Original Research

Circulating neutrophil gelatinase-associated lipocalin and gestational diabetes mellitus: a meta-analysis

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Background: Many studies have assessed the role of circulating neutrophil gelatinase-associated lipocalin (NGAL) on the risk of gestational diabetes mellitus (GDM), but the results remain uncertain. Thus, this study aimed to assess the association between NGAL and GDM risk by performing a meta-analysis. *Methods*: We carried out a systematic search of electronic databases (PubMed, Embase, Wanfang and Chinese National Knowledge Infrastructure databases) to retrieve all related studies. The estimates of standardized mean difference (SMD) and its 95% confidence interval (CI) were calculated in a random-effects model. Between-study heterogeneity was assessed using I^2. *Results*: Of all included 17 studies, 1080 pregnant women with GDM and 1736 controls were finally included in our analysis. The overall estimate indicated that circulating NGAL levels were higher in the GDM cases comparing to normal pregnant women (SMD: 3.16; 95% CI: 2.28, 4.04; $p < 0.001$). In stratified analyses, larger differences were observed in women with maternal age $<$30 years compared to those with maternal age $\geq$30 years (SMD 4.23 vs. 1.30), and among studies with BMI not matched compared to BMI matched studies (SMD: 4.29 vs. 2.63), but no difference was observed in Caucasian population (SMD: 1.68; 95% CI: –0.68, 3.99; $p = 0.157$). *Conclusion*: Our findings show that elevated levels of circulating NGAL might be more likely to be found among GDM women. Circulating NGAL might be a helpful detecting marker for the judgment of the occurrence of GDM. Nevertheless, further prospective studies are needed to assess this potential role.

Keywords

Neutrophil gelatinase-associated lipocalin; Gestational diabetes mellitus; Meta-analysis; Early diagnosis; Insulin resistance

1. Introduction

Gestational diabetes mellitus (GDM), which is the most common metabolic disorder during pregnancy, is defined as glucose intolerance that is first recognized in pregnancy and affects around 5% of all pregnancies [1–3]. Although there is no consensus on the national guidance of GDM, pregnant women with indicative results of DM on the basic of diagnostic criteria of World Health Organization (WHO) (fasting glucose $\geq$7 mmol/L, random glucose $\geq$11.1 mmol/L, 2 h-75 g oral glucose tolerance test (OGTT), or HbA1c $\geq$48 mmol/mol) should be considered to be "diabetes in pregnancy" or appropriate management initiated [4]. It was estimated that almost one in every seven live births were affected by GDM all over the world in 2017, and approximately 85% of total 21.3 million live births overwide were affected by diabetes during the whole pregnancy [5]. GDM is associated with increased risk of a wide range of serious maternal, fetal, and neonatal adverse outcomes (e.g., miscarriage, macrosomia, shoulder dystocia, and stillbirth) [6, 7]. Therefore, screening and diagnosing GDM in early pregnancy could be effective to reverses hyperglycemia and reduce the risk of associated adverse pregnancy outcomes, and could be of great importance to optimize the health of women and their children.

Insulin resistance, which has been known as one of the key pathophysiological features observed in type 2 diabetes as well as GDM [8], was found to present prior to conception and persisted across pregnancy [9], and is suggested to play a vital role in the mechanism of GDM. The insulin sensitivity is defined by the reduced sensitivity by approximately 50–60% in late pregnancy as opposed to pre-pregnancy among pregnant woman with/without normal glucose tolerance [10]. Neutrophil gelatinase-associated lipocalin (NGAL), also named lipocalin-2, first identified as a matrix protein of specific granules of human neutrophils [11], was found to exert an effect on the regulation of insulin sensitivity and was associated with insulin resistance [12]. To further investigate the potential role of NGAL in the GDM development, a broad range of studies [13–30] was conducted to evaluated the differences of circulating NGAL levels between GDM cases and healthy pregnant women. But large variations in the results were observed across studies, a little difference was obtained

from studies by Sweeting AN *et al.* [28] and Wang YY *et al.* [29] compared to the relatively significant differences obtained from most studies [13–27]. There is a need for more convincing pooled estimate, and further explorations for the source of underlying between-study heterogeneity that influences the concentrations of circulating NGAL.

Up-to-date, the most clinically and cost-effective methods of GDM screening remain controversial, and the ability to diagnose GDM in the first trimester compares to the second or third trimester of pregnancy keep inconsistent [31]. Thus, this meta-analysis was conducted to verify the circulating NGAL levels in those with GDM compared to healthy pregnant women, and potential influencing factors, which might be useful in providing more evidence to detect GDM in early pregnancy.

