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Iron metabolism and type 2 diabetes mellitus: A meta-analysis and systematic review

Jingfang Liu*, Qingxiu Li, Yaxian Yang, Lihua Ma

Department of Endocrinology, The First Hospital of Lanzhou University, Lanzhou, China

Keywords
Ferritin, Soluble transferrin receptor, Type 2 diabetes

***Correspondence**
Jingfang Liu
Tel.: +86-943-835-6470
Fax: +86-943-835-6470
E-mail address:
ljf824168@126.com

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ABSTRACT

Aims/Introduction: Iron metabolism can directly or indirectly affect the occurrence and development of type 2 diabetes. This meta-analysis and systematic review aimed to analyze the association between serum iron metabolism indicators and type 2 diabetes.

Materials and Methods: The databases PubMed and Embase were searched for studies on the correlations between serum iron metabolism indicators (iron, ferritin, transferrin, hepcidin and soluble transferrin receptor) and type 2 diabetes since January 2006. Relevant data were extracted from the included studies, and meta-analysis was carried out.

Results: A total of 12 case–control and cohort studies were analyzed. Of the 12 studies, 11 described the correlation between serum ferritin levels and type 2 diabetes. The median and high serum ferritin concentrations were significantly associated with the risks of type 2 diabetes (odds ratio [OR] 1.20, 95% confidence interval [CI] 1.08–1.33 and OR 1.43, 95% CI 1.29–1.59, respectively). However, the low concentration was not correlated with the risk of type 2 diabetes (OR 0.99, 95% CI 0.89–1.11). No significant association was observed between serum soluble transferrin receptor and type 2 diabetes, whereas the soluble transferrin receptor-to-ferritin ratio was significantly inversely related to the risk of type 2 diabetes in the median and high ratio subgroups (OR 0.71, 95% CI 0.51, 0.99 and OR 0.65, 95% CI 0.45–0.95).

Conclusions: The elevated serum ferritin was one of the risk factors for type 2 diabetes, and soluble transferrin receptor-to-ferritin ratio was inversely related to the risk of type 2 diabetes. A systematic review showed that serum transferrin and hepcidin might be directly or indirectly related to the development of diabetes.

INTRODUCTION

Diabetes is a common and frequent metabolic disease. Recently, the prevalence of diabetes has increased rapidly worldwide. The incidence rate of type 2 diabetes in Chinese adults aged >18 years has reached 11.6% (12.1% in men and 11% in women)[1]. Diabetes has become one of the most significant public health problems.

Iron, one of the essential trace mineral elements, is involved in regulating the differentiation and growth of living cells, and participates in electron transfer between cells, affecting the genomic synthesis. Furthermore, iron can combine and transport oxygen to various parts of the body, and participate in many metabolic processes essential for life[2]. The normal iron content in adults is approximately 60 g/dL. However, once the iron content in the body increases for various reasons, it might cause severe damage to the pancreatic cells through excessive oxidative stress. In addition, the ability to use insulin and gluconeogenesis in the liver are weakened, resulting in the occurrence and development of type 2 diabetes[3,4].

As a strong oxidant, iron can speed up the production of a large number of reactive oxygen radicals that participate in regulating the signal transduction process of islet β-cells, thereby affecting the secretion of insulin and interfering with the glucose metabolism process[5]. Second, iron plays an important role in mitochondria, which can promote the synthesis of adenosine triphosphate and also affect the secretion levels of insulin, ultimately leading to glucose metabolism disorder[6,7].

The blood sugar levels are closely related to the iron contents in islet β-cells. However, because of the higher expression levels of iron transport proteins in the islet β-cells[8] compared with other tissue cells, the islet β-cells are more likely to accumulate iron. Too much iron might induce excessive oxidative stress,

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promote islet β-cell apoptosis, and ultimately affect insulin secretion and increase the risk of insulin resistance.

Studies have shown that iron metabolism indicators (transferrin, ferritin, hepcidin, transferrin receptor and so on) can directly or indirectly affect the occurrence and development of type 2 diabetes. However, the results describing the correlation between iron metabolism and type 2 diabetes were inconsistent between different sex and ethnicity. Serum ferritin concentrations were significantly higher in women with diabetes than in women without diabetes in all racial/ethnic groups, but were significantly lower in Asian men with diabetes than in those without diabetes[9]. Therefore, the present meta-analysis and systematic review was carried out on the relationship between serum iron metabolism indicators and type 2 diabetes.

METHODS

Inclusion and exclusion criteria

The inclusion criteria were as follows: (i) studies based on humans; (ii) studies on the correlations of serum iron, ferritin, transferrin, hepcidin and soluble transferrin receptor with type 2 diabetes mellitus; (iii) case–control studies or prospective cohort studies; and (iv) statistical indicators, such as odds ratio (OR) or relative risk values, and 95% confidence interval (CI), provided in the studies with adjustment.

The exclusion criteria were as follows: (i) studies based on animals; (ii) patients with type 2 diabetes having other complications; (iii) patients with type 2 diabetes and other diseases; (iv) case reports or review; and (v) poor quality or incomplete data.

Literature retrieval

Databases PubMed and Embase were searched for studies on the correlations between serum iron metabolism indicators (iron, ferritin, transferrin, hepcidin and soluble transferrin receptor) and type 2 diabetes since January 2006. The related references of the studies were traced back, and the accuracy and objectivity of the viewpoints of the retrieved studies were evaluated. According to the principle of patient intervention comparison outcome, the information ("Ferritins" [Mesh] OR "Iron" [Mesh] OR "Transferrin" [Mesh] OR "Ferroprotein" [Mesh]) AND ("Diabetes Mellitus, Type 2" [Mesh]) was retrieved by matching key words or free words with each other.

