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Association Of Blood Lipocalin-2 Levels with Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis

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ABSTRACT

Lipocalin-2 (LCN2) is becoming recognized as a pleiotropic mediator of metabolic disorders. However, the relationship between LCN2 and gestational diabetes mellitus (GDM) is not well understood. We performed a systematic review and meta-analysis to explore it. A systematic search of Cochrane Library, PubMed, Embase, Scopus, Web of Science, Chinese National Knowledge Infrastructure, and Wan-fang Database was done for relevant articles published up to September 29, 2021. Standardized mean difference (SMD) with 95 % confidence intervals (CI) was calculated to explore the association of LCN2 levels with GDM using Revman 5.3 and Stata 15.1. Fifteen case-control studies were included in this meta-analysis. The patients with GDM had significantly higher levels of blood LCN2 than parturients with normal glucose tolerance (SMD = 3.41, 95 % CI = 2.24 to 4.58). Meta-regression and subgroup analysis were conducted to investigate the source of heterogeneity. Likely sources of heterogeneity were age and testing methods. This study found that GDM showed higher blood LCN2 levels than controls. However, caution is warranted on the interpretation of these findings. Standardized LCN2 measurement methods and longitudinal studies are required to disentangle and better understand the relationships observed.

Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance that begins or is initially noticed during pregnancy [1]. Being the most common pregnancy complication, GDM may complicate 15–20 % pregnancies, and its prevalence has increased by 27 % in the last 20 years in all ethnic groups [2]. GDM induces both maternal and fetal complications and gives rise to poor pregnancy outcomes, including preterm delivery, pre-eclampsia, macrosomia, and perinatal death [3]. The pathogenesis of GDM has not been completely clarified, though insulin resistance plays a fundamental role in its development [4, 5]. Increased insulin re-

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sistance, sterile inflammation, and endothelial cell dysfunction are the three central features that contribute to hyperglycemia in patients with GDM [6]. Recently, accumulating evidence indicated that adipokines are involved in the pathogenesis of GDM [7, 8].

Lipocalin-2 (LCN2), also known as neutrophil gelatinase-associated lipocalin, is a 25-kDa secreted adipokine and a member of the lipocalin superfamily [9, 10]. LCN2 was first discovered in human neutrophils [11], and is expressed in many tissues such as the liver, kidneys, and adipose tissue [12]. It was identified as a critical regulator of energy metabolism, glucose and lipid homeostasis, and insulin function [9, 13]. Metabolic disorders, as observed in diabetes and obesity, have been closely associated with the upregulation of LCN2 in blood and several other tissues [9]. There have been reports of increasing circulating LCN2 levels during pregnancy [14]. Recent evidence points to the role of LCN2 in the pathophysiology of GDM. Although a previous study proposed that blood LCN2 were higher in patients with GDM compared with parturients with normal glucose tolerance (NGT) [15], subsequent studies showed inconsistent results [16, 17]. Since the existing results from accessible studies are conflicting, evidence-based quantitative analyses evaluating the correlation between circulating LCN2 levels and GDM are indispensable.

Materials and Methods

Search strategy

We systematically searched the following 7 electronic databases: Cochrane Library, PubMed, EMBASE, Scopus, Web of Science, Chinese National Knowledge Infrastructure (CNKI) Database, and Wanfang Database. The final literature search was performed on September 29, 2021. Only articles published in English and Chinese were used. The search strategy included key terms were listed as follows: (1) "Diabetes, Gestational", "Diabetes, Pregnancy-Induced", "Diabetes, Pregnancy-Induced", "Pregnancy-Induced Diabetes", "Gestational Diabetes", "Diabetes Mellitus, Gestational", "Gestational Diabetes Mellitus" and "GDM" and (2) "Lipocalin-2", "Lipocalin 2", "NGAL Protein", "Oncogene 24p3 Protein", "Siderocalin Protein", "Neutrophil Gelatinase-Associated Lipocalin", "Neutrophil Gelatinase-Associated Lipocalin", "Lipocalin-2 Protein", "Lipocalin 2 Protein" and "NGAL". The reference lists of related original and review articles were also analyzed using a manual approach. The protocol has been registered on the INPLASY website as INPLASY202190097 (https://inplasy.com/inplasy-2021–9–0097/).