2. Materials and methods

2.1 Search strategy

Two investigators (Zhu Chen and Shuyu Wang) conducted 2-step literature searches. Firstly, the webs of knowledge database were systematically searched, including PubMed, Embase, Chinese National Knowledge Infrastructure (CNKI) [32] and Wanfang databases [33], to collect articles reported on the levels of circulating NGAL among patients with GDM. The search was extended up to October 2019 without language restriction. The following key words were used for several combinations searching: (lipocalin or NGAL or LCN-2) and (gestational diabetes[mesh] or gestational diabetes). Secondly, the reference lists of related articles or citations of possible previous reviews or meta-analyses were also investigated to perform a manual search of other eligible studies. Articles identified by these two steps of searching were then screened for the selection bias based on the abstracts. The eligibility of articles identified with the selection process were then assessed based on the full-text review.

2.2 Study selection

Studies were included in this meta-analysis on the basis of the following inclusion criteria: (1) original observational studies (case-control and cohort studies); (2) the diagnosis of GDM followed well accepted guidance or diagnostic criteria; (3) the circulating NGAL levels among GDM patients and healthy pregnant women were reported; (4) at least 20 cases were included; and (5) full text and complete data were available.

The exclusion criteria were: (1) abstracts, reviews, case reports, letters, comments or conference; (2) studies that did not provide sufficient data; (3) NGAL levels were not measured using blood sample; and (4) republished studies. For studies with overlapping study populations, only the largest study with the most recent datasets would be included in the final analysis.

2.3 Data extraction

Two reviewers applied the inclusion and exclusion criteria independently. The following data were extracted from each eligible study: first author's name, publication year, country (region) and ethnicity of the population, GDM diagnostic criteria, number of GDM patients and controls, matching methods, age, gestation weeks of recruitment, mean circulating NGAL level with standard deviation (SD) and their ranges of the participants, sample sources. The principal investigators would be contacted for further information when these data were missing, and studies would be excluded if the principal investigator could not or deny to provide further data. Any discrepancies between two reviewers were resolved by discussion among all co-authors.

2.4 Assessment of study quality

The qualities of observational studies (case-control and cohort studies) were evaluated using the Newcastle–Ottawa scale (NOS) [34]. Using this scale, the quality of each study is judged on three broad perspectives (eight items), including participant selection (3 or 4 stars), comparability of study groups (1 or 2 stars) and assessment of outcome or exposure (2 or 3 stars). One star would be awarded as one point and the highest quality of studies could be up to nine star (point), with a higher score ($\geq$7) indicates a high quality of study, as well as a lower risk of bias.

2.5 Statistical analysis

To assess the variations in circulating levels of NGAL between GDM cases and control groups, the pooled standardized mean difference (SMD) with 95% confidence interval (CI) was calculated to yield an overall effect size by using a random-effects model. Between-study heterogeneity was assessed using Cochran's Q statistic and the Higgins' I^2 statistic ($I^2 > 50\%$ suggesting substantial level of heterogeneity) [35]. Subgroup analyses were conducted to explore the potential sources of heterogeneity, with the analyses stratified by gestational weeks (first trimester, second trimester, and third trimester), ethnicity (Asians and Caucasians), maternal age ($<$30 and $\geq$30 years), and matching methods (BMI matched and not matched). We conducted the influence analyses to investigate the potential influence of each study on the overall estimate of risk by omitting one study at a time. Publication bias was quantitatively evaluated using Egger's and Begg's test [36] and visualed by the funnel plots. The statistical analyses were perfromed using Stata software version 13.0 (StataCorp LP, College Station, TX, USA), and a two-sided p value of 0.05 was taken as significant.

3. Results

3.1 Study selection

As it showed in Fig. 1, a total of 164 articles were retrieved after initial searching and 31 duplicates were excluded by endnote. After reviewing the title and abstract, 101 articles were excluded and the full texts of 32 articles were identified, and 15 articles were further excluded because they did not meet the selection criteria. In total, 17 articles (19 results) met the criteria and were finally included in our analysis [13–30].

