

Association between the ferritin level and risk of gestational diabetes mellitus: A meta-analysis of observational studies

Ce Sun¹, Qi-Jun Wu¹, Shan-Yan Gao¹, Zhi-Min Ma², Ya-Shu Liu¹, Jia-Yu Zhang¹, Yu-Hong Zhao^{1*}

¹Department of Clinical Epidemiology, Shengjing Hospital of China Medical University, Shenyang, Liaoning, and ²School of Public Health, Capital Medical University, Beijing, China

Keywords

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*Correspondence

Yu-Hong Zhao

Tel.: +86-189-0091-0777

Fax: +86-24-96615-13652

E-mail address:

zhaoyuhong@sj-hospital.org

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ABSTRACT

Aims/Introduction: The relationship between ferritin and the risk of gestational diabetes mellitus (GDM) has not been established. Thus, we carried out a meta-analysis based on the current literature.

Materials and Methods: We searched relevant databases on Embase, PubMed, Cochrane Library and Web of Science before 10 May 2019 to determine the relationship between ferritin and the risk of GDM. The relative risks and 95% confidence intervals of GDM risk were summarized using a random effects model. Studies using categories of ferritin as exposure were combined by dose–response analysis. We carried out both linear and non-linear trends. We also carried out subgroup analysis, whether or not the studies adjusted for potential confounders, and meta-regression analysis to explore the source of heterogeneity. Sensitivity analysis was carried out to explore the robustness of the meta-analysis results.

Results: A total of 10 studies involving 4,690 participants were identified. The summary relative risk comparing persons with the highest concentration categories of ferritin with the lowest concentration categories of ferritin was 1.87 (95% confidence interval 1.50–2.34; $I^2 = 20.1\%$). Linear dose–response showed that an increase in ferritin of 10 $\mu\text{g/L}$ increased the risk of GDM by 8% (1.08, 95% confidence interval 1.05–1.13, $I^2 = 55.1\%$; $n = 4$). A non-linear dose–response relationship also showed a consistently increasing risk of GDM with increased ferritin. No evidence of publication bias was detected.

Conclusions: The findings from this meta-analysis suggest that increased ferritin levels are associated with an increased risk of GDM; however, we require further prospective cohort studies to confirm the results, especially the dose–response relationship between ferritin and GDM.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance resulting in hyperglycemia with the onset or first recognition during pregnancy¹. GDM is a growing health concern as a pregnancy-associated disease worldwide², affecting 0.5–15% of all pregnancies¹. In addition, GDM is not only associated with adverse perinatal outcomes¹, but also increases the risk of maternal and newborn cardiovascular disease^{3,4}. Apart from cardiovascular disease, GDM is considered to cause several adverse outcomes during delivery, such as shoulder dystocia, perineal lacerations and blood loss⁵. Studies have

shown several predisposing factors for GDM, such as age, obesity, body mass index (BMI) and a family history of diabetes^{6,7}; however, few studies have determined the relationship between ferritin and GDM.

The physiological mechanism underlying pregnant women with GDM is complex and unclear. Some studies have shown that the main pathogenesis of GDM involves decreased insulin secretion and insulin resistance during pregnancy⁸. Iron, a redox-active transitional metal, has strong oxidative properties⁸. Iron can cause β -cell toxicity and dysfunction, eventually leading to metabolic abnormalities⁹. Therefore, iron might play an important role in the risk of GDM. Animal and epidemiological studies have shown a significant association between excess

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serum ferritin (a maker of body iron stores) storage and glucose metabolism disorders¹⁰, and studies have shown a positive association between ferritin and type 2 diabetes mellitus¹¹. In addition, pregnant women are prone to ferritin deficiency, which led the World Health Organization to recommend routine iron supplementation for pregnant women¹². Therefore, it is possible for pregnant women to increase their GDM risk; however, controversial evidence from epidemiological studies still exists. Some studies have shown a correlation between high-level serum ferritin and GDM^{8,13,14}, whereas some studies suggested that there is no such correlation^{15–17}. Recently, there have been three meta-analyses investigating the association between serum ferritin and GDM^{18–20}. Nevertheless, there were some problems in the relevant literature, such as a lack of studies, incomplete control of confounding factors and a lack of subgroup analysis to assess the source of heterogeneity. Furthermore, the meta-analyses did not assess the dose–response relationship between ferritin and the risk of GDM. Therefore, we systematically and comprehensively investigated the impact of ferritin on the risk of GDM on the basis of a dose–response meta-analysis.

METHODS

Search strategy

We carried out the meta-analysis followed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) criteria statement²¹. The search was carried out using PubMed, Web of science, Embase and Cochrane Library. Studies were selected that reported on the relationship between ferritin and the risk of GDM. We updated the search to 10 May 2019. Our search combined keywords and MeSH terms, and the search strategy for all literature databases was as follows: gestational diabetes mellitus or GDM or diabetes, gestational or diabetes, pregnancy-induced or diabetes, pregnancy induced or pregnancy-induced diabetes or gestational diabetes or diabetes mellitus, gestational; and ferritins or ferritin or isoferritin or basic isoferritin or isoferritin, Basic. In addition, the references cited in the retrieved articles were carefully checked by a manual search. The study did not check the potential gray literature.

Eligibility criteria and study selection

Published manuscripts were included based on the following selection criteria:

Title/abstract screening: the study investigated ferritin as the exposure of interest and GDM as the outcome of interest.

Full-text review: (i) the research should be an epidemiological study design (e.g., case–control study, cohort study, randomized control trial or cross-sectional study); (ii) the study used either relative risks (RRs), hazard ratios or odds ratios with 95% confidence intervals (95% CIs) for GDM.