Data extraction

Two researchers independently carried out the retrieval of relevant studies to determine whether the included studies met the aforementioned inclusion criteria. Any disagreement between the two was solved by discussion. In the final included studies, the basic features were extracted as follows: first author's name, year of publication, nationality of study, type of study, follow-up years, selection criteria for type 2 diabetes and normal control groups, sample size of the study, average age of the participants, proportion of men in the normal control and type 2 diabetes groups, diagnostic criteria for patients with type 2 diabetes, iron metabolism indicators, and variables adjusted in the study.

Ethical approval

This study complied with the Declaration of Helsinki. Given this study was a meta-analysis, no prior ethical approval was required.

Statistical analysis

First, the publication bias of the study was evaluated through Begg's and Egger's tests using the statistical analysis software Stata12.0 (StataCorp, College Station, TX, USA) Whether the distribution of funnel graphs in Begg's or Egger's test was approximately symmetric was used to subjectively evaluate the publication bias. The adjusted OR or relative risk values (or equivalent to the OR values) and 95% CI were extracted[9–13]. The combination of pure effect size and CI was used. Furthermore, a sensitivity analysis was carried out based on the heterogeneity index. $P < 0.01$ was considered statistically significant in the Begg's and Egger's test; however, in sensitivity analyses, $P < 0.05$ was considered as statistically significant.

RESULTS

Screening literature results

A total of 168 studies in the English language, describing the correlations between serum iron metabolism indicators (iron, ferritin, transferrin and soluble transferrin receptor) and type 2 diabetes, were found from the two databases. Of these studies, 145 were from PubMed and 23 from Embase; 23 repeated studies were excluded. After skimming the titles and abstracts, followed by an intensive reading of the full text, 12 case–control studies and cohort studies were obtained[10–21], which included 6,516 patients with type 2 diabetes and 43,120 control individuals without type 2 diabetes. The details of the screening process are shown in Figure 1.

Basic features of the included studies

The basic characteristics and relevant outcome indicators of the studies were extracted, including the first author's name, year of publication, country of study, type of study, follow-up years, selection criteria for type 2 diabetes and normal control groups, sample sizes of the studies, average age of the participants, proportion of men in the normal control and type 2 diabetes groups, diagnostic criteria for patients with type 2 diabetes, iron metabolism indicators, and variables adjusted in the study. The detailed features of data extraction are shown in Table 1.

The publication bias of the studies was evaluated by Begg's and Egger's tests. The distributions of funnel plots were approximately symmetric. The index of $pr > |z|$ was 0.399 in Begg's test and $P > |t|$ was 0.49 in Egger's test, showing no significant publication bias in these studies.