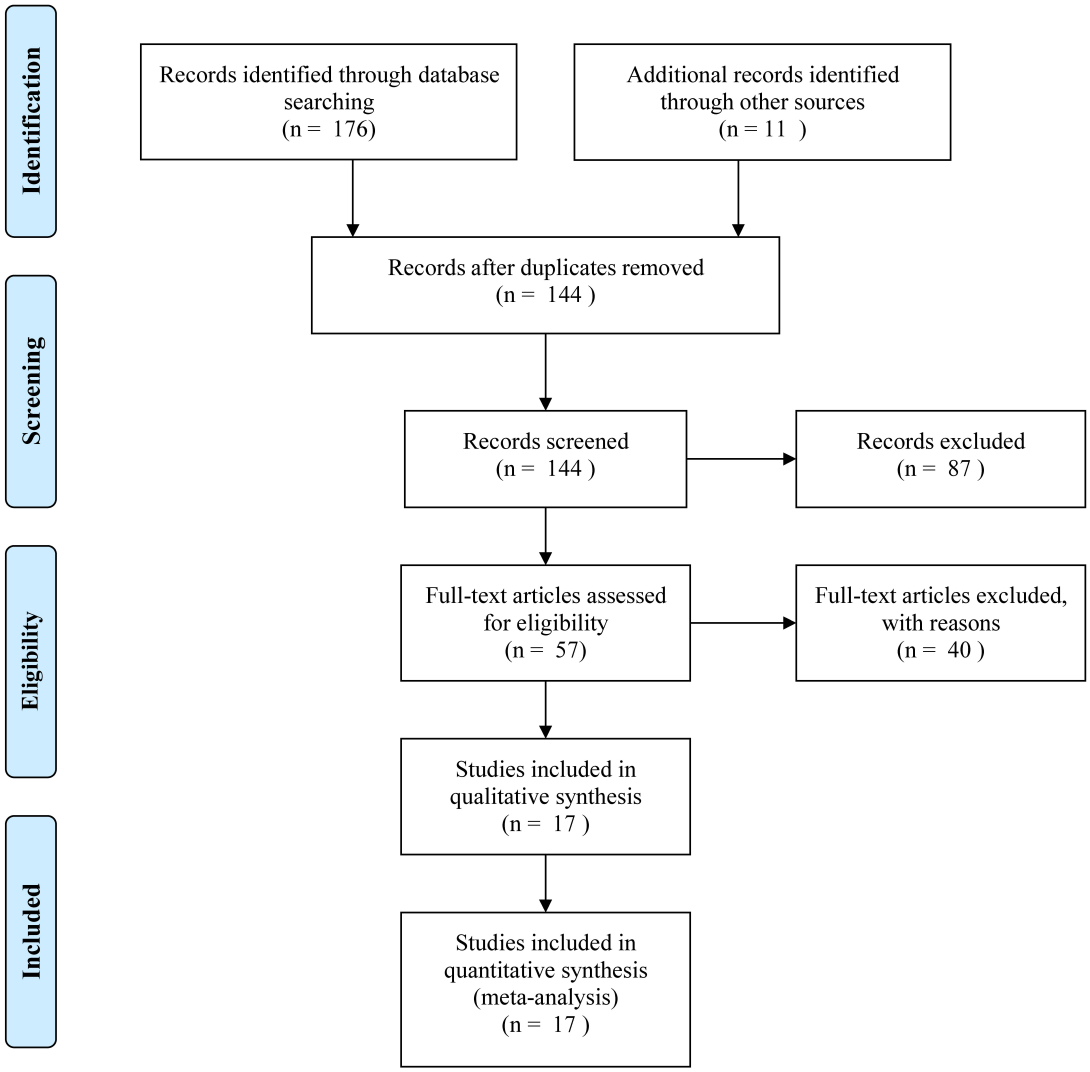

Fig. 1. Flow chart of study selection in the meta-analysis.