The topic and abstract of including articles were estimated by two independent reviewers (CS and MZM). The full-texts of potentially eligible literature that might fit the included criteria were acquired and reviewed by two independent reviewers.

When two reviewers disagreed, a third reviewer (WQJ) reviewed the paper and rendered an opinion.

Data extraction and quality assessment

In the present meta-analysis, we extracted the following information from each study: author; country; year; study design; sample number; trimester of measure ferritin concentration; adjustment confounding; GDM diagnostic criteria; and the results from each study. In addition to extracting the data information, we also evaluated the quality of the studies. As cross-sectional or randomized control trial literature were not retrieved from all databases, the Newcastle–Ottawa Scale (NOS) guidelines were used to evaluate the quality of literature in the present study. In the meta-analysis, the NOS guidelines-modified studies that achieved six or more stars were considered to be high quality²².

Statistical analysis

Because the incidence of GDM was relatively low (Approximately 7% of pregnancies)², odds ratios could be treated as RRs in most studies. After extracting and sorting the article data, we compared the RRs and 95% CIs of the highest level of ferritin to the lowest level of ferritin. To find the relationship between the exposure of ferritin and the risk of GDM, the summarized RR (SRR) and 95% CIs were assessed by random effects models to summarize the risk of all studies²³. The models also were utilized to detect within- and between-studies variation. Therefore, we summarized the study-specific RRs for comparison of pregnancies with the highest level of ferritin and pregnancies with the lowest level of ferritin.

To carry out the dose–response meta-analysis, the included studies required the following information: (i) the distribution of ferritin concentrations and risk estimates of variance had three quantitative exposure categories; and (ii) the median or mean level of exposures in each category (when the medians for this category were not reported, we used the mean of the lower and upper bounds to estimate the approximate median. When the lowest or highest categories were unbounded, we assumed the width of the category to be the same as the adjacent category when estimating the midpoint.)²⁴. Therefore, four studies were included to analyze the relationship between ferritin concentrations and GDM. After extracting the data of the relative literature, because the lowest doses in the literature were different, the dose–response relationship required centralized data²⁵. Second, we summarized the study-specific RRs for each 10- μ g/L increase in ferritin concentrations. To compute the study-specific trend from the correlated log RRs of ferritin concentrations, we used the Greenland and Longnecker method to derive a linear dose–response trend^{26,27}. This method was used to assess the study-specific dose–response slopes and 95% CIs based on the results of each ferritin concentration before combining into a pooled estimate. To examine the possibility of a non-linear dose–response relationship, we also used restricted cubic splines with four knots at fixed percentiles (5%, 35%,

65% and 95%) of the distribution of exposure^{28,29}. When the regression coefficients of the fixed effects model were simultaneously equal to zero, we calculated the overall *P*-value. The *P*-value for non-linearity was tested by the coefficient of the all spline being equal to zero³⁰. When the *P*-value for the non-linear test was near 0.05, we considered the possibility of linear and non-linear relationships^{31,32}.

To find the source of heterogeneity in this review, we used the *Z*-test to determine the significance of pooled RRs. Statistical heterogeneity between the GDM and ferritin was assessed with an *I*² statistic to quantify inconsistencies between studies²⁴. The results were defined as high heterogeneity for an *I*² >50%³³. Potential publication bias was examined by Begg's test, Egger's test and visually-inspected funnel plots. We also used stratified analysis, including geographic location, trimester, GDM diagnostic criteria, use of serum or plasma to measure ferritin, study design and whether or not adjusted potential confounders were in the analyses (e.g., BMI, age, ethnicity, parity, C-reaction protein [CRP], alcohol, smoking, medications and supplements). To determine the impact of some studies in the main analysis of the estimated RR, we carried out a sensitivity analysis that recalculated the pooled effect by deleting the low-quality studies (NOS score <6 stars). A *P* < 0.05 was

considered statistically significant in the present study. All statistical analyses were carried out using Stata 11.2 software (StataCorp, College Station, TX, USA).

Because the present study did not involve population surveys, it did not involve ethical issues.

RESULTS

Literature search

The process of this systematic review and meta-analysis was illustrated by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group (Figure 1). By searching four databases and additional records identified through other sources, we identified 361 records. After checking the records and removing duplicates, 300 articles were identified. Of these 300 articles, 28 and 264 were excluded by screening the titles and abstracts, and meeting the prespecified exclusion criteria, respectively. Finally, eight articles involving a total of 4,690 women were included in the review. In addition, because one article included two different trimesters, we extracted data as two individual studies³⁴. Another study had two different designs, so we extracted data as two individual studies¹⁵. Therefore, 10 studies from eight articles were finally included in the meta-analysis^{15-17,34-38}.