Eligibility criteria

Publications were considered eligible if the following criteria were met: (1) included pregnant women with GDM as participants; (2) circulating LCN2 levels were detected; (3) controls were pregnant women with normal glucose tolerance; (4) evaluate the association of LCN2 levels with GDM; and (5) observational study design. The exclusion criteria were: (1) review, editorial, abstract, case report, or unpublished article; (2) studies with insufficient data to calculate the mean and standard deviation (SD); (3) studies that worked on animals or cells. Studies with Newcastle-Ottawa Scale (NOS) score < 7 were of not good quality [18] and excluded in the quantitative analysis (see Quality Assessment below).

Data extraction and quality assessment

Two independent authors performed the literature search, data extraction, and quality assessment of the included studies, according to the predefined inclusion criteria. Discrepancies were resolved by discussion with a third investigator. The following data were extracted: first author of the study, publication year, study country, study design, sample size, LCN2 levels, mean age, mean pre-pregnancy body mass index (BMI), testing method, measurement trimester, and applied GDM criteria. The data were presented as median with interquartile range transformed into mean ± SD [19–21]. The quality of the studies was assessed by the NOS for case-control studies [22]. A system of points was given to the eligible categories: (I) selection (II) comparability, and (III) exposure. A study could be awarded a maximum of one point for each numbered item within the Selection and Exposure categories. A maximum of two points could be given for comparability. For case-control studies, points ranged from 0 to 9 points with ≥ 7 points classified as good quality [18].

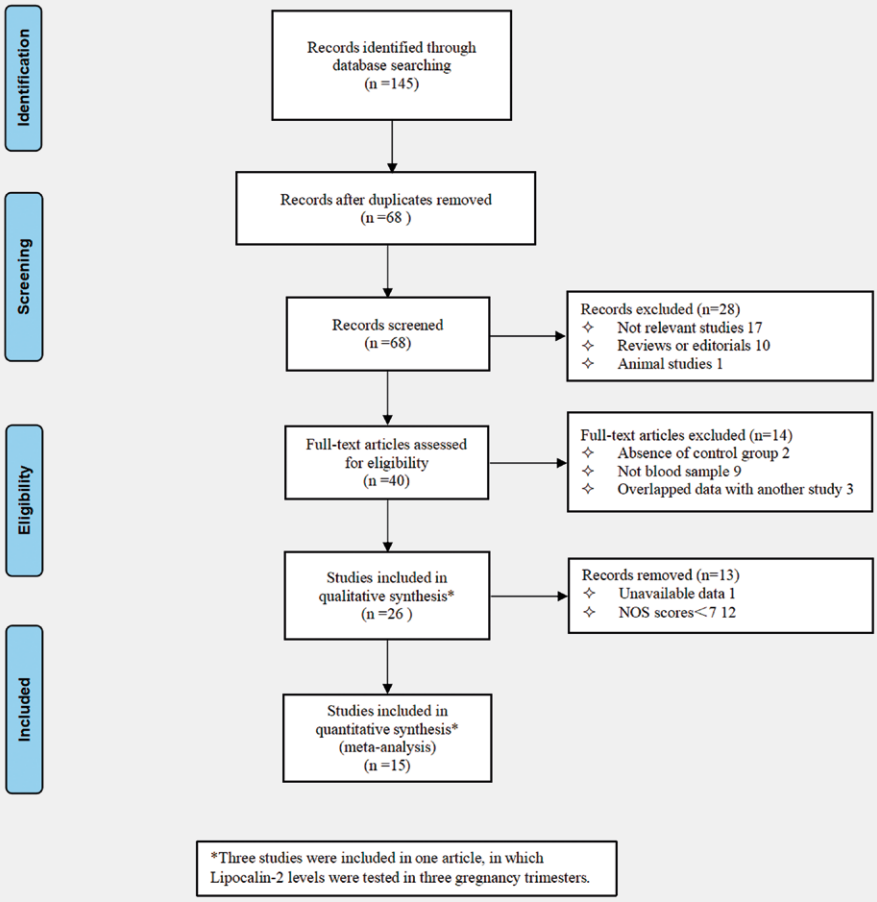
Statistical analysis

Data were analyzed using Review Manager (RevMan 5.3, The Cochrane Collaboration, Oxford, UK) and Stata software (Stata version 15.1, STATA Corporation, College Station, TX, USA). Blood LCN2 level is a continuous variable and expressed using different units depending on individual studies, therefore we used standardized mean difference (SMD) and 95 % confidence intervals (CIs) for analysis. The significance of the pooled SMD was evaluated by the Z-test. Heterogeneity across the studies was evaluated using Cochrane's Q-test and I^2 metric with a range of 0–100 %. A random-effects model was used if $I^2 > 50$ %; otherwise, the fixed-effects model was used. Sensitivity analyses, by omitting one individual study at a time, were performed to test the robustness of the results. To explore the potential cause of heterogeneity and determine whether various items affected the heterogeneity across studies, meta-regression and subgroup analysis were performed. Finally, funnel plots were used initially to evaluate visually publication bias while Egger's regression test and Begg's test were performed to inferentially evaluate publication bias. Substantial publication bias was final determined by the trim-and-fill technique. The statistical significance was defined as p-values less than 0.05.