3.2 Study characteristics

General characteristics of the included studies are presented in Table 1 (Ref. [13, 15–20, 22–28, 30, 37, 38]). All the data from 17 included articles, published from 2009 to 2020, covered 1080 GDM patients and 1736 normal pregnant women. Almost all included studies (15/17) were carried out in China, one study in Italy [13], and one conducted in multi-ethnicities populations (Caucasians, East Asians, and South Asians) [28]. The sample size ranged from 26 to 248 among GDM cases, and 21 to 732 among healthy pregnant women. There were three studies with circulating NGAL levels measured during first trimester, three studies during second trimester, eight during third trimester, and two studies at each trimester. 11 studies with matched BMI between cases and controls, whereas BMI did not match for the rest 6 studies. Almost all included studies measured circulating NGAL levels using ELISA methods and serum sample, aside from one study conducted by Sweeting AN *et al.* [28] which used DELFIA method and one study by Lou Y *et al.* [22] which used the plasma sample. The diagnose of GDM was based on various criteria: American College of Obstetricians and Gynecologists (ACOG) (n = 2), American Diabetes Association (ADA) (n = 6), The Australasian Diabetes in Pregnancy Society (ADIPS) (n = 1), Carpenter and Couston (C&C) (n = 1), The International Association of Diabetes and Pregnancy Study Groups (IADPSG) (n = 2), and WHO (n = 5). The mean/median levels of NGAL ranged from 4.8 to 105.9 ng/mL in patients with GDM, and from 3.66 to 87.2 ng/mL in healthy controls. The quality score assessed by the NOS of included studies ranged from 5 to 8 points.

3.3 Overall meta-analysis

The overall estimates were calculated in a random-effect model due to the tremendous heterogeneity between studies (I^2 = 98.4%, $p < 0.001$). Due to two studies which had provided the circulating NGAL levels at each trimester [24, 25], we used the data for the first trimester as the main analysis (Table 2 and Fig. 2). In the pooled analysis of 17 studies, the overall levels of circulating NGAL in GDM cases were signif-

Table 1. Main characteristics of the studies included in this meta-analysis.

First author	Year	Study location	Case group				Control group				Measurement trimester	BMI matched	GDM diagnostic criterion	Quality score
			Sample size	Age, years	Gestation weeks	NGAL, ng/mL	Sample size	Age, years	Gestation weeks	NGAL, ng/mL				
Yin X [30]	2020	China	49	32.47 ± 4.68	39.14 ± 0.62	4.80 ± 1.99	39	31.77 ± 4.96	39.00 ± 0.46	4.80 ± 1.99	3	0	IADPSG	7
Sweeting AN [28]	2019	Australia	248	33 (30–36)	11–13	Caucasians: 105.9 (73.9–141.7) East Asians: 70.9 (57.9–95.8) South Asians: 76.0 (51.9–91.5)	732	32 (29–35)	11–13	Caucasians: 87.2 (65.9–111.6) East Asians: 73.7 (55.1–94.9) South Asians: 64.8 (47.2–109.0)	1	1	ADIPS	9
He XJ [26]	2018	China	37	31.6 ± 3.1	38.9 ± 1.4	49.811 ± 10.367	34	29.3 ± 3.6	38.8 ± 1.0	14.438 ± 4.413	2	0	ADA	6
Kang YS [27]	2018	China	107	28.8 ± 3.9	9.3 ± 1.4	13.72 ± 1.575	110	29.3 ± 4.1	9.4 ± 1.1	8.045 ± 1.048	1	0	WHO	6
Lu SL [25]	2017	China	42	28.2 ± 6.8	38.5 ± 7.5	1st: 21.8 ± 3.2[a] 2nd: 49.6 ± 4.4 3rd: 50.1 ± 4.9	42	28.4 ± 6.6	38.9 ± 7.1	1st: 10.2 ± 2.8[a] 2nd: 14.6 ± 4.4 3rd: 14.7 ± 4.3	1–3	0	ADA	6
Ma QP [24]	2015	China	97	29.9 ± 3.5	38.5 ± 2.8	1st: 25.32 ± 3.13[a] 2nd: 56.84 ± 6.98 3rd: 49.87 ± 6.01	100	28.95 ± 3.17	39.06 ± 2.81	1st: 10.32 ± 1.24[a] 2nd: 17.64 ± 1.87 3rd: 14.32 ± 4.72	1–3	1	IADPSG	7
Liu YH [23]	2015	China	30	32.5 ± 4.2	35.2 ± 2.7	32.61 ± 3.71	30	29.3 ± 2.5	36.5 ± 2.3	14.37 ± 3.29	3	0	ACOG	5
Hu J [20]	2014	China	55	33.02 ± 3.42	34.98 ± 3.28	42.56 ± 11.52	55	28.12 ± 3.12	34.92 ± 3.42	17.63 ± 5.39	3	0	ACOG	6
Guo J [37]	2014	China	28	28.5 ± 3.1	37.3 ± 1.8	57.5 ± 13.8	21	27.9 ± 2.9	37.5 ± 2.5	21.7 ± 5.4	3	1	WHO	6
Fu XM [19]	2014	China	30	29.4 ± 5.1	35.7 ± 2.9	32.5 ± 3.7	30	28.5 ± 5.5	36.3 ± 2.8	14.5 ± 3.2	3	1	ADA	6
Lou Y [22]	2014	China	96	27.88 ± 2.16	NA	49.47 ± 8.19	164	28.38 ± 2.42	271.4 ± 3.46	15.95 ± 6.18	3	1	ADA	7
Wang F [18]	2013	China	26	NA	20–32	52.94 ± 10.25	66	NA	20–32	15.44 ± 4.62	2	0	ADA	5
Ren GH [17]	2012	China	35	29.4 ± 4.4	38.2 ± 2.2	61.9 ± 14.7	32	28.7 ± 3.7	39.1 ± 1.4	24.0 ± 6.7	3	1	WHO	5
Duan DM [16]	2012	China	77	29.5 ± 6.0	35.7 ± 1.0	43.99 ± 14.82	77	28.0 ± 5.0	36.1 ± 3.8	17.80 ± 5.78	3	1	ADA	6
Jiang J [15]	2011	China	42	29.07 ± 2.05	14–18	45.83 ± 6.93	42	28.78 ± 2.17	14–18	19.72 ± 5.77	2	1	WHO	7
Chen Q [38]	2011	China	40	31.7 ± 4.60	24–28	42.2 (32.4–55.5)	80	31.28 ± 5.11	24–28	28.7 (22.8–35.4)	2	1	WHO	6
D'Anna R [13]	2009	Italy	41	27.2 ± 4.4	9–12	51.3 (39.8–66.1)	82	28.4 ± 3.9	9–12	17.8 (15.5–20.9)	1	1	C&C	7

