/L.

[b]Anemia defined as hemoglobin <11.0 g/dL.

[c]Iron deficiency anemia defined as hemoglobin <11.0 g/dL and serum ferritin <12 µg/L).

Note that definitions used in some studies varied slightly from the above definitions.

Bolded values show a statistically significant difference.

Table 7. Effect of Maternal Iron Supplementation vs. Placebo on Infant Birth Outcomes

Study, year *Quality*	Country N randomized	Iron supplement dose and formulation, initiation	Preterm delivery[a]	Small for gestational age[b]	Low birth weight[c]	Infant mortality
Barton 1994[63] *Fair*	Ireland N=97	120 mg elemental iron daily starting at end of first trimester	-	-	<2700 g: 9.4% (5/53) vs. 15.9% (7/44), RR 0.59 (95% CI 0.20 to 1.74)	1.9% (1/53) vs. 0% (0/44), RR 2.50 (95% CI 0.10 to 59.88)
Chan 2009[64] *Fair*	Hong Kong N=1,164	60 mg elemental iron daily starting at <16 weeks gestation	6.4% (27/419) vs. 6.8% (30/443); RR 0.95 (95% CI 0.58 to 1.57)	3.58% (15/419) vs. 7.45% (33/443), **OR 0.46, 95% CI 0.24 to 0.85**	-	-
Falahi 2011[69] *Fair*	Iran N=148	60 mg elemental iron daily starting at <20 weeks gestation	3% (2/70) vs. 6.4% (5/78), RR 0.45 (95% CI 0.09 to 2.22)	-	3% (2/70) vs. 6.4% (5/78), RR 0.45 (95% CI 0.09 to 2.22)	-
Liu 2013[72] *Good*	China (rural) N=12,513	30 mg elemental iron daily starting at <20 weeks gestation	5.7% (340/5926) vs. 6.0% (353/5906), RR 0.96 (95% CI 0.83 to 1.11) Spontaneous preterm birth (20 to 36 weeks): 5.6% vs.5.7%, RR 0.99 (95% CI 0.85 to 1.16)	-	2.2% (129/5922) vs. 2.1% (125/5905), RR 1.03 (95% CI 0.81 to 1.31)	Cases per 1000 for mortality outcomes Perinatal mortality (stillbirth + early neonatal): 8.73 vs. 8.76, RR 1.00 (95% CI 0.68 to 1.46) Stillbirth (28 weeks to delivery): 4.70 vs. 4.72, RR 1.00 (95% CI 0.59 to 1.68) Early neonatal mortality (birth to 6 days after delivery): 4.05 vs. 4.06, RR 1.00 (95% CI 0.57 to 1.75) Neonatal mortality (birth to 28 days after delivery): 5.40 vs. 4.91, RR 1.10 (95% CI 0.67 to 1.82) Infant mortality (first year of life): 7.42 vs. 7.62, RR 0.97 (95% CI 0.64 to 1.48)
Makrides 2003[74] *Good*	Australia N=430	20 mg elemental iron daily starting at 20 weeks gestation	-	-	5.4% (12/216) vs. 4.2% (9/214), RR 1.32 (95% CI 0.57 to 3.07)	0.5% (1 case) vs 0%, p=NS (infant born at 22 weeks with bilateral intrauterine pneumonia)
Meier 2003[76] *Fair*	U.S. N=144	60 mg elemental iron daily starting at 1st prenatal visit	-	-	Adolescents 0% vs 0%, p=NS Adults 5.4% (2/38) vs. 2.9% (1/36), RR 1.89 (95% CI 0.18 to 20.00)	0% vs 0%, p=NS

Table 7. Effect of Maternal Iron Supplementation vs. Placebo on Infant Birth Outcomes

Study, year *Quality*	Country N randomized	Iron supplement dose and formulation, initiation	Preterm delivery[a]	Small for gestational age[b]	Low birth weight[c]	Infant mortality
Milman 1994[78] *Fair*	Denmark N=248	66 mg elemental iron daily starting at 14 to 16 weeks gestation	-	-	-	-
Ouladsahebmadarek, 2011[80] *Fair*	Iran N=960	30 mg elemental iron daily starting at 13 weeks gestation	Delivery at 20 to 38 weeks: 3.9% (16/410) vs. 4.8% (18/372), RR 0.81 (95% CI 0.42 to 1.56)	14.1% (58/410) vs, 17.5% (65/372), RR 0.81 (95% CI 0.59 to 1.12)	-	-
Romslo 1983[81] *Fair*	Norway N=52	200 mg elemental iron daily starting within 10 weeks gestation	-	-	-	-
Zeng 2008[85] *Fair*	China (rural) N=3,929	60 mg elemental iron daily starting at 14 weeks gestation	4.9% (76/1537) vs. 6.1% (102/1666), RR 0.81 (95% CI 0.61 to 1.08) <34 weeks: 0.98% vs. 1.80%, **RR 0.50 (95% CI 0.27 to 0.94)**	18.9% vs. 18.1%, RR 1.04 (95% CI 0.89 to 1.22)	4.5% (66/1470) vs. 5.3% (82/1545), RR 0.85 (95% CI 0.62 to 1.16)	Rates per 1000: Stillbirths (≥28 weeks through labor): 30.4 vs. 30.8, RR 1.01 (95% CI 0.67 to 1.51) All neonatal deaths (within 28 days): 10.7 vs. 20.2, **RR 0.53 (95% CI 0.29 to 0.97)** Early neonatal deaths (within 7 days): 6.7 vs. 14.7, **RR 0.46 (95% CI 0.21 to 0.98)** Perinatal deaths (stillbirth + early neonatal deaths): 36.9 vs. 45.0, RR 0.84 (95% CI 0.59 to 1.19)
Ziaei 2007[89] *Good*	Iran N=750	50 mg elemental iron daily starting at 20 weeks gestation		15.4% (57/370) vs. 10.1% (36/357), **RR 1.53 (95% CI 1.03 to 2.26)**	-	0.8% (3/370) vs. 1.7% (6/357), RR 0.48 (95% CI 0.12 to 1.91)

Abbreviation: CI, confidence interval; NS, not significant; RR, relative risk

[a]Preterm delivery is defined as <37 weeks.

[b]Small for gestational age is defined as <10th percentile of birth weight for gestational age.

[c]Low birth weight is defined as <2,500g.

Bolded values show a statistically significant difference.

Table 8. Harms of Maternal Iron Supplementation

Study, year *Quality*	Country N randomized	Iron supplement dose and formulation, initiation	Maternal adverse outcomes	Non-adherence
Chan 2009[64] *Fair*	Hong Kong N=1,164	60 mg elemental iron daily starting at <16 weeks gestation	"No major adverse events from study drugs"	At 36 weeks: 68% overall (of n=473 with data), p=0.34 between groups
Cogswell 2003[66] *Fair*	U.S. N=275	30 mg elemental iron daily starting at <20 weeks gestation	Side effects reported at >1 visit from enrollment to week 28: 24.6% vs. 18.5%, p=NS	At week 28: 36.6% vs 34.8%, p=NS
Eskeland 1997[68] *Fair*	Norway N=90	27 mg elemental iron daily starting at 20 weeks gestation	No difference in fatigue or other side effects, p=NS	19% (both iron arms) vs. 18%, p=NS
Jafarbegloo 2015[70]	Iran N=179	50 mg ferrous sulfate daily starting at 20 weeks gestation	At 32-36 weeks gestation: Nausea: 16.1% vs. 14%, p=0.74 Vomiting: 3.2% vs. 10%, p=0.09 Diarrhea: 0% vs. 2%, p=0.17 Constipation: 12.9% vs. 4%, p=0.09 Loss of appetite: 4.3% vs. 4%, p=0.93 Heart burn: 16.1% vs. 8%, p=0.17 Abdominal pain: 2.2% vs. 2%, p=0.30	-
Liu 2013[72] *Good*	China (rural) N=12,513	30 mg elemental iron daily starting at <20 weeks gestation	Serious adverse events: none reported Gastrointestinal discomfort (e.g. nausea, vomiting; denominators at 24 to 28 weeks): 3.6% (212/5913) vs. 2.3% (133/5896), **RR 1.59 (95% CI 1.28 to 1.97)**	7.2% vs. 6.7%
Makrides 2003[74] *Good*	Australia N=430	20 mg elemental iron daily starting at 20 weeks gestation	At 36 weeks gestation: Nausea: 29% vs 28%, RR 1.04, 0.76 to 1.42 Stomach pain: 35% vs 30%, RR 1.19, 0.89 to 1.58 Heartburn: 68% vs 69%, RR 0.99, 0.86 to 1.13 Vomiting: 12% vs 13%, RR 0.89, 0.53 to 1.50 Bowel ≤3 times/week: 4% vs 1.6%, RR 2.56, 0.69 to 9.51 Rash: 7.5% vs 6.2%, RR 1.21, 0.58 to 2.51	14% vs. 15%, p=NS
Meier 2003[76] *Fair*	U.S. N=144	60 mg elemental iron daily starting at 1st prenatal visit	<u>Adolescents</u>: Nausea: 53% vs 65%, p=NS Vomiting: 41% vs 41%, p=NS Constipation: 29% vs 12%, p=NS Diarrhea: 13% vs 17%, p=NS <u>Adults</u>: Nausea: 63% vs 53%, p=NS Vomiting: 35% vs 21%, p=NS Constipation: 24% vs 28%, p=NS Diarrhea: 14% vs 24%, p=NS	Adolescents: 4.5% vs 12.6%, p=0.320 Adults: 2.2% vs 16.1%, **p=0.036**

Table 8. Harms of Maternal Iron Supplementation

Study, year *Quality*	Country N randomized	Iron supplement dose and formulation, initiation	Maternal adverse outcomes	Non-adherence
Ouladsahebmadarek, 2011[80] *Fair*	Iran N=960	30 mg elemental iron daily starting at 13 weeks gestation	No difference in means of complications including septicemia.	-
Romslo 1983[81] *Fair*	Norway N=52	200 mg elemental iron daily starting within 10 weeks gestation	No discomfort attributed to the medication was reported.	45% overall, p=NS
Siega-Riz 2006[83] *Fair*	US N=429	30 mg elemental iron daily starting at <20 weeks gestation	-	34% vs. 37%, p=0.27
Zeng 2008[85] *Fair*	China (rural) N=3,929	60 mg elemental iron daily starting at 14 weeks gestation	Withdrawals due to adverse events: Nausea: 1.6% (31/1912) vs. 1.3% (26/2017), RR 1.26 (95% CI 0.75 to 2.11) Vomiting: 2.1% (40/1912) vs. 1.4% (28/2017), RR 1.51 (95% CI 0.93 to 2.43)	Mean % of days when supplements not consumed: 8.1% vs. 6.6%
Zhao 2015[86] *Fair*	China (rural) N=2,371	60 mg elemental iron daily starting at enrollment	"Minor adverse symptoms such as nausea, vomiting, diarrhea, or constipation:" 68.4% vs. 68.2%	14.9% vs. 9.9% (women with complete data, ns NR)

Abbreviations: CI, confidence interval; Hb, hemoglobin; MCV, mean corpuscular volume; MD, mean difference; NS, not significant; RCT, randomized control trial; RR, relative risk; SES, socioeconomic status; SF, serum ferritin; U.S., United States

Note: Bolded values show a statistically significant difference.

Table 9. Summary of Evidence for Routine Iron Supplementation in Pregnant Women

Key question *Outcome*	No. of studies (k) No. of participants (N) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Body of evidence limitations	*Overall quality*	*Strength of evidence*	Applicability
KQ 1. Benefits, maternal *QOL*	k=1 RCT n=430	No differences in quality of life for iron supplementation versus placebo in one trial at 36 weeks of gestation, 6 weeks, 6 months, or 4 years postpartum	Unable to assess consistency (1 trial) Imprecise No reporting bias detected	Single trial Outcome based on SF-36; reported as secondary outcome	Fair	Insufficient	1 trial conducted in Australia Applicability limited due to insufficient evidence
KQ 1. Benefits, maternal *Hypertensive disorders of pregnancy*	k=5 RCTs N=14,468	Iron supplementation vs. placebo or no iron: (5 trials; RR, 1.24 [95% CI, 0.75 to 2.06]; I^2=48% No difference in stratified analyses by HDI country or supplement dose	Inconsistent Imprecise Some reporting bias detected	Poorly defined outcome definition: 3 studies reported pregnancy induced hypertension, 1 study reported preeclampsia and PIH, 2 studies reported the category of hypertensive diseases of pregnancy	Fair	Low for no effect of iron supplementation on hypertensive disorders of pregnancy	Studies conducted in Ireland, Iran (3), and rural China Stratified analysis by HDI country or supplement dose did not affect results
KQ 1. Benefits, maternal *Gestational diabetes*	k=2 N=2,214	Two studies reported no differences in rates of gestational diabetes for iron supplementation versus placebo	Consistent Imprecise No reporting bias detected	Diagnostic criteria defined in one of two studies	Fair	Insufficient	Studies conducted in Hong Kong and Iran; unclear diagnostic criteria

Table 9. Summary of Evidence for Routine Iron Supplementation in Pregnant Women

Key question *Outcome*	No. of studies (k) No. of participants (N) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Body of evidence limitations	*Overall quality*	*Strength of evidence*	Applicability
KQ 1. Benefits, maternal *Cesarean delivery*	k=8 RCTs N=6,160	Iron supplementation vs. placebo or no iron: 8 trials; RR, 1.01 [95% CI, 0.90 to 1.14]; I^2=42.7% In 1 trial (n=1,164): Reduced risk of cesarean for 60 mg elemental iron daily versus placebo (25.2% vs 33.1%; OR, 0.58, [95% CI, 0.37 to 0.89]) No difference in stratified analyses by HDI country or supplement dose	Inconsistent Some imprecision No reporting bias detected	Cesarean delivery may occur for a variety of indications, including elective reasons	Fair	Low for no effect on cesarean delivery	Studies conducted in Ireland, Hong Kong, Australia, U.S., Iran (3), rural China. Cesarean rates were unusually high in two studies Stratified analysis by HDI country or supplement dose did not affect results
KQ 1. Benefits, maternal *Hemorrhage*	k=2 RCTs N=341	Two studies report no difference in rates of maternal hemorrhage	Consistent Imprecise No reporting bias detected	Low event rates in both studies	Fair	Insufficient for maternal hemorrhage	Studies conducted in Ireland and Iran

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Key question *Outcome*	No. of studies (k) No. of participants (N) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Body of evidence limitations	*Overall quality*	*Strength of evidence*	Applicability
KQ1. Benefits, maternal *Iron deficiency anemia*	k=7 RCTs N=4,045	Iron supplementation vs. placebo or no iron: 3rd trimester: 3 trials; RR, 0.63 [95% CI, 0.41 to 0.97]; I^2=0%; ARD, -4% [95% CI, -8% to 0%]) Term: 4 trials; RR, 0.40 [95% CI, 0.26 to 0.61]; I^2=20.5%; ARD, -10% [95% CI, -16% to -3%] Statistically significant difference in stratified analyses, at term: By HDI country: very high HDI: RR, 0.29 [95% CI, 0.15 to 0.55]; I^2=0.0%; ARD, -12% [95% CI, -19% to -6%] vs. medium to high HDI: RR, 0.49 [95% CI, 0.38 to 0.62]; I^2=NA; ARD, -5% [95% CI, -16% to 5%] By supplement dose: low dose: RR, 0.28 [95% CI, 0.12 to 0.68]; I^2=NA; ARD, -8% [95% CI, -13% to -3%] vs. high dose: RR, 0.42 [95% CI, 0.24 to 0.71]; I^2=21.0%; ARD, -11% [95% CI, -19% to -2%]	Consistent Some imprecision No reporting bias detected	Variable doses of iron supplements	Fair	Moderate for reduced risk of IDA during third trimester and at term	Studies conducted in the U.S. (3) Iran, Australia, Denmark, and rural China; similar results in subgroup analysis by country The clinical significance of differences is uncertain

Table 9. Summary of Evidence for Routine Iron Supplementation in Pregnant Women

Key question *Outcome*	No. of studies (k) No. of participants (N) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Body of evidence limitations	*Overall quality*	*Strength of evidence*	Applicability
KQ1. Benefits, maternal *Iron deficiency*	k=9 RCTs N=16,556	Iron supplementation vs. placebo or no iron: 3rd trimester: 4 trials; RR, 0.70 [95% CI, 0.53 to 0.92]; I^2=77.4%; ARD, -17% [95% CI, -24% to -10%]) Term: 6 trials; RR, 0.47 [95% CI, 0.33 to 0.67]; I^2=81.9%; ARD, -34% [95% CI, -46% to -22%] Mostly statistically significant differences in stratified analyses, at term: By HDI country: very high HDI: RR, 0.35 [95% CI, 0.18 to 0.65]; I^2=79.3%; ARD, -44% [95% CI, -63% to -25%] though medium to high HDI analysis showed no difference By supplement dose: low dose: RR, 0.57 [95% CI, 0.46 to 0.69]; I^2=0.0%; ARD, -32% [95% CI, -52% to -11%] vs. high dose: RR, 0.26 [95% CI, 0.09 to 0.77]; I^2=86.0%; ARD, -36% [95% CI, -54% to -18%]	Consistent Some Imprecision No reporting bias detected	Study heterogeneity (I^2) was high Variable doses of iron supplements	Fair	Moderate for reduced risk of iron deficiency during third trimester and at term	Studies conducted in the U.S. (2), Norway (2), Iran, Australia, rural China (2), Denmark Largest studies in rural China; analysis stratified by country showed similar results for very high HDI countries, but the medium to high countries analysis was no longer statistically significant The clinical significance of differences is uncertain

Table 9. Summary of Evidence for Routine Iron Supplementation in Pregnant Women

Key question *Outcome*	No. of studies (k) No. of participants (N) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Body of evidence limitations	*Overall quality*	*Strength of evidence*	Applicability
KQ1. Benefits, maternal *Anemia*	k=9 RCTs N=20,330	Iron supplementation vs. placebo or no iron: 3rd trimester: 7 trials; RR, 0.71 [95% CI, 0.51 to 0.97]; I^2=64.2%; 3 studies were statistically significant; ARD, -7.97% [95% CI -15.28% to -0.66%] Term: 4 trials; RR, 0.43 [95% CI, 0.26 to 0.72]; I^2=43.7%; ARD, -11.73% [95% CI, -14.87 to -8.60%] Mostly statistically significant differences in stratified analyses, at term: By HDI country: very high HDI: RR, 0.22 [95% CI, 0.06 to 0.84]; I^2=49.3%; ARD, -12.42% [95% CI, -18.76% to -6.08%] vs. medium to high HDI: RR, 0.53 [95% CI, 0.43 to 0.66]; I^2=NA; ARD, -11.67% [95% CI, -15.48% to -7.87%] By supplement dose: low dose: RR, 0.45 [95% CI, 0.25 to 0.82]; I^2=NA; ARD, -8.54% [95% CI, -14.76% to -2.33%] vs. high dose: RR, 0.22 [95% CI, 0.05 to 1.02]; I^2=61.1% Anemia rates ranged from 0% to 45% in the supplementation and 4.5% to 61% in the placebo group	Inconsistent Imprecise Some reporting bias detected	Type of anemia not defined in most studies	Fair	Low	Studies conducted in the U.S. (2), Norway, Australia, rural China (3), Denmark Largest studies conducted in rural China

Table 9. Summary of Evidence for Routine Iron Supplementation in Pregnant Women

Key question *Outcome*	No. of studies (k) No. of participants (N) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Body of evidence limitations	*Overall quality*	*Strength of evidence*	Applicability
KQ1. Benefits, maternal *Hemoglobin*	k=15 RCTs N=20,069	Findings were inconsistent during the 3rd trimester and postpartum, and mostly significant at term with higher hemoglobin values with supplementation versus placebo Hemoglobin levels ranged from 11.0 to 13.9 g/dL in the supplementation and 10.5 to 13.4 g/dL in the placebo group	Inconsistent Imprecise No reporting bias detected	Hemoglobin values decrease during pregnancy due to physiologic blood volume expansion and, in isolation, have unclear clinical significance	Fair	Low for increased hemoglobin	Studies conducted in the U.S. (3), Iran (5), Hong Kong, Australia, Ireland, Norway, Denmark, and rural China (2)
KQ1. Benefits, maternal *Serum ferritin*	k=13 RCTs N=19,075	Reported ferritin levels were inconsistent during the 3rd trimester and postpartum, and mostly significant at term with higher serum ferritin values with supplementation versus placebo in most studies Serum ferritin ranged from 7.4 to 34 µg/L in the supplementation group and 6.0 to 26 µg/L in the placebo group	Inconsistent Imprecise Reporting bias not detected	Ferritin levels are associated with inflammation and in isolation, have unclear clinical significance	Fair	Low for increased serum ferritin	Studies conducted in the U.S. (3), Hong Kong, Iran (3), Australia, Ireland, Norway, Denmark, rural China (2) The clinical significance of these findings remains unclear
KQ 1. Benefits, infant *Mortality*	k=6 trials N=17,863	Five trials reported no association between maternal iron supplementation and infant mortality, while 1 study reported a statistically significant difference in rates of neonatal deaths (1.1% vs. 2.0%, RR, 0.53 [95% CI, 0.29 to 0.97])	Some inconsistency Imprecise No reporting bias detected	Not a pre-specified outcome in any study; event rates were generally low	Fair	Insufficient	Studies conducted in Ireland, rural China (2), Australia, U.S. and Iran

Table 9. Summary of Evidence for Routine Iron Supplementation in Pregnant Women

Key question *Outcome*	No. of studies (k) No. of participants (N) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Body of evidence limitations	*Overall quality*	*Strength of evidence*	Applicability
KQ 1. Benefits, infant *Preterm birth*	k=5 RCTs N=18,714	Iron supplementation vs. placebo: 5 trials; RR, 0.92 [95% CI, 0.81 to 1.04]; I^2=0% No difference in stratified analyses by HDI country or supplement dose	Consistent Precise No reporting bias detected	Reported as a secondary outcome	Fair	Moderate for no effect of iron supplementation on preterm birth	Studies conducted in Hong Kong, Iran (3), rural China (2) Stratified analysis by HDI country or supplement dose did not affect results
KQ 1. Benefits, infant *Small for gestational age*	k=4 RCTs N=6,803	Iron supplementation vs. placebo: 4 trials; RR, 0.94 [95% CI, 0.67 to 1.31]; I^2=75.5% Mostly no difference in stratified analyses by HDI country or supplement dose, with one exception: the 1 very high HDI trial (RR, 0.48 [95% CI, 0.26 to 0.87])	Inconsistent Imprecise No reporting bias detected	Reported as a secondary outcome	Fair	Insufficient	Studies conducted in Hong Kong, rural China, and Iran
KQ1. Benefits, infant *Low birth weight*	k=6 RCTs N=17,261	Iron supplementation versus placebo: 6 trials; RR, 0.95; [95% CI, 0.79 to 1.14]; I^2=0.0% No difference in stratified analyses by HDI country or supplement dose	Some inconsistency Some imprecision No reporting bias detected	Reported as a secondary outcome	Fair	Moderate for no effect of iron supplementation on LBW	Studies conducted in Ireland, Iran, rural China (2), Australia, U.S. Stratified analysis by HDI country or supplement dose did not affect results

Table 9. Summary of Evidence for Routine Iron Supplementation in Pregnant Women

Key question *Outcome*	No. of studies (k) No. of participants (N) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Body of evidence limitations	*Overall quality*	*Strength of evidence*	Applicability
KQ1. Benefits, infant *Hematologic outcomes*	k=2 RCTs N=12,943	Infant hemoglobin and anemia reported at 6 months and 1 year in 1 trial, and infant hemoglobin, ferritin, ID, and IDA reported in another trial at 6 months No differences reported between groups for any hematologic indices or time points	Consistent Imprecise No reporting bias detected	Changes in infant intermediate outcomes up to one year could be multifactorial; only the smaller trial (n=430) reported ID and IDA outcomes and event rates were low	Fair	Insufficient	Studies conducted in rural China and Australia
KQ 2. Harms	k=12 RCTs N=22,716	12 trials (11 included in KQ1) assessed harms of routine iron supplementation in pregnant women Most reported harms included transient treatment effects such as nausea, constipation, and diarrhea, and all but one found no difference in harms; 1 large trial conducted in rural China found a higher rate of gastrointestinal discomfort for those receiving supplementation 3.6% vs. 2.3%; RR, 1.59 (95% CI, 1.28 to 1.97) 9 trials found no difference in non-adherence to supplementation versus placebo between groups; however, 1 trial had lower non-adherence in the supplementation than the placebo group	Mostly consistent Some imprecision Some reporting bias detected	Outcomes mostly reported as ad hoc events	Fair	Moderate for no major harms and some transient side effects of prenatal iron supplementation	Studies conducted in Hong Kong, the U.S. (3), Norway, rural China (3), Australia, Iran (2), Norway

Table 9. Summary of Evidence for Routine Iron Supplementation in Pregnant Women

Key question *Outcome*	No. of studies (k) No. of participants (N) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Body of evidence limitations	*Overall quality*	*Strength of evidence*	Applicability
KQ 3. Association	k=1 observational study N=20,690	Response to iron therapy was associated with a reduction in the odds of preeclampsia and preterm delivery compared with those with untreated anemia or those who did not respond to treatment	Unable to assess consistency Imprecise Reporting bias detected	Inconsistent methods for defining anemia; included participants already using iron supplementation; lack of reporting on methods for outcome assessment Comparison groups were based on all persons with anemia compared with specific groups within the whole population (e.g. refractory to treatment or successful treatment) rather than comparing outcomes in responders versus non-responders	Fair	Insufficient	Conducted in U.S.; some participants already using iron supplementation; lack of information on dosing, timing, or duration of treatment

Abbreviations: CI, confidence interval; GI, gastrointestinal; ID, iron deficiency; IDA, iron deficiency anemia; KQ, Key Question; LBW, low birth weight; PIH, pregnancy induced hypertension; RCT, randomized control trial; RR, relative risk; SGA, small for gestational age; U.S., United States.