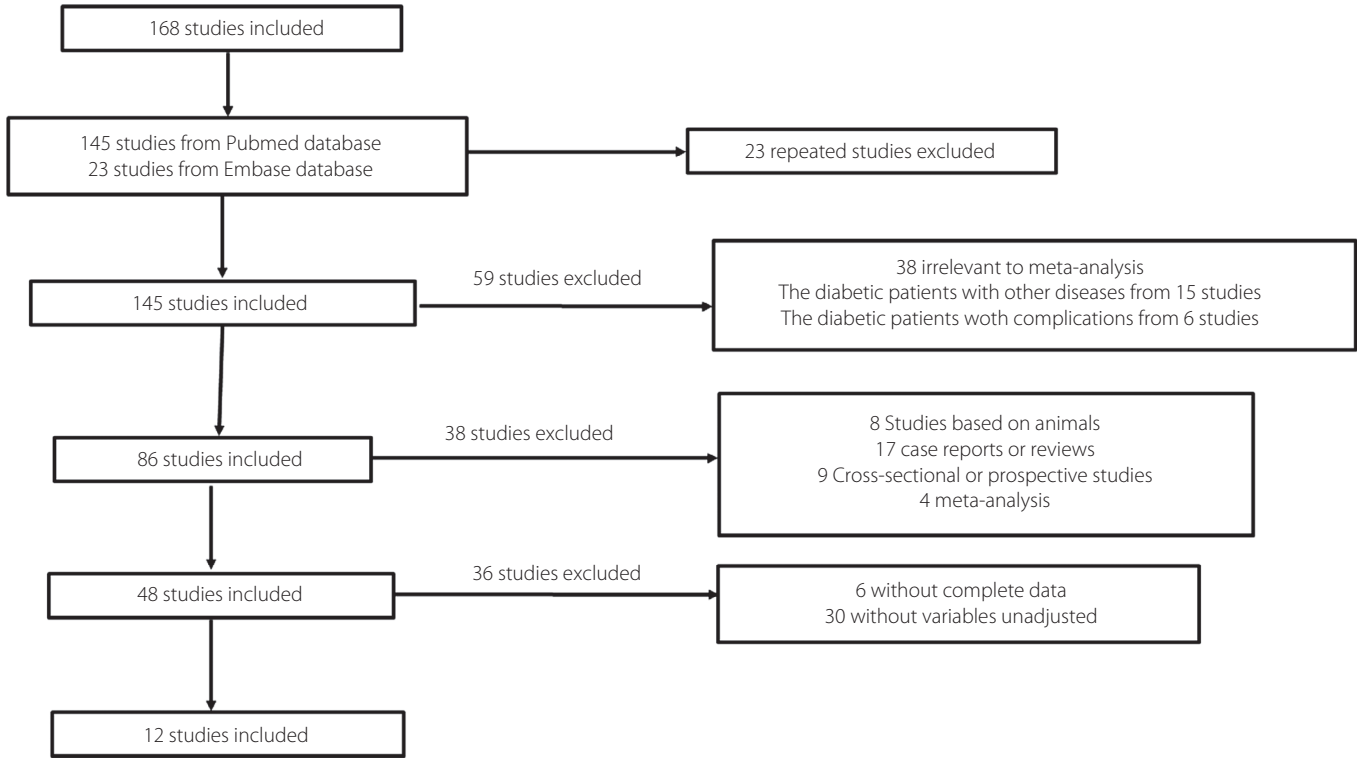

Figure 1 | Literature screening flowchart.

Serum ferritin levels and the risks of type 2 diabetes

Of the 12 studies, 11 described the correlation between serum ferritin levels and type 2 diabetes[10–20]. Eight studies were categorized into three subgroups (low, medium and high concentration) according to the quartiles or quintile of ferritin levels, respectively. The other three serum ferritin unstratified studies constituted an independent subgroup. Eventually, the effect sizes (adjusted OR or relative risk) and 95% CI were extracted. After taking the natural logarithm of the upper and lower limits of effect sizes and the 95% CI, the pure effect sizes and 95% CI were combined using the random effects models, and the forest maps were constructed.

The results showed that the median and high serum ferritin concentrations were significantly associated with the risks of type 2 diabetes (OR 1.20, 95% CI 1.08–1.33 and OR 1.43, 95% CI 1.29–1.59). However, no significant association was shown between the low serum ferritin concentration and the risks of type 2 diabetes (OR 0.99, 95% CI 0.89–1.11; Figure 2). In addition, serum ferritin levels remained a risk factor for type 2 diabetes in the unstratified subgroup (OR 1.35, 95% CI 1.23–1.48; 3).

Sensitivity analysis

Figure 2 showed that in the high concentration subgroup, I^2 was 81.2% ($P = 0.000$), suggesting high heterogeneity among the eight included studies. The sensitivity analysis was carried out to explore the source of heterogeneity.

The natural logarithms of the corresponding effect sizes were taken, and the standard error of effect size logarithms was calculated. The results showed that the effect and 95% CI were evenly distributed on both sides of the baseline in each study. However, one study[13] deviated from the baseline level further, as compared with the other seven studies, showing distinct heterogeneity, and hence, was eliminated.

After removing a reference with obvious heterogeneity, the effect size and 95% CI were again combined by the same method, and the forest map was drawn. As shown in Figure 4, the high serum ferritin concentrations were significantly associated with the risk of type 2 diabetes (OR 2.32, 95% CI 1.90–2.83). Furthermore, compared with the statistical variables ($I^2 = 81.2\%$, $P = 0.000$) in the eight studies, the I^2 values were significantly decreased ($I^2 = 1.1\%$, $P = 0.416$), which suggested that the excluded study was the main source of heterogeneity in the high concentration subgroup.

Serum soluble transferrin receptor levels and the risk of type 2 diabetes

Of the 12 studies, three described the correlations between serum soluble transferrin receptor and type 2 diabetes[12,18,21]. The effect size OR values and 95% CI were extracted from these two studies. As shown in Figure 5, no significant correlation was found between serum soluble transferrin receptor levels and the risk of type 2 diabetes in the low concentration (OR 1.36, 95% CI 0.90–2.07), median concentration (OR 1.10,

Table 1 | Basic characteristics of the included studies

First author's name	Publication year	Country	Type of study	Follow-up years	Patient/ control	Sample size (patient/ control)	Average age, years (patient/ control)	Outcome indicators	Variables adjusted
Xin Guo	2013	China	Case–control study	–	T2DM/normal control	555/704	64/58	SF, hepcidin	1, 2, 6
Chang Hee Jung	2013	Korea	Case–control study	4	T2DM/normal control	186/1,843	54/50	SF	1, 5, 7, 8, 9, 11, 13, 14, 15, 16, 17, 18, 19
Victoria Arija	2014	Caucasus	Case–control study	6	T2DM/normal control	153/306	66/66	SF, sTfR	3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 16, 19, 20
Clemens Wittenbecher	2015	Potsdam	Cohort study	7	T2DM/normal control	688/2,047	49/49	SF	1, 2, 3, 6, 7, 9, 10, 11, 12
Sunyong Kim	2015	Korea	Cohort study	3	T2DM/normal control	2,655/27,347	42/43	SF	1, 6, 7, 8, 9, 11, 14, 19, 22
Jose C. Fernández-Cao	2016	Spain	Case–control study	6	T2DM/normal control	153/306	66/66	sTfR	3, 4, 5, 7, 9, 10, 13, 16, 19, 20, 21, 23, 24, 25
Liang Sun	2008	China	Case–control study	–	T2DM/normal control	440/2,812	50/50	SF	1, 2, 3, 6, 7, 8, 9, 10, 13, 16, 23, 25, 26
DeChun Luan	2008	China	Case–control study	–	T2DM/normal control	146/2,851	46/46	SF	1, 2, 5, 6, 7, 8, 10, 11, 12, 13,
N. G. Forouhi	2007	Norwich	Cohort Study	5	T2DM/normal control	360/758	62/62	SF	1, 2, 6, 17, 18, 27
J. Montonen H	2012	Potsdam	Cohort Study	7	T2DM/normal control	849/2,500	50/50	SF, sTfR	1, 2, 3, 5, 6, 7, 8, 9, 12, 13, 16, 17, 18, 19, 20, 27
S.N. Rajpathak	2009	USA	Case–control study	–	T2DM/normal control	280/280	50/50	SF	1, 2, 6, 9, 13, 15
Zumin Shi	2006	China	Cohort Study	–	T2DM/normal control	51/1366	47/47	SF	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 13, 23