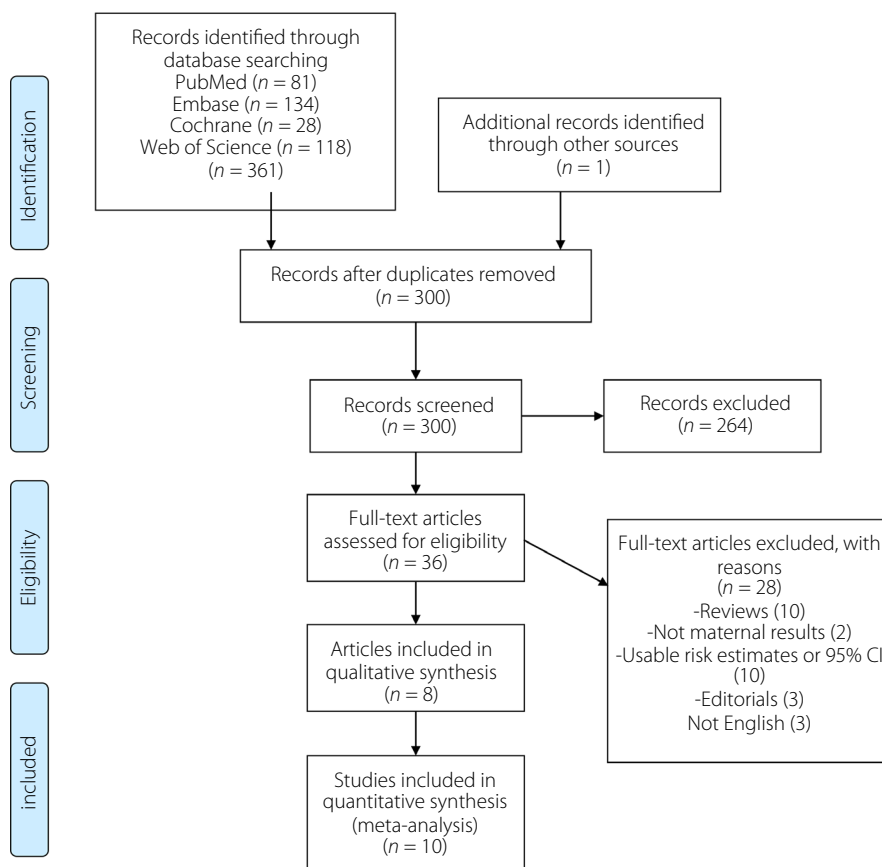


Figure 1 | Flow chart of the study selection.

Characteristics of the included studies

The baseline characteristics of the included studies are summarized in Table 1. The quality assessment results showed that seven studies had six or more stars on the modified NOS (Table 2,3). Of the included studies, 1,040 pregnant women had GDM and 3,650 pregnant women were euglycemic. Three studies were cohort studies^{15,16,35} and seven studies were case-control studies^{15,17,34,36–38}.

Of the included studies, five were carried out in Western countries^{15,34,36} (USA $n = 4$, Denmark $n = 1$) and five studies were carried out in Asian countries^{16,17,35,37,38} (Iran $n = 3$, China $n = 1$, Lebanon $n = 1$). Seven studies^{15–17,35,37,38} used serum to measure the ferritin concentrations, and three studies^{34,36} used plasma to measure the ferritin concentrations. GDM was diagnosed based on several methods, as follows: three studies used World Health Organization screening criteria^{16,35,36} (75-g oral glucose tolerance test), six studies used the Carpenter/Coustan diagnostic criteria^{15,17,34,38}, and one study³⁷ used gynecology and obstetrics diagnostic criteria. Of the included studies, six studies^{16,17,34–37} determined the relationship between the ferritin concentration in the first trimester and GDM risk, and four studies^{15,34,38} determined the ferritin concentration in the second trimester. Most studies matched or adjusted for BMI ($n = 6$) and age ($n = 7$); however, fewer studies controlled for ethnicity ($n = 4$), parity ($n = 5$), CRP ($n = 5$), alcohol consumption ($n = 2$), smoking ($n = 5$), and medications and supplements ($n = 2$).

Overall meta-analysis

Data extracted from 10 studies that compared pregnant women with GDM in the top level of ferritin and GDM in the bottom level of ferritin yielded an SRR of 1.87 (95% CI 1.50–2.34; Figure 2). No significant publication bias existed in the meta-analysis by Begg's test ($P = 0.17$), Egger's test ($P = 0.09$) and the funnel plot with 95% CI limits, as shown in Figure 3. No significant heterogeneity among studies was shown in the present study ($I^2 = 20.1\%$, $P = 0.26$).

Four studies^{34,36,37} were included to analyze the dose-response relationship. The fixed effects model was fitted for the dose-response ($P < 0.01$). There was the possibility of linearity ($P = 0.061$), therefore a linear dose-response meta-analysis was used (Figure 4). An increase in the ferritin concentration of 10 $\mu\text{g/L}$ resulted in an 8% increase in the risk of GDM (1.08, 95% CI 1.05–1.13, $P < 0.01$), with slight high heterogeneity ($I^2 = 55.1\%$, $P = 0.08$; Figure 5). A non-linear dose-response analysis showed a consistently increasing risk with increased ferritin (Figure 6); however, a non-linear dose-response relationship also showed a flat curve over a broad range of typical concentrations of ferritin, suggesting that higher risks were associated with higher concentrations in which data were limited and CIs were wider.

Subgroup, sensitivity and meta-regression analyses

The results of all stratified analyses by study characteristics are shown in Table 4. The subgroup analysis contained geographic location, GDM diagnosis, serum or plasma, trimester, design of included studies and adjustment for confounders that were associated with exposure or outcome. The results showed that when we stratified data by geographic location, the review was categorized by Western and Asian countries. The SRR was 2.22 (95% CI 1.60–3.10) for Western countries, and 1.76 (95% CI 1.24–2.49) for Asian countries. Western countries had a slightly higher risk of GDM than Asian countries.

When stratified using serum or plasma ferritin to measure the content of ferritin in pregnant women, the SRR for plasma ferritin was higher than serum ferritin (2.51, 95% CI 1.64–3.86 vs 1.63, 95% CI 1.33–2.15). In addition, when stratifying by study design, the SRR of case-control studies (2.07, 95% CI 1.63–2.61, $I^2 = 0.1\%$, $P = 0.42$) was higher than the cohort studies (1.39, 95% CI 1.05–1.85, $I^2 = 0.0\%$, $P = 0.65$).