Results

Search results

The literature search yielded 145 relevant articles, of which 12 were from PubMed, 25 from Embase, 16 from Web of Science, 11 from Scopus, 48 from CNKI, and 33 from Wan-fang. No relevant publications were identified in the Cochrane Library. After removing duplicates, and further eliminating unrelated articles, reviews or editorials and animal studies, 40 articles were assessed for eligibility by full-text screening. From these, two articles had no control group, nine articles did not use peripheral blood sample, and three articles had overlapped data with other studies. Of the remaining



▶ **Fig. 1** Flowchart of database search and study identification.

26 articles, data presented as "Median (first quartile- third quartile)" in 1 article was significantly skewed away from normality, and not recommended to data transformation. Hence, mean and SD were unavailable in this article. Twelve articles that scored < 7 according to the NOS quality assessment criteria were not of good quality. These 12 articles were therefore also excluded. This left 13 articles (containing 15 studies), which were eventually analyzed in this meta-analysis, among which LCN2 levels in one article were tested in three pregnancy trimesters [23]. The flow chart of the study selection is shown in ▶ **Fig. 1**.

Study characteristics are described in ▶ **Table 1**. Overall, 15 studies with 1882 individuals were included. The studies were performed in Denmark [16], Italy [15], Mexico [17], Poland [24], and China [4, 12, 23, 25–30]. All included studies were case-control studies and five were nested case-control studies. Blood samples were collected in different trimesters of pregnancy. Thirteen studies used enzyme-linked immunosorbent assay (ELISA) for measurements, and mass spectrometer and Magpix technology were used in the other studies. ADA and IADPSG diagnostic criteria for GDM were used in most studies, and other diagnostic criteria were supported by references in original articles. The NOS scores of the included studies ranged 7–9, indicating generally good study quality.

Meta-Analysis of Association of Lipocalin-2 Levels and GDM

Fifteen studies (1882 participants included in 13 articles) compared the LCN2 levels between patients with GDM and controls. Patients with GDM had significantly higher levels of blood LCN2 than parturients with NGT (SMD = 3.41; 95 % CI 2.24–4.58; $p < 0.001$; ▶ **Fig. 2**). Random-effects models were used due to significant heterogeneity among the studies ($I^2 = 98.9\%$; $p < 0.001$).

Meta-regression and subgroup analysis

Since significant heterogeneity was observed among studies ($I^2 = 98.9\%$; $p < 0.001$), meta-regression was performed to find the sources of heterogeneity, such as mean pre-pregnancy BMI, measurement trimesters, testing methods, mean age, and fasting sample. Testing methods and mean age were found to moderate the results ($p = 0.018$ and $p = 0.035$, ▶ **Table 2**), While measurement trimesters, mean pre-pregnancy BMI, and fasting sample did not affect the findings.

As shown in ▶ **Fig. 3**, subgroup analyses revealed that compared to pregnant women with NGT, significantly higher blood LCN2 concentrations in patients in GDM were detected using ELISA (SMD = 3.98; 95 % CI: 2.86–5.09, $p < 0.001$). No significant difference was exhibited using other testing methods (SMD = –0.24; 95 %

▶ **Table 1** Characteristics of the included articles.