Adjusted variables: 1: age; 2: sex; 3: education level; 4: marital status; 5: waist circumference; 6: body mass index; 7: smoking; 8: drinking alcohol; 9: sports; 10: dietary intake; 11: hypertension; 12: hyperlipidemia; 13: family history of diabetes; 14: homeostasis model of insulin resistance; 15: glycosylated hemoglobin; 16: high sensitivity C-reactive protein; 17: glutamyl transpeptidase; 18: alanine aminotransferase; 19: triglyceride, high-density lipoprotein, low-density lipoprotein; 20: fasting blood glucose; 21: fasting insulin; 22: white blood cells; 23: saturated, monounsaturated and polyunsaturated fatty acids; 24: center (Pamplona/Barcelona/Tarragona); 25: intervention group (Mediterranean diet supplemented with nuts or olive oil/ control group); 26: inflammatory factors (interleukin-6, and tumor necrosis factor receptor 2); 27: adipokines (adiponectin, plasminogen activator inhibitor-1 and retinol-binding protein 4). SF, serum ferrtin; sTfR, soluble transferrin receptor-to-ferritin ratio; T2DM, type 2 diabetes.

95% CI 0.79–1.52) and high concentration (OR 0.95, 95% CI 0.67–1.34) subgroups.

Soluble transferrin receptor-to-ferritin ratio and the risks of type 2 diabetes

Of the 12 studies, two described the correlations between serum soluble transferrin receptor-to-ferritin ratio and type 2 diabetes[12,18]. The effect size OR values and 95% CI were extracted from these two studies. As shown in Figures 5, 6, soluble transferrin receptor-to-ferritin ratios were significantly inversely related to the risk of type 2 diabetes in median (OR 0.71, 95% CI 0.51–0.99) and high ratio subgroups (OR 0.65, 95% CI 0.45–0.95); however, no correlation was observed in the low soluble transferrin receptor-to-ferritin ratios subgroup (OR 0.87, 95% CI 0.63–1.20).

Other iron metabolism indicators and the risks of type 2 diabetes

In addition, during the process of retrieving and selecting the studies, just one study described the correlation between serum hepcidin level and type 2 diabetes[10]. No related studies on the correlation between serum transferrin and type 2 diabetes were