Table 10. Summary of Evidence for Screening for Iron Deficiency and Iron Deficiency Anemia in Pregnancy

Key question	Number of studies (k) Number of participants* (n) Study design	Summary of findings by outcome	Consistency/ precision Reporting bias	Body of evidence limitations	*Overall quality*	*Strength of evidence*	Applicability
KQ 1. Screening benefits	No studies	-	-	-	-	Insufficient	-
KQ 2. Screening harms	No studies	-	-	-	-	Insufficient	-
KQ 3. Treatment benefits	No studies	-	-	-	-	Insufficient	-
KQ 4. Treatment harms	No studies	-	-	-	-	Insufficient	-
KQ 5. Association (Same KQ as KQ 3 in the supplementation framework)	k=1 observational study N=20,690	Response to iron therapy was associated with a reduction in the odds of preeclampsia and preterm delivery compared with those with untreated anemia or those who did not respond to treatment	Unable to assess consistency Imprecise Some reporting bias detected	Inconsistent methods for defining anemia; included participants already using iron supplementation; lack of reporting on methods for outcome assessment Comparison groups were based on all persons with anemia compared with specific groups within the whole population (e.g. refractory to treatment or successful treatment) rather than comparing outcomes in responders versus non-responders	Fair	Insufficient	Conducted in U.S.; some participants already using iron supplementation; lack of information on dosing, timing, or duration of treatment

Abbreviations: KQ, Key Question; U.S., United States.

Appendix A1. Search Strategies

Database: Ovid MEDLINE

Pregnancy Iron Screening

1 exp pregnancy/
2 exp pregnancy complications/
3 exp Maternal Nutritional Physiological Phenomena/
4 (pregnan* or prenatal* or antenatal* or obstetric* or trimester* or gestat*or maternal* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid or (expect* adj3 mother*)).mp.
5 1 or 2 or 3 or 4
6 exp Mass Screening/ or screen$.mp. or exp Diagnostic Tests, Routine/ or (routin* adj3 (diagnos* or detect*)).mp. or ((routin* or repeat* or frequen*) adj3 (test* or assess* or assay* or status or measur* or (blood adj2 (sampl* or draw*)))).mp.
7 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (defic* or lack* or insuffic* or ("not" adj2 (suffic* or adequa*)) or inadequa* or scarc* or shortag* or deplet*)).mp. or exp Iron Deficiencies/ or exp Anemia, Iron-Deficiency/ or ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 ((an?emi* or (reduc* or low or lower* or inadeq* or insuffic* or lack* or shortag*)) adj3 (h?emoglob* or hgb or h?ematocrit* or rbc* or red blood cell*))).mp.
8 exp iron/bl or exp iron compounds/bl or ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj3 (level* or serum* or blood or status)).mp.
9 7 or 8
10 5 and 6 and 9
11 ((screen* or (routin* adj3 (diagnos* or detect*)) or (routin* adj3 (test* or assess* or assay* or measur* or (blood adj2 draw*)))) adj10 (((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (defic* or lack* or status or insuffic* or ("not" adj2 (suffic* or adequa*)) or inadequa* or scarc* or shortag* or deplet*)) or ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj10 (an?emi* or (reduc* or defic* or low or lower* or inadeq* or insuffic* or lack* or shortag*)) adj3 (h?emoglob* or hgb or h?ematocrit* or rbc* or (red adj2 cell*) or blood)))).mp.
12 5 and 11
13 ((pregnan* or prenatal* or antenatal* or obstetric* or trimester* or gestat* or maternal* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid* or (expect* adj3 mother*)) adj15 ((screen* or (routin* adj3 (diagnos* or detect*)) or ((routin* or repeat* or frequen*) adj3 (test* or assess* or assay* or measur* or (blood adj2 draw*)))) adj10 (((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (defic* or lack* or status or insuffic* or ("not" adj2 (suffic* or adequa*)) or inadequa* or scarc* or shortag* or deplet*)) or ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj10 (an?emi* or (reduc* or defic* or low or lower* or inadeq* or ("not" adj2 (suffic* or adequa*)) or insuffic* or lack* or status or shortag* or deplet*)) adj3 (h?emoglob* or hgb or h?ematocrit* or rbc* or (red adj2 cell*) or blood))))).mp.
14 10 or 12 or 13
15 limit 14 to english language

16 limit 14 to abstracts
17 15 or 16

Pregnancy Iron Only Anemia

1 exp Iron/ or exp iron compounds/ or exp iron, dietary/
2 exp Dietary Supplements/
3 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (pill* or tablet* or capsule* or liquid* or syrup* or elixir* or supplemen* or intraven* or parenteral* or oral*)).mp.
4 exp Iron, Dietary/ad or exp iron compounds/ad or exp iron/ad
5 1 and 2
6 3 or 4 or 5
7 exp pregnancy/
8 (pregnan* or prenatal* or antenatal* or obstetric* or trimester* or gestat* or maternal* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid).mp.
9 exp pregnancy complications/
10 exp Maternal Nutritional Physiological Phenomena/
11 7 or 8 or 9 or 10
12 6 and 11
13 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj7 (pill* or tablet* or capsule* or liquid* or syrup* or elixir* or supplemen* or intraven* or parenteral* or oral*) adj10 (pregnan* or prenatal* or antenatal* or obstetric* or trimester* or gestat* or maternal* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid)).mp.
14 12 or 13
15 limit 14 to english language
16 limit 14 to abstracts
17 15 or 16
18 limit 17 to humans
19 exp Iron/ad, tu or exp iron compounds/ad, tu or exp iron, dietary/ad, tu or exp Iron Deficiencies/dt, th, dh
20 exp Iron/ or exp iron compounds/ or exp iron, dietary/ or exp Iron Deficiencies/
21 exp Dietary Supplements/
22 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (pill* or tablet* or capsule* or liquid* or syrup* or elixir* or supplemen* or intraven* or parenteral* or oral*)).mp.
23 20 and 21
24 19 or 22 or 23
25 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (defic* or lack* or insuffic* or ("not" adj2 (suffic* or adequa*)) or inadequa* or scarc* or shortag* or deplet* or missing)).mp. or exp Iron Deficiencies/ or exp Anemia, Iron-Deficiency/
26 exp anemia/th, dh, dt, pc
27 24 and 26

28 exp pregnancy/ or exp pregnancy complications/ or exp Maternal Nutritional Physiological Phenomena/ or (pregnan* or prenatal* or antenatal* or obstetric* or trimester* or gestat* or maternal* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid* or (expect* adj3 mother*)).mp.
29 24 and 25 and 28
30 27 and 28
31 29 or 30
32 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (defic* or lack* or insuffic* or ("not" adj2 (suffic* or adequa*)) or inadequa* or scarc* or shortag* or deplet* or missing) adj10 (pregnan* or prenatal* or antenatal* or obstetric* or maternal* or trimester* or gestat* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid* or (expect* adj3 mother*))).mp.
33 31 or 32
34 limit 33 to english language
35 limit 33 to abstracts
36 34 or 35
37 limit 36 to humans
38 18 and 37
39 18 not 38
40 37 not 38
41 limit 38 to (systematic reviews pre 2019 or systematic reviews)
42 limit 38 to (adaptive clinical trial or controlled clinical trial or pragmatic clinical trial or randomized controlled trial)
43 42 not 41
44 exp Epidemiologic Studies/
45 exp "Outcome and Process Assessment, Health Care"/
46 exp Comparative Study/
47 44 or 45 or 46
48 38 and 47
49 48 not (42 or 43)
50 38 not (42 or 43 or 49)
51 limit 39 to (systematic reviews pre 2019 or systematic reviews)
52 limit 39 to (adaptive clinical trial or controlled clinical trial or pragmatic clinical trial or randomized controlled trial)
53 52 not 51
54 39 and 47
55 54 not (51 or 52)
56 39 not (51 or 52 or 55)
57 limit 40 to (systematic reviews pre 2019 or systematic reviews)
58 limit 40 to (adaptive clinical trial or controlled clinical trial or pragmatic clinical trial or randomized controlled trial)
59 58 not 57
60 40 and 47
61 60 not (57 or 58)

62 40 not (57 or 58 or 61)

Pregnancy Iron Only Supplementation

1 exp Iron/ or exp iron compounds/ or exp iron, dietary/
2 exp Dietary Supplements/
3 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (pill* or tablet* or capsule* or liquid* or syrup* or elixir* or supplemen* or intraven* or parenteral* or oral*)).mp.
4 exp Iron, Dietary/ad or exp iron compounds/ad or exp iron/ad
5 1 and 2
6 3 or 4 or 5
7 exp pregnancy/
8 (pregnan* or prenatal* or antenatal* or obstetric* or trimester* or gestat* or maternal* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid).mp.
9 exp pregnancy complications/
10 exp Maternal Nutritional Physiological Phenomena/
11 7 or 8 or 9 or 10
12 6 and 11
13 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj7 (pill* or tablet* or capsule* or liquid* or syrup* or elixir* or supplemen* or intraven* or parenteral* or oral*) adj10 (pregnan* or prenatal* or antenatal* or obstetric* or trimester* or gestat* or maternal* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid)).mp.
14 12 or 13
15 limit 14 to english language
16 limit 14 to abstracts
17 15 or 16
18 limit 17 to humans
19 exp Iron/ad, tu or exp iron compounds/ad, tu or exp iron, dietary/ad, tu or exp Iron Deficiencies/dt, th, dh
20 exp Iron/ or exp iron compounds/ or exp iron, dietary/ or exp Iron Deficiencies/ (168831)
21 exp Dietary Supplements/
22 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (pill* or tablet* or capsule* or liquid* or syrup* or elixir* or supplemen* or intraven* or parenteral* or oral*)).mp.
23 20 and 21
24 19 or 22 or 23
25 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (defic* or lack* or insuffic* or ("not" adj2 (suffic* or adequa*)) or inadequa* or scarc* or shortag* or deplet* or missing)).mp. or exp Iron Deficiencies/ or exp Anemia, Iron-Deficiency/ [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol

supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
26 exp anemia/th, dh, dt, pc
27 24 and 26
28 exp pregnancy/ or exp pregnancy complications/ or exp Maternal Nutritional Physiological Phenomena/ or (pregnan* or prenatal* or antenatal* or obstetric* or trimester* or gestat* or maternal* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid* or (expect* adj3 mother*)).mp.
29 24 and 25 and 28
30 27 and 28
31 29 or 30
32 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (defic* or lack* or insuffic* or ("not" adj2 (suffic* or adequa*)) or inadequa* or scarc* or shortag* or deplet* or missing) adj10 (pregnan* or prenatal* or antenatal* or obstetric* or maternal* or trimester* or gestat* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid* or (expect* adj3 mother*))).mp.
33 31 or 32
34 limit 33 to english language
35 limit 33 to abstracts
36 34 or 35
37 limit 36 to humans
38 18 and 37
39 18 not 38
40 37 not 38
41 limit 38 to (systematic reviews pre 2019 or systematic reviews)
42 limit 38 to (adaptive clinical trial or controlled clinical trial or pragmatic clinical trial or randomized controlled trial)
43 42 not 41
44 exp Epidemiologic Studies/
45 exp "Outcome and Process Assessment, Health Care"/
46 exp Comparative Study/
47 44 or 45 or 46
48 38 and 47
49 48 not (42 or 43)
50 38 not (42 or 43 or 49)
51 limit 39 to (systematic reviews pre 2019 or systematic reviews)
52 limit 39 to (adaptive clinical trial or controlled clinical trial or pragmatic clinical trial or randomized controlled trial)
53 52 not 51
54 39 and 47
55 54 not (51 or 52)
56 39 not (51 or 52 or 55)
57 limit 40 to (systematic reviews pre 2019 or systematic reviews)

58 limit 40 to (adaptive clinical trial or controlled clinical trial or pragmatic clinical trial or randomized controlled trial)
59 58 not 57
60 40 and 47
61 60 not (57 or 58)
62 40 not (57 or 58 or 61)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1 exp Iron/ or exp iron compounds/ or exp iron, dietary/
2 exp Dietary Supplements/
3 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (pill* or tablet* or capsule* or liquid* or syrup* or elixir* or supplemen* or intraven* or parenteral* or oral*)).mp.
4 exp Iron, Dietary/ad or exp iron compounds/ad or exp iron/ad
5 1 and 2
6 3 or 4 or 5
7 exp pregnancy/
8 (pregnan* or prenatal* or antenatal* or obstetric* or trimester* or gestat* or maternal* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid).mp.
9 exp pregnancy complications/
10 exp Maternal Nutritional Physiological Phenomena/
11 7 or 8 or 9 or 10
12 6 and 11
13 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj7 (pill* or tablet* or capsule* or liquid* or syrup* or elixir* or supplemen* or intraven* or parenteral* or oral*) adj10 (pregnan* or prenatal* or antenatal* or obstetric* or trimester* or gestat* or maternal* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid)).mp.
14 12 or 13
15 limit 14 to english language
16 limit 14 to abstracts
17 15 or 16
18 exp Iron/ad, tu or exp iron compounds/ad, tu or exp iron, dietary/ad, tu or exp Iron Deficiencies/dt, th, dh
19 exp Iron/ or exp iron compounds/ or exp iron, dietary/ or exp Iron Deficiencies/
20 exp Dietary Supplements/
21 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (pill* or tablet* or capsule* or liquid* or syrup* or elixir* or supplemen* or intraven* or parenteral* or oral*)).mp.
22 19 and 20
23 18 or 21 or 22

24 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (defic* or lack* or insuffic* or ("not" adj2 (suffic* or adequa*)) or inadequa* or scarc* or shortag* or deplet* or missing)).mp.
25 exp anemia/th, dh, dt, pc
26 23 and 25
27 exp pregnancy/ or exp pregnancy complications/ or exp Maternal Nutritional Physiological Phenomena/ or (pregnan* or prenatal* or antenatal* or obstetric* or trimester* or gestat* or maternal* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid* or (expect* adj3 mother*)).mp.
28 23 and 24 and 27
29 26 and 27
30 28 or 29
31 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (defic* or lack* or insuffic* or ("not" adj2 (suffic* or adequa*)) or inadequa* or scarc* or shortag* or deplet* or missing) adj10 (pregnan* or prenatal* or antenatal* or obstetric* or maternal* or trimester* or gestat* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid* or (expect* adj3 mother*))).mp.
32 30 or 31
33 limit 32 to english language
34 limit 32 to abstracts
35 33 or 34
36 17 and 35
37 17 not 36
38 35 not 36

Database: EBM Reviews - Cochrane Database of Systematic Reviews

1 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (pill* or tablet* or capsule* or liquid* or syrup* or elixir* or supplemen* or intraven* or parenteral* or oral*)).mp.
2 (pregnan* or prenatal* or antenatal* or obstetric* or trimester* or gestat* or maternal* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid).mp.
3 1 and 2
4 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj7 (pill* or tablet* or capsule* or liquid* or syrup* or elixir* or supplemen* or intraven* or parenteral* or oral*) adj10 (pregnan* or prenatal* or antenatal* or obstetric* or trimester* or gestat* or maternal* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid)).mp.
5 3 or 4
6 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (pill* or tablet* or capsule* or liquid* or syrup* or elixir* or supplemen* or intraven* or parenteral* or oral*)).mp.

7 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (defic* or lack* or insuffic* or ("not" adj2 (suffic* or adequa*)) or inadequa* or scarc* or shortag* or deplet* or missing)).mp.
8 [exp pregnancy/ or exp pregnancy complications/ or exp Maternal Nutritional Physiological Phenomena/ or (pregnan* or prenatal* or antenatal* or obstetric* or trimester* or gestat* or maternal* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid* or (expect* adj3 mother*)).mp.
9 6 and 7 and 8
10 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (defic* or lack* or insuffic* or ("not" adj2 (suffic* or adequa*)) or inadequa* or scarc* or shortag* or deplet* or missing) adj10 (pregnan* or prenatal* or antenatal* or obstetric* or maternal* or trimester* or gestat* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid* or (expect* adj3 mother*))).mp.
11 9 or 10
12 5 and 11
13 5 not 12
14 11 not 12
15 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (pill* or tablet* or capsule* or liquid* or syrup* or elixir* or supplemen* or intraven* or parenteral* or oral*)).mp.
16 (pregnan* or prenatal* or antenatal* or obstetric* or trimester* or gestat* or maternal* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid).mp.
17 15 and 16
18 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj7 (pill* or tablet* or capsule* or liquid* or syrup* or elixir* or supplemen* or intraven* or parenteral* or oral*) adj10 (pregnan* or prenatal* or antenatal* or obstetric* or trimester* or gestat* or maternal* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid)).mp.
19 17 or 18
20 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (pill* or tablet* or capsule* or liquid* or syrup* or elixir* or supplemen* or intraven* or parenteral* or oral*)).mp.
21 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (defic* or lack* or insuffic* or ("not" adj2 (suffic* or adequa*)) or inadequa* or scarc* or shortag* or deplet* or missing)).mp.
22 (pregnan* or prenatal* or antenatal* or obstetric* or trimester* or gestat* or maternal* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid* or (expect* adj3 mother*)).mp.
23 20 and 21 and 22
24 ((iron or ferric or ferrous or ferritin* or fe or "fe2+" or "fe+2" or "fe++") adj5 (defic* or lack* or insuffic* or ("not" adj2 (suffic* or adequa*)) or inadequa* or scarc* or shortag* or

deplet* or missing) adj10 (pregnan* or prenatal* or antenatal* or obstetric* or maternal* or trimester* or gestat* or nulliparous* or nullipara or nulligravid* or primapara or primaparous or primagravid* or unipara or uniparous or unigravid* or multipara or multiparous* or multigravid* or gravid* or (expect* adj3 mother*))).mp.
25 23 or 24
26 19 and 25
27 19 not 26
28 25 not 26

Appendix A2. Inclusion and Exclusion Criteria

Framework	PICOTS	Include	Exclude
Routine Iron Supplementation in Pregnancy	Populations	Asymptomatic adults (age ≥18 years) and adolescents (ages 13 to <18 years) regardless of iron status who are pregnant, and their infants	Non-pregnant persons; those with underlying diagnosis or symptoms of anemia; severely malnourished populations not representative of those in the United States
	Interventions	Oral iron supplementation; iron-fortified foods	Non-oral forms of iron
	Comparators	No supplementation A change in maternal iron deficiency and/or iron deficiency anemia status (KQ 3)	No comparison
	Outcomes	Maternal health outcomes: Mortality; health related quality of life; preeclampsia (severe), postpartum hemorrhage, blood transfusion; postpartum depression (KQ 1) Maternal Intermediate outcomes: Incidence of iron deficiency anemia; Incidence of iron deficiency; Hematologic indices and ferritin levels; Cesarean delivery rates, (KQ 1) Infant health outcomes: perinatal mortality, respiratory distress, NICU admission Infant intermediate outcomes: hematologic indices and ferritin levels; Low birth weight, small for gestational age, preterm delivery (KQ 1) More serious harms; harms leading to discontinuation; accidental overdose (KQ 2)	Infant outcomes >1 year of age
	Timing	Long-term outcomes (KQ 1) Short- or long-term outcomes (KQ 2)	
	Settings	U.S. primary care relevant settings	
	Study Designs	Randomized controlled trials, controlled cohort studies and other controlled observational studies* (KQ 1) Studies from KQ 1 and large uncontrolled observational studies* (KQ 2)	Uncontrolled studies (KQ 1)

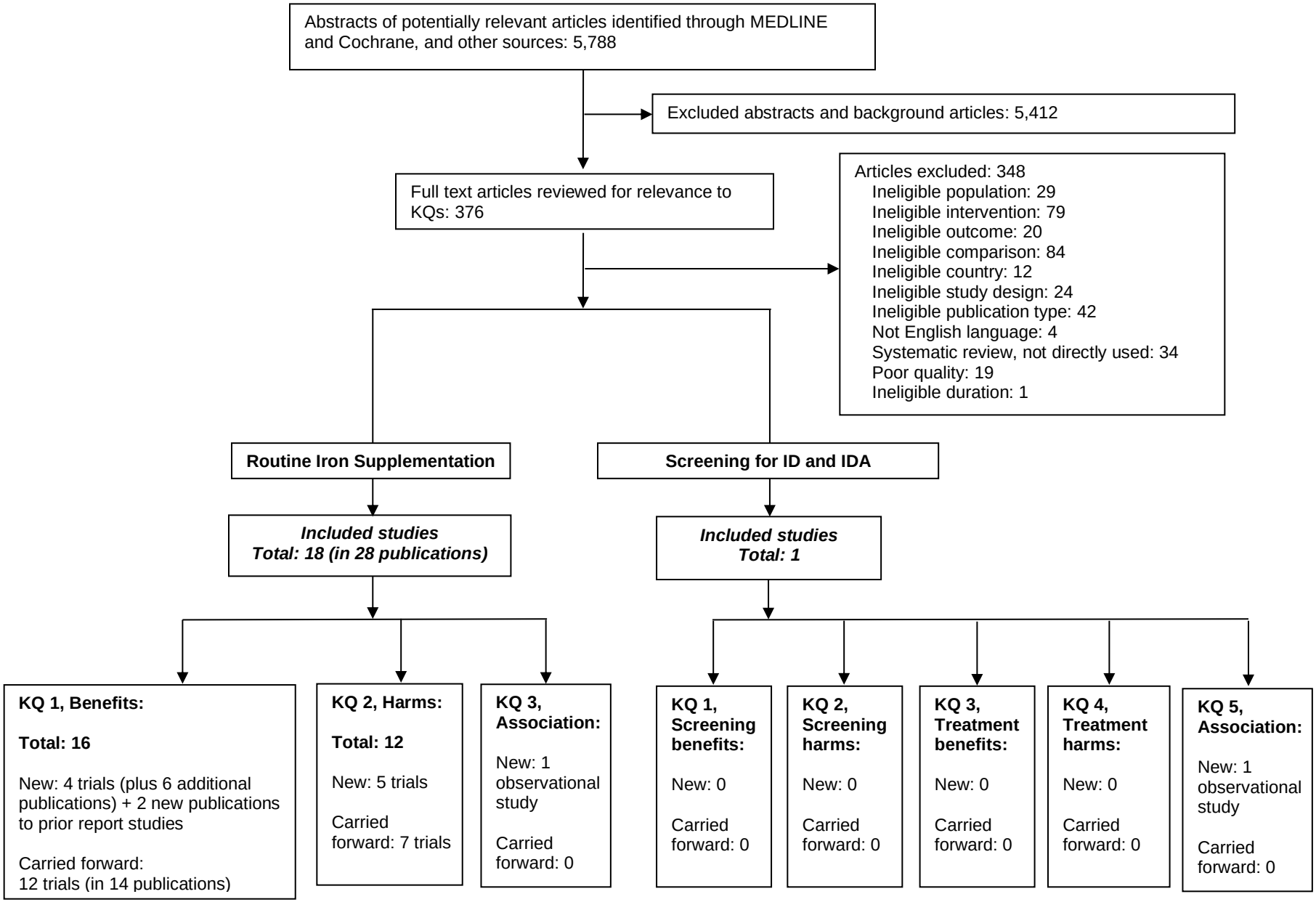
*For the supplementation framework, observational studies were not included since randomized controlled trials were available.

Appendix A2. Inclusion and Exclusion Criteria

Framework	PICOTS	Include	Exclude
Screening for Iron Deficiency Anemia in Pregnancy	Populations	Pregnant adolescents and adults and their infants asymptomatic for iron deficiency or iron deficiency anemia (KQs 1 and 2) Pregnant adolescents and adults with iron deficiency anemia and their infants (KQs 3, 4) Pregnant persons with iron deficiency, with or without anemia, and their infants (KQ 5)	Non-pregnant persons; severely malnourished populations not representative of those in the United States; Those symptomatic for iron deficiency or iron deficiency anemia
	Interventions	Screening for iron deficiency anemia (KQs 1 and 2) Oral or intravenous iron supplementation, iron-fortified foods (KQs 3 and 4)	Non-oral and non-intravenous forms of iron
	Comparators	No screening for iron deficiency anemia (KQs 1 and 2) No treatment (KQs 3 and 4) A change in maternal iron deficiency and/or iron deficiency anemia status (KQ 5)	No comparison
	Outcomes	Maternal health outcomes: Mortality; health related quality of life; preeclampsia (severe); postpartum hemorrhage, blood transfusion; postpartum depression (KQs 1, 3, 5) Maternal Intermediate outcomes: Cesarean delivery rates (KQ1,3,5); Incidence of iron deficiency anemia, incidence of iron deficiency; Hematologic indices and ferritin levels (KQ 3) Infant Health outcomes: perinatal mortality, morbidity (NICU admission, respiratory distress) Infant Intermediate outcomes: hematologic indices and ferritin levels; low birth weight, small for gestational age, preterm delivery (KQs 1, 3, 5) Overdiagnosis, anxiety, labeling, etc. (KQ 2) More serious harms; harms leading to discontinuation; overtreatment (KQ 4)	Infant outcomes >1 year of age
	Settings	U.S. primary care relevant	
	Timing	Long-term outcomes (KQs 1 and 3) Short- or long-term outcomes (KQs 2, 4, 5)	
	Study Designs	Randomized controlled trials, controlled cohort studies and other controlled observational studies (KQs 1 and 3) Studies included from other KQs and large uncontrolled observational studies (KQs 2 and 4) Association studies (KQ 5)	Uncontrolled studies (KQs 1 and 3)

Abbreviation: KQ=Key Question

Appendix A3. Literature Flow Diagram



Note 1: The sum of the number of studies per KQ exceeds the total number of studies because some studies were applicable to multiple KQs.
Note 2: KQ3 in the routine iron supplementation framework and KQ5 in the screening for ID and IDA framework are the same KQ and therefore cover the same evidence.

Abbreviations: ID=iron deficiency, IDA=iron deficiency anemia; KQ=Key Question.