Study [Ref]	Country	Study Design	Sample Size (GDM/ controls)	Mean Age	Mean BMI	Fasting	Methods	Measurement trimesters	GDM criteria	NOS score
D'Anna et al. (2009) [15]	Italy	NCC	41/82	27.2	26.7	Yes	ELISA	First	C & C	9
Duan et al. (2012) [25]	China	CC	77/77	29.5	22.7	Yes	ELISA	Third	ADA	7
Wang et al. (2013) [29]	China	CC	26/66	NA	NA	Yes	ELISA	Third	IADPSG	9
Lou et al. (2014) [12]	China	CC	84/96	28.31	20.43	Yes	ELISA	Third	ADA	7
Guo (2014) [26]	China	CC	28/21	28.5	NA	Yes	ELISA	Third	CSOG	7
Ma et al. (2015) [23]	China	NCC	101/100	29.92	22.78	Yes	ELISA	First, Second, third	IADPSG	9
Ravnsborg et al. (2016) [16]	Denmark	NCC	101/104	32.35	≥27	No	MRMMS	First	EDPSG	7
He et al. (2018) [30]	China	CC	37/34	31.6	22.9	Yes	ELISA	Second	ADA	7
Kang (2018) [28]	China	NCC	107/110	28.8	25.81	Yes	ELISA	First	CSOG	8
Guo et al. (2019) [27]	China	CC	85/50	29.12	22.54	Yes	ELISA	Third	ADA	7
Yin et al. (2020) [4]	China	CC	49/39	32.47	23.15	Yes	ELISA	Third	IADPSG	7
Mierzynski et al. (2021) [24]	Poland	NCC	153/84	27.59	23.71	Yes	ELISA	Second	WHO	8
Saucedo et al. (2021) [17]	Mexico	CC	65/65	31.65	32.36	Yes	Magpix	Third	IADPSG	7

BMI: Body Mass Index; NCC: Nested case-control; CC: Case-control; ELISA: Enzyme Linked Immuno Sorbent Assay; MRM-MS: Multiple Reaction Monitoring- Mass Spectrometry; C & C: Carpenter and Coustan's criteria; EDPSG: European Diabetic Pregnancy Study Group; ADA: American Diabetes Association; IADPSG: International Association of Diabetes and Pregnancy Study Group; CSOG: Chinese Society of Obstetrics and Gynecology; WHO: World Health Organization; NOS: Newcastle-Ottawa Scale; NA: Not available.

CI: –0.74–0.25, p = 0.34). As shown in ▶ **Fig. 4**, for women aged ≤ 30 years, women with GDM showed higher circulating LCN2 levels (SMD = 4.12; 95 % CI: 2.87–5.37, p < 0.001). However, for women aged > 30 years, the difference was not significant (SMD = 1.06; 95 % CI: − 0.20–2.32, p = 0.10).

Sensitivity analysis and publication bias

Sensitivity analyses showed that none of the studies were extremely outliers (▶ **Fig. 5**). Sensitivity analysis results indicated that the results were stable and credible by omitting one study at a time.

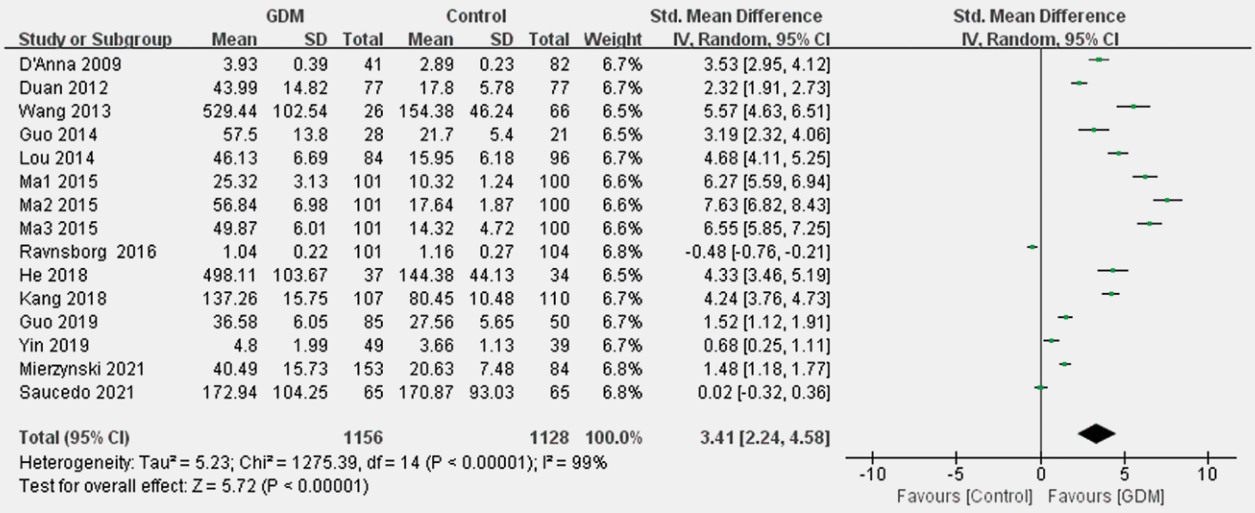
Publication bias was measured by funnel plots and quantified by Begg's and Egger's tests. Asymmetry was observed by visual inspection of funnel plots (▶ **Fig. 6**). Begg's and Egger's tests revealed the existence of potential publication bias (p = 0.008 and p < 0.001, respectively). We further used the trim-and-fill method to evaluate the publication bias. There were no indications of publication bias with the trim-and-fill method (no new studies added).