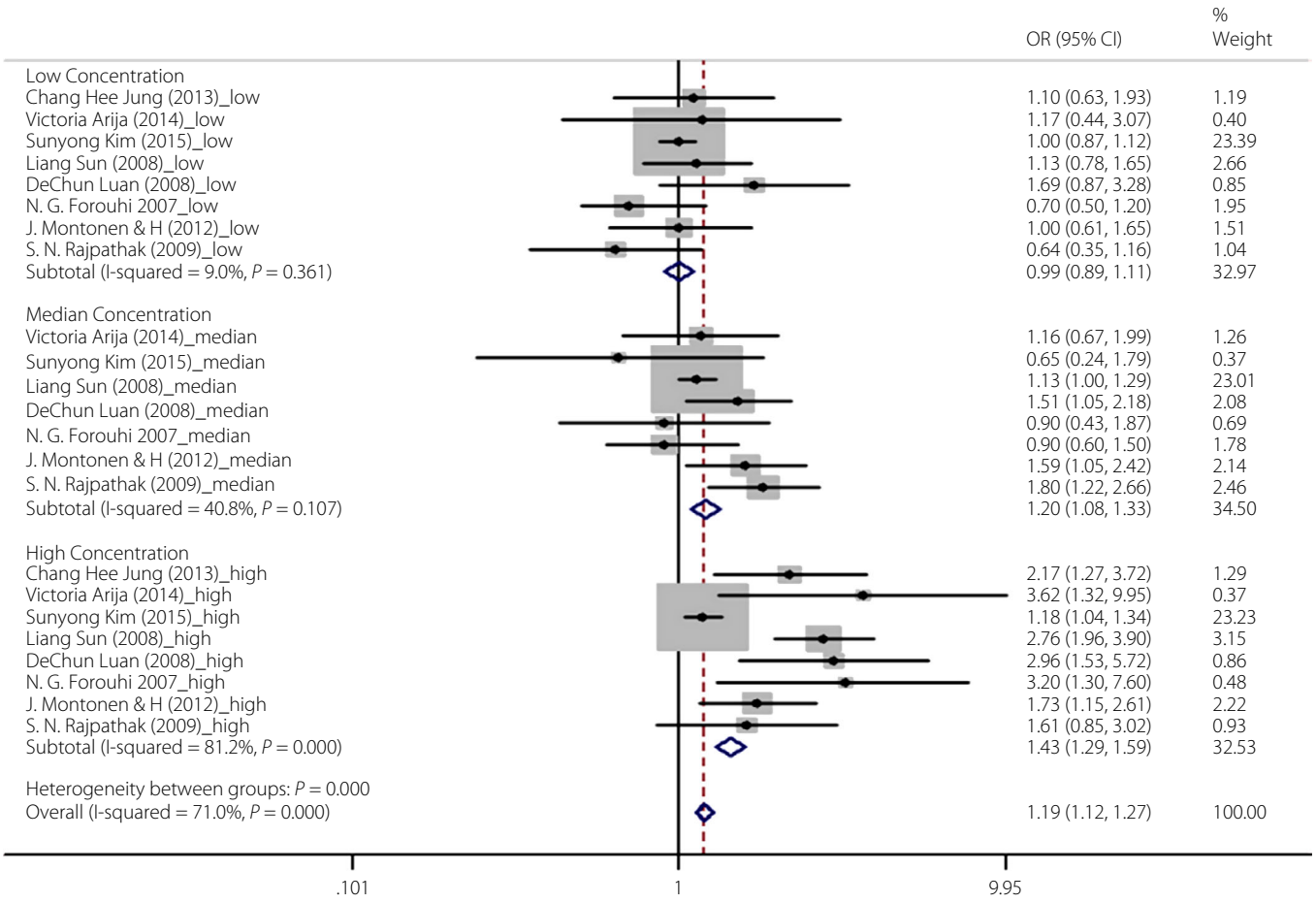

Figure 2 | The association between serum ferritin and type 2 diabetes in ferritin concentration stratified group. CI, confidence interval; OR, odds ratio.

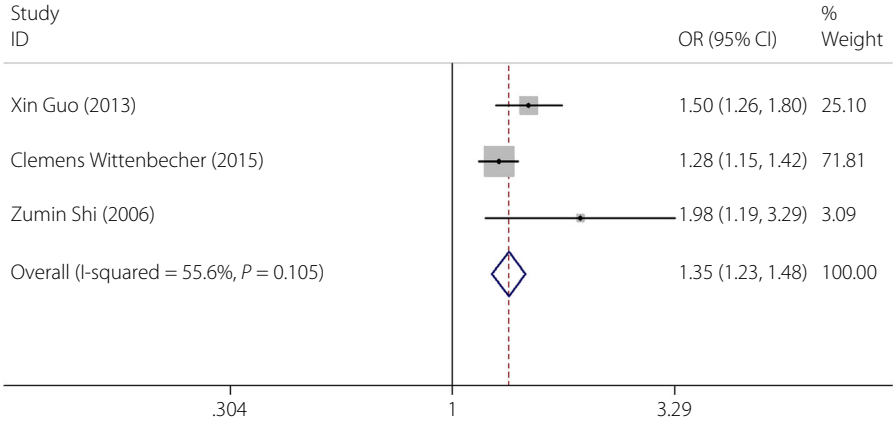

Figure 3 | The association between serum soluble transferrin receptor and type 2 diabetes in the ferritin unstratified group. CI, confidence interval; OR, odds ratio.

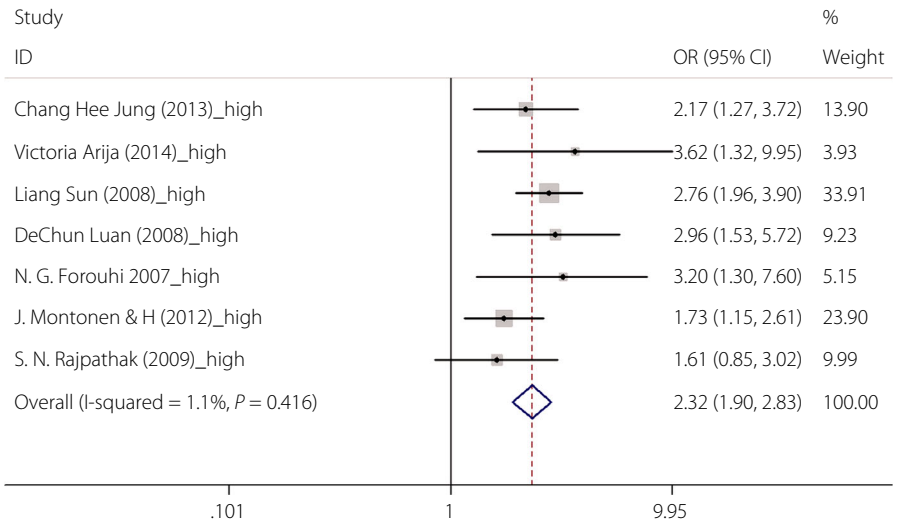

Figure 4 | The association between serum ferritin and type 2 diabetes, excluding one study. CI, confidence interval; OR, odds ratio.