When stratified by trimester of ferritin measurement, the study was categorized as first and second trimesters. In the first trimester group, the SRR was 2.05 (95% CI 1.39–3.02); the second trimester results approximated the first trimester group (1.79, 95% CI 1.36–2.36). All the meta-regression analysis showed no evidence of significant heterogeneity in stratified analyses.

The result of the sensitivity analysis showed that the SRR was 1.77 (95% CI 1.36–2.31, $I^2 = 12.8\%$, $P = 0.33$) after excluding the studies of Sharifi³⁸, Amiri¹⁷ and Guo³⁷.

DISCUSSION

The results of a meta-analysis involving 4,690 pregnant women have shown that there was a positive association between ferritin and the risk of GDM. The prevalence of GDM in pregnant women with the highest level of ferritin was increased by 87% (1.87, 95% CI 1.50–2.34), compared with the lowest level of ferritin.

Although these findings were consistent with the findings of three previous meta-analyses, the previous meta-analyses had some limitations that could be improved. For example, previous meta-analyses included literature in which the retrieval strategy only involved serum ferritin (the effect of plasma ferritin was not considered)²⁰. The present meta-analysis was the first analysis to systematically and comprehensively assess the ferritin concentration and GDM risk. For example, we included the results from eight studies that involved 1,000 cases of GDM from >4,500 pregnant women. Compared with the limited sample size of individual studies, the present meta-analysis included a large number of GDM cases. The large number of cases not only allowed us to determine the relationship between ferritin and the risk of GDM, but also led us to stratify data and carry out sensitivity analyses to evaluate heterogeneity. Seven included studies were of high quality (the score of all studies was ≥ 6 stars). We considered using plasma or serum ferritin concentrations to adjust for confounders on outcome. In addition, the

Table 1 | Characteristics of studies included in the meta-analysis

Author	Study design	Ethnicity	No. participants	Trimester of ferritin	GDM diagnosis	Matching/adjustment/variables	Relative risks (RRs)
Chen USA, 2006	Prospective cohort study Nested case-control study	Hispanic, African American, Caucasian, Asian	1,456	Second trimester	Carpenter and Coustan's diagnostic criteria	Age, ethnicity, parity, family history of diabetes in a first-degree relative, gestational age at blood collection and cigarette smoking, prepregnant BMI	Q1: <79 pmol/L Q2: ≥80 pmol/L Q1: <92.0 pmol/L Q2: ≥92.1 pmol/L
							1 1.84 (0.95–3.58) 1 1.88 (0.81–4.36)
Rawal, USA, 2017	Case-control study	Non-Hispanic white, non-Hispanic black, Hispanic or Asian/Pacific Islander	321	First trimester	Carpenter and Coustan's diagnostic criteria	Age, ethnicity, parity, education, smoking, alcohol; BMI; family history of diabetes	Q1: ≤77.05 pmol/L Q2: 77.06–118.70 pmol/L Q3: 118.80–173.90 pmol/L Q4: ≥174.00 pmol/L Q1: ≤496 pmol/L Q2: 497–77.9 pmol/L Q3: 78.0–119.3 pmol/L Q4: ≥119.4 pmol/L
							1 1.57 (0.69–3.56) 1.71 (0.75–3.90) 2.43 (1.12–5.28) 1 4.45 (1.61–12.3) 3.42 (1.26–9.30) 3.95 (1.38–11.30)
Bowers, USA, 2016	Case-control study	Not available from publication	699	First trimester	WHO	Age, family history of diabetes, parity, prepregnancy BMI, C-reactive protein and oxidized LDL	Q1: 25.0 µg/L Q2: 45.0 µg/L Q3: 66.0 µg/L Q4: 87.0 µg/L Q5: 141.0 µg/L
							1 1.17 (0.65–2.11) 1.84 (1.03–3.28) 0.77 (0.43–1.40) 2.22 (1.23–4.01)
Zein, Lebanon, 2015	Prospective cohort study	Not available from publication	104	First trimester	WHO	Not available from publication	Q1: <38.5 µg/L Q2: ≥38.5 µg/L
							1 1.62 (0.20–12.95)
Amiri, Iran, 2013	Case-control study	Ayan	200	First trimester	Carpenter and Coustan's diagnostic criteria	Age, gestational age, parity	Q1: <20 ng/mL Q2: >80 ng/mL
							2.37 (0.80–7.01) 0.20 (0.09–0.44)
Faranak Sharifi, Iran, 2010	Case-control study	Ayan	128	Second trimester	Carpenter and Coustan's diagnostic criteria	Age, BMI, blood pressure, fasting plasma glucose, HbA1c, C-reactive protein, insulin concentrations	Q1: >84.7 pmol/L Q2: <84.7 pmol/L
							1 2.3 (1.06–5.1)
Sohelykhah, Iran, 2017	Prospective cohort study	Ayan	1,279	First trimester	WHO	Age; level of education, reproductive medical histories	Q1: <45 ng/mL Q2: ≥45 ng/mL
							1 1.3 (0.95–1.8)
Wenchen, China, 2018	Case-control study	Asian	362	First trimester	Gynecology and Obstetrics	Not available from publication	Q1: <38.5 µg/L Q2: 38.5–62.7 µg/L Q3: 62.7–80.8 µg/L Q4: >80.8 µg/L
							1 1.74 (0.82–3.72) 2.31 (1.28–4.35) 3.75 (1.72–8.01)

Gynecology and Obstetrics, Gynecology and Obstetrics diagnostic criteria; Carpenter and Coustan, Carpenter and Coustan diagnostic criteria. BMI, body mass index; CRP, C-reactive protein; WHO, World Health Organization diagnostic criteria.