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to summarize the association of blood LCN2 with GDM. The main findings of the meta-analysis were as follows: Patients with GDM had significantly higher levels of blood LCN2 than parturients with NGT. Sensitivity analyses revealed that these pooled results were stable. Meta-regression analysis suggested that the testing methods and age were the sources of heterogeneity. Subgroup analyses showed that, compared to pregnant women with NGT, significantly higher LCN2 levels were observed in GDM samples using the ELISA. For women aged < 30, the same trend was found. Taken together, these results indicated that LCN2 might be involved in the pathogenesis of GDM.

As a common pregnancy complication, GDM affects about 1 in 7 pregnancies worldwide, and is associated with adverse outcomes for both mothers and babies. Although the exact mechanisms of GDM are still unclarified, insulin resistance was considered as the main mechanism elaborated in the pathogenesis of GDM [31]. During normal pregnancy, more insulin was produced to meet the progressive demands of fetus development, which caused insulin resistance occurring at the start of the second trimester of pregnancy [32, 33]. The dysfunction of insulin signaling in peripheral tissues made GDM mediated insulin resistance further exacerbated by nearly 56 % [6]. Maternal and placental hormones, such as estrogen, placental lactogen, and placental growth hormone, also participated in pregnancy insulin resistance [34]. Moreover, inflammation and endothelial cell dysfunction also played essential roles in the pathogenesis of GDM.

A lot of evidence emphasized the association between LCN2 and metabolic diseases, such as obesity, type 2 diabetes, and nonalcoholic fatty liver disease, which partly shared the same underlying pathogenesis with GDM [35, 36]. Above all, a positive correlation between LCN2 and pregnancy had been recognized from very early [14]. It was widely recognized that LCN2 is involved in insulin resistance, and the potential mechanisms were multifaceted [37, 38]. LCN2 deficiency in mice caused an improvement in insulin resistance and inhibited gluconeogenesis in mice, which was probably



▶ **Fig. 2** The forest plot about the association of blood LCN2 levels with GDM.

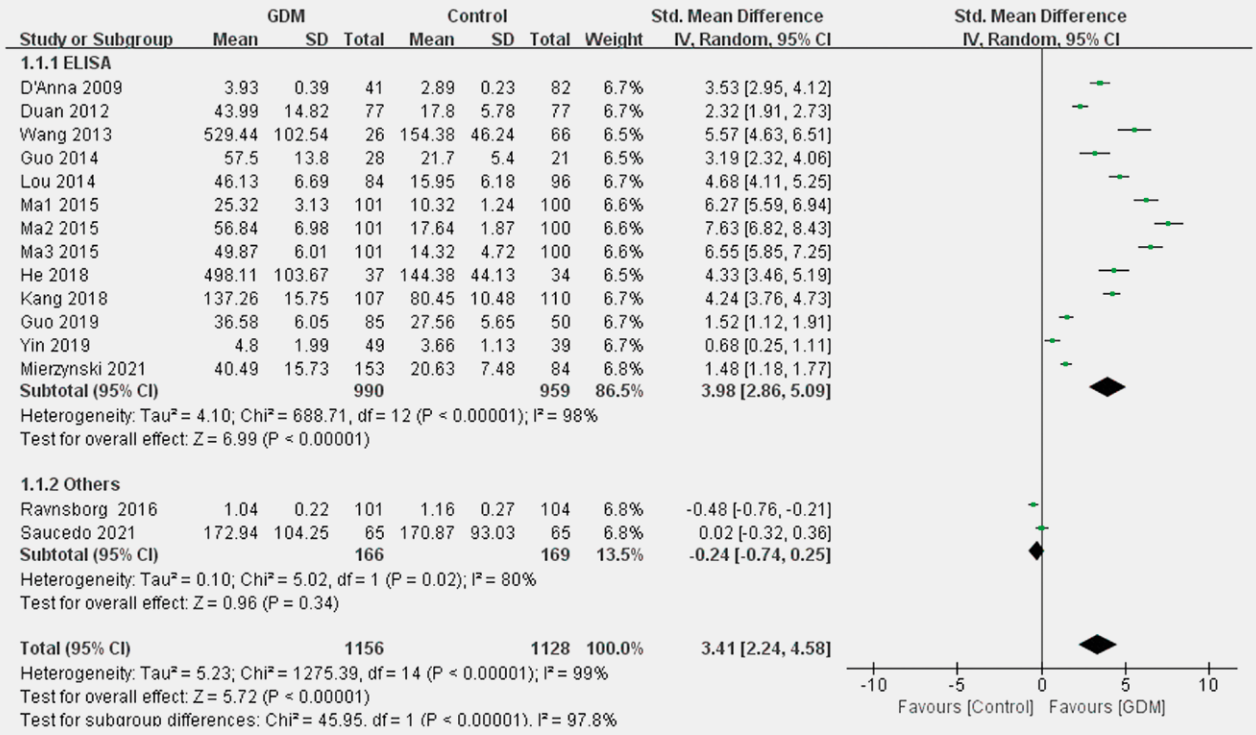
▶ **Table 2** The results of Meta-regression analysis.