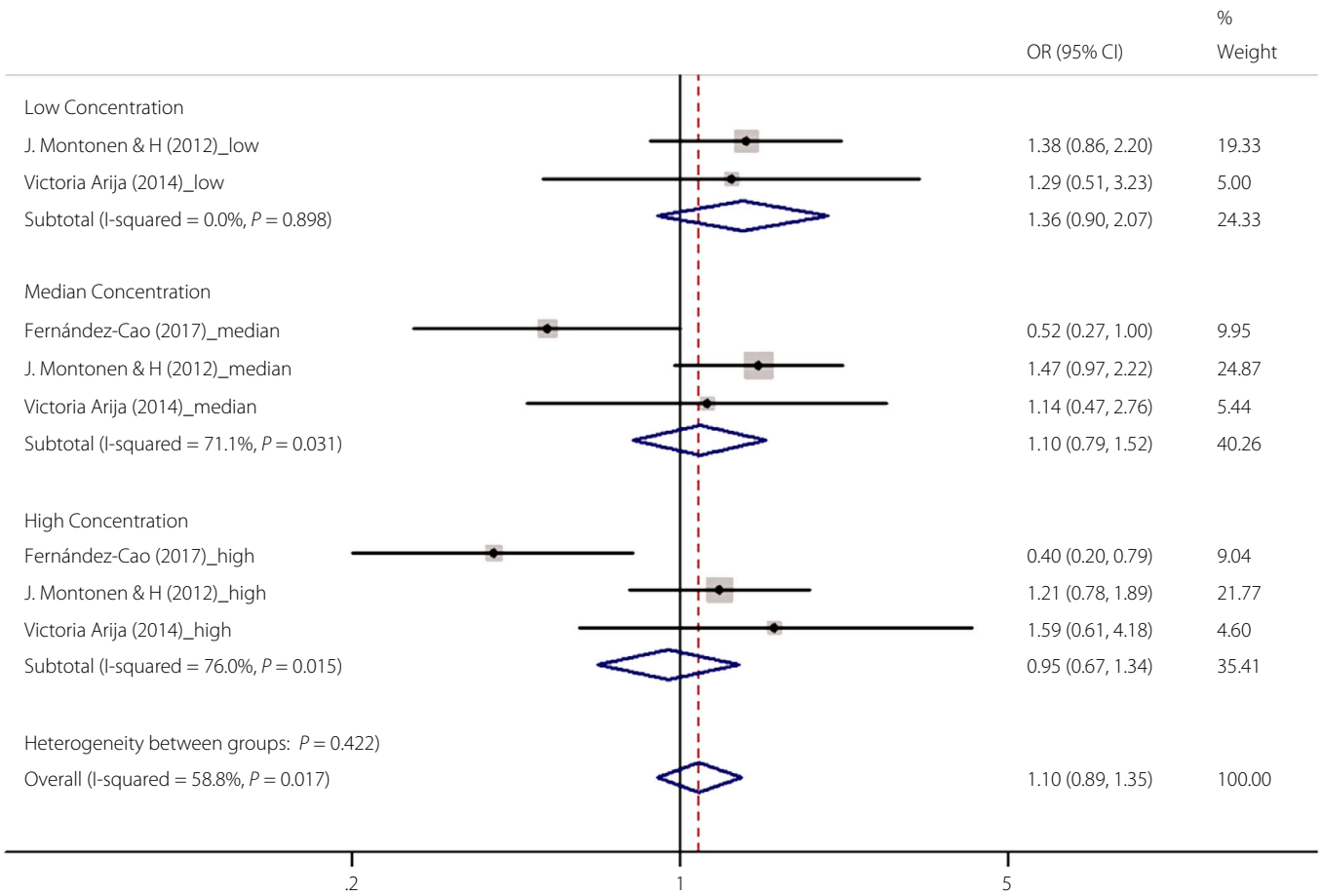

Figure 5 | The association between serum soluble transferrin receptor and type 2 diabetes. CI, confidence interval; OR, odds ratio.