Appendix A4. List of Included Studies

1. Barton DP, Joy MT, Lappin TR, et al. Maternal erythropoietin in singleton pregnancies: a randomized trial on the effect of oral hematinic supplementation. Am J Obstet. Gynecol. 1994;170(3):896-901. doi: 10.1016/s0002-9378(94)70305-1. PMID: 8141223.
2. Chan KKL, Chan BCP, Lam KF, et al. Iron supplement in pregnancy and development of gestational diabetes--a randomised placebo-controlled trial. BJOG. 2009;116(6):789-8. doi: 10.1111/j.1471-0528.2008.02014.x. PMID: 19432567.
3. Chen S, Li N, Mei Z, et al. Micronutrient supplementation during pregnancy and the risk of pregnancy-induced hypertension: a randomized clinical trial. Clin Nutr. 2019;38(1):146-51. doi: 10.1016/j.clnu.2018.01.029. PMID: 29428785.
4. Cogswell ME, Parvanta I, Ickes L, et al. Iron supplementation during pregnancy, anemia, and birth weight: a randomized controlled trial. Am J Clin Nutr. 2003;78(4):773-81. doi: 10.1093/ajcn/78.4.773. PMID: 14522736.
5. Detlefs SE, Jochum MD, Salmanian B, et al. The impact of response to iron therapy on maternal and neonatal outcomes among pregnant women with anemia. Am J Obstet Gynecol MFM. 2022;4(2):100569. doi: 10.1016/j.ajogmf.2022.100569. PMID: 35033748.
6. Eskeland B, Malterud K, Ulvik RJ, et al. Iron supplementation in pregnancy: is less enough? A randomized, placebo controlled trial of low dose iron supplementation with and without heme iron. Acta Obstet Gynecol Scand. 1997;76(9):822-8. doi: 10.3109/00016349709024359. PMID: 9351406.
7. Falahi E, Akbari S, Ebrahimzade F, et al. Impact of prophylactic iron supplementation in healthy pregnant women on maternal iron status and birth outcome. Food Nutr Bull. 2011;32(3):213-7. doi: 10.1177/156482651103200305. PMID: 22073795.
8. Jafarbegloo E, Ahmari Tehran H, Dadkhah Tehrani T. Gastrointestinal complications of ferrous sulfate in pregnant women: a randomized double-blind placebo-controlled trial. Iran Red Crescent Med J. 2015 Aug 29;17(8):e15001. doi: 10.5812/ircmj.15001. PMID: 26430520; PMCID: PMC4587092.
9. Li Z, Mei Z, Zhang L, et al. Effects of prenatal micronutrient supplementation on spontaneous preterm birth: a double-blind randomized controlled trial in China. Am J Epidemiol. 2017;186(3):318-25. doi: 10.1093/aje/kwx094. PMID: 28472219.
10. Liu J-m, Mei Z, Ye R, et al. Micronutrient supplementation and pregnancy outcomes: double-blind randomized controlled trial in China. JAMA Intern Med. 2013;173(4):276-82. doi: 10.1001/jamainternmed.2013.1632. PMID: 23303315.
11. Liu Y, Li N, Mei Z, et al. Effects of prenatal micronutrients supplementation timing on pregnancy-induced hypertension: secondary analysis of a double-blind randomized controlled trial. Matern Child Nutr. 2021;17(3):e13157. doi: 10.1111/mcn.13157. PMID: 33594802.
12. Makrides M, Crowther CA, Gibson RA, et al. Efficacy and tolerability of low-dose iron supplements during pregnancy: a randomized controlled trial. Am J Clin Nutr. 2003;78(1):145-53. doi: 10.1093/ajcn/78.1.145. PMID: 12816784.

13. Mei Z, Serdula MK, Liu J-M, et al. Iron-containing micronutrient supplementation of Chinese women with no or mild anemia during pregnancy improved iron status but did not affect perinatal anemia. J Nutr. 2014;144(6):943-8. doi: 10.3945/jn.113.189894. PMID: 24744317.

14. Meier PR, Nickerson HJ, Olson KA, et al. Prevention of iron deficiency anemia in adolescent and adult pregnancies. Clin Med Res. 2003;1(1):29-36. doi: 10.3121/cmr.1.1.29. PMID: 15931282.

15. Milman N, Agger AO, Nielsen OJ. Iron supplementation during pregnancy. Effect on iron status markers, serum erythropoietin and human placental lactogen. A placebo controlled study in 207 Danish women. Dan Med Bull. 1991;38(6):471-6. PMID: 1802636.

16. Milman N, Agger AO, Nielsen OJ. Iron status markers and serum erythropoietin in 120 mothers and newborn infants. Effect of iron supplementation in normal pregnancy. Acta Obstet Gynecol Scand. 1994;73(3):200-4. doi: 10.3109/00016349409023439. PMID: 8122498.

17. Milman N, Byg KE, Agger AO. Hemoglobin and erythrocyte indices during normal pregnancy and postpartum in 206 women with and without iron supplementation. Acta Obstet Gynecol Scand. 2000;79(2):89-98. doi: 10.1034/j.1600-0412.2000.079002089.x. PMID: 10696955.

18. Ouladsahebmadarek E S-MM, Taghavi S, Abbasalizadeh S, Seyedhejazie M. The effect of supplemental iron elimination on pregnancy outcome. Pak J Biol Sci. 2011;23(3):641-5.

19. Romslo I, Haram K, Sagen N, et al. Iron requirement in normal pregnancy as assessed by serum ferritin, serum transferrin saturation and erythrocyte protoporphyrin determinations. BJOG. 1983;90(2):101-7. doi: 10.1111/j.1471-0528.1983.tb08891.x. PMID: 6824608.

20. Serdula MK, Zhou Y, Li H, et al. Prenatal iron containing supplements provided to Chinese women with no or mild anemia had no effect on hemoglobin concentration in post-partum women or their infants at 6 and 12 months of age. Eur Journal Clin Nutr. 2019;73(11):1473-9. doi: 10.1038/s41430-018-0365-x. PMID: 30446762.

21. Siega-Riz AM, Hartzema AG, Turnbull C, et al. The effects of prophylactic iron given in prenatal supplements on iron status and birth outcomes: a randomized controlled trial. Am J Obstet Gynecol. 2006;194(2):512-9. doi: 10.1016/j.ajog.2005.08.011. PMID: 16458655.

22. Wang L, Mei Z, Li H, et al. Modifying effects of maternal Hb concentration on infant birth weight in women receiving prenatal iron-containing supplements: a randomised controlled trial. Br J Nutr. 2016;115(4):644-9. doi: 10.1017/S0007114515004870. PMID: 26824731.

23. Zeng L, Dibley MJ, Cheng Y, et al. Impact of micronutrient supplementation during pregnancy on birth weight, duration of gestation, and perinatal mortality in rural western China: double blind cluster randomised controlled trial. BMJ. 2008;337:a2001. doi: 10.1136/bmj.a2001. PMID: 18996930.

24. Zhao G, Xu G, Zhou M, et al. Prenatal iron supplementation reduces maternal anemia, iron deficiency, and iron deficiency anemia in a randomized clinical trial in rural china, but iron deficiency remains widespread in mothers and neonates. J Nutri. 2015;145(8):1916-23. doi: 10.3945/jn.114.208678. PMID: 26063068.

25. Zhou SJ, Gibson RA, Makrides M. Routine iron supplementation in pregnancy has no effect on iron status of children at six months and four years of age. J Pediatr. 2007;151(4):438-40. doi: 10.1016/j.jpeds.2007.06.001. PMID: 17889086.

26. Zhou SJ, Gibson RA, Crowther CA, Baghurst P, Makrides M. Effect of iron supplementation during pregnancy on the intelligence quotient and behavior of children at 4 y of age: long-term follow-up of a randomized controlled trial. Am J Clin Nutr. 2006 May;83(5):1112-7. doi: 10.1093/ajcn/83.5.1112. PMID: 16685054.

27. Ziaei S, Mehrnia M, Faghihzadeh S. Iron status markers in nonanemic pregnant women with and without iron supplementation. Int J Gynaecol Obstet. 2008;100(2):130-2. doi: 10.1016/j.ijgo.2007.07.027. PMID: 17977537.

28. Ziaei S, Norrozi M, Faghihzadeh S, et al. A randomised placebo-controlled trial to determine the effect of iron supplementation on pregnancy outcome in pregnant women with haemoglobin > or = 13.2 g/dl. BJOG. 2007;114(6):684-8. doi: 10.1111/j.1471-0528.2007.01325.x. PMID: 17516958.

Appendix A5. List of Excluded Studies With Reasons for Exclusion

1. Gastrointestinal complications of iron supplement in pregnant women. 2003. Exclusion reason: Not a study.
2. Impact of prenatal vitamin/mineral supplements on perinatal mortality. Impact of iron/folic acid versus multimicronutrient versus folic acid supplements during pregnancy on mortality, morbidity, and complications during pregnancy, labor, and delivery: a randomized controlled trial in China. 2005. Exclusion reason: Not a study.
3. A randomized placebo-controlled trial to determine the effect of iron supplementation on hematological indices in pregnant women with hemoglobin =13.2 g/dl. 2009. Exclusion reason: Not a study.
4. Which iron supplementation regime for pregnant women provides the best maternal and infant outcomes? A randomised controlled trial to compare the impact on birth weight of daily iron-folic acid, twice weekly iron-folic acid and twice weekly multiple micronutrient supplementation for pregnant women in Ha Nam province, Vietnam. 2010. Exclusion reason: Not a study.
5. Impact of iron/folic acid vs folic acid supplements during pregnancy on maternal and child health. Impact of iron/folic acid versus folic acid supplements during pregnancy on maternal and children's health: a randomized controlled trial in China. 2014. Exclusion reason: Not a study.
6. The effect of iron supplementation in pregnant women with high hemoglobin. The effect of iron supplementation on iron status markers in pregnant women with high hemoglobin. 2014. Exclusion reason: Not a study.
7. Lactoferrin supplementation and iron metabolism in healthy pregnant women. Effect of daily bovine lactoferrin supplementation on fetal development and iron metabolism in healthy pregnant women: a randomized double-blind controlled trial. 2016. Exclusion reason: Not a study.
8. The IRONWOMAN pilot feasibility study: oral versus intravenous iron therapy for iron deficiency anaemia in late pregnancy. The IRONWOMAN pilot feasibility study: a double blind randomised trial to compare feasibility of blinding of intravenous or oral iron replacement to placebo intravenous or oral therapy for iron deficiency anaemia in pregnancy. 2019. Exclusion reason: Ineligible comparator.
9. Effect of ayurvedic medicines in combination with conventional therapy for healthy pregnancy and post partum period. Feasibility of introducing Ayurveda intervention in Reproductive and Child Health (RCH) in PHCs of selected district (Gadchiroli) of Maharashtra - (Effectiveness of Ayurvedic intervention for ante-natal care (Garbhini Paricharya) at primary health care level: a multi centre operational study. 2019. Exclusion reason: Not a study.
10. Role of jeevantyadi avaleha on foetal growth and maternal well-being in second trimester of pregnancy: a randomized controlled clinical trial. 2021. Exclusion reason: Not a study.

11. Aaseth J, Thomassen Y, Ellingsen DG, et al. Prophylactic iron supplementation in pregnant women in Norway. J Trace Elem Med Biol. 2001;15(2-3):167-74. doi: 10.1016/S0946-672X(01)80062-6. PMID: 11787984. Exclusion reason: Ineligible intervention.
12. Abbas AM, Abdelbadee SA, Alanwar A, et al. Efficacy of ferrous bis-glycinate versus ferrous glycine sulfate in the treatment of iron deficiency anemia with pregnancy: a randomized double-blind clinical trial. J Matern Fetal Neonatal Med. 2019;32(24):4139-45. doi: 10.1080/14767058.2018.1482871. PMID: 29843553. Exclusion reason: Ineligible comparator.
13. Abdel Moety GAF, Ali AM, Fouad R, et al. Amino acid chelated iron versus an iron salt in the treatment of iron deficiency anemia with pregnancy: a randomized controlled study. Eur J Obstet Gynecol Reprod Biol. 2017;210:242-6. doi: 10.1016/j.ejogrb.2017.01.003. PMID: 28073037. Exclusion reason: Ineligible comparator.
14. Abdulrehman J, Lausman A, Tang GH, et al. Development and implementation of a quality improvement toolkit, iron deficiency in pregnancy with maternal iron optimization (IRON MOM): a before-and-after study. PLoS Med. 2019;16(8):e1002867. doi: 10.1371/journal.pmed.1002867. PMID: 31430296. Exclusion reason: Ineligible study design for key question.
15. Abraha I, Bonacini MI, Montedori A, et al. Oral iron-based interventions for prevention of critical outcomes in pregnancy and postnatal care: an overview and update of systematic reviews. J Evid Based Med. 2019;12(2):155-66. doi: 10.1111/jebm.12344. PMID: 31144465. Exclusion reason: Systematic review used as a source document only to identify individual studies.
16. Abu MA, Borhan AS, Abdul Karim AK, et al. Comparison between Iberet Folic and Zincofer in treatment of iron deficiency anaemia in pregnancy. Horm Mol Biol Clin Investig. 2020;42(1):49-56. doi: 10.1515/hmbci-2020-0034. PMID: 33781008. Exclusion reason: Ineligible comparator.
17. Afkhami-Ardekani M, Rashidi M. Iron status in women with and without gestational diabetes mellitus. J Diabetes Complications. 2009;23(3):194-8. doi: 10.1016/j.jdiacomp.2007.11.006. PMID: 18413178. Exclusion reason: Ineligible study design for key question.
18. Akyol S, Karatas K, Tunali H. Relationship of iron supplementation during pregnancy with the opsonization and complement components. AJRI. 2014;71(s1):31. doi: doi.org/10.1111/aji.12255. Exclusion reason: Not a study.
19. Al RA, Unlubilgin E, Kandemir O, et al. Intravenous versus oral iron for treatment of anemia in pregnancy: a randomized trial. Obstet Gynecol. 2005;106(6):1335-40. doi: 10.1097/01.AOG.0000185260.82466.b4. PMID: 16319260. Exclusion reason: Ineligible comparator.

20. Alfawaz HA, Khan N, AlOteabi N, et al. Factors associated with dietary supplement use in Saudi pregnant women. Reprod Health. 2017;14(1):104. doi: 10.1186/s12978-017-0357-7. PMID: 28851385. Exclusion reason: Ineligible intervention.

21. Ali MK, Abbas AM, Abdelmagied AM, et al. A randomized clinical trial of the efficacy of single versus double-daily dose of oral iron for prevention of iron deficiency anemia in women with twin gestations. J Matern Fetal Neonatal Med. 2017;30(23):2884-9. doi: 10.1080/14767058.2016.1266478. PMID: 27894198. Exclusion reason: Ineligible comparator.

22. Alizadeh L, Salehi L. Is routine iron supplementation necessary in pregnant women with high hemoglobin? Iranian Red Crescent Med J. 2016;18(1):e59314. doi: 10.5812/ircmj.22761. PMID: 26889391. Exclusion reason: Ineligible population.

23. Alizadeh L, Salehi L, Mehraban Z, et al. Effect of iron supplementation in pregnant women with high hemoglobin on neonatal jaundice: a randomized double-blind clinical trial. IJOGI. 2019;22(4):18-24. doi: 10.22038/IJOGI.2019.13441. Exclusion reason: Not English language.

24. Allen LH, Peerson JM, Maternal Micronutrient Supplementation Study Group. Impact of multiple micronutrient versus iron-folic acid supplements on maternal anemia and micronutrient status in pregnancy. Food Nutr Bull. 2009;30(4 Suppl):S527-32. doi: 10.1177/15648265090304S407. PMID: 20120794. Exclusion reason: Ineligible intervention.

25. Allen LH, Peerson JM, Olney DK. Provision of multiple rather than two or fewer micronutrients more effectively improves growth and other outcomes in micronutrient-deficient children and adults. J Nutr. 2009;139(5):1022-30. doi: 10.3945/jn.107.086199. PMID: 19321586. Exclusion reason: Ineligible intervention.

26. Alwan N, Cade J. Routine iron supplementation in pregnancy: why is the UK different? Perspect Public Health. 2011;131(5):207-8. doi: 10.1177/1757913911419152. PMID: 21999024. Exclusion reason: Not a study.

27. Alwan NA, Greenwood DC, Simpson NAB, et al. Dietary iron intake during early pregnancy and birth outcomes in a cohort of British women. Hum Reprod. 2011;26(4):911-9. doi: 10.1093/humrep/der005. PMID: 21303776. Exclusion reason: Ineligible intervention.

28. Angulo-Barroso RM, Li M, Santos DCC, et al. Iron supplementation in pregnancy or infancy and motor development: a randomized controlled trial. Pediatrics. 2016;137(4):e20153547. doi: 10.1542/peds.2015-3547. PMID: 26936859. Exclusion reason: Ineligible population.

29. Aranda N, Ribot B, Garcia E, et al. Pre-pregnancy iron reserves, iron supplementation during pregnancy, and birth weight. Early Hum Dev. 2011;87(12):791-7. doi: 10.1016/j.earlhumdev.2011.06.003. PMID: 21723050. Exclusion reason: Ineligible comparator.

30. Arija V, Ribot B, Aranda N. Prevalence of iron deficiency states and risk of haemoconcentration during pregnancy according to initial iron stores and iron supplementation. Public Health Nutr. 2013;16(8):1371-8. doi: 10.1017/S1368980013000608. PMID: 23472860. Exclusion reason: Ineligible comparator.

31. Asadi N, Vafaei H, Kasraeian M, et al. Effects of prophylactic iron supplementation on outcome of nonanemic pregnant women: a non-randomized clinical trial. J Chin Med Assoc. 2019;82(11):840-4. doi: 10.1097/JCMA.0000000000000184. PMID: 31517773. Exclusion reason: Ineligible comparator.

32. Auerbach M, James SE, Nicoletti M, et al. Results of the first American prospective study of intravenous iron in oral iron-intolerant iron-deficient gravidas. Am J Med. 2017;130(12):1402-7. doi: 10.1016/j.amjmed.2017.06.025. PMID: 28739199. Exclusion reason: Ineligible intervention.

33. Bah A, Wegmuller R, Cerami C, et al. A double blind randomised controlled trial comparing standard dose of iron supplementation for pregnant women with two screen-and-treat approaches using hepcidin as a biomarker for ready and safe to receive iron. BMC Pregnancy Childbirth. 2016;16(1):157. doi: 10.1186/s12884-016-0934-8. PMID: 27411564. Exclusion reason: Ineligible country.

34. Banhidy F, Acs N, Puho EH, et al. Iron deficiency anemia: pregnancy outcomes with or without iron supplementation. Nutrition. 2011;27(1):65-72. doi: 10.1016/j.nut.2009.12.005. PMID: 20381313. Exclusion reason: Ineligible intervention.

35. Baraka MA, Steurbaut S, Laubach M, et al. Iron status, iron supplementation and anemia in pregnancy: ethnic differences. J Matern Fetal Neonatal Med. 2012;25(8):1305-10. doi: 10.3109/14767058.2011.632036. PMID: 22010638. Exclusion reason: Ineligible intervention.

36. Barton JC, Barton JC, Acton RT. Insulin resistance and metabolic syndrome: clinical and laboratory associations in African Americans without diabetes in the hemochromatosis and iron overload screening study. Metab Syndr Relat Disord. 2018;16(6):267-73. doi: 10.1089/met.2018.0036. PMID: 29851359. Exclusion reason: Ineligible population.

37. Bayoumeu F, Subiran-Buisset C, Baka N-E, et al. Iron therapy in iron deficiency anemia in pregnancy: intravenous route versus oral route. Am J Obstet Gynecol. 2002;186(3):518-22. doi: 10.1067/mob.2002.121894. PMID: 11904617. Exclusion reason: Ineligible comparator.

38. Beard JL. Effectiveness and strategies of iron supplementation during pregnancy. Am J Clin Nutr. 2000;71(5 Suppl):1288S-94S. doi: 10.1093/ajcn/71.5.1288s. PMID: 10799404. Exclusion reason: Not a study.

39. Beard JL, Hendricks MK, Perez EM, et al. Maternal iron deficiency anemia affects postpartum emotions and cognition. J Nutr. 2005;135(2):267-72. doi: 10.1093/jn/135.2.267. PMID: 15671224. Exclusion reason: Ineligible population.

40. Behboudi-Gandevani S, Safary K, Moghaddam-Banaem L, et al. The relationship between maternal serum iron and zinc levels and their nutritional intakes in early pregnancy with gestational diabetes. Biol Trace Elem Res. 2013;154(1):7-13. doi: 10.1007/s12011-013-9703-y. PMID: 23743666. Exclusion reason: Ineligible intervention.

41. Bencaiova G, Breymann C. Mild anemia and pregnancy outcome in a Swiss collective. J Pregnancy. 2014;2014:307535. doi: 10.1155/2014/307535. PMID: 25478229. Exclusion reason: Ineligible comparator.

42. Bencaiova G, von Mandach U, Zimmermann R. Iron prophylaxis in pregnancy: intravenous route versus oral route. Eur J Obstet Gynecol Reprod Biol. 2009;144(2):135-9. doi: 10.1016/j.ejogrb.2009.03.006. PMID: 19406557. Exclusion reason: Ineligible comparator.

43. Beyens M-N, Guy C, Ratrema M, et al. Prescription of drugs to pregnant women in France: the HIMAGE study. Therapie. 2003;58(6):505-11. doi: 10.2515/therapie:2003082. PMID: 15058494. Exclusion reason: Ineligible intervention.

44. Bhatla N, Kaul N, Lal N, et al. Comparison of effect of daily versus weekly iron supplementation during pregnancy on lipid peroxidation. J Obstet Gynaecol Res. 2009;35(3):438-45. doi: 10.1111/j.1447-0756.2008.00972.x. PMID: 19527380. Exclusion reason: Ineligible intervention.

45. Bhavi SB, Jaju PB. Intravenous iron sucrose v/s oral ferrous fumarate for treatment of anemia in pregnancy. A randomized controlled trial. BMC Pregnancy Childbirth. 2017;17(1):137. doi: 10.1186/s12884-017-1313-9. PMID: 28482869. Exclusion reason: Ineligible comparator.

46. Bloxam DL, Williams NR, Waskett RJ, et al. Maternal zinc during oral iron supplementation in pregnancy: a preliminary study. Clin Sci (Lond). 1989;76(1):59-65. doi: 10.1042/cs0760059. PMID: 2920535. Exclusion reason: Poor quality.

47. Bo S, Menato G, Villois P, et al. Iron supplementation and gestational diabetes in midpregnancy. Am J Obstet Gynecol 2009;201(2):158.e1-6. doi: 10.1016/j.ajog.2009.04.049. PMID: 19527900. Exclusion reason: Ineligible intervention.

48. Bokhari F, Derbyshire EJ, Hickling D, et al. A randomized trial investigating an iron-rich bread as a prophylaxis against iron deficiency in pregnancy. Int J Food Sci Nutr. 2012;63(4):461-7. doi: 10.3109/09637486.2011.634790. PMID: 22081981. Exclusion reason: Ineligible intervention.

49. Bozhinova S, Ivanova I, Lukanova M. How to avoid a haemotransfusion which is not lifesaving? Our experience with administration of intravenous iron to pregnant women and young mothers. Akush Ginekol (Sofiia). 2004;43(6):13-7. PMID: 15669646. Exclusion reason: Ineligible study design for key question.

50. Bresani Salvi CC, Braga MC, Figueiroa JN, et al. Could the erythrocyte indices or serum ferritin predict the therapeutic response to a trial with oral iron during pregnancy? Results from the Accuracy study for Maternal Anaemia diagnosis (AMA). BMC Pregnancy

Childbirth. 2016;16(1):218. doi: 10.1186/s12884-016-1005-x. PMID: 27516193. Exclusion reason: Ineligible intervention.

51. Breymann C. Treatment of iron deficiency anaemia in pregnancy and postpartum with special focus on intravenous iron sucrose complex. J Med Assoc Thai. 2005;88 Suppl 2:S108-9. PMID: 17718296. Exclusion reason: Not a study.

52. Breymann C, Milman N, Mezzacasa A, et al. Ferric carboxymaltose vs. oral iron in the treatment of pregnant women with iron deficiency anemia: an international, open-label, randomized controlled trial (FER-ASAP). J Perinat Med. 2017;45(4):443-53. doi: 10.1515/jpm-2016-0050. PMID: 27278921. Exclusion reason: Ineligible comparator.

53. Brough L, Rees GA, Crawford MA, et al. Effect of multiple-micronutrient supplementation on maternal nutrient status, infant birth weight and gestational age at birth in a low-income, multi-ethnic population. Br J Nutr. 2010;104(3):437-45. doi: 10.1017/S0007114510000747. PMID: 20412605. Exclusion reason: Ineligible intervention.

54. Bumrungpert A, Pavadhgul P, Piromsawasdi T, et al. Efficacy and safety of ferrous bisglycinate and folinic acid in the control of iron deficiency in pregnant women: a randomized, controlled trial. Nutrients. 2022;14(3):452. doi: 10.3390/nu14030452. PMID: 35276810. Exclusion reason: Ineligible comparator.

55. Butler EB. Effect of iron and folic acid on red cell and plasma volume in pregnancy. J Obstet Gynaecol Br Commonw. 1968;75(5):497-510. doi: 10.1111/j.1471-0528.1968.tb00153.x. PMID: 5742694. Exclusion reason: Poor quality.

56. Buytaert G, Wallenburg HC, van Eijck HG, et al. Iron supplementation during pregnancy. Eur J Obstet Gynecol Reprod Biol. 1983;15(1):11-6. doi: 10.1016/0028-2243(83)90291-5. PMID: 6884561. Exclusion reason: Poor quality.

57. Byg KE, Milman N, Agger AO. Correlations between iron status markers during normal pregnancy in women with and without iron supplementation. Hematology. 1999;4(6):529-39. doi: 10.1080/10245332.1999.11746481. PMID: 27420749. Exclusion reason: Ineligible outcome.

58. Byg KE, Milman N, Hansen S, et al. Serum ferritin is a reliable, non-invasive test for iron status in pregnancy: comparison of ferritin with other iron status markers in a longitudinal study on healthy pregnant women. Hematology. 2000;5(4):319-25. doi: 10.1080/10245332.2000.11746526. PMID: 11399631. Exclusion reason: Ineligible intervention.

59. Cantlie GS, De Leeuw NK, Lowenstein L. Iron and folate nutrition in a group of private obstetrical patients. Am J Clin Nutr. 1971;24(6):637-41. doi: 10.1093/ajcn/24.6.637. PMID: 5581003. Exclusion reason: Poor quality.

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345. Zhao L, Lian J, Tian J, et al. Dietary intake of heme iron and body iron status are associated with the risk of gestational diabetes mellitus: a systematic review and meta-analysis. Asia Pac J Clin Nutr. 2017;26(6):1092-106. doi: 10.6133/apjcn.022017.09. PMID: 28917236. Exclusion reason: Systematic review used as a source document only to identify individual studies.

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348. Zhu B, Liang C, Xia X, et al. Iron-related factors in early pregnancy and subsequent risk of gestational diabetes mellitus: the Ma'anshan Birth Cohort (MABC) study. Biol Trace

Elem Res. 2019;191(1):45-53. doi: 10.1007/s12011-018-1595-4. PMID: 30515713. Exclusion reason: Ineligible intervention.