Table 2 | Newcastle–Ottawa Scale of cohort studies

Author	Representativeness of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present	Comparability of exposure and non-exposure	Ascertainment of outcome	Follow up enough for outcome	Adequacy of follow up
Chen, USA, 2006	★	★	★	★	★★	★	★	★
Zein, Lebanon, 2015	★	★	★	★	★★	★		
Soheilykhah, Iran, 2017	★	★	★	★	★★	★		

Table 3 | Newcastle–Ottawa Scale of case–control studies

Author	Case definition adequate	Representativeness of the cases	Selection of controls	Definition of control	Comparability of cases and controls	Ascertainment of exposure	Same method of cases and controls	Non-response rate
Chen, USA, 2006	★	★	★	★	★★		★	★
Rawal, USA, 2017	★	★	★	★	★★	★	★	
Bowers, USA, 2016	★	★	★	★	★★		★	
Amiri, Iran, 2013	★			★	★★		★	
Faranak Sharifi, Iran, 2010	★			★	★★		★	
Wenchen, China, 2018	★			★	★★		★	

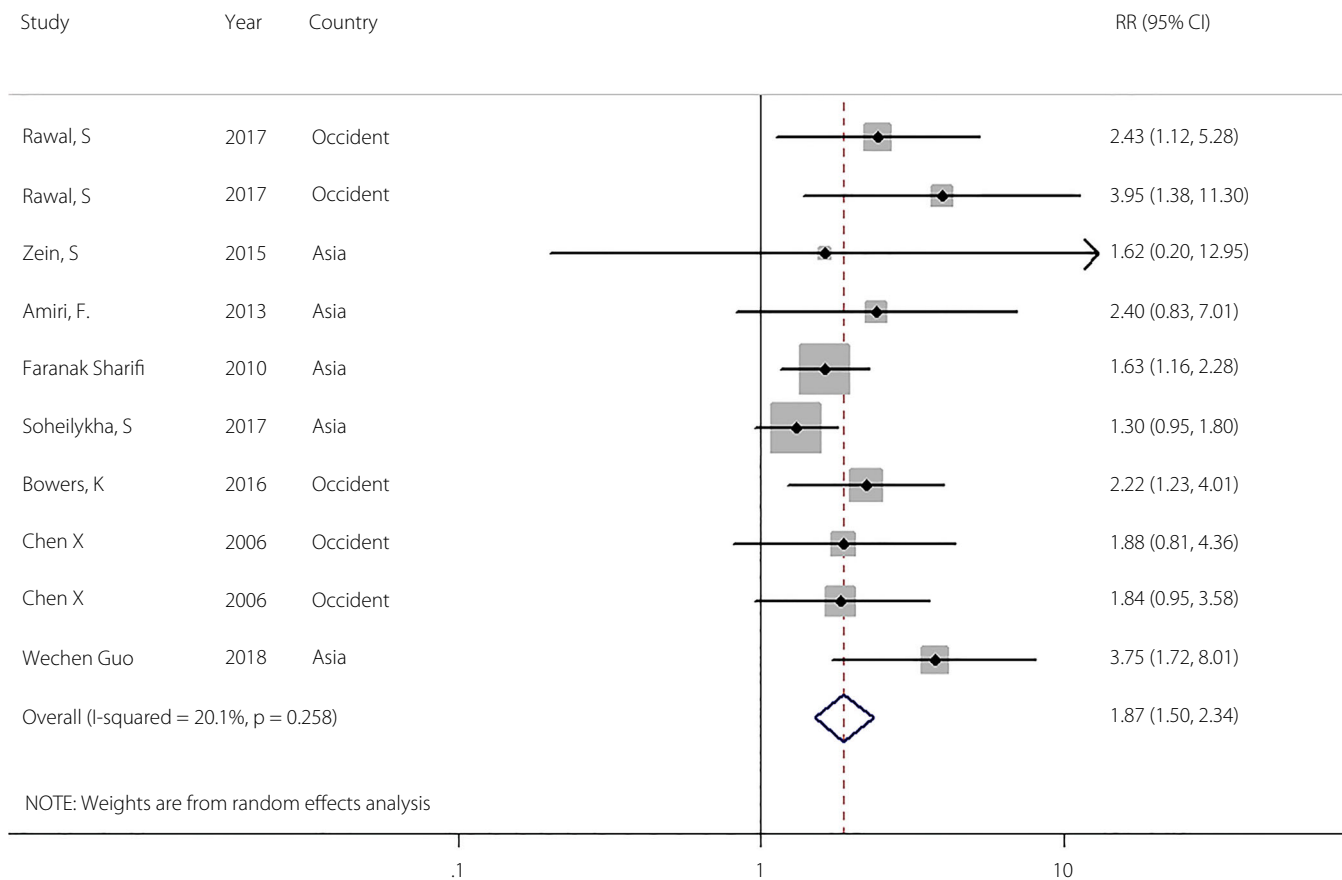


Figure 2 | Forest plots (random effects model) of meta-analysis on the association between the concentration of ferritin and the risk of gestational diabetes mellitus.

present meta-analysis was the first to explore the dose–response trends between ferritin and GDM, and the first to investigate the possibility of non-linear and linear associations. The linear dose–response showed that a 10- $\mu\text{g/L}$ increase in the ferritin concentration increased the risk of GDM by 8%. Because the results of linear testing showed a P -value near 0.05 ($P = 0.061$), we used linear and non-linear dose–response trends to combine studies. The results of the non-linear dose–response meta-analysis consistently showed an increased risk of GDM associated with increased ferritin. The heterogeneity for linear ($P = 0.08$) and non-linear dose–responses ($P = 0.09$) had statistical significance. The reason for this finding might contribute to fewer included studies (4 studies), fewer included participants, using different blood specimen sources (serum or plasma) and not adjusting for CRP in some studies¹⁵.