	Coef.	t-Value	p	95 % CI
Mean pre-pregnancy BMI	−2.10	−1.40	0.190	−5.409, 1.209
Sampling trimesters	−0.25	−0.33	0.749	−1.930, 1.423
Detecting methods	−4.21	−2.71	0.018	−7.570, −0.850
Mean age	−3.02	−2.38	0.035	−5.783, −0.253
Fasting sample	−4.18	−1.75	0.103	−9.333, 0.973

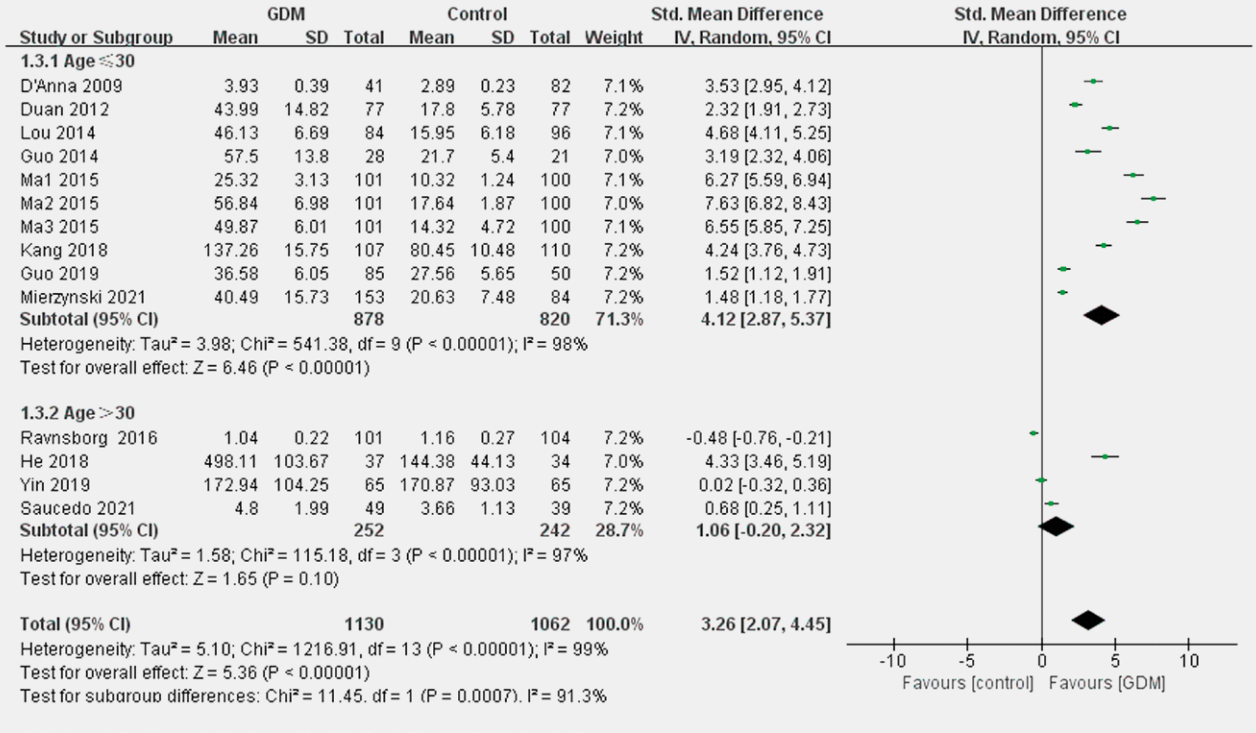
BMI: Body mass index; Coef: Coefficient; CI: Confidence interval.