Randomized Controlled Trials and Cohort Studies

Criteria:

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

Definition of ratings based on above criteria:

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

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

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

Source: U.S. Preventive Services Task Force. Procedure Manual. *Appendix VI. Criteria for Assessing Internal Validity of Individual Studies*. https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual/procedure-manual-appendix-vi-criteria-assessing-internal-validity-individual-studies

Appendix A7. Expert Reviewers of the Draft Report

Jeanne Conry, MD, PhD, President, International Federation of Gynecology and Obstetrics; President, Environmental Health Leadership Foundation; Chair, U.S. Women's Preventive Services Initiative

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Federal Partner Reviewers

National Institute on Minority Health and Health Disparities - *2 reviewers*
Office of Research on Women's Health - *1 reviewer*

Appendix B Table 1. Data Abstraction of Iron Supplementation Trials

Author, year Quality rating	Setting Country	Interventions (N)	Study duration	Population characteristics (age, sex/gender, race/ethnicity, gestational age, other factors reported)	Baseline hematologic indices, iron deficiency, and anemia	Eligibility criteria	Number randomized, analyzed	Withdrawals Loss to followup	Funding source
Barton 1994[63] Fair	Maternity hospital Dublin, Ireland	A. 120 mg elemental iron and folic acid daily (n=53) B. Placebo (n=44) Supplementation started at end of first trimester	Through delivery	Age: NR Race/ethnicity: NR Gestational age, mean: 12 weeks SES: NR Nulliparous: 47% vs. 45% Smoking: 47% vs. 32%, p>0.05	Mean hemoglobin: 14.3 vs. 14.4 g/dL Mean ferritin: 47.53 vs. 43.93 µg/L Mean hematocrit: 0.425 vs. 0.429 Mean serum erythropoietin: 22.86 vs. 21.57 mU/mL Anemia: excluded at baseline (0%)	Women with a singleton pregnancy and hemoglobin ≥14 gm/dL (patients not anemic during first trimester) Exclude: Recent blood transfusion, chronic respiratory disease, chronic hypertension, renal disease, diabetes mellitus, history of a hematologic disorder, or alcohol dependence	Randomized: 97 Analyzed: varies per outcome and time point (hemoglobin at week 36: 89% vs. 91%; week 40: 57% vs. 41%; ferritin at week 36: 81% vs. 77%)	A vs B 36 weeks: 9%-19% vs. 9%-23% 40 weeks: 43%-45% vs. 59%-64% (fewer data in placebo group due to delivery before 40 weeks or blood sampling errors) Patients would be withdrawn if anemia (hemoglobin <10 gm/dL) developed, but no instances	NR
Chan 2009[64] Fair	Single center Pok Fu Lam, Hong Kong	A: 60 mg daily iron supplement (300 mg ferrous sulfate tablet) (n=565) B: Placebo tablet (n=599) Supplementation started at <16 weeks gestation	Through delivery	A vs. B Mean age: 31.3 vs. 31.3 years Race: NR (Hong Kong) SES: NR Gestational age: 11.4 vs. 11.2 weeks Family history of diabetes: 23% vs 24% BMI: 20.8 vs. 21.0 Parity >2: 0.18% vs. 0.50%	A vs. B Mean hemoglobin: 12.5 vs. 12.6 g/dL Mean ferritin: 182.0 vs. 196.9 pmol/L ID: NR Anemia: NR	1164 women with singleton pregnancy <16 weeks gestation with HB level 8-14 g/dl and no pre-existing diabetes or haemoglobinopathies Exclude: >16 weeks gestation, gestational diabetes, history of diabetes, Hb<8 or >14	Randomized: 1164 Analyzed: 1164	Withdrawals: NR Lost: 21% (239/1,164) of participants delivered elsewhere and could not be traced.	Research Grant Council, Hong Kong

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Cogswell 2003[66] Fair	Prenatal clinic, WIC eligible population U.S., Cleveland, Ohio	Gestational week 20-27: A. 30 mg Fe as ferrous sulfate (assume elemental) daily (n=146) B. Placebo (n=129) Gestational week 28: Reassigned to either 30 mg (n=54), 60 mg (n=118), placebo (n=15) Gestational week 38: Reassigned again based on iron measures	Through delivery	A vs. B Age: 24.3 vs. 24.5 years Race/ethnicity: 56% vs. 57% White, 24% vs. 26% Black, 16% vs. 17% Hispanic Gestational age: 11 vs. 11 weeks SES: 100% enrolled in WIC Prepregnancy weight: 72.5 vs. 77.9 kg, p=0.049 Parity >2: 31% vs 24% Smokers: 40% vs. 36%	A vs. B Mean hemoglobin: 12.9 vs. 12.7 g/dL Mean ferritin: 45 vs. 49 µg/L, p=0.0168 MCV: 89 vs. 89 fL Erythrocyte protoporphyrin: 54 vs. 56 µg/dL Anemia: excluded at baseline (0%)	Iron-replete, nonanemic pregnant women at <20 weeks of gestation, enrolled in WIC	Randomized: 275 Analyzed: 275	Loss to followup at week 28: 25% (36/146) vs. 33% (43/129) Excluded for medical intervention at week 28: 3.4% (5/146) vs. 3.1% (4/129)	U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, and National Institutes of Health grant

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Eskeland 1997[68] Fair	Single maternity center, inner city Bergen, Norway	A. Heme iron: 3 tablets containing 1.2 mg heme iron plus 8 mg Fe^{2+} as iron fumarate per tablet (total iron 27.6 mg; elemental), plus 1 placebo tablet daily (n=31) B. Non-heme iron: 1 tablet containing 27 mg Fe^{2+} as iron fumarate with 100 mg vitamin C, plus 3 placebo tablets daily (n=30) C. Placebo, 4 tablets daily (n=29) Supplementation started at 20th week of gestation through delivery	Through 6 months post-partum	A vs. B vs. C Mean age: 28 vs. 26 vs. 28 years Race/ethnicity: NR Gestational age: NR SES: NR Living single: 3% vs 17% vs 3% Elementary school only: 3% vs 7% vs 10% BMI: 23 vs. 22 vs. 23 Parity 0: 65% vs. 70% vs. 55%	A vs. B vs. C s-ferritin <15 µg/L: 14% (4/29) vs. 3% (1/30) vs. 21% (6/28), p=ns Anemia: NR	Healthy pregnant women at <13 weeks of gestation Excluded: Uncertain gestational age, hemoglobin <11.0 or >14.8 g/dL, chronic disease or pregnancy complications, multiple pregnancy, liver enzymes out of normal range, or practical difficulties such as planned moving during study period	Randomized: 90 Analyzed: 71	A vs. B vs. C Missing data due to non-attendance: 22.6% (7/31) vs. 20% (6/30) vs. 20.7% (6/29)	NR

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Falahi 2011[69] Fair	"Gynecology center" Khorramabad City, Iran	A. Iron, 60 mg elemental as ferrous sulfate daily (n=70) B. Placebo (n=78) Supplementation started at <20 weeks	Through delivery	A vs. B Age: 24.6 vs. 23.1 years (p=0.02) Race/ethnicity: NR SES: NR Gestational age at study entry: 12.2 vs. 11.9 weeks BMI: 24.8 vs. 24.4 kg/m^2	A vs. B Hemoglobin: 13.0 vs. 13.1 g/dL Ferritin: 36.6 vs. 31.7 µg/L ID: 0% Anemia: 0% (excluded)	Nonanemic pregnant women with gestational age <20 weeks, primigravidae, age between 20 and 35 years, BMI >25 and <30, hemoglobin >11.0 g/dL, and serum ferritin >20 µg/L Excluded: Diabetes mellitus, coronary heart disease, thalassemia, renal disease, respiratory disease, use of supplementary multivitamins or minerals, drug use, special diet; anemic or iron deficient women were referred for medical evaluation and treatment	Randomized: 148 Analyzed: NR	Withdrawals: NR Loss to followup: NR	NR

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Author, year Quality rating	Setting Country	Interventions (N)	Study duration	Population characteristics (age, sex/gender, race/ethnicity, gestational age, other factors reported)	Baseline hematologic indices, iron deficiency, and anemia	Eligibility criteria	Number randomized, analyzed	Withdrawals Loss to followup	Funding source
Jafarbeglo 2015[70] Fair NEW	Prenatal care clinic Tehran, Iran	A. Iron, 50 mg ferrous sulfate daily (n=90) B. Placebo (n=89) Supplementation started at the 20th week	Through delivery	A vs. B Age: 27 vs. 26 years Race/ethnicity: NR Completed high school: 75% vs. 81% Housewife: 90% vs. 90% Gestational age at study entry: 13.6 vs. 13.9 weeks BMI: 23.4 vs. 23.6 kg/m^2	A vs. B Hemoglobin: 13.9 vs. 14.0 g/dL	Pregnant women ages 17 to 35 years, Hb ≥13.2 g/dL between the 13th and 18th week, singleton pregnancy, pregestational BMI of 19.8-26 Excluded: those with a drop of serum Hb level below 10.5 g/dL in 24th - 28th weeks or below 11.0 g/dL in 32nd - 36th weeks, and those with diseases associated with polycythemia such as asthma and chronic hypertension, history of GI diseases such as peptic ulcer, reflux esophagitis, gastritis, GI bleeding, diseases resulting in nausea, vomiting, diarrhea, constipation, heartburn and abdominal pain before pregnancy, systemic diseases or hyperemesis gravidarum in present pregnancy	Randomized 179 Analyzed: 176	Withdrawals: 0 Loss to followup: 0, but 3 excluded due to consumption of additional supplement containing iron	NR

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Liu 2013[72] *NEW* Also: Chen 2019[65] Li 2017[71] Liu 2021[73] Mei 2014[75] Serdula 2019[82] Wang 2016[84] Good	Village clinics and township hospitals for prenatal care, county hospitals for delivery China, 5 rural counties in northeast (Yuanshi, Mancheng, Xianghe, Fengrun, and Laoting)	A: Iron (ferrous fumarate [assume elemental], 30 mg Fe) + folic acid (400 µg) daily (n=6252) B: Folic acid alone (400 µg) (n=6261) (Third arm with iron, folic acid, and multiple micronutrients not abstracted) Supplementation started at <20 weeks through delivery	Through 1 year post-partum	A vs. B Age, mean: 23.7 vs. 23.7 years Ethnicity: Han, 98.9% vs. 98.7% Gestational age, mean: 12.0 vs. 11.9 weeks Education, ≥high school: 18.0% vs. 18.5% BMI: <18.5, 5.9% vs. 5.8%; ≥30, 1.9% vs. 2.1%	A vs. B Hemoglobin, g/dL (finger puncture, capillary blood, n=11,809): 10.0 to 10.9: 6.0% vs. 5.9% 11.0 to 11.9: 23.3% vs. 22.5% 12.0 to 12.9: 42.0% vs. 42.2% ≥13.0: 28.7% vs. 29.4% Venous blood (n=562): Ferritin, µg/L: 54.8 vs. 51.4, p>0.05 ID (ferritin <12 µg/L): 5.4% vs. 4.6%, p>0.05 Hemoglobin, g/dL: 12.15 vs. 12.15, p>0.05 Anemia (Hb <11.0 g/dL): 6.2% vs. 6.9%, p>0.05	Eligible: ≥20 years old, nulliparous, "no or mild anemia," recorded menstruation dates for ≥2 months before conception, ≤20 weeks gestation, no recent micronutrient supplements other than folic acid, Hb>10.0 g/dL Excluded: multiple pregnancies (not singleton)	Randomized: 12,513 (2 of 3 arms) Analyzed: 11,888	Withdrawals: 33 Lost: 28	Peking University Health Science Center and the U.S. Centers for Disease Control and Prevention

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Makrides 2003[74] Also: Zhou 2007[87] Zhou 2006[90] Good	Prenatal clinic North Adelaide, Australia	A: 20 mg daily elemental iron supplement (as ferrous sulfate) (n=216) B: Placebo (n=214) Supplementation started at 20 weeks gestation through delivery	Through 6 months post-partum	A vs. B Age: 28.5 vs. 28.0 years Race: 95.4% vs. 95.3% White, 0.9% vs. 3.3% Aboriginal, 2.3% vs. 1.4% Asian, 1.4% vs. 0% other Highest level of education: year ≤10 12% vs. 15%, year 11 27% vs. 28%, year 12 33% vs. 28%, trade certificate or diploma 5% or 8%, tertiary degree 21% vs. 21% Gestational age: NR Maternal smoking: 19% vs. 20% Multiparous: 52% vs 53% BMI: 26.0 vs 25.5 kg/m^2	Hemoglobin: 13.1 vs. 13.0 g/dL Ferritin: NR ID: NR Anemia: NR (excluded Hb < 11.0 g/dL)	Attending antenatal clinics at the Women & Children's hospital in Adelaide Excluded: Pre-existing anemia, thalassemia, history of drug or alcohol abuse, already taking vitamin and mineral preparations containing iron	Randomized: 430 Analyzed: 430 for pregnancy outcomes, 362 to 383 for hematologic outcomes and adverse effects; 299 women for 4 year outcomes	Withdrawals: 32 Lost: 0 4 year outcomes: 30% lost to followup (131/430 women)	Channel 7 Children's Medical Research Foundation, Women's & Children's Hospital Perinatal Pathology Fund, Gunn & Gunn Medical Research Foundation, Soul Pattinson Manufacturing

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Meier 2003[76] Fair	Prenatal clinic Marshfield Wisconsin U.S.	A. Iron supplementation 60 mg elemental iron (200 mg ferrous sulfate) + 1 mg folic acid daily (n=58, including 20 adolescents) B. Placebo + 1 mg folic acid (n=53, including 17 adolescents) If IDA occurred at 2nd trimester, 180 mg elemental iron was initiated (3 women in iron group and 9 women in placebo group)	Through delivery	A vs. B Adolescents: Age: 18.2 vs. 17.7 years Race: NR Gestational age: 14.1 vs. 12.1 weeks Adults: Age 25.2 vs. 28.8 years Race: NR Gestational age: 10.6 vs. 12.3 weeks	A vs. B Adolescents: Serum ferritin: 31.1 vs. 34.0 ng/mL Hemoglobin: 12.6 vs. 13.1 g/dL Adults: Serum ferritin: 39.3 vs. 37.0 ng/mL Mean hemoglobin: 13.0 vs. 12.9 g/dL ID: NR Anemia: NR IDA: 0%	Pregnant adolescents (1st pregnancy) and adults (1st or later pregnancy) ages 15 and older seeking prenatal care at a private group practice Excluded: Those with IDA at 1st prenatal visit	Randomized: Unclear, assume 144 Analyzed: 111	Withdrawals: 20 had inadequate data or failed to comply with medication requirements Lost: 3 moved or were lost to followup	National Institutes of Health, Marshfield Medical Research Foundation, Mead-Johnson Nutritional Division, and Hybritech, Inc.

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Milman 1991[77] Also: Milman 1994[78] Milman 2000[79] Fair	"Birth Clinic" Copen-hagen, Denmark	A: 66 mg elemental iron (200 mg ferrous fumarate) daily (n=100) B: Placebo (n=107) Patients with ferritin measured (n=120): A: (n=63) B: (n=57) Supplementation started at 14-16 weeks gestation through delivery	Through 8 weeks post-partum	A vs. B (n=207): Age: 27 vs. 27 years Race/Ethnicity: NR Gestational age: NR Parity: 2 vs. 2	A vs. B 14 to 18 weeks Hemoglobin <11.0 g/dL (n=207): 2.9% vs. 6.1% Hemoglobin, mean (n=206): 12.2 vs. 11.9 g/dL, p=0.02 N=120: Ferritin ≤20 µg/L: 6.8% vs. 5.5% Mean ferritin: 45 vs 40 µg/L, p=NS Mean hemoglobin: 12.2 vs 11.9 g/dL, p=NS Anemia: NR	Healthy women with a normal, single pregnancy, 14-16 weeks gestation, and an uncomplicated delivery Excluded: Uterine bleeding, placental insufficiency, placenta previa, abruptio placentae, preeclampsia, premature birth, excessive smoking (≥10 cig/day) (some exclusions after treatment allocation)	Randomized: unclear, assume 248 Analyzed: 207 or 206 All patients (n=207; n=206 in 2000 paper, one more excluded for missing data)	Withdrawals: 10 Lost: NR	Sundhed-spuljen and Fund for Medical Science Research grants
Ouladsa-hebmadar ek 2011[80] *NEW* *Fair*	Prenatal clinic at university hospital Tehran, Iran	A. 30 mg elemental iron + multivitamin daily (n=480) B. Placebo + multivitamin daily (n=480) Supplementation started at 13 weeks gestation	Through delivery	A vs. B Age: 26.3 vs. 25.5 years Race: NR Ethnicity: NR Gestational age: NR SES: NR Parity: 0.53 vs. 0.41	A vs. B Hemoglobin: 13.8 vs. 13.3 g/dL Hematocrit: 41.48% vs. 41.22% Ferritin: 41.05 vs. 35.01 µg/L ID: NR Anemia: 0%	Healthy women in 1st trimester with single fetus and Hb >12 g/dL, no iron supplements in last month, and BP <140/90 Excluded: patients with Hb <10.5 g/dL at end of 2nd trimester or Hb <11 at end of 3rd trimester; miscarriage of current pregnancy; fetal abnormality	Randomized: 960 Analyzed: 782	Withdrawals: NR Lost: 105	Tabriz University of Medical Sciences

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Romslo 1983[81] Fair	Prenatal clinic Bergen, Norway	A. 200 mg elemental iron (as ferrous sulfate) daily starting within first 10 weeks gestation (n=22) B. Placebo (n=23) Supplementation started within 10 weeks gestation	Through delivery	A vs. B Age 27.8 vs. 26.7 years Race/ethnicity: NR Gestational age: NR	A vs. B At 10 to 12 weeks: Hemoglobin: 12.8 vs. 12.4 g/dl Ferritin: 28.0 vs. 27.0 µg/L Anemia: NR	Healthy women with a normal pregnancy ending in an uncomplicated delivery of a single, normal infant at between 37-42 weeks gestation Excluded: NR	Randomized: unclear, assume 52 Analyzed: 43	Withdrawals reported: 7	NR

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Siega-Riz 2006[83] Fair	Prenatal clinic, serves WIC - eligible population Raleigh, North Carolina, U.S.	A. Prenatal supplementation with 30 mg iron as ferrous sulfate daily (assume elemental) (n=218) B. Prenatal supplementation without iron (n=211) Supplementation started at first prenatal visit; at 26-29 weeks, active participation (RCT) ended and all received at least 30 mg iron	Through delivery	A vs. B Age 13-18 years: 14% vs. 15% Age 19-24 years: 73% vs. 71% Race/ethnicity: 65% vs. 58% Black, 31% vs. 37% White Gestational age at study entry: 12.3 vs. 12.4 weeks SES: 100% eligible for WIC Single marital status: 75% vs. 75% High school education or less: 76% vs. 73% Previous live births: 68% vs. 66% Parity >2: 44% vs. 41%	A vs. B Mean hemoglobin: 12.4 vs. 12.4 g/dL Mean ferritin: 83.1 vs. 84.2 µg/L Anemia: 0%	Iron-replete, nonanemic pregnant women at <20 weeks gestation, hemoglobin ≥11.0 g/dL and serum ferritin ≥40 µg/L, spoke English, had not taken supplements that contained iron in the last month, singleton pregnancy, receiving prenatal care, eligible for Women, Infants and Children (WIC) program Excluded: NR	Randomized: 867, of which 429 had eligible hematologic values and were included in the study Analyzed: 316 at 3rd trimester	26% missing data at 3rd trimester on anemia 22% missing data on birth weight 19.5% missing data on gestational age 32% missing data on more than one variable Missing data: 204 Miscarriage: 13 Multiple births: 6	Association of Schools of Public Health, Centers for Disease Control and Prevention, National Institute of Child Health and Human Development to the Carolina Population Center

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Author, year Quality rating	Setting Country	Interventions (N)	Study duration	Population characteristics (age, sex/gender, race/ethnicity, gestational age, other factors reported)	Baseline hematologic indices, iron deficiency, and anemia	Eligibility criteria	Number randomized, analyzed	Withdrawals Loss to followup	Funding source
Zeng 2008[85] *NEW* Fair	Prenatal clinics, township and county hospitals, and in patients' homes China, "two poor rural counties" in the northwest	Cluster randomized trial (by village, total 561 villages) A: Iron (60 mg elemental) + folic acid (400 µg) daily (n=1470 infants) B: Folic acid (400 µg) daily (n=1545 infants) Supplementation started at mean 14 weeks gestation through delivery (Third arm with iron, folic acid, and multiple micronutrients not abstracted)	Through 6 weeks post-partum	A vs. B Age: 24.8 vs. 24.8 years Race/ethnicity: NR Education ≥high school: 15.1% vs. 12.9% Wealth index, highest third: 35.2% vs. 31.1% Gestational age: 13.6 vs. 13.8 weeks Parity: 0, 61.9% vs. 60.6%; 1, 35.0% vs. 35.4%; ≥2, 3.1% vs. 4.0% BMI: 20.9 vs. 20.8 kg/m^2	NR	Included all women residing in the 2 counties who became pregnant between August 2002 and January 2006 Excluded: gestation >28 weeks, taking other supplements, serious illness, abnormal reproductive history, planning to work outside of county	Randomized: 3929 women Analyzed: 3015 infants Birth outcome (stillbirth or live birth): 3306 births in 3270 women Birth weight: 3015 births	Withdrawals: 175 Lost: 87	United Nations Children's Fund, U.S. Centers for Disease Control and Prevention, National Natural Science of Foundation of China

Appendix B Table 1. Data Abstraction of Iron Supplementation Trials

Author, year Quality rating	Setting Country	Interventions (N)	Study duration	Population characteristics (age, sex/gender, race/ethnicity, gestational age, other factors reported)	Baseline hematologic indices, iron deficiency, and anemia	Eligibility criteria	Number randomized, analyzed	Withdrawals Loss to followup	Funding source
Zhao 2015[86] *NEW* Fair	Three partici-pating hospitals with prenatal clinics Sanhe County, Hebei Province, China, one rural county in the northeast	A: Iron (300 mg ferrous sulfate = 60 mg elemental iron) + 0.40 mg folate daily (n=814) B: Placebo + 0.40 mg folate daily (n=802) Supplementation started at enrollment through delivery	Through 1 day post-partum	A vs. B Age: 24.7 vs. 24.5 years Race/ethnicity: NR Education ≤middle school: 67.5% vs. 66.0% Low income: 56.0% vs. 53.2% Gestational age: 15.9 vs. 15.8 weeks Primiparous: 78.6% vs. 78.0% BMI, prepregnancy: 21.9 vs. 21.9 kg/m^2	A vs. B Hemoglobin, mean: 12.3 vs. 12.3 g/dL Ferritin, mean: 30.7 vs. 30.7 µg/L Anemia (Hb<11.0 g/dL): 7.5% vs. 8.8% ID (ferritin < 15 µg/L): 18.9% vs. 19.0% IDA: 2.1% vs. 2.5%	A vs. B Uncomplicated singleton pregnancy at ≤20 weeks gestation, aged ≥18 years, and with hemoglobin ≥10.0 g/dL Excluded: chronic illness, prior medicinal iron	Randomized: 2371 Analyzed: 1616 women, 1595 neonates	Withdrawals: 10 Lost: 647	Vifor Pharma Ltd. and U.S. National Institutes of Health

Appendix B Table 1. Data Abstraction of Iron Supplementation Trials

Author, year Quality rating	Setting Country	Interventions (N)	Study duration	Population characteristics (age, sex/gender, race/ethnicity, gestational age, other factors reported)	Baseline hematologic indices, iron deficiency, and anemia	Eligibility criteria	Number randomized, analyzed	Withdrawals Loss to followup	Funding source
Ziaei 2007[89] Good	6 clinical centers; within routine health services with help of comm-unity midwives Tehran, Iran	A: One 150 mg tablet ferrous sulfate (containing 50 mg elemental iron) daily (n=375) B: Placebo (n=375) Supplementation started at 20 weeks gestation through delivery Everyone also received 1 mg of folic acid and received dietary counseling from midwives	Through 6 weeks post-partum	A vs. B Age: 25.7 vs. 25.7 years Race/ethnicity: NR Gestational age, mean: 13.07 vs. 13.66 weeks SES: NR University: 12% vs. 9.9% BMI: 23.6 vs. 23.8 Gravidity, mean: 1.6 vs. 1.7	A vs. B Mean hemoglobin: 13.98 vs. 14.01 g/dL Anemia: excluded at baseline (0%)	Pregnant women in early stage of 2nd trimester with Hb >13.2 g/dL, BMI 19.8-26, single pregnancy, age 17-35, nonsmoking, no diseases related to polycythemia like asthma or chronic HTN, "no history of threatened abortion in present pregnancy" Excluded: Smoking, disease related to polycythemia; asthma, chronic hypertension; history of threatened abortion in present pregnancy	Randomized: 750 Analyzed: 727	A vs B 1.3% (5/375) vs. 4.8% (18/375) Excluded if developed anemia (Hb <10.5 g/dL in 2nd trimester or <11 g/dL in 3rd trimester) 2 developed anemia in placebo arm and were excluded from analyses	NR

Appendix B Table 1. Data Abstraction of Iron Supplementation Trials

Author, year Quality rating	Setting Country	Interventions (N)	Study duration	Population characteristics (age, sex/gender, race/ethnicity, gestational age, other factors reported)	Baseline hematologic indices, iron deficiency, and anemia	Eligibility criteria	Number randomized, analyzed	Withdrawals Loss to followup	Funding source
Ziaei 2008[88] Good	Prenatal clinic Tehran, Iran	A: One 150 mg tablet ferrous sulfate (50 mg elemental iron) daily (n=122) B: Placebo (n=122) Supplementation started at 20 weeks gestation through delivery; after delivery, all women received iron supplementation (RCT ended at delivery) All received dietary counseling from midwives	Through 6 weeks post-partum	A vs. B Age: 26.9 vs. 25.7 years Race/ethnicity: NR Gestational age: NR SES: NR BMI: 24.1 vs. 23.7 Gravidity, mean: 1.7 vs. 1.7	A vs. B Hemoglobin, mean: 13.99 vs. 13.94 g/dL, p=0.48 Hematocrit, mean: 41.55% vs. 41.38% Ferritin, mean: 28.07 vs. 28.21 µg/L Anemia: excluded at baseline (0%; only enrolled those with higher hemoglobin)	Women 17 to 35 years old with a Hgb concentration ≥13.2g/dL and serum ferritin ≥15 µg/L, between 13th and 18th week of pregnancy; BMI 19.8 to 26; singleton pregnancy Excluded: Smoking, disease related to polycythemia; asthma, chronic hypertension; history of threatened abortion in present pregnancy	Randomized: 244 Analyzed: 234 at delivery; 205 at 1 week postpartum	A vs B At delivery: 4.1% Excluded: 1 due to Hb <10.5 g/dL in 2nd trimester 9 due lost to followup	NR