Based on subgroup analyses, we found that the Western population with high ferritin concentrations had a higher risk of GDM. It has been suggested that the Western Dietary Model might play an important role in GDM. A meta-analysis also showed that a high intake of red meat and processed meat increased the risk of GDM³⁹. The present study showed that

different study designs and using serum or plasma ferritin had a large effect on the outcome, which might have resulted in few studies in the plasma group and cohort studies in this subgroup. One study showed that people with normal/high serum ferritin levels (women 15–200 ng/mL; men 30–300 ng/mL) had an average plasma ferritin level 51% of the serum ferritin level (range 36–69%)⁴⁰. Thus, the value of ferritin measured by plasma might be less than that measured by serum; however, this study is only applicable to the general population, and further research is required involving pregnant women. According to the results of the subgroup, we found that higher levels of ferritin were associated with a similar risk of GDM in the first and second trimesters of pregnancy. Does this result mean ferritin is a stable indicator for pregnancy? At present, studies have shown that ferritin is a robust biomarker for type 2 diabetes mellitus^{41,42}. Furthermore, the dose–response relationship between ferritin and GDM showed that the risk of GDM is on the rise. Based on an increased concentration of ferritin in pregnant women, the ferritin level can be used as a biomarker to predict the risk of GDM. Additional studies should be evaluated.

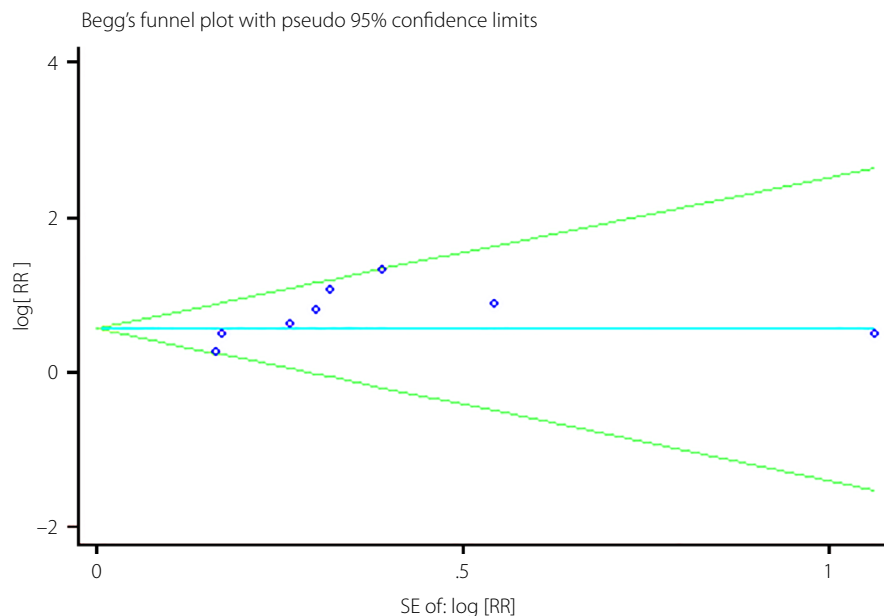


Figure 3 | Funnel plot of included studies for potential publication bias between gestational diabetes mellitus patients and healthy pregnant women. RR, relative risk; SE, standard error.

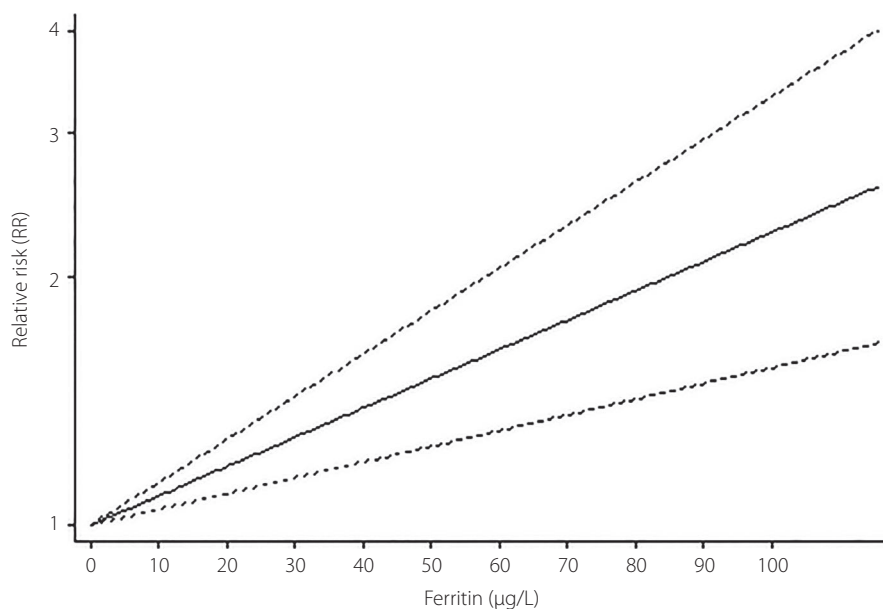


Figure 4 | The linear dose–response analysis between the concentration of ferritin and the risk of gestational diabetes mellitus. The restricted cubic splines in a fixed effect were used to model the ferritin concentration, and the lowest concentration (1.0 $\mu\text{g/L}$) served as a reference. The middle line represents the estimated relative risk, and the lines on both sides represent the corresponding 95% confidence intervals.