mediated by decreasing AMP-activated protein kinase activity, and regulating forkhead transcription factor O1 and its downstream genes phosphoenolpyruvate carboxykinase/glucose-6-phosphatase, a hepatic gluconeogenesis moderator [39, 40]. In H9c2 cells, LCN2 aggravated insulin resistance by inhibition of autophagy [41]. LCN2 probably also caused mitochondrial dysfunction through inhibiting the estrogen receptor α-polymerase gamma 1 axis [42]. Moreover, insulin itself is an inducer of LCN2, and LCN2 interfered with insulin signaling [43]. Glucose transporter (GLUT) 1 and GLUT4, the primary transporter responsible for glucose uptake, were declined in isolated human subcutaneous adipocytes after treating with recombinant LCN2 [44]. Furthermore, LCN2 played a role in GDM via inflammation and endothelial cell dysfunction. LCN2 induced many pro-inflammatory mediators, such as interleukin-6, matrix metalloproteinase 2 (MMP2), and MMP9 [45, 46]. Interestingly, LCN2 induced the expression of tumor necrosis factor α, a critical insulin resistance–inducing factor, in fat tissue [40]. LCN2 was critically involved in diet-induced endothelial dysfunction by modulating cytochrome P450 2 C9 activity [47].

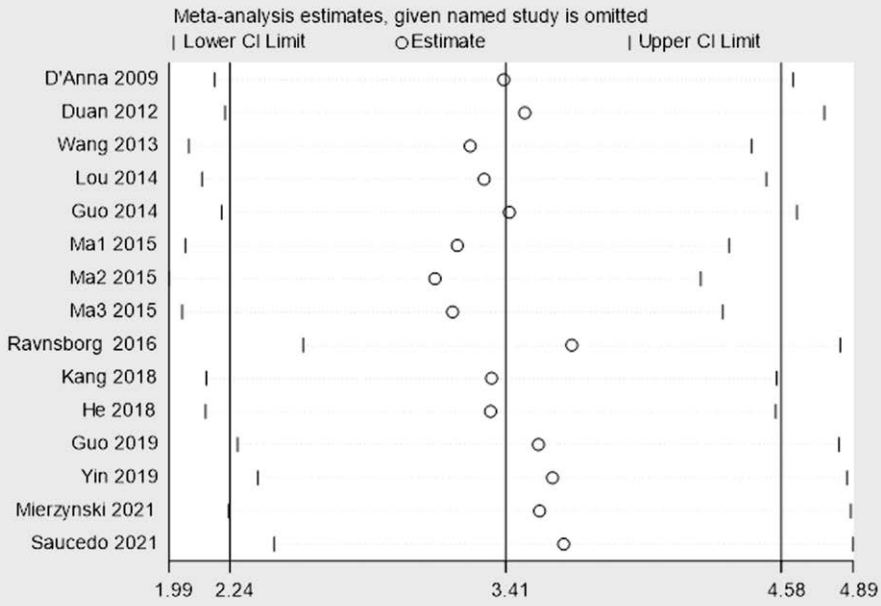
Given the substantial heterogeneity among studies, meta-regression and subgroup analyses were carried out to investigate possible reasons for this heterogeneity. The plausible sources of heterogeneity were detecting method and age. Human LCN2 was originally purified from the supernatants of phorbol myristate acetate-stimulated neutrophils. Due to ligand-binding, post-translational modifications, and protein–protein interactions, different variants carried out different functions. The unknown sources and structural diversity of the variants of LCN2 lead to significant variabilities for clinical assessment [48]. LCN2 levels in most studies included were tested by ELISA, the difference between subjects with GDM and subjects in the control group were significant, whereas two studies [16, 17] using other methods did not show the same trend. According to recent reviews, there is currently no “gold standard” method for detecting and measuring LCN2. ELISA was the first analytical procedure set up for measurement of LCN2 in blood samples and is currently the most widely used method [48, 49]. It seems that other methods are still far from being extensively production ready. Standardization and quality control of LCN2 measurement are needed in future studies. For other testing