Appendix B Table 1. Data Abstraction of Iron Supplementation Trials

Author, year	Hematologic outcomes, maternal	Hematologic outcomes, infant	Clinical outcomes, maternal	Clinical outcomes, infant	Adverse events, maternal	Adverse events, infant
Barton 1994[63]	A vs. B **At 36 weeks**: Mean hemoglobin: 13.5 vs. 12.6 g/dL, p=0.043 (adjusted for smoking p=0.25) Mean ferritin: 32.6 vs. 12.8 µg/L, p=0.04 Mean hematocrit: 0.399 vs. 0.375, p<0.001 Mean serum erythropoietin: 42.67 vs. 54.39 mU/mL, p=0.045 (adjusted for smoking p=0.20) **At 40 weeks**: Mean hemoglobin: 13.7 vs. 12.0 g/dL, p<0.001 Mean ferritin NR Mean hematocrit: 0.410 vs. 0.366, p<0.001 Mean serum erythropoietin: 37.33 vs. 60.49 mU/mL, p=0.0001 Anemia (hg <10 gm/dL): "no patients were withdrawn from the study due to anemia"	Cord blood not abstracted	A vs. B Cesarean delivery: 7.5% (4/53) vs. 9.1% (4/44), p=0.78 Hypertensive disorder: 7.5% (4/53) vs. 9.0% (4/44), p=0.78 Antepartum hemorrhage: 5.7% (3/53) vs. 4.5% (2/44), p=0.81	A vs. B Low birth weight: (<2700 g): 9.4% (5/53) vs. 15.9% (7/44), p=0.34 Perinatal death: 1.9% (1/53) vs. 0% (0/44), p=0.57	NR	NR
Chan 2009[64]	A vs. B **At delivery**: Mean hemoglobin: 12.2 vs. 11.8 g/dL; p<0.001 Mean ferritin: 67.5 vs. 55.9 pmol/L; p=0.003	NR	A vs. B Delivery method Vaginal: 63.5% (290/457) vs. 56.0% (262/468); p=0.021 Cesarean: 25.2% (115/457) vs. 33.1% (155/468); p=0.008 Gestational diabetes at 28 weeks: 9.9% (56/565) vs. 10% (60/599); OR 1.04, 95% CI 0.7 to 1.53 Gestational diabetes, cumulative at 36 weeks: 13% (72/565) vs. 13% (77/599)	A vs. B Mean gestational age at delivery: 38.8 vs. 38.7 weeks; p=0.322 Preterm delivery: 6.4% (27/419) vs. 6.8% (30/443); p=0.85 Apgar score @ 1min: 8.8 vs. 8.8, p=0.625 Apgar score @ 5min: 9.7 vs. 9.8, p=0.352SGA: 3.58% (15/419) vs. 7.45% (33/443); OR 0.46, 95% CI 0.24 to 0.85, p=0.013 Birth weight for term infants: 3247.3 g vs. 3151.9 g; p=0.001	A vs. B No major adverse events from study drugs Non-adherence at 36 weeks: 68% overall (of n=473 with data), p=0.34 between groups	NR

Appendix B Table 1. Data Abstraction of Iron Supplementation Trials

Author, year	Hematologic outcomes, maternal	Hematologic outcomes, infant	Clinical outcomes, maternal	Clinical outcomes, infant	Adverse events, maternal	Adverse events, infant
Cogswell 2003[66]	A vs. B **Week 28** (RCT phase): Mean hemoglobin: 11.7 vs. 11.6 g/dL, p=0.499 Mean ferritin: 7.4 vs. 7.4 µg/L, p=0.985 MCV: 90.8 vs. 90.3 fL, p=0.443 Erythrocyte protoprophyrin: 59.3 vs. 62.9 µg/dL, p=0.140 Anemia (hemoglobin <11.0 g/dL): 19.8% vs. 26.7%, p=0.251 Absent iron stores (serum ferritin <12 µg/L): 56.4% (62/110) vs. 65.1% (56/86), p=0.214 Iron deficiency anemia (hemoglobin <11.0 g/dL and serum ferritin <12 µg/L): 12.7% (14/110) vs. 20.9% (18/86), p=0.123 After adjustment for prepregnancy weight and initial ferritin: Absent iron stores: 14.3 percentage points lower for those on supplementation, p=0.031 Iron deficiency anemia: 10 percentage points lower for those on supplementation, p=0.062	NR	NR	Outcomes from non-RCT phase not abstracted (ended at week 28)	Side effects reported at >1 visit from enrollment to week 28: 24.6% vs. 18.5% Non-adherence at week 28: 36.6% vs 34.8%, p=NS	NR

Appendix B Table 1. Data Abstraction of Iron Supplementation Trials

Author, year	Hematologic outcomes, maternal	Hematologic outcomes, infant	Clinical outcomes, maternal	Clinical outcomes, infant	Adverse events, maternal	Adverse events, infant
Eskeland 1997[68]	A vs. B vs. C **During pregnancy** (timing not specified): Hemoglobin <11.0 g/dL: 25% iron supplemented vs. 52% unsupplemented, p<0.05 Hemoglobin <10.0 g/dL and s-ferritin <15 µg/L: 0 vs. 0 vs. 4 (14%) (denominators NR) **Week 38**: s-ferritin <15 µg/L (ID): 29% (7/24) vs. 52% (13/25) vs. 85% (17/20); p<0.001 for A vs. C and p<0.05 for B vs. C **1 week postpartum**: Anemia (hemoglobin <10.0 g/dL): 11.5% (7/61) vs. 20.7% (6/29), p=0.25 **6-10 weeks postpartum**: s-ferritin <15 µg/L (ID): 8% (2/25) vs. 27% (7/26) vs. 52% (12/23); p<0.01 for A vs. C <1st trimester value and s-ferritin <15 µg/L: 0 vs. 2 vs. 3 people (denominators NR) **24 weeks postpartum**: s-ferritin <15 µg/L (ID): 4% (1/24) vs. 17% (4/24) vs. 51% (12/23); p<0.001 for A vs. C and p<0.05 for B vs. C Total supplementation "failures" over the study period: High dose iron (100 mg) medication was given if failed to maintain an acceptable hematologic status (abstracted above), but these individuals were included in the analyses: 10% (3/31) vs. 20% (6/30) vs. 45% (13/29), p<0.01 for both treatment groups combined vs. placebo Median hemoglobin was significantly lower in placebo group compared to both intervention groups from 28 weeks to the end of pregnancy (data reported in a figure)	NR	"There were no significant differences in weight gain in pregnancy (mean 14 kg in all groups) or in number of complications in pregnancy or at birth (data from birth reports not shown)"	A vs. B Birthweight: 3690 vs. 3620 vs. 3610 g A vs. B vs. C Fetal weight: 3690 vs. 3620 vs. 3610 g	No difference in fatigue or other side effects, p=ns Non-adherence: 19% (combined 2 iron groups) vs 18%, p=ns A vs. B vs. C Compliance: 81% vs. 81% vs. 82% Compliance <50%: 4% vs. 12% vs. 5%	NR

Appendix B Table 1. Data Abstraction of Iron Supplementation Trials

Author, year	Hematologic outcomes, maternal	Hematologic outcomes, infant	Clinical outcomes, maternal	Clinical outcomes, infant	Adverse events, maternal	Adverse events, infant
Falahi 2011[69]	A vs. B **At delivery**: Hemoglobin: 12.3 vs. 12.1 g/dL Ferritin: 28.1 vs. 22.1 µg/L ID (serum ferritin <12 µg/L): 10.0% (7/70) vs. 28.2% (22/78), p<0.05 IDA (hemoglobin <110g/L and serum ferritin <12 µg/L): 0% vs. 0% **At 28 weeks**: ID 5.7% (4/70) vs. 24.4% (19/78) IDA: 1.4% (1/70) vs. 3.8% (3/78)	NR	A vs. B Pregnancy-induced hypertension: 1.4% (1/70) vs. 0% (0/78)	A vs. B Birthweight: 3.31 vs. 3.27 kg Birth length: 49.1 vs. 49.3 cm Low birthweight (<2500 g): 3% (2/70) vs. 6.4% (5/78) Preterm delivery (<37 weeks): 3% (2/70) vs. 6.4% (5/78) Gestational age at delivery: 38.9 vs. 38.8 weeks	NR	NR
Jafarbegloo 2015[70]	NR	NR	NR	NR	A vs. B **At 24-28 weeks**: Nausea: 2.3% vs. 3.9%, p=0.58 Vomiting: 0% vs. 2%, p=0.19 Diarrhea: 0% vs. 2%, p=0.19 Constipation: 4.5% vs. 3.2%, p=0.36 Loss of appetite: 0% vs. 0%, p=0.16 Heart burn: 3.4% vs. 2%, p=0.62 Abdominal pain: 0% vs. 2%, p=0.19 **At 32-36 weeks**: Nausea: 16.1% vs. 14%, p=0.74 Vomiting: 3.2% vs. 10%, p=0.09 Diarrhea: 0% vs. 2%, p=0.17 Constipation: 12.9% vs. 4%, p=0.09 Loss of appetite: 4.3% vs. 4%, p=0.93 Heart burn: 16.1% vs. 8%, p=0.17 Abdominal pain: 2.2% vs. 2%, p=0.30	NR

Appendix B Table 1. Data Abstraction of Iron Supplementation Trials

Author, year	Hematologic outcomes, maternal	Hematologic outcomes, infant	Clinical outcomes, maternal	Clinical outcomes, infant	Adverse events, maternal	Adverse events, infant
Liu 2013[72] *NEW* Also: Chen 2019[65] Li 2017[71] Liu 2021[73] Mei 2014[75] Serdula 2019[82] Wang 2016[84]	A vs. B **24 to 28 weeks gestation** (finger puncture, n= 11,809) Hemoglobin: 12.2 vs. 12.2 g/dL, MD 0.04 (95% CI 0.01 to 0.07) Anemia (Hb <11.0 g/dL, n=11,809): 5.5% vs. 7.7%, RR 0.72 (95% CI 0.63 to 0.83) **28 to 32 weeks gestation** (venous blood, n=562; Mei, 2014): Ferritin: 16.7 vs. 11.3 µg/L, p<0.05 ID (serum ferritin <12 µg/L): 35.3% (98/278) vs. 59.6% (168/282), p<0.05 Hemoglobin: 12.4 vs. 12.5 g/dL, p>0.05 Anemia: 7.2% (20/278) vs. 5.3% (15/284), p>0.05 **4 to 6 weeks postpartum** (n=11,544; Serdula 2019): Hemoglobin: 12.4 vs. 12.4 g/dL, MD 0.015 (95% CI -0.014 to 0.045) Anemia: 26.8% (1547/5779) vs. 27.2% (1568/5765), OR 0.98 (95% CI 0.93 to 1.05) Also reported stratified by baseline hemoglobin, with similar findings across hemoglobin levels and no statistically significant interaction between supplementation and baseline hemoglobin level in effects on postpartum hemoglobin or anemia	A vs. B **6 months of age**: Hb, g/dL: 12.17 vs. 12.17, MD -0.005 (95% CI -0.036 to 0.027) Anemia: 6.7% (386/5779) vs. 6.9% (400/5765), OR 0.96 (95% CI 0.84 to 1.10) **12 months of age**: Hb, g/dL: 12.22 vs. 12.21, MD 0.005 (95% CI -0.025 to 0.034) Anemia: 5.0% (287/5779) vs. 5.2% (300/5765), OR 0.95 (95% CI 0.82 to 1.12) Also reported stratified by baseline maternal hemoglobin, with similar findings across hemoglobin levels and no statistically significant interaction between supplementation and baseline hemoglobin level in effects on infant hemoglobin or anemia at 6 or 12 months	A vs. B Pregnancy-induced hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg from ≥20 weeks of gestation among women with previously normal BP): 6.3% (374/5933) vs. 7.1% (423/5923), OR 0.88 (95% CI 0.76 to 1.01) No statistically significant association between timing of iron supplementation (before/after 12 weeks) and PIH	A vs. B (Cases per 1000 for mortality outcomes) Perinatal mortality (stillbirth + early neonatal): 8.73 (52/5954) vs. 8.76 (52/5934), RR 1.00 (95% CI 0.68 to 1.46) Stillbirth (28 weeks to delivery): 4.70 (28/5954) vs. 4.72 (28/5934), RR 1.00 (95% CI 0.59 to 1.68) Early neonatal mortality (birth to 6 days after delivery): 4.05 (24/5926) vs. 4.06 (24/5906), RR 1.00 (95% CI 0.57 to 1.75) Neonatal mortality (birth to 28 days after delivery): 5.40 (32/5926) vs. 4.91 (29/5906), RR 1.10 (95% CI 0.67 to 1.82) Infant mortality (first year of life): 7.42 (44/5926) vs. 7.62 (45/5906), RR 0.97 (95% CI 0.64 to 1.48) Spontaneous preterm birth (20 to 36 weeks): 5.6% (334/5920) vs. 5.7% (335/5888), RR 0.99 (95% CI 0.85 to 1.16) Birth weight: 3292.5 vs. 3290.6 g, MD 1.91 (95% CI -12.16 to 15.98) LBW (<2500 g): 2.2% (129/5922) vs. 2.1% (125/5905), RR 1.03 (95% CI 0.81 to 1.31)	A vs. B Serious adverse events: none reported Gastrointestinal discomfort (e.g. nausea, vomiting; denominators at 24 to 28 weeks): 3.6% (212/5913) vs. 2.3% (133/5896), p<0.0001 across 2 groups Non-adherence: 7.2% vs. 6.7%	NR

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Author, year	Hematologic outcomes, maternal	Hematologic outcomes, infant	Clinical outcomes, maternal	Clinical outcomes, infant	Adverse events, maternal	Adverse events, infant
				Birth length: 50.0 vs.50.0 cm, MD 0.01 (95% CI -0.03 to 0.05) Preterm birth (<37 weeks): 5.7% (340/5926) vs. 6.0% (353/5906), RR 0.96 (95% CI 0.83 to 1.11) Gestational age: 39.6 vs. 39.6 weeks, MD -0.03 (95% CI -0.09 to 0.03) Also reported birth weight stratified by baseline maternal hemoglobin. No difference for birth weight for patients with hemoglobin up to 14.5 g/dL; for those with hemoglobin >14.5 g/dL, iron supplementation associated with a statistically significant but very small increase in birth weight (3280 g vs. 3195 g)		

Appendix B Table 1. Data Abstraction of Iron Supplementation Trials

Author, year	Hematologic outcomes, maternal	Hematologic outcomes, infant	Clinical outcomes, maternal	Clinical outcomes, infant	Adverse events, maternal	Adverse events, infant
Makrides 2003[74] Also: Zhou 2007[87] Zhou 2006[90]	A vs. B **At 28 weeks**: Hemoglobin: 12.0 vs. 11.6 g/dL; MD 0.34 (95% CI 0.17 to 0.53) Anemia: 9.7% (20/206) vs. 24.9% (51/205), RR 0.39 (95% CI 0.24 to 0.63) **At delivery:** Hemoglobin: 12.7 vs. 12.0 g/dL; MD 0.69 (95% CI 0.44 to 0.93) Ferritin: 21 vs. 14 ug/L; MD 7.1 (95% CI 4.0 to 10.2)ID: 35% (65/186) vs. 58% (102/176); RR 0.60 (95% CI 0.48 to 0.76) Anemia: 7% (14/200) vs. 16% (30/193); RR 0.45 (95% CI 0.25 to 0.82) IDA: 3% (6/198) vs. 11% (20/185); RR 0.28 (95% CI 0.12 to 0.68) **At 6 months postpartum**: Hemoglobin: 13.5 vs. 13.4 g/dL; MD 0.16 (95% CI -0.01 to 0.33) Ferritin: 34 vs. 26; MD 7.9 (95% CI 3.5 to 12.3)ID: 16% (31/190) vs. 29% (51/177); RR 0.57 (95% CI 0.38 to 0.84) Anemia: 3.7% (7/189) vs. 4.5% (8/177); RR 0.82 (95% CI 0.30 to 2.21) IDA: 2.6% (5/190) vs. 1.7% (3/177); RR 1.55 (95% CI 0.38 to 6.40)	A vs. B **At 6 months postpartum** Hemoglobin: 12.1 vs. 11.9 g/dL, p=0.10 Ferritin: 32.5 vs. 30.8 ug/L, p=0.48 ID: 6% (11/170) vs. 4% (6/159), p=0.27 IDA: 0% vs. 0%, p=NS	A vs. B Cesarean: 23.6% (51/216) vs 22.0% (47/214), p=NS **At 36 weeks of gestation, 6 weeks postpartum, 6 months postpartum** Quality of life (Short Form-36): no significant differences between women receiving iron-supplementation and those in the placebo group in any of the 8 health concepts (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and general mental health) (specific data only displayed in a figure) **At 4 years (ns 151 vs. 148):** Quality of life (Short Form-36): no significant differences on any of the same 8 health concepts, p-values 0.20 to 0.80	A vs. B Gestational age at birth: 39.4 vs. 39.2 weeks, p=NS Birth weight: 3406 vs. 3449 g, p=NS Apgar score <7 at 5 min: 1.4% vs. 1.9%, p=NS Low birth weight: 5.4% (12/216) vs. 4.2% (9/214), p=NS Birth length: 49.9 vs. 50.0 cm, p=NS Neonatal death: 0.5% (1 case) vs. 0%, p=NS Level III nursery care: 2.7% (6/216) vs. 3.3% (7/214), p=NS	A vs. B **At 36 weeks** Nausea: 29% (58/200) vs. 28% (54/193) RR 1.04 (95% CI 0.76 to 1.42) Stomach pain: 35% (70/200) vs. 30% (57/193); RR 1.19 (95% CI 0.89 to 1.58) Heartburn: 68% (136/200) vs. 69% (133/193); RR 0.99 (95% CI 0.86 to 1.13) Vomiting: 12% (24/200) vs. 13% (26/193); RR 0.89 (95% CI 0.53 to 1.50) Rash: 7.5% (15/200) vs. 6.2% (12/193); RR 1.21 (95% CI 0.58 to 2.51) Bowel actions ≤3 times/week: 4% (8/200) vs. 1.6% (3/192); RR 2.56 (95% CI 0.69 to 9.51) Non-adherence: 14% vs 15%, p=NS	NR

Appendix B Table 1. Data Abstraction of Iron Supplementation Trials

Author, year	Hematologic outcomes, maternal	Hematologic outcomes, infant	Clinical outcomes, maternal	Clinical outcomes, infant	Adverse events, maternal	Adverse events, infant
Meier 2003[76]	A vs. B **At 36-40 weeks**: *Adolescents*: Median serum ferritin: 12.0 vs. 6.2 ng/mL, p=0.010 Median hemoglobin: 12.2 vs. 11.5 g/dL, p=0.024 IDA: 5% (1/20) vs. 29.4% (5/17), p=0.090 *Adults*: Median serum ferritin: 12.9 vs. 7.6 ng/mL, p=0.027 Median hemoglobin: 12.1 vs. 11.7 g/dL, p=0.135 IDA: 10.5% (4/38) vs. 22.2% (8/36), p=0.187	NR	A vs. B *Adolescents*: Cesarean delivery: 20% (4/20) vs. 6.2% (1/16), p=NS *Adults*: Cesarean delivery: 14.3% (5/38) vs. 25% (9/36), p=NS Combined cesarean delivery: 16% vs. 19%, p=NS	A vs. B *Adolescent mothers*: Apgar scores of ≤7 in 1 minute: 30% (6/20) vs. 25% (4/16), p=NS Mean length: 50.0 vs. 51.6 cm, p=NS Mean gestational age: 39.9 vs. 39.8 weeks, p=NS Birth weight <2,500g: 0% vs. 0%, p=NS *Adult mothers*: Apgar scores of ≤7 in 1 minute: 29.7% (11/38) vs. 16.7% (6/36), p=NS Mean length: 52.4 vs. 51.8 cm, p=NS Mean gestational age: 39.2 vs. 39.5 weeks, p=NS Birth weight <2,500g: 5.4% (2/38) vs. 2.9% (1/36), p=NS Infant mortality: 0% vs 0%, p=NS	A vs. B *Adolescents*: Nausea: 53% vs. 65%, p=NS Vomiting: 41% vs. 41%, p=NS Constipation: 29% vs. 12%, p=NS Diarrhea: 13% vs. 17%, p=NS Adults: Nausea: 63% vs. 53%, p=NS Vomiting: 35% vs. 21%, p=NS Constipation: 24% vs. 28%, p=NS Diarrhea: 14% vs. 24%, p=NS Non-adherence: *Adolescents*: 4.5% vs 12.6%, p=0.320 *Adults*: 2.2% vs 16.1%, p=0.036	NR

Appendix B Table 1. Data Abstraction of Iron Supplementation Trials

Author, year	Hematologic outcomes, maternal	Hematologic outcomes, infant	Clinical outcomes, maternal	Clinical outcomes, infant	Adverse events, maternal	Adverse events, infant
Milman 1991[77] Also: Milman 1994[78] Milman 2000[79]	A vs. B **27 to 30 weeks** (N=207, 1991 paper): Hb <11.0 g/dL: 8.8% vs. 22.0% (n/N NR) **Approximate term, 39 to 43 weeks:** (N=207), (1991 paper): Hb <11.0 g/dL: 0% vs. 14.3% (n/N NR) Mean hemoglobin (n=206): 12.9 vs. 11.9 g/dL, p<0.0001 **At term** (n=120): Mean ferritin: 22 vs 14 µg/L, p<0.0001 Ferritin ≤20 µg/L: 34.0% vs. 91.9% Mean hemoglobin: 12.7 vs 11.6 g/dL, p<0.0001 ID (ferritin <20 µg/L + transferrin saturation <15%; 1994 paper): 6.3% (4/63) vs. 54.4% (31/57) IDA (ferritin <20 µg/L, transferrin saturation <15%, Hb <11.0 g/dL; 1994 paper): 0% (0/63) vs. 17.5% (10/57) **8 weeks postpartum**: Ferritin ≤20 µg/L (n=120): 16.1% vs. 40.4% Mean hemoglobin (n=121, reason for discrepancy unclear): 13.4 vs. 12.9 g/dL, p<0.001 Hb <12.1 g/dL (n=207): 3.2% vs. 21.1%	NR (cord blood only)	NR	N=207: Pregnancy duration (n=207): 282 vs. 282 days Weight, median: 3375 vs. 3500 g Height, median: 52 vs. 52 cm Apgar, median, 1 to 10 min: 10 vs. 10 N=120: Median birth weight: 3350 vs. 3450 g, p>0.5	NR	NR

Appendix B Table 1. Data Abstraction of Iron Supplementation Trials

Author, year	Hematologic outcomes, maternal	Hematologic outcomes, infant	Clinical outcomes, maternal	Clinical outcomes, infant	Adverse events, maternal	Adverse events, infant
Ouladsaheb-madarek 2011[80] *NEW*	A vs. B **At delivery**: Hemoglobin: 13.46 vs. 12.48 g/dL, p=0.03 Hematocrit: 41.48% vs. 37.36%, p=0.01 Ferritin: 26.91 vs. 9.26 µg/dL, p=0.048	NR	A vs. B Pregnancy-induced hypertension: 6.7% (25/410) vs. 3.4% (14/372), p=0.04 Preeclampsia: 3.9% (16/410) vs. 2.7% (10/372), p=0.42 Gestational diabetes: 0.5% (2/410) vs. 0.8% (3/372), p=0.67 Cesarean: 51.2% (210/410) vs. 45.8% (NR/372), p=0.09	A vs. B Gestational age at birth: 39 vs. 39 weeks, p=0.74 Preterm delivery (20 to 38 weeks): 3.9% (16/410) vs. 4.8% (18/372), p=0.6 Birth weight: 3260 vs. 3217 g, p=0.28 IUGR (BW < 10th percentile for GA): 14.1% (58/410) vs, 17.5% (65/372), p=0.23 IUFD (not defined): 0.5% (2/410) vs. 0.8% (3/372), p=0.67 Apgar 1 min: 8.89 vs. 8.93, p=0.5 Apgar 5 min: 9.96 vs. 9.99, p=0.11 NICU admission duration (min): 165 vs. 132, p=0.12	"No meaningful differences were found between the means of…complications includ[ing]...septicemia in [the] two groups"	"No meaningful differences were found between the means of…complications includ[ing] hyaline membrane disease, asphyxia, convulsion, and septicemia in [the] two groups" (NR for infants vs. mothers)

Appendix B Table 1. Data Abstraction of Iron Supplementation Trials

Author, year	Hematologic outcomes, maternal	Hematologic outcomes, infant	Clinical outcomes, maternal	Clinical outcomes, infant	Adverse events, maternal	Adverse events, infant
Romslo 1983[81]	A vs. B **At 28 to 32 weeks**: Anemia (hemoglobin <11.0 g/dL): 9.1% (2/22) vs. 21.7% (5/23) **At 38 to 42 weeks**: Anemia (hemoglobin <11.0 g/dL): 4.5% (1/22) vs. 30.4% (7/23) **At 37-40 weeks**: Mean hemoglobin: 12.6 vs. 11.3 g/dL, p-value NR Mean ferritin: 24.0 vs. 6.0 µg/L, p-value Low serum ferritin, low serum transferrin saturation and high erythrocyte protoprophyrin values: 0% (0/22) vs. 65.2% (15/23), p=0.02	NR (cord blood only)	NR	A vs. B Gestation: 39.9 vs. 39.5 weeks, p-value NR Birthweight: 3546 vs. 3510 g, p-value NR Apgar 1 min score: 8.7 vs. 8.8, p-value NR Apgar 5 min score: 9.0 vs. 9.0, p-value NR	A vs. B Non-adherence: 45% overall, p=NS ("did not vary significantly between the two groups")" None of the women complained of discomfort that could be attributed to the medication"	NR
Siega-Riz 2006[83]	A vs. B **At 26-29 weeks**: Mean hemoglobin: 11.4 vs. 11.4 g/dL, p=0.81 Mean ferritin: 22.0 vs. 20.3 µg/L, p=0.48 Anemia (hemoglobin <11.0 g/dL): 21% (34/160) vs. 19% (30/156), p=0.65 Iron depletion (serum ferritin <20 µg/L): 53% (85/160) vs. 65% (101/156), p=0.08 IDA (hemoglobin <11.0 g/dL and serum ferritin <20 µg/L): 10% (16/160) vs. 15% (23/156), p=0.23	NR	NR	Outcomes from non-RCT phase not abstracted (ended at week 26-29)	A vs. B Non-adherence: 34% vs 37%, p=0.27	NR