According to existing research, the biological mechanisms between high ferritin and GDM are not clear⁴³. Studies considered that a high CRP (a biomarker of inflammation) level was associated with GDM¹⁴. Therefore, the biological mechanisms of diabetes mellitus might be related to inflammation. Some

studies found that ferritin–inflammatory–GDM mechanism is the basic pathophysiological basis, as well as an important part in the development of GDM^{44–46}. They considered that ferritin was an acute-phase response protein, which would increase in inflammation⁴⁷. Therefore, high-level ferritin could lead to an

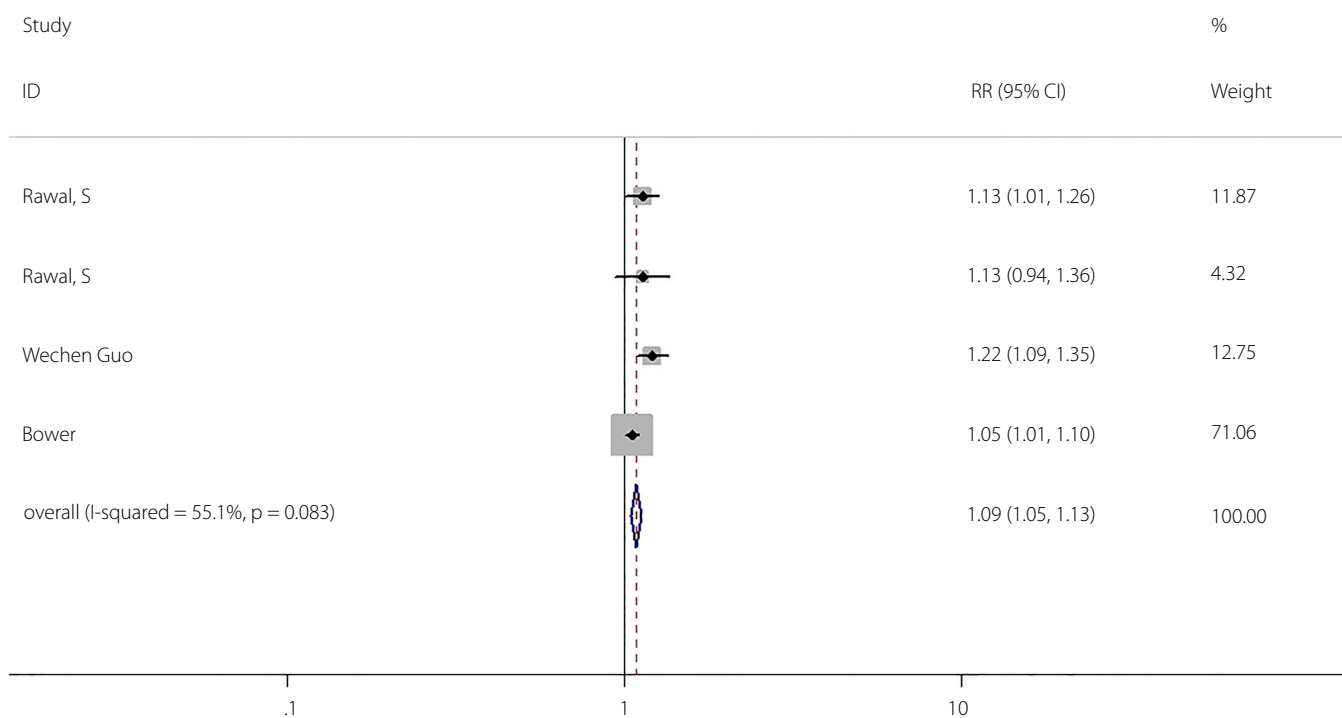


Figure 5 | Forest plots of linear dose–response trends with pooled estimates from fixed-effects meta-analysis.

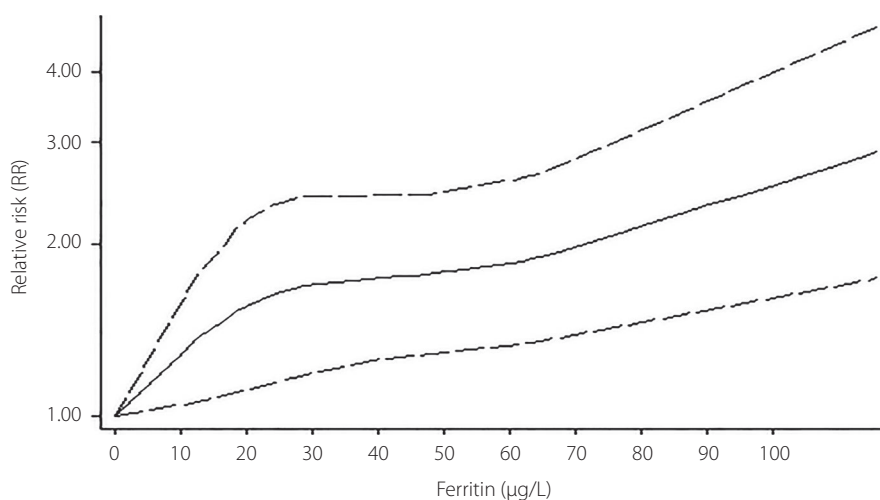


Figure 6 | The non-linear dose–response analysis between the concentration of ferritin and the risk of gestational diabetes mellitus. The restricted cubic splines in a fixed effects model were used to model the ferritin concentration. The lowest concentration (1.0 µg/L) served as a reference. The middle line represents the estimated relative risk, and the lines on both sides represent the corresponding 95% confidence intervals.

inflammation state in the body⁴⁷. Therefore, the ferritin concentration level could increase with subclinical systemic inflammation, which was associated with insulin resistance in GDM⁴⁸. However, studies found that high CRP is associated with GDM risk due to BMI as an intermediate factor⁴⁹. However, some studies showed that the increased risk of GDM associated with a higher CRP was independent of maternal obesity⁵⁰. The

present data showed that adjusting BMI has a significant impact on the heterogeneity of the study. Therefore, further research is required to explore whether iron is directly related to diabetes mellitus.