Abbreviations: GDM, gestational diabetes mellitus; BMI, body mass index; ADIPS, The Australasian Diabetes in Pregnancy Society; IADPSG, The International Association of Diabetes and Pregnancy Study Groups; ADA, American Diabetes Association; C&C, Carpenter and Couston; ACOG, American College of Obstetricians and Gynecologists; WHO, World Health Organization; NGAL, neutrophil gelatinase-associated lipocalin; NA, not available. [a] Two studies provided the NGAL for all three trimesters.

Table 2. Subgroup analyses of the association between NGAL and gestational diabetes mellitus.

Subgroups	Studies	GDM	Control	SMD	95% CI	p for Z[b]	I^2 (%)	p for I^2[c]
Total 1[a]	19	1078	1722	3.16	2.28–4.04	<0.001	98.4	<0.001
Total 2[a]	19	1078	1722	3.43	2.51–4.36	<0.001	98.6	<0.001
Total 3[a]	19	1078	1722	3.36	2.45–4.28	<0.001	98.5	<0.001
Gestational weeks								
First trimester	6	491	1010	2.34	0.79–3.89	0.003	99.1	<0.001
Second trimester	3	108	188	3.58	0.75–6.40	0.013	98.1	<0.001
Third trimester	10	479	524	3.54	2.55–4.53	<0.001	96.0	<0.001
Countries								
Asians	17	929	1110	3.34	2.34–4.35	<0.001	98.5	<0.001
Caucasians	2	149	612	1.68	–0.65–3.99	0.157	98.3	<0.001
Maternal age, years								
<30	12	651	796	4.23	3.50–4.96	<0.001	93.3	<0.001
≥30	7	427	926	1.30	0.55–2.04	0.001	96.5	<0.001
BMI matched								
Yes	13	781	1385	2.63	1.64–3.62	<0.001	98.5	<0.001
No	6	297	337	4.29	3.48–5.10	<0.001	87.2	<0.001

Abbreviations: GDM, gestational diabetes mellitus; NGAL, neutrophil gelatinase-associated lipocalin; BMI, body Mass Index; SMD, standardized mean difference.

[a] Because two studies provided the NGAL for all three trimesters, we combined the data for these two studies added each trimester independently (total 1: 1st trimester; total 2: 2nd trimester; and total 3: 3rd trimester).

[b] p-value of Z-test for significance.

[c] p-value of Q-test for significance.

icantly higher compared to healthy pregnant women (SMD: 3.16; 95% CI: 2.28, 4.04; $p < 0.001$). The results strengthened but did not significantly changed when we use data from the second or third trimester for the two studies mentioned above (Table 2 and Fig. 2).

