Introduction

Gestational diabetes mellitus (GDM), characterized by glucose intolerance with onset or first recognition during pregnancy, is one of the most common obstetrical complications. It is estimated that GDM affects 1–14% of all pregnancies depending on the population and the diagnostic criteria [1–3]. Although extensive research was performed, the precise mechanism responsible for the pathogenesis of GDM is still not completely understood. Mounting evidence demonstrated that enhanced systemic insulin resistance played a crucial role in the etiology of GDM [4,5]. Previous studies also suggested that women with obesity, metabolic syndrome as well as type 2 diabetes [14,15]. Although the association between RBP4 and metabolic dysfunction is well established, studies on the relationship between circulating RBP4 levels and the risk of GDM have yielded inconclusive results [16–29]. For instance, several studies suggested significantly enhanced serum levels of RBP4 in GDM compared with those of controls [18,21,22,24,29]. As the association between RBP4 and GDM were far from clear, we performed a meta-analysis to systematically review the current literature to investigate whether women with GDM had higher circulating RBP4 levels than the normglycemic pregnant women.

Methods

The present meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [30].

Search strategy and data sources

Three electronic databases (PubMed, Web of Science and EMBASE) were searched up to August 1st, 2014 using the combinations of terms “GDM” or “gestational diabetes” or “diabetes” or “pregnancy” and “RBP4” or “retinol-binding protein” or “adipokine”. We sifted through potentially relevant articles, firstly by titles and abstracts, and then we retrieved the...
full texts of articles for detailed review. Further, we scanned the reference lists of the articles that met the inclusion criteria in our analysis, and searched for those articles or citations in Google Scholar and Google to obtain additional studies.

Inclusion and exclusion criteria

Original case-control or cohort studies comparing serum/plasma RBP4 levels in pregnant women with GDM as well as healthy pregnant women were included. Studies which did not report the absolute RBP4 concentrations and/or an indication of the variation (demonstrated as standard error, standard deviation or interquartile range) in their original data were excluded from this meta-analysis. For multiple publications based on the same population, only the study with the latest or the most complete data were selected.

Data extraction

A form designed a priori was used to extract the information from the included studies. Two independent investigators performed the data extraction. Concentrations of serum/plasma RBP4 were the main exposure and GDM was the primary outcome. The following information was recorded: first author’s last name; year of publication; study location; number of GDM and controls; covariates adjusted for in the analysis.

Assessment of methodological quality

Two independent investigators assessed the quality of each study included using the Newcastle-Ottawa Quality Assessment Scale (NOS) (Table S1) [31]. Studies of low, intermediate and high quality were defined with NOS scores of 1–3, 4–6 and 7–9 in the meta-analysis, respectively.

Statistical analysis

The results were presented as the standardized mean difference (SMD) and 95% confident interval (95% CI) to estimate the size of the effect. Studies were weighted with consideration of both the sample size and the standard deviation. The SMDs were combined in a meta-analysis using a fixed-effects model when heterogeneity observed among studies was absent to moderate. When heterogeneity was high ($I^2 > 50\%$), a random-effects model was used. Heterogeneity among these studies was evaluated by two parameters. $p < 0.10$ for the Cochran’s $Q$ test or $I^2 > 50\%$ for Higgins statistic were regarded statistically significant heterogeneity [32]. The publication bias was investigated by two methods. Visual detection was used to analyze the funnel plots. Quantitative analysis was performed by the Begg’s regression asymmetry test [33]. Subgroup analysis was performed with respect to study type, diagnostic criteria of GDM, countries, maternal age as well as maternal BMI in order to explore the influence of these factors on the association.

Results

Selection flow and Study characteristics

The detailed search procedures were demonstrated in Figure 1. Full texts of 19 identified articles were retrieved for further assessment. Five of these articles were excluded because 2 studies explored serum RBP4 concentrations between women with previous history of GDM and their normal controls and three studies investigated the cord blood, adipose tissues or placental other than circulating concentrations in women with GDM as well as their controls (Figure 2). Finally, the remaining 14 independent articles were used for this meta-analysis. The main characteristics of the included studies are presented in Table 1. According to the NOS scoring, three of the 14 studies selected in this meta-analysis were of intermediate quality [21,24,26], and 11 studies were of high quality [16–20,22,23,25,27–29]. None of the studies included were of low quality (Table S1).

Main results

A total of 14 studies comprised of 884 women with GDM and 1251 normoglycemic pregnant women were included. In a pooled analysis of all studies, the results indicated that maternal circulating level of RBP4 was significantly higher in women with GDM than their normal controls (SMD: 0.49µg/ml, 95% CI: 0.23–0.75µg/ml, $p < 0.001$, random effect model) with significant heterogeneity among these studies ($Q = 89.17$, $I^2 = 85\%$, $p < 0.001$).