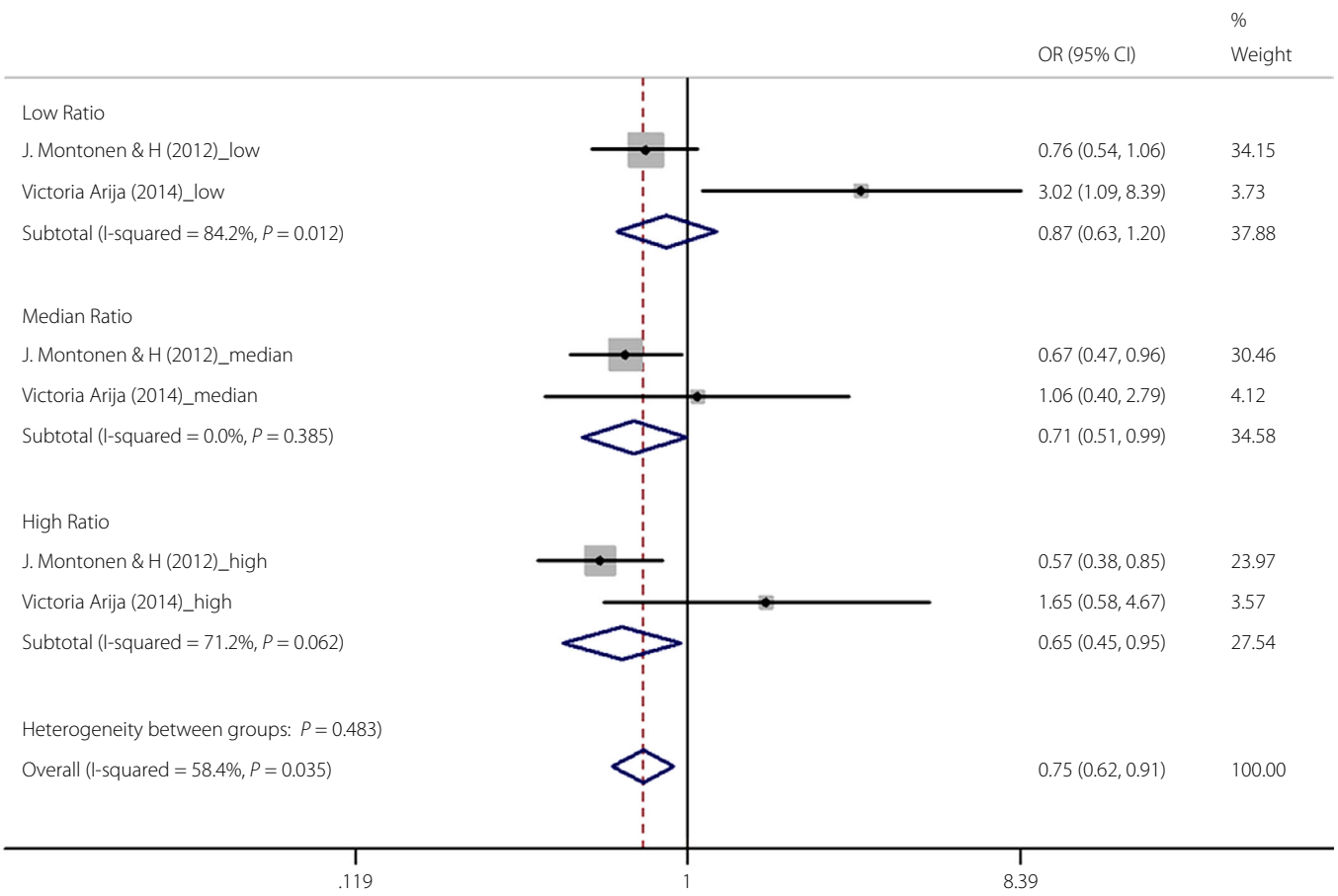

Figure 6 | The association between serum soluble transferrin receptor to ferritin ratio and type 2 diabetes. CI, confidence interval; OR, odds ratio.

found; therefore, it was impossible to extract and analyze relevant data. Hence, the relationships of serum transferrin and hepcidin with type 2 diabetes were not evaluated by the meta-analysis, and only discussed in the systematic review.

DISCUSSION

Iron is one of the essential trace elements for the human body. The body contains 3–5 g iron. The body regulates the amount of iron mainly through absorption. When iron is deficient or excessive, it causes dysfunction of the body. Excessive iron stores have been suggested to be associated with a high risk of type 2 diabetes by causing damage to the pancreatic β-cells and insulin resistance through increased oxidative stress[22].

Ferritin, a key protein regulating iron homeostasis, is the main form of iron storage in the body. The level of ferritin might be increased due to the injury of non-stored iron organs, which could be used as a sensitive indicator of excessive iron load in the body. Some studies have shown that serum ferritin levels are elevated in type 2 diabetes patients, and increased serum ferritin levels in Western and Asian populations are associated with an increased risk of diabetes[10–14].

In the present study, OR for the risk of type 2 diabetes was significant in the median and high concentration subgroups. However, no correlation was established between the low concentration subgroup and type 2 diabetes. The results showed that the risk of type 2 diabetes increased with the increase in serum ferritin concentration. Consistent with the current results, three meta-analyses evaluated the correlations between serum ferritin levels and the risk of type 2 diabetes, suggesting that high ferritin levels were associated with the risk of type 2 diabetes[23–25]. Therefore, Jung *et al.*[11] speculated a threshold between serum ferritin and the risk of type 2 diabetes, above which, the risk is increased.

Serum ferritin levels were a risk factor for type 2 diabetes in the unstratified subgroup, which might be related to the high average serum ferritin levels of participants in these three studies.

The sensitivity analysis showed that a study might be the main resource of high heterogeneity in the serum ferritin high concentration subgroup[13]. The reason might be related to the following factors. First, the participants were young compared with the participants of the other studies. Age has a significant

effect on ferritin level, which is related to the weakening of the body protection mechanism and the decline in the metabolic capacity after aging[26]. Second, each study had different variables to adjust, and as compared with the other three studies, the present study adjusted relatively few parameters. Third, serum ferritin concentrations varied according to sex and ethnicity[27]. A previous study identified innate biological differences in serum ferritin levels between races. Asian men and women were reported to have higher adjusted mean serum ferritin concentrations compared with white men and women[27]. In addition, the body composition of different races had different effects on the levels of serum ferritin[28]. The levels of the high ferritin subgroup (the 4th quartiles, ≥149.2 mg/mL) in the present study were lower than the levels in the other seven studies.

The mechanisms underlying the relationship between serum ferritin and type 2 diabetes might be as follows. First, the elevated serum ferritin might interact with other kinds of pathogenic factors, impair the function of islet β-cells, affect the secretion of insulin and increase the risks of type 2 diabetes[29]. Second, insulin is involved in regulating the transcription of serum ferritin and increasing the use of iron in the peripheral tissues. When the body iron content is in excess, insulin secretion is affected, and the iron use in peripheral tissues is reduced. The overload iron causes excessive oxidative stress to influence normal physiological functions of various tissues and organs[30]. Third, serum ferritin is also considered as an acute-phase reaction marker. When the body is affected by factors, such as inflammation, the serum ferritin levels increase, thereby affecting the insulin secretion and disrupting the normal glucose metabolism process. This leads to insulin resistance, which increases the risk of type 2 diabetes. Fourth, the elevated ferritin levels leading to an increased risk of type 2 diabetes are associated with oxidative stress. This phenomenon is caused by an increase in iron-catalyzed hydroxyl radicals, which leads to systemic insulin resistance and hyperglycemia[31].