3.4 Subgroup analyses

In the stratified analyses, the significant findings were observed among all strata except for studies conducted among Caucasians (SMD: 1.68; 95% CI: –0.68, 3.99; $p = 0.157$). According to the overlaps of the 95% CIs among strata, we observed that higher difference among those with lower maternal age (<30 years) than those with higher maternal age (≥30 years) (SMD: 4.23 vs. 1.30), and among those with BMI not matched than those with BMI matched among cases and controls (SMD: 4.29 vs. 2.63). However, significant heterogeneity among studies unchanged within each stratum (range: 87.2%–99.1%).

3.5 Influence analysis and publication bias

According to the result of influence analysis, no significant effect of any individual study has been found to been exerted on the association between circulating NGAL levels between GDM patients and controls, with the SMD ranged from 1.57 (1.46, 1.68) to 2.14 (2.02, 2.26) (Fig. 3).

The possibility of publication bias was detected by the Egger's test ($p < 0.001$) and Begg's Test ($p = 0.003$). However, using Trim and fill method, no study was needed for further adjustment (Fig. 4).

4. Discussion

In this meta-analysis, we firstly pool the current evidence on the role of circulating NGAL in detection of GDM. Result from comparation between 1080 GDM cases and 1736 controls, our finding shows that the circulating NGAL levels in GDM patients are higher than that of healthy pregnant women, although significant heterogeneity of results was detected. Subgroup analyses further indicated that these differences were more significant in women with younger maternal age (<30 years), as well as in studies comparing to not BMI-matched controls, but not in studies conducted among Caucasian population.

Over the last decades, the need and interest in the identification of molecules for the detection of disease onset and progression has wildly emerged. Since first identified in 1994, NGAL has become increasingly relevant as a biomarker in several diseases (e.g., acute kidney injury, Alzheimer's disease, multiple sclerosis, cardiovascular diseases, depression, etc.) [12, 39]. By pooling the current evidence, our results were in chord with findings from previous studies mainly conducted in Chinese population [13–30], showing that circulating NGAL levels were higher in GDM cases compared to healthy controls. For instance, in a cohort study involving 41 women with a singleton pregnancy, who developed GDM in the past 12 months, and healthy group of 82 normal pregnancies, the levels of circulating NGAL were significantly higher in those with GDM than that of control group [51.3 ng/mL (39.8–66.1) vs. 17.8 ng/mL (15.5–20.9); $p < 0.001$] in the first trimester [13]. Furthermore, another study including 49 GDM subjects and 39 age-matched