Subgroup analysis

An analysis of the results according to study type (cohort [16,18,19,22–25,29], case-control [20,26–28] or Cross-section [17,21]), diagnostic criteria of GDM (ADA [16,22–24,28], WHO [17,21,25–27], Carpenter & Coustan [18,29] or NDDG [19,20]), countries (Asia [16,19,20,23,26,29], Europe [17,21,22,25,27] or North America [18,24,28]), maternal age (matched [16–20,22,23,25,27,29] or higher in GDM [21,24,26,29]), maternal BMI (matched [16–20,22,23,25] or higher in GDM [21,24,26–29]) and gestational weeks of RBP4 measurement (first trimester [27] or second or early third trimesters [16–26,28,29]) are summarized in Table 2. Stratification by countries indicated that circulating RBP4 levels were higher in patients with GDM in Asia than their normal controls (SMD: 0.78µg/ml, 95% CI: 0.30–1.26µg/ml), while no significant difference of circulating RBP4 levels were observed when patients with GDM were compared to their normal controls in non-Asian population. Moreover, subgroup analysis according to matched maternal age and BMI still demonstrated that women with GDM had higher circulating RBP4 levels than their normal controls (SMD: 0.67µg/ml, 95% CI: 0.37–0.97µg/ml) and (SMD: 0.80µg/ml, 95% CI: 0.50–1.10µg/ml), respectively.

Publication bias

The publication bias was investigated by Begg’s funnel plot (Figure S1). The shape of this funnel plot was symmetrical, indicating a low probability of publication bias ($p = 0.381$).

Discussion

While elevated maternal circulating RBP4 levels has been associated with increased rate of obstetrical complications such as preeclampsia and fetal growth restriction [34,35], one intriguing observation was regarding the occurrence of GDM. Previous reports on the association between circulating RBP4 levels and the risk of GDM have yielded inconsistent results. Although the overall pooled results indicated that circulating levels of RBP4 were significantly higher in women with GDM than their normal controls, these results should be interpreted with caution, since subgroup analysis with respect to studies locations suggested that this observation was limited to Asian population [16,19,20,23,26,29]. And no significant differences of serum RBP4 levels were found between women with GDM and their control from European [17,21,22,25,27] or North American countries [18,24,28].

Previously, several studies reported elevated plasma RBP4 was associated with increased risk of insulin resistance and type 2 diabetes in Asian population [36–38], whereas some clinical studies demonstrated lack of association between plasma RBP4 levels and increased risk of insulin resistance as well as type 2 diabetes in non-Asian population [39,40]. Previous studies
suggested GDM has a strong genetic basis [41]. Under the influence of environment, lifestyles, and genetic factors, the association between RBP4 and the pathophysiology of GDM might vary in different regions [42,43]. A very recent meta-analysis investigated the association between RBP4 and polycystic ovary syndrome (PCOS), which [44] seemed to support our hypothesis by demonstrating that RBP4 levels were higher in PCOS patients in Asian countries, but not in European countries. Since GDM
Table 1. Characteristics of studies of GDM versus control on RBP4.