Appendix B Table 1. Data Abstraction of Iron Supplementation Trials

Author, year	Hematologic outcomes, maternal	Hematologic outcomes, infant	Clinical outcomes, maternal	Clinical outcomes, infant	Adverse events, maternal	Adverse events, infant
Zeng 2008[85] *NEW*	A vs. B At weeks **28 to 32 weeks** (in 411 women): Hemoglobin: 11.0 vs. 10.5 g/dL, MD 0.50 (95% CI 0.20 to 0.80) Anemia (Hb <110g/L): 45.1% (87/193) vs. 61.0% (133/218), RR 0.74 (95% CI 0.61 to 0.91) Estimates adjusted for effects of multiple births and cluster randomization	NR	NR	A vs. B Birth weight: 3173.9 vs, 3153.7, MD 24.3 (95% CI −10.3 to 59.0) Low birth weight (<2500 g): 4.5% (66/1470) vs. 5.3% (82/1545), RR 0.85 (95% CI 0.62 to 1.16) Small for gestational age (below 10th centile, U.S. reference): 18.9% (278/1470) vs. 18.1% (280/1545), RR 1.04 (95% CI 0.89 to 1.22) Birth length: 49.1 vs. 48.8 cm, MD 0.24 (95% CI 0.02 to 0.46) Duration of gestation: 39.84 vs. 39.63 weeks, MD 0.23 (95% CI 0.10 to 0.36) Preterm delivery (<37 weeks): 4.9% (76/1537) vs. 6.1% (102/1666), RR 0.81 (95% CI 0.61 to 1.08) Early preterm delivery (<34 weeks): 0.98% (15/1537) vs. 1.80% (30/1666), RR 0.50 (95% CI 0.27 to 0.94) Rates per 1000:Stillbirths (≥28 weeks through labor): 30.4 vs. 30.8, RR 1.01 (95% CI 0.67 to 1.51) All neonatal deaths (within 28 days): 10.7 vs. 20.2, RR 0.53 (95% CI 0.29 to 0.97) Early neonatal deaths (within 7 days): 6.7 vs. 14.7, RR 0.46 (95% CI 0.21 to 0.98)	A vs. B Withdrawals due to adverse events: 3.7% (71/1912) vs. 2.7% (54/2017), RR 1.39, 95% CI 0.98 to 1.97 Nausea: 1.6% (31/1912) vs. 1.3% (26/2017) Vomiting: 2.1% (40/1912) vs. 1.4% (28/2017) Non-adherence, mean % of days when supplements not consumed: 8.1% vs. 6.6%	NR

Appendix B Table 1. Data Abstraction of Iron Supplementation Trials

Author, year	Hematologic outcomes, maternal	Hematologic outcomes, infant	Clinical outcomes, maternal	Clinical outcomes, infant	Adverse events, maternal	Adverse events, infant
				Perinatal deaths (stillbirth + early neonatal deaths): 36.9 vs. 45.0, RR 0.84 (95% CI 0.59 to 1.19)		
Zhao 2015[86] *NEW*	A vs. B **At or near term**, mean 39.4 weeks GA: Hemoglobin, mean: 12.2 vs. 11.7 g/dL, p<0.001 Ferritin, mean: 15.3 vs. 11.1 µg/L, p<0.001 Anemia (Hb<11.0 g/dL): 13.4% (109/814) vs. 25.1% (201/802), RR 0.53 (95% CI 0.43 to 0.66) ID (ferritin < 15 µg/L): 56.8% (462/815) vs. 77.1% (618/802), RR: 0.74 (95% CI 0.69 to 0.79) IDA: 10.6% (86/814) vs. 21.7% (174/802), RR 0.49 (95% CI 0.38 to 0.62) Postpartum anemia (day 1): RR 0.71 (95% CI 0.66 to 0.78)	NR (cord blood only)	A vs. B Cesarean delivery: 70.1% (571/815) vs. 66.0% (527/799), p=0.08	A vs. B Gestational age, mean: 39.6 vs. 39.7 weeks, p=0.76 Birth weight, mean: 3355 vs. 3368 g, p=0.55 Birth length, mean: 49.7 vs. 49.7 cm, p=0.65 Serious adverse birth outcomes (miscarriage, stillbirth, prematurity, congenital malformation): 0.95% (8/840) vs. 1.81% (15/831), p=0.13	A vs. B "Minor adverse symptoms such as nausea, vomiting, diarrhea, or constipation:" 68.4% vs. 68.2% Non-adherence, 14.9% vs. 9.9% (women with complete data, ns NR)	NR
Ziaei 2007[89]	A vs. B **At 3rd trimester**: Mean hemoglobin: 13.75 vs. 12.56 g/dL, p<0.001 2 developed anemia in placebo arm and were excluded from analyses	NR	A vs. B Caesarean "for obstetrics reasons": 25.9% (96/370) vs. 23% (82/357), p=NS Weight gain, mean: 12.4 vs. 12.8 kg, p=NS Hypertensive disorder: 2.7% (10/370) vs. 0.8% (3/357), p=0.07	A vs. B Apgar score at 10 min: 9.9 vs. 9.8, p=NS SGA: 15.4% (57/370) vs. 10.1% (36/357), p=0.035 Perinatal mortality: 0.8% (3/370) vs. 1.7% (6/357), p=NS Premature labor, number: 4.6% (17/370) vs. 3.6% (13/357), p=NS	NR	NR

Appendix B Table 1. Data Abstraction of Iron Supplementation Trials

Author, year	Hematologic outcomes, maternal	Hematologic outcomes, infant	Clinical outcomes, maternal	Clinical outcomes, infant	Adverse events, maternal	Adverse events, infant
Ziaei 2008[88]	A vs. B **At delivery** (n=234) Hemoglobin, mean: 13.88 vs. 12.78 g/dL, p<0.0001 Ferritin, mean: 26.18 vs. 19.08 µg/L, p<0.0001 Hematocrit, mean: 41.12% vs. 40.08%, p<0.001 After delivery, all women received iron supplementation, therefore 6 week postpartum outcomes not abstracted	NR	A vs. B Cesarean delivery: 10.5% (12/114) vs. 10.8% (13/120), RR 0.97 (95% CI 0.46 to 2.04) Postpartum hemorrhage: 1.8% (2/114) vs. 1.7% (2/120), RR 1.05 (95% CI 0.15 to 7.35)	NR	NR	NR

Abbreviations: BMI=body mass index; BP=blood pressure; BW=birth weight; CI=confidence interval; DBP=diastolic blood pressure; GA=gestational age; Hb=hemoglobin; HTN=hypertension; ID=iron deficiency; IDA=iron deficiency anemia; IUFD=intrauterine fetal demise; IUGR=intrauterine growth restriction; LBW=low birth weight; MCV=mean corpuscular volume; MD=mean difference; NICU=neonatal intensive care unit; NR=not reported; NS=not significant; OR= odds ratio; PIH=pregnancy induced hypertension; RCT=randomized control trial; RR=relative risk; SBP=systolic blood pressure; SES=socioeconomic status; SF=serum ferritin; SGA=small for gestational age; U.S.=United States; WIC=women and infant children.

Appendix B Table 2. Quality Assessment of Iron Supplementation Trials

Author, year	Random-ization adequate?	Allocation conceal-ment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and with-drawals reported?	Loss to follow-up: differential/ high?	Analyze people in the groups in which they were randomized?	Quality rating
Barton 1994[63]	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No/no	Yes	Fair
Chan 2009[64]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No/Yes	Yes	Fair
Cogswell 2003[66]	Yes	Unclear	No	Yes	Yes	Unclear	Yes	Yes	No/Somewhat high	Yes	Fair
Eskeland 1997[68]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No/no	Yes	Fair
Falahi 2011[69]	Unclear	Unclear	No	Yes	Yes	Yes	Yes	No	Unclear	Unclear	Fair
Jafarbegloo 2015[70]	Unclear	Unclear	Yes	Yes	No	Yes	Yes	Yes	No/No	Yes	Fair
Liu 2013[72]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Makrides 2003[74]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
Meier 2003[76]	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No	Yes	Fair
Milman 1991[77]	Unclear	Unclear	No	Yes	Unclear	Yes	Yes	Yes	No/Unclear	Unclear	Fair
Ouladsahe-bmadarek 2011[80]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes/No	Yes	Fair
Romslo 1983[81]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear/No	Unclear	Fair
Siega-Riz 2006[83]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No/Unclear	No	Fair
Zeng 2008[85]	Yes	Yes	Yes	Yes	Yes?	Yes	Yes	Yes	No	No	Fair
Zhao 2015[86]	Yes	Yes	Yes	Yes	Yes?	Yes	Yes	Yes	No/Yes	No	Fair
Ziaei 2007[89]	Yes	Unclear	Yes	Yes	No	Yes	Yes	Yes	No/No	Yes	Good
Ziaei 2008[88]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No/No	Yes	Good

Appendix B Table 3. Data Abstraction of Association Study

Author, year Quality	Study design	N	Country Setting	Condition definition	Intervention	Comparison (Definition)	Duration of follow up Loss to followup	Eligibility criteria
Detlefs, 2022[67] Fair	Population based cohort study	20,690	U.S. University medical center	Anemic (N=7,416): Treated with an iron supplement outside of prenatal vitamin or presented to labor and delivery with anemia as defined by the ACOG criteria. Included a hemoglobin level of <11 g/dL in the third trimester of pregnancy or 10.5 g/dL if delivered in the second trimester of pregnancy. Patients initially treated with iron supplementation if hemoglobin below ACOG cutoffs for anemia. Patients continued on supplementation throughout pregnancy if iron studies were performed and indicated iron deficiency. Patients who received iron therapy other than that included in a prenatal vitamin were considered to have a diagnosis of iron deficiency.	a. Refractory anemic (N=1,319): anemic on admission to labor and delivery despite taking an iron supplement b. Successfully treated (N=2,695): arrived with normal hemoglobin and reported taking iron supplementation c. Untreated and anemic (N=3,402): anemic on admission to labor and delivery and did not receive iron supplementation	Non-anemic N=13,274 (Hgb >11)	Through delivery NA	Singleton pregnancy and sufficient prenatal care (prenatal care beginning <20 weeks; attending 50 to 100% of recommended visits) identified from PeriBank database from August 2011 to November 2019

Appendix B Table 3. Data Abstraction of Association Study

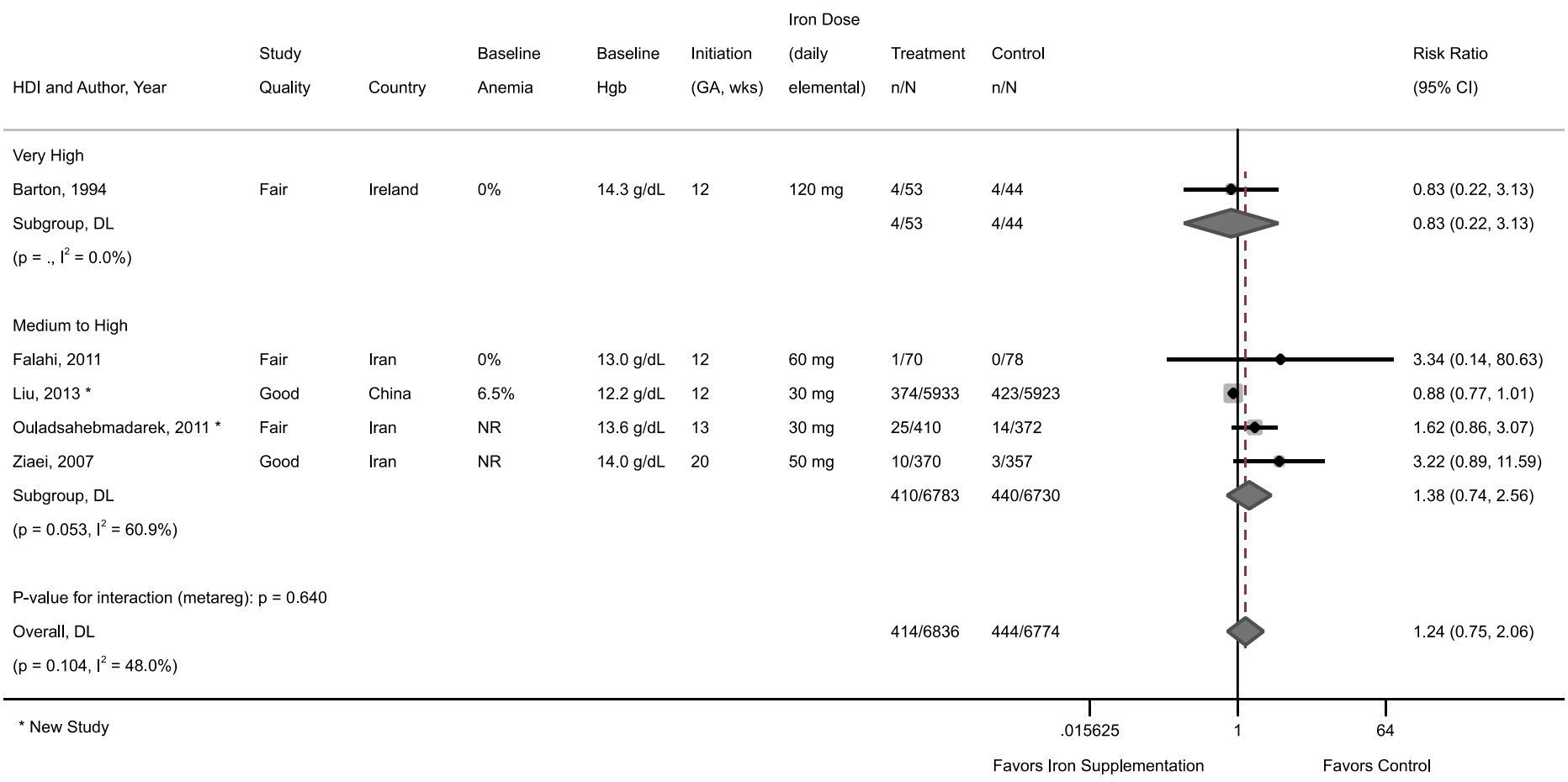
Author, year	N (number receiving supplementation)	Population characteristics (age, sex/gender, race/ethnicity, gestational age, other factors reported)	Proportion of patients with intermediate outcome	Confounders adjusted for in analysis	Results (by clinical outcome)
Detlefs, 2022[67]	Successfully treated (N=2,695): arrived with normal hemoglobin and reported taking iron supplementation Refractory anemic (N=1,319): anemic on admission to labor and delivery despite taking an iron supplement Dosing, timing, and duration unclear: very little information about what supplementation people actually received or for how long	Anemic (a; b; c) vs nonanemic **Maternal age, n (%)** <18: 17 (1.3); 17 (0.6); 76 (2.2) vs 122 (0.9) 18-35: 1078 (81.8); 2095 (77.9); 2594 (76.3) vs 10,112 (76.2) >35: 222 (16.9); 579 (21.5); 730 (21.5) vs 3029 (22.8) **Nulliparous** 325 (24.6); 956 (35.5); 967 (25.5) vs 3923 (29.6) **Body mass index at time of delivery** <18.5: 1 (0.1); 1 (0); 0; vs 6 (0.1) 18-25: 112 (9.1); 253 (9.9); 223 (7.0) vs 1063 (8.6) 25-30: 372 (30.3); 929 (36.5); 922 (28.9) vs 4136 (33.3) 30-40: **Race and ethnicity** African American: 307 (23.5); 437 (16.4); 546 (16.3) vs 1170 (9) Hispanic: 726 (55.5); 1150 (43.3); 2122 (63.6) s 7094 (54.4) White: 235 (18); 863 (32.5); 591 (17.7) vs 3899 (30) Asian: 37 (2.8); 201 (7.6); 75 (2.3) vs 838 (6.4) Other: 2 (0.2); 5 (0.2); 4 (0.1); vs 22 (0.2) **Insurance type** Federal: 895 (70); 1236 (46.9); 2320 (72) vs 6947 (55) Private: 380 (29.7); 1391 (52.8); 880 (27.3) vs 5621 (44.5) None: 4 (0.3); 7 (0.3); 22 (0.7) vs 47 (0.5)	Anemic (Hgb <11), N=7416 Intermediate measures not reported	Adjusted for age, nulliparity, education status, race and ethnicity, composite medical condition, and tobacco use	**Maternal outcomes**: Cesarean delivery, n (%) A: 473 (35.9) B:874 (32.4) C:1182 (34.8) Nonanemic: 3858 (29.1); P<0.0001 Preeclampsia; AOR (95% CI) A:136 (11.5); 1.54 (1.24-1.89) B: 136 (5.1); 0.75 (0.61-0.91) C: 410 (12.1); 1.44 (1.25-1.67) Nonanemic: 1014 (8.3); P<0.0001 Postpartum hemorrhage; AOR (95% CI) A: 47 (3.6); 2.04 (1.40-2.89) B: 69 (2.6); 1.20 (0.70−1.97) C: 101 (3); 1.23 (0.74−1.98) Nonanemic: 242 (1.8); P<0.0001 Blood transfusion A: 72 (5.5); 6.05 (4.29−8.48) B: 41 (1.5); 1.49 (0.97−2.23) C: 118 (3.5); 3.70 (2.76−4.98) Nonanemic: 130 (1.0); P<0.0001 Composite maternal morbidity A: 377 (29.6) B: 517 (19.8) C: 935 (30) Nonanemic: 2709 (21.7); P<0.0001 Maternal death = 0 **Infant outcomes**: Preterm birth; AOR (95% CI) A: 145 (11); 1.44 (1.16-1.76) B: 136 (5.1); 0.59 (0.47-0.72) C: 410 (12.1); 1.45 (1.26-1.67) Nonanemic: 1106 (8.3); P<0.0001 There was a significant reduction in the odds of preterm birth (aOR, 0.59; 95% CI, 0.47−0.72) and preeclampsia (aOR, 0.75; 95% CI, 0.61−0.91) among successfully treated patients vs reference population SGA; n (%); AOR (95% CI) A: 231 (17.5); 0.71 (0.59−0.84 B: 502 (18.6); 0.82 (0.72−0.93 C: 655 (19.3); 0.71 (0.63−0.80

Abbreviations: ACOG=American College of Obstetricians and Gynecologists; AOR=adjusted odds ratio; CI=confidence interval; Hgb=hemoglobin; NA=not applicable; RR=relative risk; SGA=small for gestational age.

Appendix B Table 4. Quality Assessment of Association Study

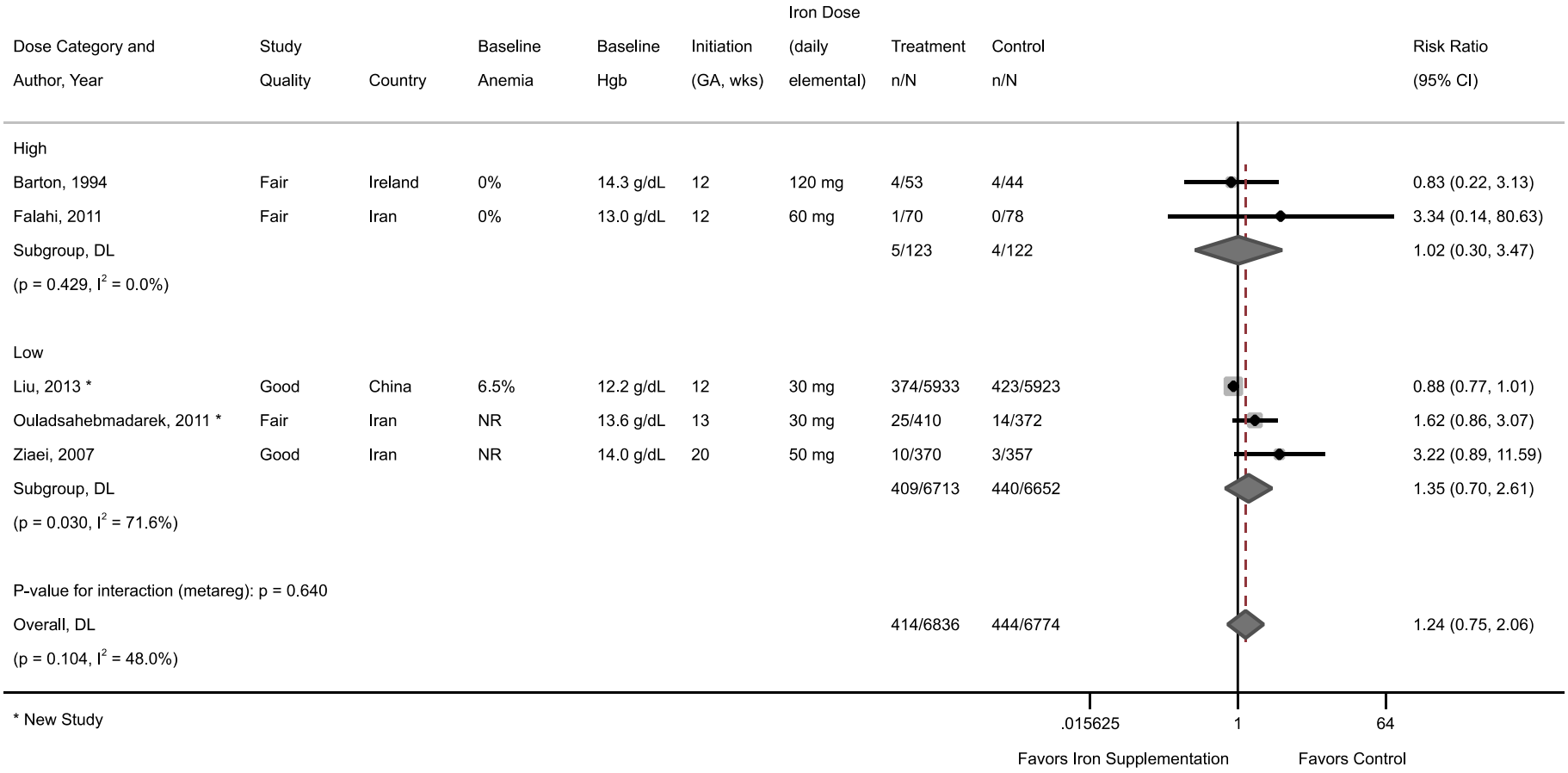
Author, year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining intermediate outcomes?	Were outcome assessors and/or data analysts blinded to treatment?	Did the article report the number of patients who met inclusion criteria excluded due to missing data or loss to follow up?	Did the study perform appropriate statistical analyses on potential confounders, or appropriately account for them (should evaluate at least age, gestational stage, anemia status)?	Is there important (overall or differential) exclusion of patients due to missing data or loss to follow up?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality rating	Funding source
Detlefs 2022[67]	No	No	Unclear	Unclear (not reported)	NA	Yes	Not applicable	Yes	Fair	National Institutes of Health; National Institute of Child Health and Human Development

Appendix C Figure 1. Meta-Analysis: Hypertensive Disorders of Pregnancy, Stratified by HDI Country



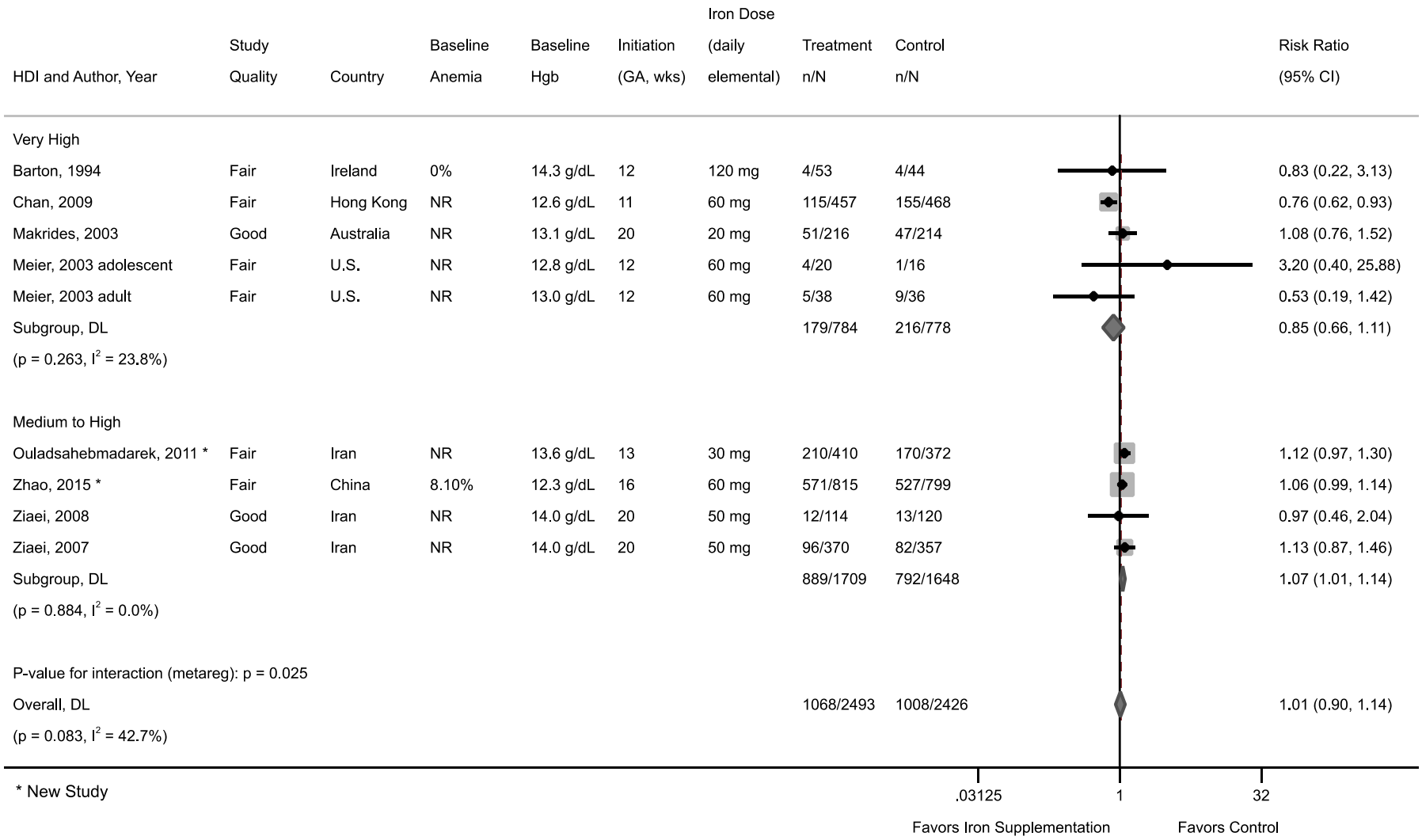
Abbreviations: CI=confidence interval; DL=DerSimonian Laird; GA, wks=gestational age, weeks; HDI=United Nations Human Development Index; Hgb=hemoglobin; NR=not reported.