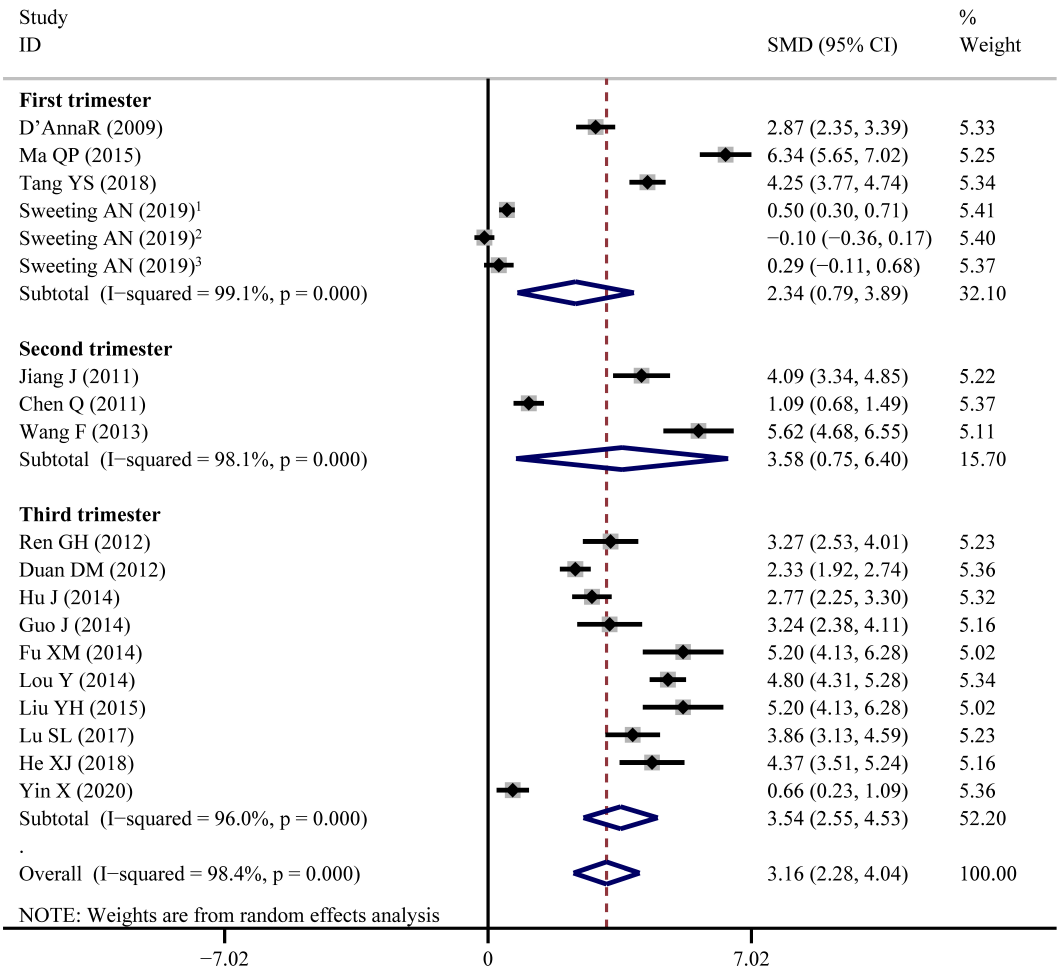

Fig. 2. Forest plots of association between circulating neutrophil gelatinase-associated lipocalin and gestational diabetes mellitus by trimesters.

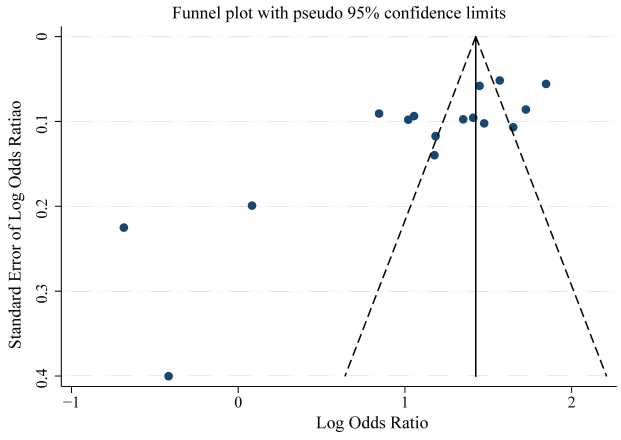

Fig. 3. Funnel plot of association between circulating neutrophil gelatinase-associated lipocalin and gestational diabetes mellitus.

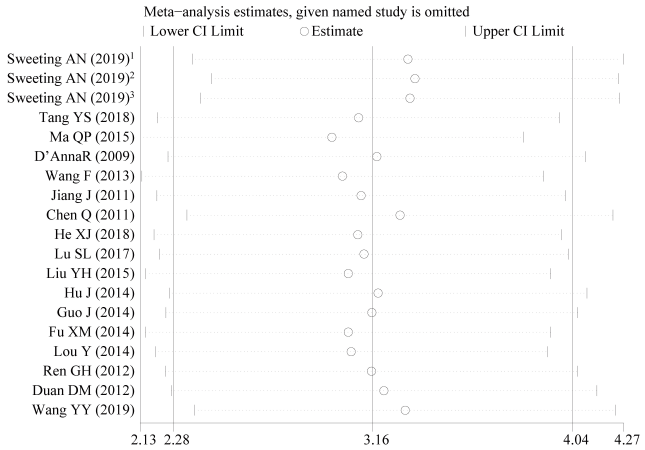

Fig. 4. Influence analysis for association between circulating neutrophil gelatinase-associated lipocalin and gestational diabetes mellitus.

women with heathy pregnancies not only reported significantly higher level of serum NGAL in GDM women compared with the control in maternal blood (4.80 ± 1.99 vs. 3.66 ± 1.13, p = 0.001) and cord blood (4.70 ± 2.08 vs. 3.85 ± 1.44, p = 0.027), but also found positive correlation between NGAL levels and different clinical markers of insulin resistance (Pearson's correlation coefficient or Spearman's corre-

lation coefficient ranged from 0.253 to 0.624, all $p < 0.05$) [30]. Consistently, a Chinese study involving 260 pregnant women showed that, plasma NGAL concentrations tended to be statistically higher in women with GDM and normal pre-pregnancy BMI (group 2) and in those with GDM and overweighted BMI (group 3) compared with healthy pregnant women with normal BMI (group 1) ($p < 0.001$ for both group comparisons) [22]. All these evidence consistently suggested that plasma NGAL might play a significant role in the development of GDM.