| Author          | Year   | Study type     | Location     | GDM/Control | Gestation age for RBP4 measurement (weeks) | Age* (years) | Pregnancy BMI* (kg/m²) | RBP4 levels* (mg/l) | Assay       | GDM diagnostic criterion | GDM treatments | Adjustment                      |
|-----------------|--------|----------------|--------------|-------------|-------------------------------------------|--------------|------------------------|--------------------|-------------|--------------------------|----------------|------------------------------------------------|
| Kim et al. [16] | 2008   | Retrospective cohort | South Korea | 10/9        | GDM: 32.6 ± 3.0 Control: 32.6 ± 3.3     | 24–28        | NR                     | Serum GDM: 39.1 ± 6.3 Control: 30.0 ± 10.0 | ELISA       | ADA                      | Diet control | Age, BMI, gestational week |
| Lewandowski et al. [17] | 2008 | Cross-sectional | UK           | 15/20       | GDM: 34.0 (29.0–36.0) Control: 32.0 (29.0–35.0) | 28           | GDM: 26.3 (24.9–30.1) Control: 25.1 (23.5–28.2) | Serum GDM: 53.9 ± 17.9 Control: 29.7 ± 13.9 | NR          | WHO                      | NR            | Age, BMI               |
| Tepper et al. [18] | 2010 | Prospective cohort | USA          | 12/10       | GDM: 28.6 ± 4.9 Control: 28.8 ± 6.2     | 24–28        | GDM: 31.1 ± 0.6 Control: 31.1 ± 0.9          | Serum GDM: 44.1 ± 8.4 Control: 37.8 ± 12.6 | EIA         | Carpenter & Coustan     | NR            | Age, BMI, ethnicity       |
| Chan et al. [19] | 2007   | Prospective cohort | China        | 20/20       | GDM: 32.7 ± 5.0 Control: 32.7 ± 5.0     | 24           | GDM: 26.1 ± 4.7 Control: 25.9 ± 2.9       | Serum GDM: 42.4 ± 13.8## Control: 32.0 ± 8.7## | ELISA       | NDDG                     | NR            | Age, BMI, parity           |
| Liang et al. [20] | 2014  | Case-control    | China        | 35/35       | GDM: 29.0 ± 2.5 Control: 29.3 ± 3.1     | 24–27        | GDM##: 20.2 ± 1.5 Control##: 20.3 ± 1.5   | Serum GDM: 22.9 ± 3.1 Control: 17.9 ± 3.9 | ELISA       | NDDG                     | NR            | Age, pre-pregnant BMI, gestational week, glycosylated hemoglobin |
| Krzyzanowska et al. [21] | 2008 | Cross-sectional | Austria      | 42/45       | GDM: 33.0 (29.0–35.0) Control: 28 (24–34)     | 29           | GDM: 34.0 (29.0–38.0) Control: 29.0 (25.0–31.0) | Serum GDM: 25.1 ± 3.6 Control: 26.6 ± 2.1 | WB          | ADA                      | Diet control and/or insulin therapy | BP, fasting insulin, 1 h insulin, 2 h insulin |
| Klein et al. [22] | 2010 | Retrospective cohort | Austria     | 63/38       | GDM: 32.7 ± 5.2 Control: 33.3 ± 4.8     | 24–28        | GDM: 27.7 ± 5.6 Control: 28.1 ± 6.2       | Serum GDM: 18.0 ± 3.7 Control: 16.9 ± 5.1 | ELISA       | ADA                      | Insulin therapy | Age, BMI, parity          |
| Su et al. [23] | 2010  | Retrospective cohort | China        | 63/58       | GDM: 28.8 ± 1.8 Control: 28.4 ± 2.4     | 24–29        | GDM: 25.5 ± 2.6 Control: 249 ± 2.1       | Serum GDM: 41.6 ± 12.2 Control: 34.5 ± 9.8 | ELISA       | ADA                      | NR            | Age, BMI, BP             |
| Study                | Year   | Study Design | Country  | Sample Size | Age Range | GDM Mean ± SD or Median (IQR) | Control Mean ± SD or Median (IQR) | Test Method | GDM Mean ± SD or Median (IQR) | Control Mean ± SD or Median (IQR) | GDM Mean ± SD or Median (IQR) | Control Mean ± SD or Median (IQR) | Age, BMI, parity | Notes |
|----------------------|--------|--------------|----------|-------------|------------|-----------------------------|----------------------------------|-------------|-----------------------------|----------------------------------|-----------------------------|----------------------------------|-----------------|-------|
| Saucedo et al. [24]  | 2011   | Prospective cohort | Mexico  | 60/60       | 30         | GDM: 31.9 ± 5.6**<sup>**</sup><br>Control: 24.8 ± 6.4 | GDM: 30.2 ± 4.9<br>Control: 28.4 ± 7.3 | RIA | GDM: 4.7 ± 1.9<br>Control: 5.3 ± 1.8 | EIA WHO Diet control or insulin therapy | Age, BMI, parity | None |
| Kuzmicki et al. [25] | 2011   | Prospective cohort | Poland  | 68/68       | 24–30      | GDM: 29.5 (27.0–33.0)<br>Control: 29.5 (27.0–31.5) | GDM: 27.2 (25.2–30.1)<br>Control: 27.3 (23.1–29.4) | ELISA | GDM: 58.1 ± 12.3<br>Control: 51.0 ± 12.6 | None |
| Maghbooli et al. [26] | 2010   | Case-control | Iran     | 92/100      | 24–28      | GDM: 32.5 ± 5.2**<sup>**</sup><br>Control: 27.9 ± 7.1 | GDM: 28.2 ± 4.1<br>Control: 25.2 ± 3.7 | ELISA | GDM: 0.5 ± 0.1<br>Control: 0.4 ± 0.1 | None |
| Nanda et al. [27]    | 2013   | Case-control | UK       | 60/240      | 11–13      | GDM: 32.0 (28.5–35.6)<br>Control: 33.0 (27.3–35.9) | GDM: 28.6 (24.6–34.2)<br>Control: 23.8 (21.7–26.2) | ELISA | GDM: 13.8 ± 2.4<br>Control: 12.6 ± 2.2 | None |
| Abetew et al. [28]   | 2013   | Case-control | USA      | 173/187     | 13–19      | GDM: 34.2 ± 4.6<br>Control: 33.0 ± 4.3 | GDM: 26.6 ± 6.5<br>Control: 23.4 ± 5.1 | ELISA | GDM: 47.1 ± 30.0<br>Control: 41.4 ± 21.3 | Education, smoking, parity, gestational week |
| Khovidhunkit et al. [29] | 2012 | Retrospective cohort | Thailand | 171/361 | 24–32 | GDM: 33.0 (29.0–37.0)<br>Control: 33.0 (28.0–36.0) | GDM: 23.1 (20.6–26.2)<br>Control: 21.9 (19.9–25.3) | ELISA | GDM: 36.0 ± 10.4<br>Control: 35.6 ± 10.9 | Age, gestational week, history of macrosomia |