Appendix C Figure 2. Meta-Analysis: Hypertensive Disorders of Pregnancy, Stratified by Dose



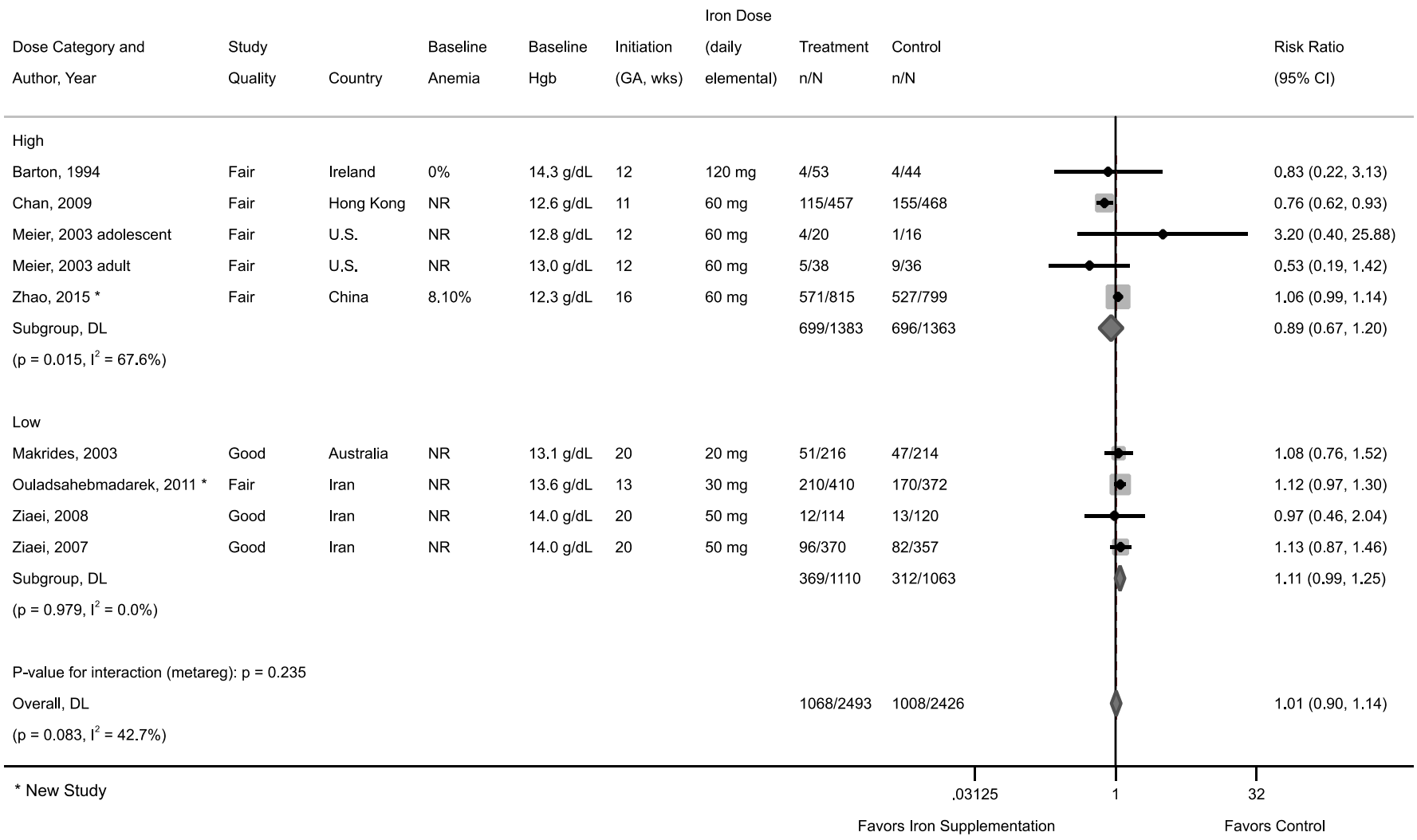
Abbreviations: CI=confidence interval; DL=DerSimonian Laird; GA, wks=gestational age, weeks; Hgb=hemoglobin; NR=not reported.

Appendix C Figure 3. Meta-Analysis: Cesarean Delivery, Stratified by HDI Country



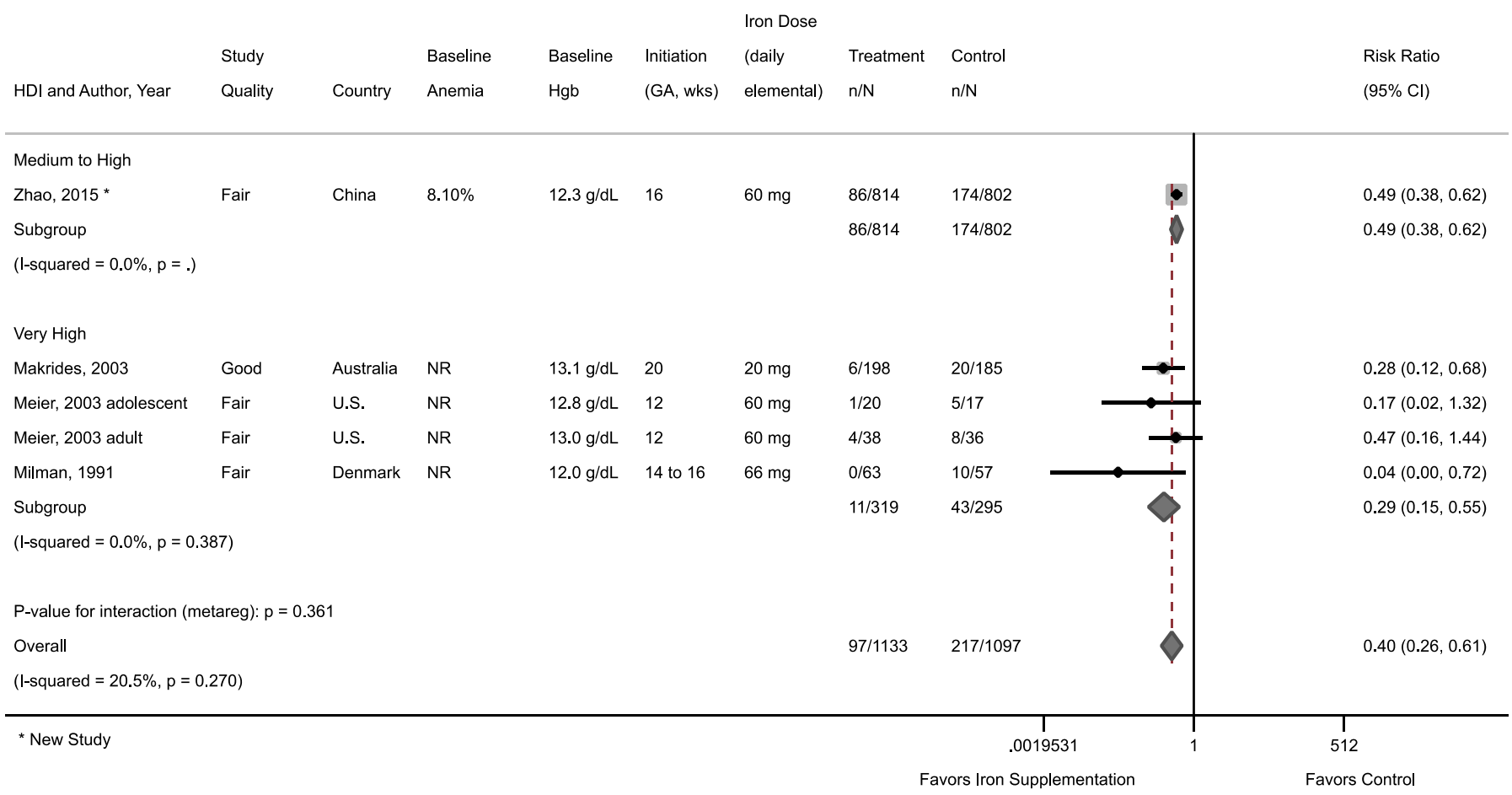
Abbreviations: CI=confidence interval; DL=DerSimonian Laird; GA, wks=gestational age, weeks; HDI=United Nations Human Development Index; Hgb=hemoglobin; NR=not reported.

Appendix C Figure 4. Meta-Analysis: Cesarean Delivery, Stratified by Dose



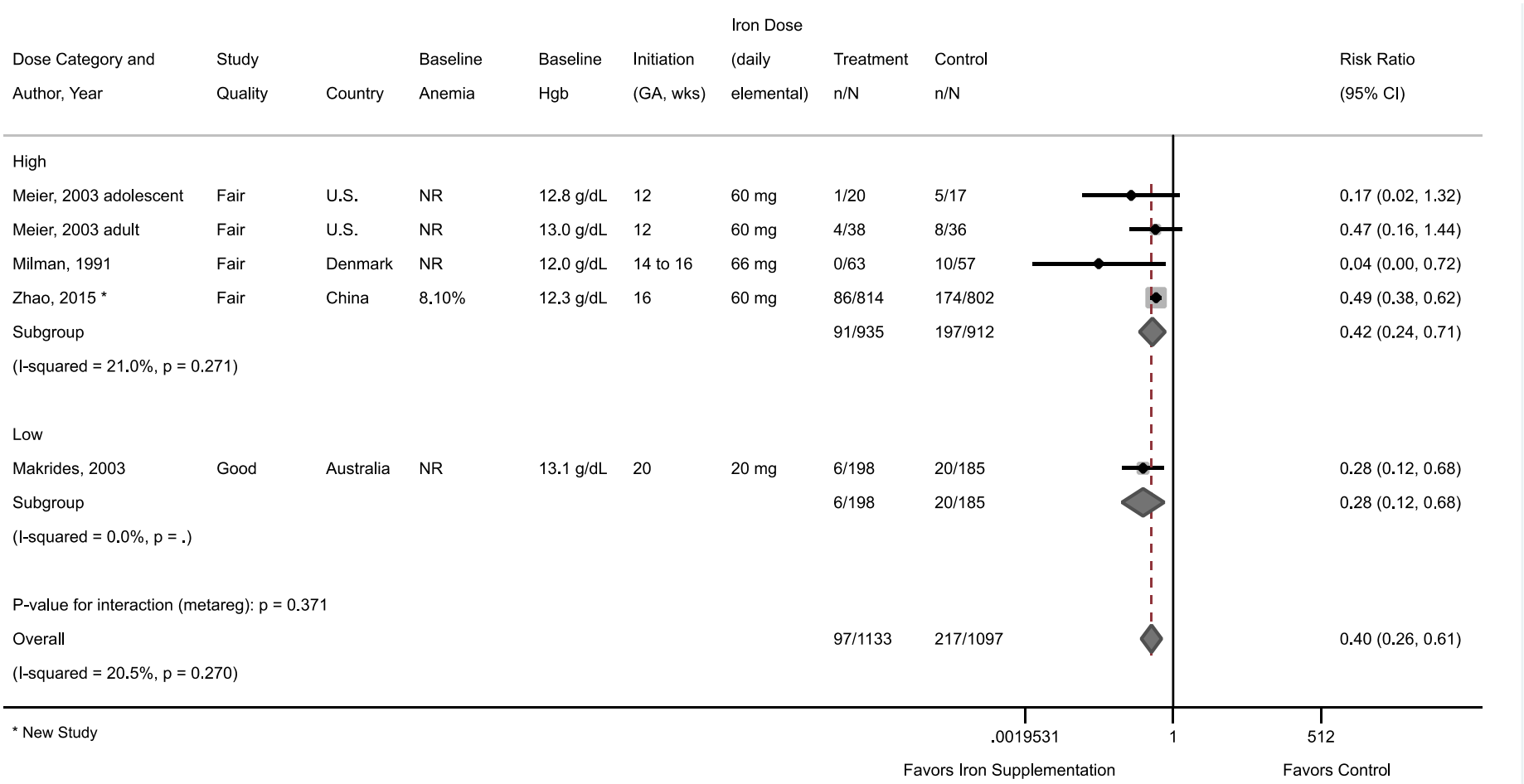
Abbreviations: CI=confidence interval; DL=DerSimonian Laird; GA, wks=gestational age, weeks; Hgb=hemoglobin; NR=not reported; U.S.=United States.

Appendix C Figure 5. Meta-Analysis: Iron Deficiency Anemia at Term, Stratified by HDI Country



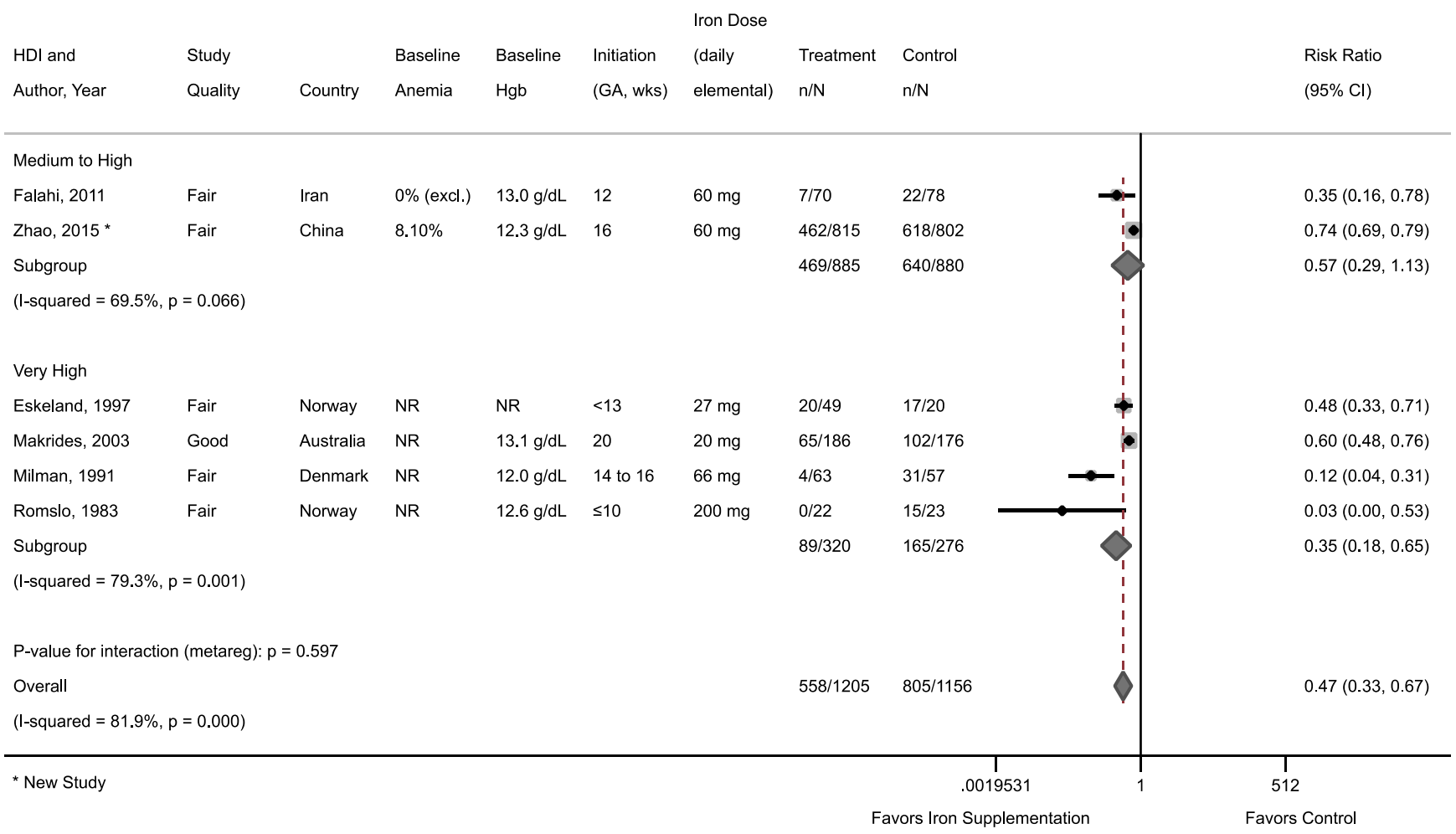
Abbreviations: CI=confidence interval; GA, wks=gestational age, weeks; HDI=United Nations Human Development Index; Hgb=hemoglobin; NR=not reported; U.S.=United States.

Appendix C Figure 6. Meta-Analysis: Iron Deficiency Anemia at Term, Stratified by Dose



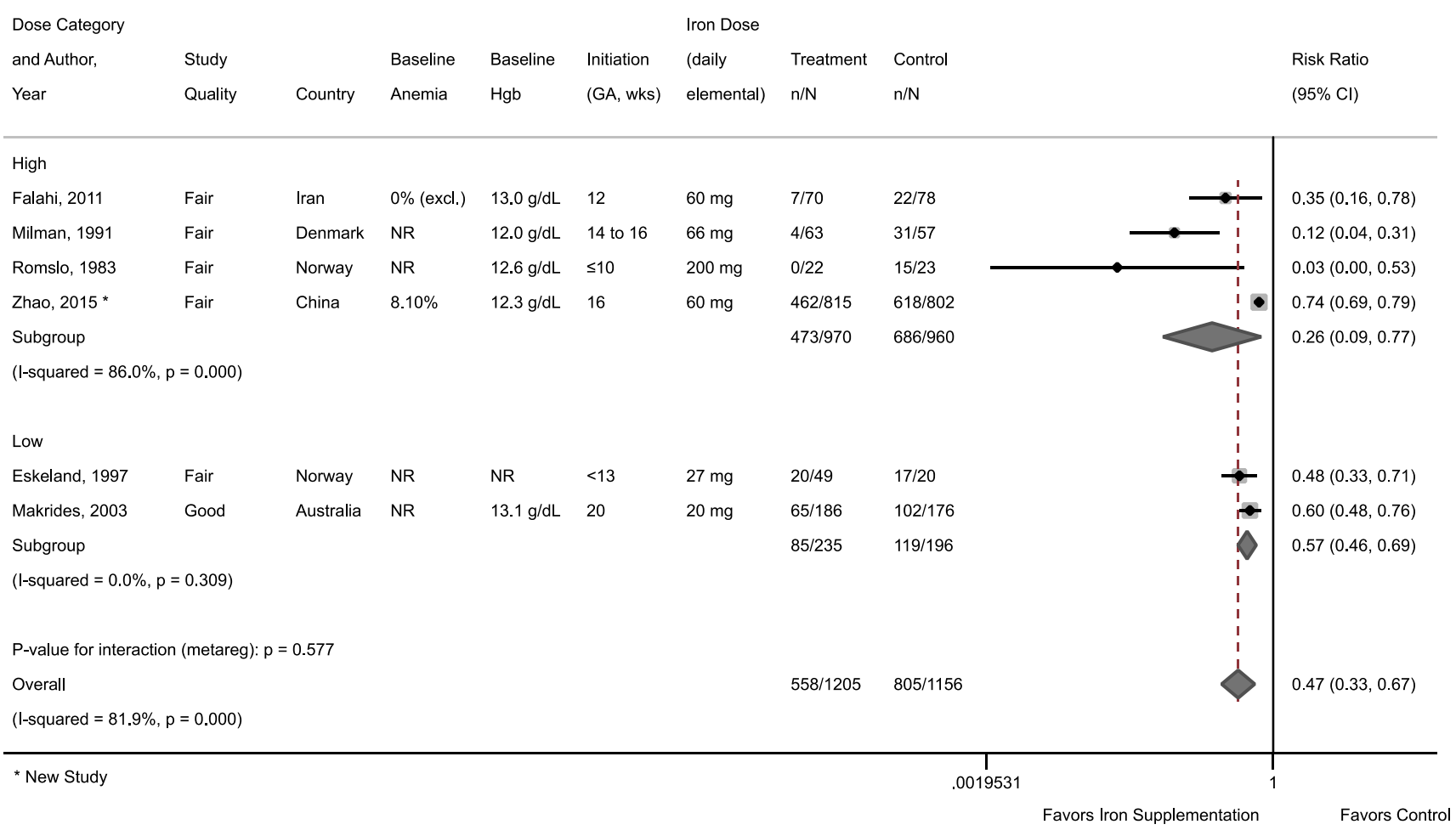
Abbreviations: CI=confidence interval; GA, wks=gestational age, weeks; Hgb=hemoglobin; NR=not reported; U.S.=United Sates

Appendix C Figure 7. Meta-Analysis: Iron Deficiency at Term, Stratified by HDI Country



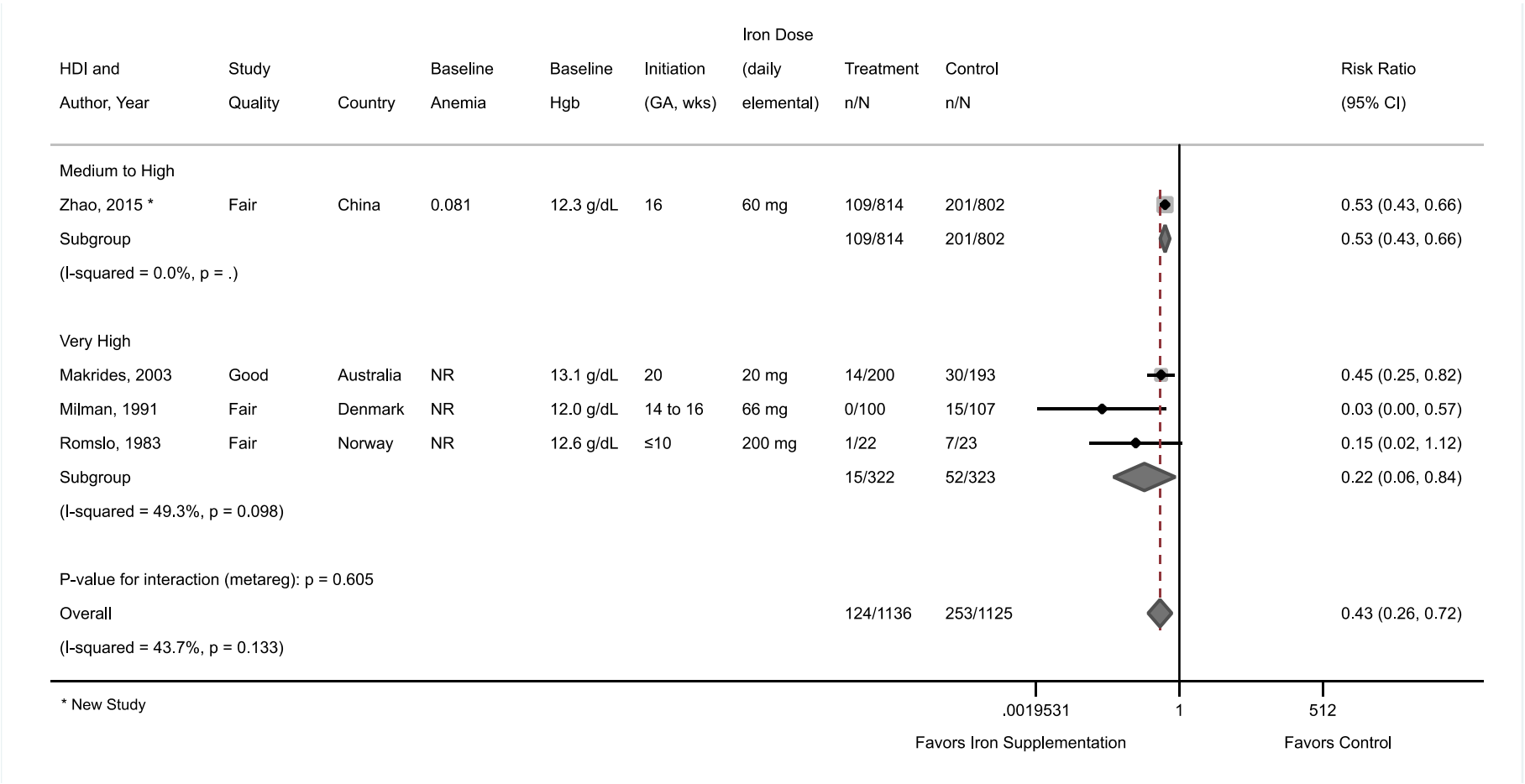
Abbreviations: CI=confidence interval; GA, wks=gestational age, weeks; HDI=United Nations Human Development Index; Hgb=hemoglobin; NR=not reported.

Appendix C Figure 8. Meta-Analysis: Iron Deficiency at Term, Stratified by Dose



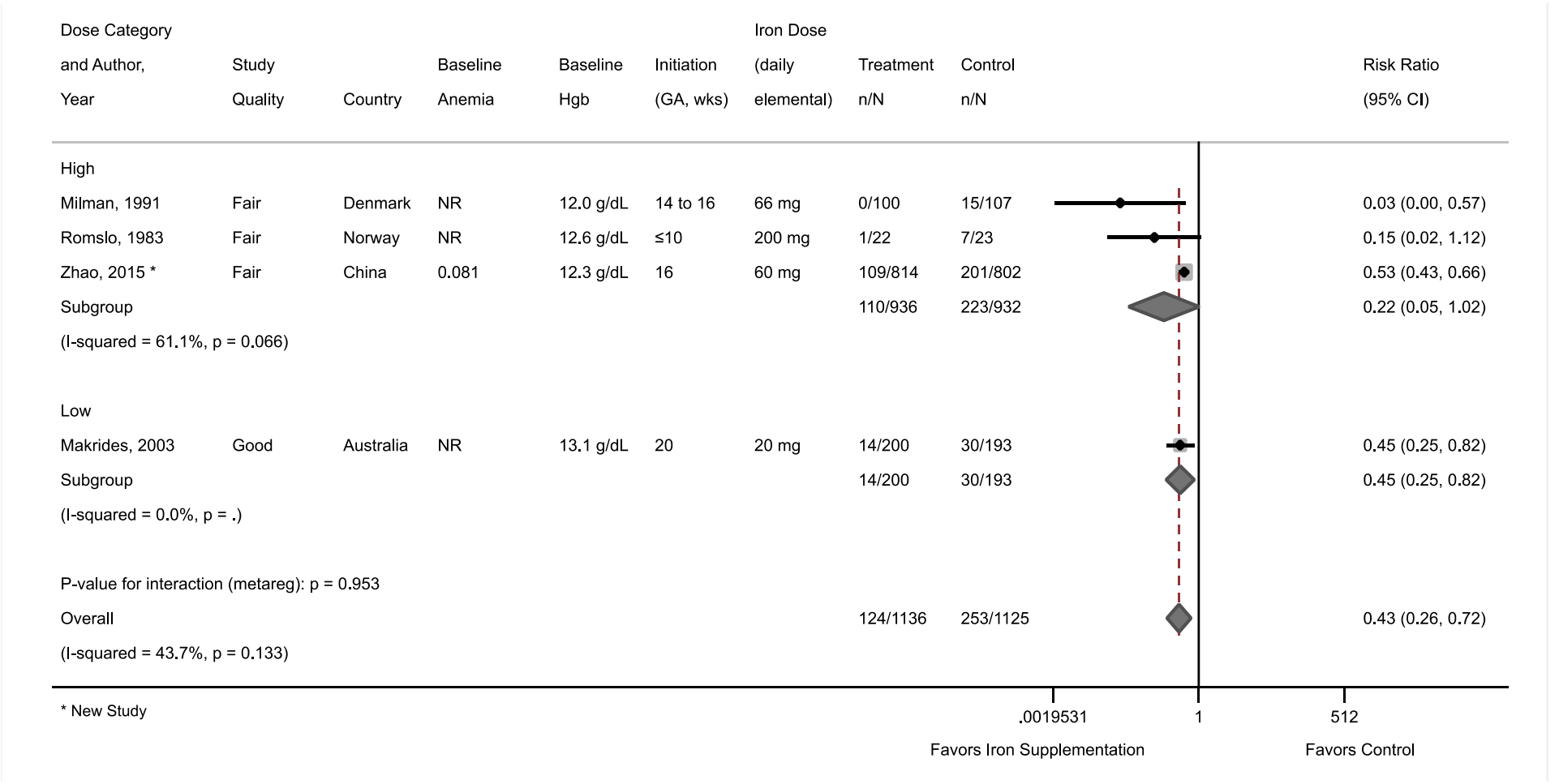
Abbreviations: CI=confidence interval; GA, wks=gestational age, weeks; Hgb=hemoglobin; NR=not reported.