Although the broad functions of NGAL have been described, including innate immune response (e.g., chelator of bacterial siderophores and anti-plasmodial regulator) [40], iron homeostasis (e.g., inductor of cell proliferation/cell differentiation and inductor of cell death) [41], modulation of the inflammatory response (e.g., anti-inflammatory modulator and pro-inflammatory modulator) [11], the exact mechanism by which NGAL has potential role in the occurrence and development of GDM were still unclear. Agent-mediated decreases in NGAL concentrations significantly correlated with increases in insulin sensitivity [12]. Moreover, NGAL was found to promote insulin resistance in cultured adipocytes and hepatocytes [42]. According to the current evidence, NGAL has not only been proposed to be an iron delivery protein [41], but also been probably involved in the regulation of insulin sensitivity through the influence on iron homeostasis [39, 42]. During an oral glucose tolerance test, the GDM Serum ferritin levels might be independent predictors of 2-h glucose [43], and iron intake in healthy women has been found to be positively associated with higher risk of type 2 diabetes [44]. Consistent with this surmise that iron is required for the effect of NGAL on insulin action, the iron-free NGAL might be ineffective in causing insulin resistance in cultured hepatocytes [42]. Consequently, NGAL may play a role in the development of GDM through insulin resistance; still, whether the increase circulating NGAL levels contributes to GDM progression is not yet known.

Subgroup analyses indicated that the variation of circulating NGAL levels between GDM cases and healthy pregnant women increased when studies were performed in women with maternal age <30 years. As a modulator of the inflammatory response, NGAL involved in progression of inflammatory/anti-inflammatory states [11]. Relatively stronger immune function in young pregnant women could result in higher increased production of NGAL when exposed diverse pro-inflammatory stimuli. However, the inconsistency between studies might be partly ascribed to the difference in diagnostic tools and methods used in the detection of NGAL [45]. Besides, more significant difference in the levels of circulating NGAL was observed in BMI not matched studies, which could interpret by the interaction between NGAL and BMI. Circulating NGAL was a marker for obesity and its associated pathologies by providing both clinical and experimental evidence [12]. In addition, nutritional status among pregnant women might exert an effect on the result because Asian population tend to consume more carbohydrates (rice) in their diet than other populations and this might affect their insulin resistance [46]. Of note, heterogeneity of definitions for GDM [47], parity [48], gestational age at GDM diagnosis [49], and concurrent diseases (e.g., hypertension or hyperglycemia) [50] might exert great effects on the results. Hence, findings of our subgroup analyses still need to be further confirmed.

At present, GDM presents a particular public health challenge given its rapidly increasing prevalence in the context of the global obesity epidemic [51]. Screening and diagnosing GDM in early pregnancy are beneficial to reduce the burden of disease caused by GDM. Our study suggested that NGAL may be helpful for early identification of GDM, but this potential role needed more evidence to prove, further prospective studies are needed.

This meta-analysis had several limitations. Firstly, between-study heterogeneity was significantly assessed for overall estimate (I^2: 98.4%), but subgroup analyses showed that the main source of heterogeneity was not well described with high I^2 (ranged from 87.2% to 99.1%) observed in all stratums. However, the significant heterogeneity in meta-analysis might be susceptible to the influence of bias, confounding, potential measurement error. Secondly, most included studies were conducted in Asian population, while only two studies measured circulating NGAL in Caucasian participants [13, 28], and no relevant studies were found for Africans. Moreover, subgroup analyses for Caucasians did not obtain any difference, probably due to the different measurement and small sample size. Thus, this finding should be interpreted with more care. Finally, all included studies were case-control studies with variations in matching method, and the bias was unavoidable.

5. Conclusions

Our findings imply that the expression levels of NGAL in patients with GDM were higher than in healthy pregnant women, indicating that NGAL might be a useful detecting index for the judgment of the occurrence of GDM. This suggests that NGAL should be valued at the GDM screening in order to improve the maternal and fetus health. However, more evidence from larger prospective studies are needed to demonstrate the exact role of circulating NGAL during the early pregnancy.

Author contributions

Study concept and design—LX and HH. Data extraction—ZC, and SYW. Data analysis—JCH and SYW. Manuscript drafting—ZC and HH. HH, JCH and LX contributed to the article revise. All authors gave final approval of the version to be published.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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