The present meta-analysis also had several limitations. First, one of the main limitations was a lack of ferritin data. Although we have already identified many studies to assess

Table 4 | Subgroup analysis of the risk of gestational diabetes mellitus and ferritin

		No. studies	Summary RR (95% CI)	I ² (%)	P*	P**
Overall		10	1.87 (1.50–2.34)	20.1	0.26	
Subgroup						
Geographic location	Western	5	2.22 (1.60–3.10)	0.0	0.80	0.25
	Asia	5	1.76 (1.24–2.49)	42.0	0.14	
GDM diagnosis	WHO	3	1.54 (1.07–2.20)	18.2	0.29	0.09
	Carpenter–Coustan	6	1.88 (1.46–2.42)	0.0	0.67	
	Gynecology and Obstetrics	1	3.75(1.74–8.09)	–	–	
Serum or plasma	Serum	7	1.69 (1.33–2.15)	16.4	0.31	0.18
	Plasma	3	2.51 (1.64–3.86)	0.0	0.64	
Trimester	First trimester	6	2.05 (1.39–3.02)	42.8	0.12	0.88
	Second trimester	4	1.79 (1.36–2.36)	0.0	0.48	
Design	Case–control	7	2.07 (1.63–2.61)	0.1	0.42	0.11
	Cohort	3	1.39 (1.05–1.85)	0.0	0.65	
Adjustment for potential confounders						
BMI	Adjusted	6	1.91 (1.51–2.42)	0.0	0.65	0.72
	Unadjusted	4	2.03 (1.18–2.08)	56.3	0.08	
Age	Adjusted	7	1.66 (1.34–2.05)	6.4	0.38	0.14
	Unadjusted	3	2.63 (1.67–4.16)	0.0	0.51	
Ethnicity	Adjusted	4	2.22 (1.49–3.32)	0.0	0.65	0.43
	Unadjusted	6	1.81 (1.34–2.44)	37.2	0.16	
Parity	Adjusted	5	2.25 (1.54–3.26)	0.0	0.79	0.34
	Unadjusted	5	1.79 (1.29–2.49)	46.5	0.11	
CRP	Adjusted	5	2.22 (1.60–3.10)	0.0	0.79	0.25
	Unadjusted	5	1.76 (1.24–2.49)	42.0	0.14	
Alcohol consumption	Adjusted	2	2.88 (1.55–5.38)	0.0	0.47	0.22
	Unadjusted	8	1.74 (1.40–2.17)	13.8	0.32	
Cigarette smoking	Adjusted	5	2.22 (1.60–3.10)	0.0	0.79	0.25
	Unadjusted	5	1.76 (1.24–2.49)	42.0	0.14	
Medication and supplements	Adjusted	2	2.88 (1.55–5.38)	0.0	0.47	0.22
	Unadjusted	8	1.74 (1.40–2.17)	13.8	0.32	

P*-value for heterogeneity within each subgroup. *P*-value for heterogeneity between subgroups with meta-regression analysis. BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; RR, relative risk.

the overall dose–response, the relationship between ferritin and GDM, whether linear or non-linear, has not been defined. Even though the results of linear testing showed that the relationship between ferritin and GDM was linear ($P = 0.061$), we still considered the possibility of a non-linear relationship^{8,34}. A future meta-analysis requires more studies to obtain a more precise assessment of the impact of the dose–response relationship of ferritin and GDM risk. Second, we included all observational studies compared with prospective cohort studies, and case–control studies use post-diagnostic blood samples, which might introduce reverse causality. Therefore, this meta-analysis showed that the point estimate of case–control studies was higher than cohort studies. Third, it is possible that the positive relationship between ferritin and GDM might reflect that not all of the included studies measured the residual or incomplete potential confounding factors (e.g., BMI, age, parity and CRP) that might affect the results of meta-analysis in the original study. For example,

because the BMI was not adjusted, the point estimates of Soheilykhah *et al.*³⁵ differed from other studies. In addition, the results from heterogeneity of subgroups showed that not adjusting for BMI and CRP will yield higher heterogeneity. Therefore, the correlation between ferritin and GDM should be analyzed and summarized after the potential confounding factors are fully considered or adjusted. Further studies should report analyses stratified by BMI and CRP to rule out residual confounding. Finally, the present meta-analysis might have inclusion criteria bias due to excluding the non-English literature and gray literature.

Based on the above results, it would be reasonable to conclude that higher ferritin was associated with GDM risk. Additionally, the present study suggested that pregnant women should pay attention to the level of ferritin during pregnancy to prevent GDM risk. Ferritin might become a new biomarker to prevent GDM risk. Further large-scale prospective cohort studies are warranted to confirm the results and explore the underlying physiological mechanism.

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DISCLOSURE

The authors declare no conflict of interest.

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