Appendix C Figure 9. Meta-Analysis: Anemia at Term, Stratified by HDI Country



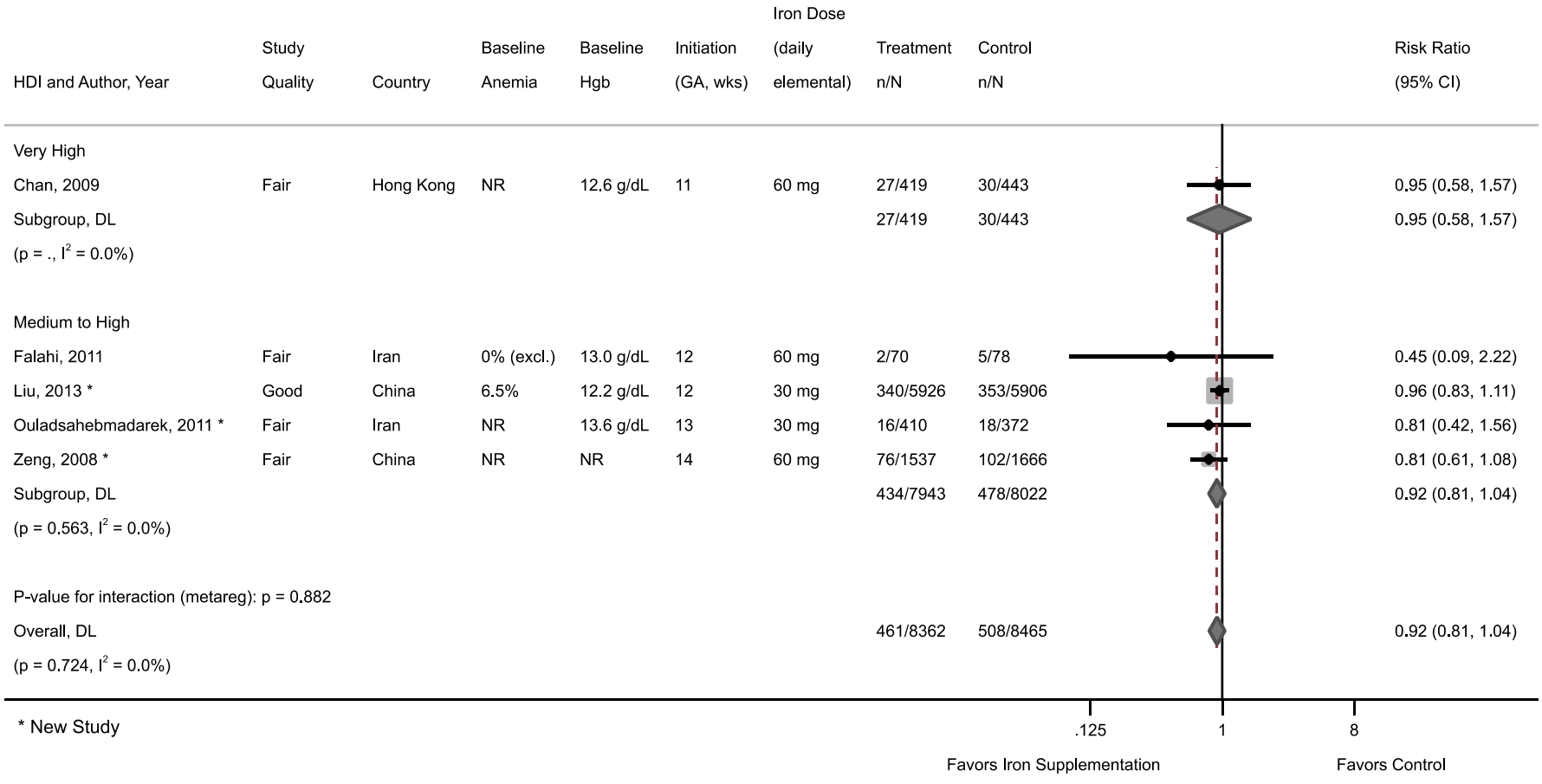
Abbreviations: CI=confidence interval; GA, wks=gestational age, weeks; HDI=United Nations Human Development Index; Hgb=hemoglobin; NR=not reported.

Appendix C Figure 10. Meta-Analysis: Anemia at Term, Stratified by Dose



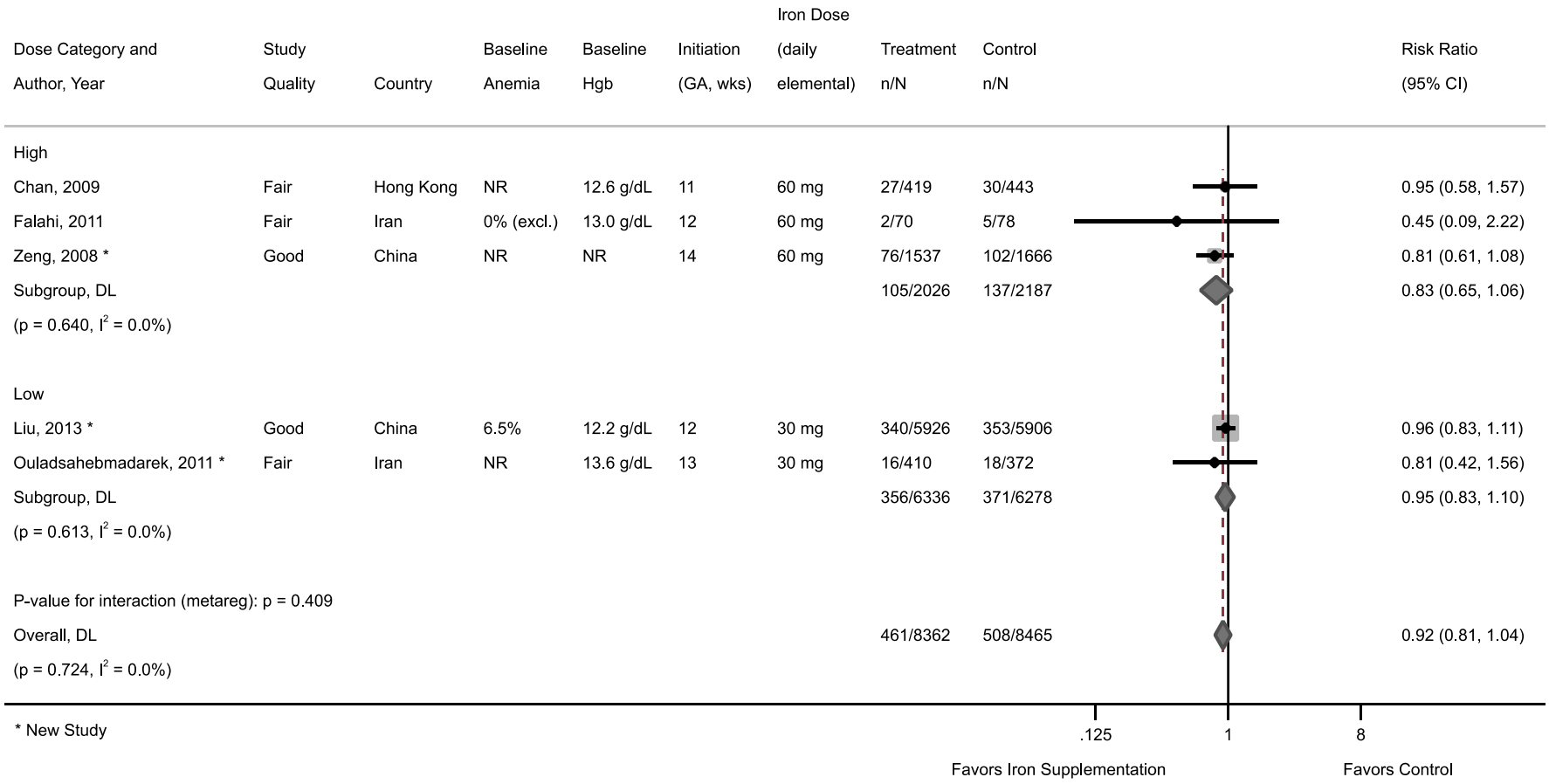
Abbreviations: CI=confidence interval; GA, wks=gestational age, weeks; Hgb=hemoglobin; NR=not reported.

Appendix C Figure 11. Meta-Analysis: Preterm Birth, Stratified by HDI Country



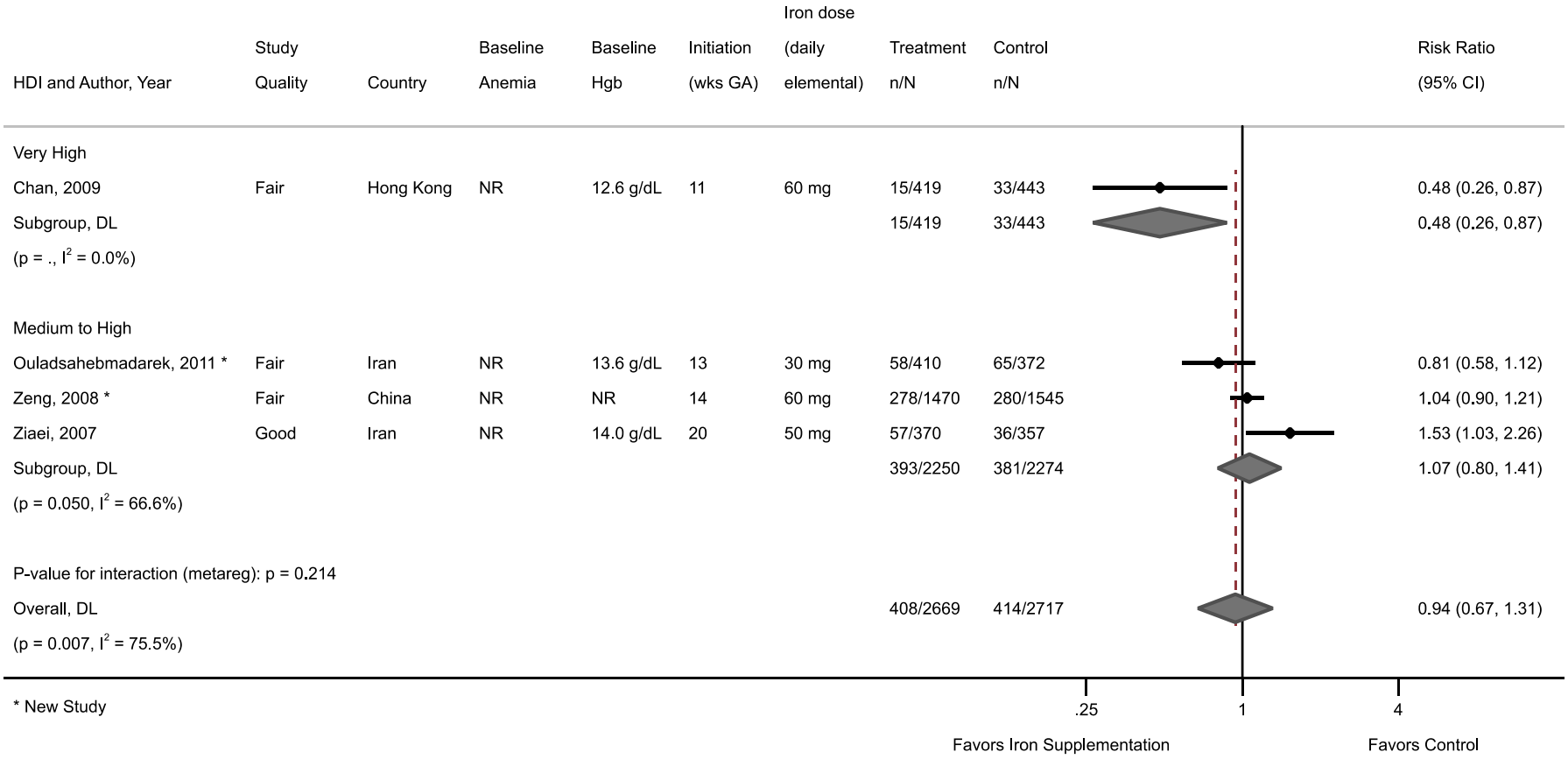
Abbreviations: CI=confidence interval; DL=DerSimonian Laird; GA, wks=gestational age, weeks; HDI=United Nations Human Development Index; Hgb=hemoglobin; NR=not reported.

Appendix C Figure 12. Meta-Analysis: Preterm Birth, Stratified by Dose



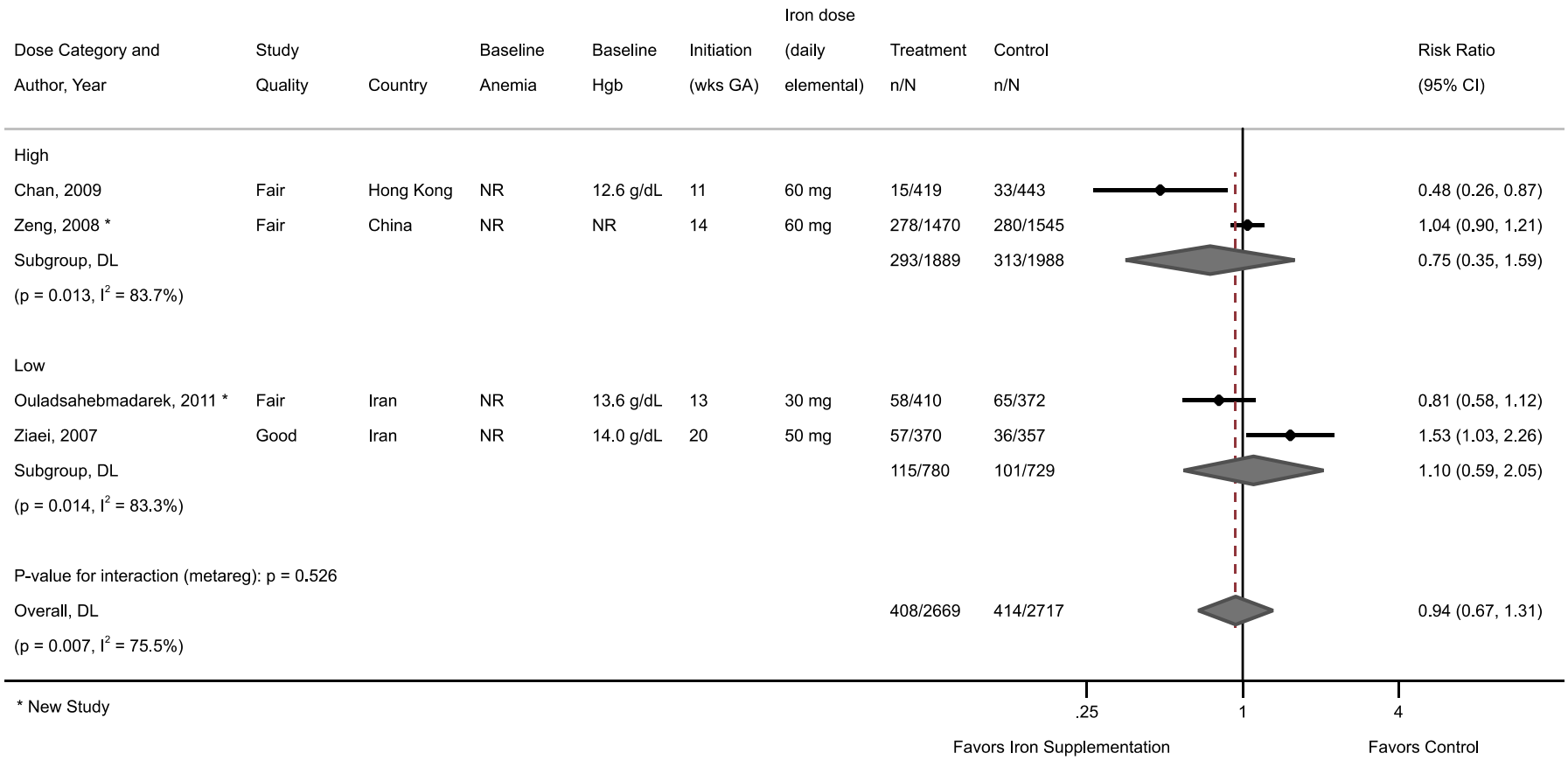
Abbreviations: CI=confidence interval; DL=DerSimonian Laird; GA, wks=gestational age, weeks; Hgb=hemoglobin; NR=not reported.

Appendix C Figure 13. Meta-Analysis: Small for Gestational Age, Stratified by HDI Country



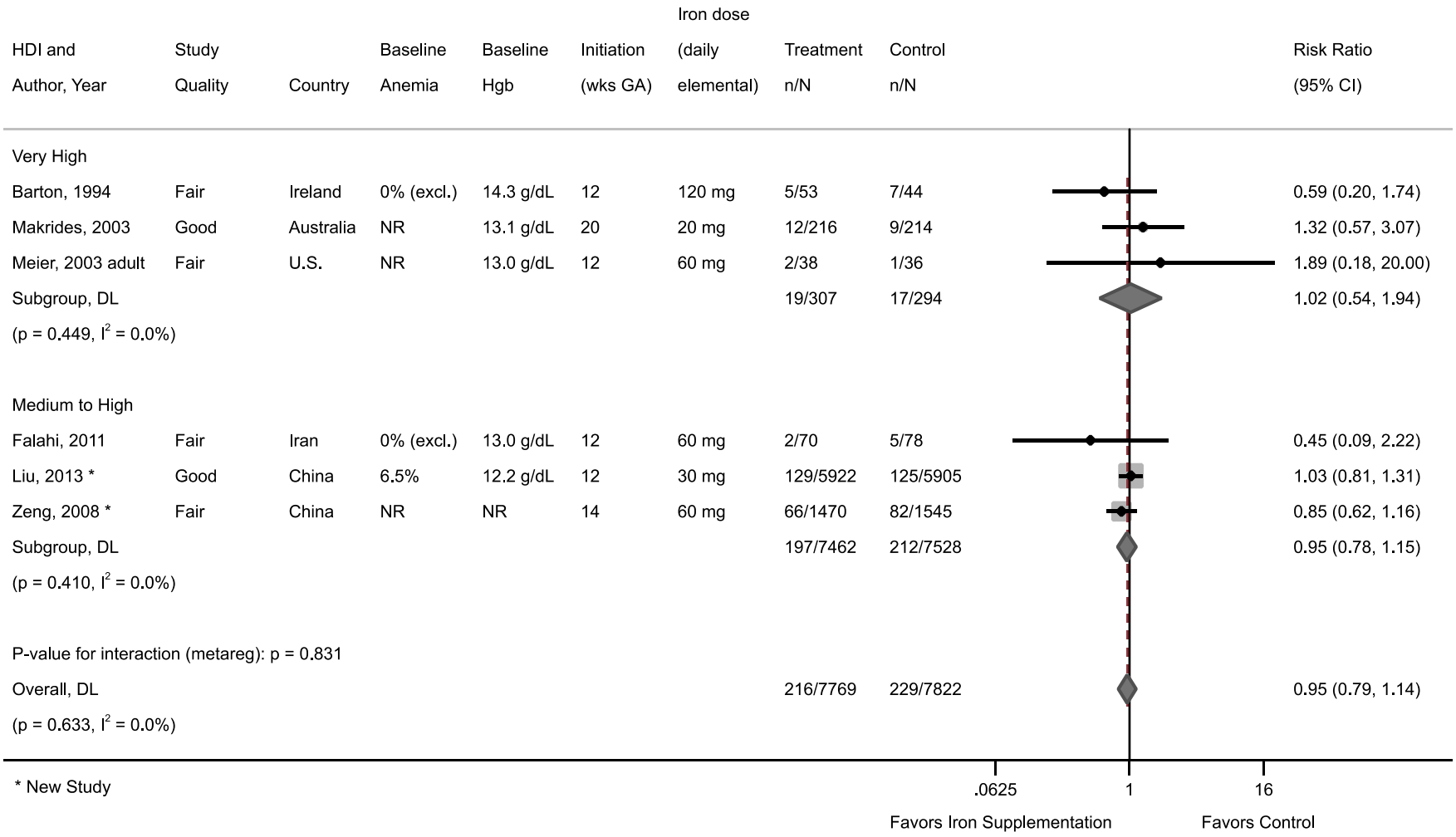
Abbreviations: CI=confidence interval; DL=DerSimonian Laird; GA, wks=gestational age, weeks; HDI=United Nations Human Development Index; Hgb=hemoglobin; NR=not reported.

Appendix C Figure 14. Meta-Analysis: Small for Gestational Age, Stratified by Dose



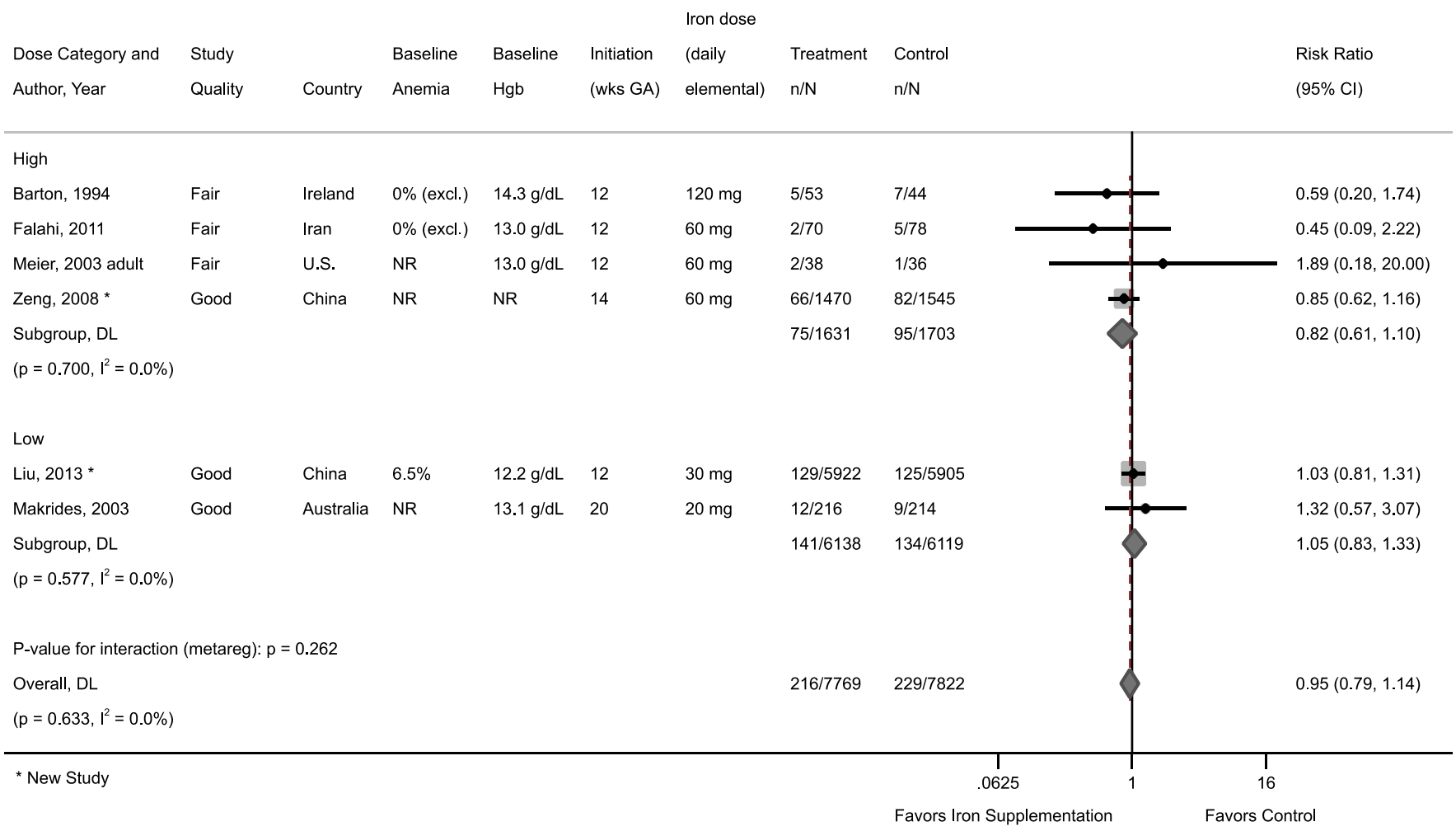
Abbreviations: CI=confidence interval; DL=DerSimonian Laird; GA, wks=gestational age, weeks; Hgb=hemoglobin; NR=not reported.

Appendix C Figure 15. Meta-Analysis: Low Birth Weight, Stratified by HDI Country



Abbreviations: CI=confidence interval; DL=DerSimonian Laird; GA, wks=gestational age, weeks; HDI=United Nations Human Development Index; Hgb=hemoglobin; NR=not reported.

Appendix C Figure 16. Meta-Analysis: Low Birth Weight, Stratified by Dose



Abbreviations: CI=confidence interval; DL=DerSimonian Laird; GA, wks=gestational age, weeks; Hgb=hemoglobin; NR=not reported; U.S.=United States