Soluble transferrin receptor and type 2 diabetes

Serum soluble transferrin receptor, an indicator reflecting the intracellular iron storage, often binds to serum transferrin, which can transport iron from outside into the cell[32]. Soluble transferrin receptor, as a truncated form of transferrin receptor, is located in the serum proportional to the transmembrane protein, and therefore, to cell iron demands. Soluble transferrin receptor is considered as an optimal biomarker of iron deficiency. Hitherto, just a few studies have evaluated the association between soluble transferrin receptor and the risk of type 2 diabetes.

Montonen *et al.*[18] reported that no significant association was observed between the serum levels of soluble transferrin receptor and the risk of type 2 diabetes. In the present meta-analysis, three studies described the correlations between serum soluble transferrin receptor and type 2 diabetes[12,15], and no significant correlation was established between the levels of serum soluble transferrin receptor and the risk of type 2 diabetes. To date, the independent association between serum soluble transferrin receptor and risk of diabetes was reported in only one study[19]; the elevated levels of soluble transferrin receptor levels were associated with an increased risk of diabetes among overweight and obese persons with impaired glucose tolerance. The study suggested that iron overload in the body leads to an excessive oxidative stress response; free iron is consumed, and in turn, serum soluble transferrin receptor increases the risk of patients with type 2 diabetes having abnormal glucose metabolism[19]. In addition, serum soluble transferrin receptor might be a biomarker of some other factor (such as obesity, insulin resistance or inflammation etc.) that is causally related to the development of diabetes and possibly unrelated to the iron load.

Soluble transferrin receptor-to-ferritin ratio and type 2 diabetes

Soluble transferrin receptor levels might be affected by other factors, such as the degree of glucose tolerance, insulin resistance, hyperinsulinemia, inflammation and obesity. Recent studies showed that the ratio of serum soluble transferrin receptor-to-ferritin could be used as an indicator to evaluate the iron content *in vivo*[18]. Arija *et al.*[12] reported a low soluble transferrin receptor-to-ferritin ratio level and the incidence of type 2 diabetes, but no association with soluble transferrin receptor. In addition, the present study showed serum soluble transferrin receptor-to-ferritin ratios were significantly inversely related to the risk of type 2 diabetes in median (OR 0.71, 95% CI 0.51–0.99) and high ratio subgroups (OR 0.65, 95% CI 0.45–0.95). However, as relatively few studies have been included to date, there might be some bias in the results; hence, additional studies are required to further confirm the correlation between the soluble transferrin receptor-to-ferritin ratio level and type 2 diabetes. At the same time, no association was observed in the low ratio subgroup, and whether the negative correlation between soluble transferrin receptor-to-ferritin ratio and type 2 diabetes in median and high ratio subgroups was related to increased serum ferritin levels might require further confirmation.

Hepcidin and type 2 diabetes

Only one study on the relationship between serum hepcidin and type 2 diabetes was included[10]. A previous study showed that serum hepcidin concentrations correlated with serum hemoglobin and ferritin concentrations. No difference was found in serum hepcidin concentrations between diabetes and control groups. The serum hepcidin concentrations were not significantly correlated with the risk factors for type 2 diabetes (body mass index, glycosylated hemoglobin, fasting blood glucose levels etc.).

Although no accurate evidence of a direct correlation between serum hepcidin and the risks of type 2 diabetes was found, serum hepcidin, as an important negative regulator of iron homeostasis in the body, might directly regulate the expressional levels of iron. Serum hepcidin might be mediated

by the interaction between serum transferrin and cell membrane. On the one hand, with the increase in the body's iron levels, iron levels in the liver also increase, inhibit the transcription and expression of iron transport protein on the cell membrane of the duodenum, and prevent the transfer of iron from the cells into circulation, ultimately reducing the absorption of iron in the gut. On the other hand, serum hepcidin can also act on liver cells and macrophages, and reduce the release of iron from the tissues, thereby decreasing the levels of iron in the body[33,34]. Serum hepcidin is involved in the balance of iron by preventing the absorption, use and release of iron from the tissues[35]. The animal experiments confirmed that insulin might directly induce serum hepcidin production[36]. Under the influence of dietary factors, gluconeogenesis is continuously activated and serum hepcidin levels also rise, which induce iron accumulation and excessive oxidative stress, and interfere with glucose metabolism by activating p38 mitogen-activated protein kinase and peroxisome proliferator-activated receptor-γ coactivator-1α signaling pathways and CCAAT/enhancer-binding protein alpha phosphorylation[37]. In addition, serum hepcidin might also affect the function of mitochondria and participate in glycogen synthesis. The excessive expression of serum hepcidin causes iron accumulation in the liver and an increase in active oxygen free radicals. The excessive oxidative stress eventually damages pancreatic cells, affects insulin secretion and increases the occurrence of type 2 diabetes[38].

Serum transferrin and type 2 diabetes

Very few studies reported on the direct link between serum transferrin and type 2 diabetes. Because of the molecular weight and negative charges, serum transferrin is susceptible to leakage from glomeruli. Therefore, monitoring urinary transferrin levels might help in the early evaluation of the progression of diabetic nephropathy[39]. At the same time, serum transferrin can also induce lipolysis of the body's fat cells, cause an increase in free fatty acids and affect the secretion function of the pancreas, ultimately leading to insulin resistance and an increased risk of type 2 diabetes[40].

In conclusion, the elevated level of serum ferritin is one of the risk factors for type 2 diabetes. The serum soluble transferrin receptor-to-ferritin ratio was inversely related to the risk of type 2 diabetes. Serum soluble transferrin receptors might not be associated with the risk of type 2 diabetes. A systematic review showed that serum transferrin and hepcidin might be directly or indirectly related to the development of diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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