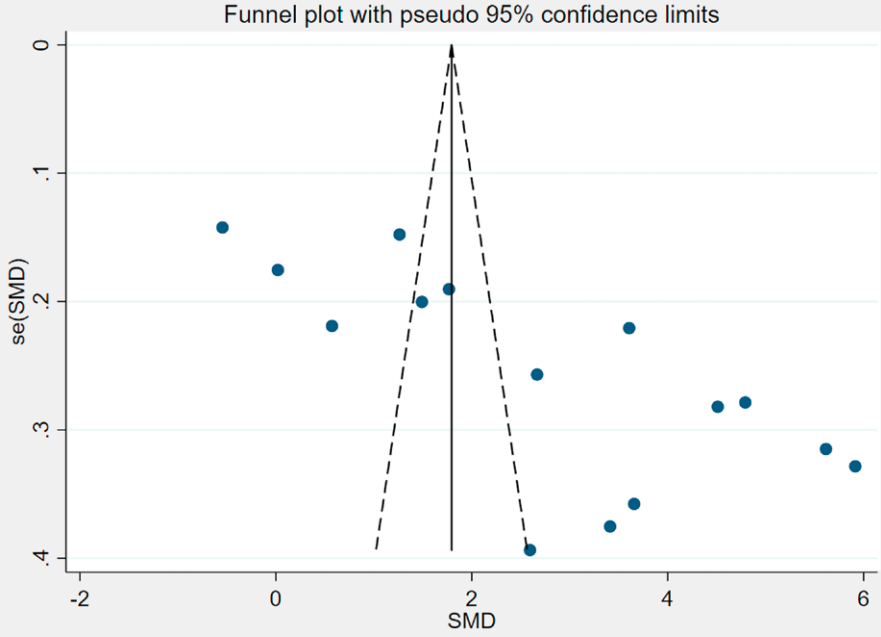
▶ **Fig. 3** Forest plots for the subgroup analysis for the difference of blood LCN2 level between patients with GDM and parturients with NGT according to testing methods.



▶ **Fig. 4** Forest plots for the subgroup analysis for the difference of blood LCN2 level between patients with GDM and parturients with NGT according to age.



▶ **Fig. 5** The plot of sensitivity analysis about the association of blood LCN2 levels with GDM.



▶ **Fig. 6** Funnel plots for the publication bias underlying the meta-analysis of the association of blood LCN2 levels with GDM.

methods, the number of studies was insufficient to draw clear conclusions. Age was considered as another factor leading to heterogeneity. Many studies have confirmed blood LCN2 correlated with age in both humans and mice. Previous studies have noticed the positive correlation between blood LCN2 levels and age in patients with GDM, while the explanations of mechanisms were not presented due to lack of evidence [24]. The increase of maternal age is paralleled by the progressive increase of maternal adipose tissue deposition, which means more adipocytokines produced [50]. In our study, younger patients with GDM showed significantly higher LCN2 levels than pregnant women with NGT. The recent study revealed that LCN2 may play a protective role in younger mice [51]. Nonetheless, the relationship between LCN2 and age is ambiguous, and research on age fertility demand further attention.

The heterogeneity did not decrease significantly, which suggests that not all heterogeneity sources could be found. Additional factors influencing LCN2 levels like exogenous insulin dosages and diet style might contribute to heterogeneity. Insulin can upregulate circulating LCN2 levels in humans, an effect that was mediated by phosphatidylinositol 3-kinase and mitogen-activated protein [52]. Diet lifestyle had been confirmed as a regulatory factor in blood LCN2 levels. The intake of saturated fatty acids contributed to changes in LCN2 levels after weight loss in obese subjects [53]. These factors are rarely mentioned in studies included; therefore subgroup analyses are unavailable and future research should take these variables into consideration.

There are limitations to our study. First, only case-control studies were included and heterogeneity between studies was high [54]. Existing uncontrolled factors in original studies might influence the heterogeneity of the meta-analysis. Though the trend of the relationship between LCN2 and GDM from these studies was clear, longitudinal cohort studies are optimal for further research. The evolution of LCN2 levels in GDM and their causality can be further confirmed if longitudinal cohort studies are conducted. Second, LCN2 testing methods in different laboratories lack standardization. Hemolysis, storage temperature, and manual measurement impact assay outcome and reduce comparability between different laboratories [49]. Third, most of the studies were from China, with limited data from other countries, and thus the regional effect must be considered. Therefore, there were strict quality control measures for studies included and quantitative analyses were conducted with a NOS score subject of ≥ 7.

Conclusion

In conclusion, our study found that GDM is associated with higher LCN2 levels. However, caution should be taken in the generalization of the conclusions of this study. Large scale longitudinal studies covering more influencing factors with a unified standard detection method are needed to validate this finding, and whether LCN2 changes are causative or a consequence of GDM may be further investigated.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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