GDM: gestational diabetes mellitus; RBP4: retinol-binding protein-4; UK: the United Kingdom; BMI: body Mass Index; EIA: enzyme immunometric assay; ELISA: enzyme linked immuno-sorbent assay; RIA: radio immunoassay; WB: western blot; ADA: American Diabetes Association; WHO: World Health Organization; NDDG: National Diabetes Data Group; BP: blood pressure; GCT: glucose challenge test. * Values are given as mean ± SD or media (interquartile ranges); # Pre-pregnancy BMI; ## ng/ml.
and increased risk of GDM. RBP4 might serve as a link between the metabolic dysfunction and advanced age [11,14,15,46]. Moreover, several studies showed that elevated circulating RBP4 levels were increased and positively correlated with body mass index (BMI) in obese non-diabetic and diabetic subjects [47–49]. Prior studies indicated that higher pre-pregnancy maternal BMI and advanced maternal age were associated with increased risk for GDM [50,51]. Therefore, it was proposed that women with GDM were more likely have a higher BMI status and/or advanced age, which might be important confounders in the current study. It should be noted that several studies included in this meta-analysis also reported a higher BMI status and/or advanced maternal age among the GDM cases [21,24,27,29]. Our findings could avoid these biases, since subgroup analysis of all the studies with matched maternal BMI as well as maternal age still demonstrated higher circulating RBP4 levels in women with GDM when compared with their normal controls.

Mounting evidence demonstrated that enhanced systemic insulin resistance played a crucial role in the etiology of GDM [4,5]. Prior studies suggested that women with previous history of GDM were more likely to experience increased subsequent risk for developing type 2 diabetes mellitus in their future life time [52]. One recent study investigated the correlation between serum RBP4 level and various risk factors related to cardiovascular diseases (CVD) and found a strong association between circulating RBP4 levels and various well-established CVD risk factors and suggested RBP4 might serve as an independent predictor of CVD in women [53]. Therefore, it was reasonable to propose that RBP4 might serve as a link between the metabolic dysfunction and increased risk of GDM.

Regarding diagnostic criteria of GDM, the pooled results using the ADA criteria [16,22–24,28] suggested no significant difference between GDM and their normal controls, while the WHO criteria [17,21,25–27] demonstrated that an increased circulating levels of RBP4 in GDM. Although the ADA criteria had higher sensitivity and less strict inclusion criteria when compared with the WHO criteria [54], it also meant that the ADA criteria may contain more mild GDM cases than those diagnosed by the WHO criteria. Since higher levels of RBP4 could be associated with more severe glycemic metabolic dysfunction [11,14,15,46], this may partially explain why the higher circulating levels of RBP4 in GDM were not obvious when using the ADA criteria. As for the Carpenter and Coustan [18,29] as well as the NDDG criteria [19,20], the results seemed still inconclusive, since both the studies number and the sample sizes were limited.

In this meta-analysis, although we observed significantly higher levels of RBP4 in women with GDM in the second/third trimesters of pregnancy, only one study investigated this relationship in the first trimester [27], which suggested no significant association between RBP4 concentrations and subsequent increased risk of GDM. Since insufficient data on the first trimester was available, it was still inconclusive whether there was significant difference of circulating RBP4 levels between GDM and their normal controls. Another issue which should be taken into account was that the methods used for RBP4 determination might contribute to the moderate to high heterogeneity observed among these studies. Therefore, large prospective cohorts were performed in the first trimester, with standardized assays required to confirm whether elevated circulating RBP4 levels during early gestational age were associated with subsequent increased risk of GDM in the future.

To the best of our knowledge, this is the first comprehensive systematic review to explore whether women with GDM had

### Table 2. Subgroup analysis of the association between GDM and RBP4.

| Study type               | Studies | GDM | Control | SMD   | 95%CI       | I²   |
|-------------------------|---------|-----|---------|-------|------------|------|
| Cohort                  | 8       | 467 | 624     | 0.37  | 0.07 to 0.67 | 76%  |
| Case-control            | 4       | 360 | 562     | 0.72  | 0.28 to 1.15 | 88%  |
| Cross-sectional         | 2       | 57  | 65      | 0.47  | −1.50 to 2.44 | 95%  |
| Diagnostic criteria of GDM |          |     |         |       |            |      |
| ADA                     | 6       | 411 | 397     | 0.15  | −0.21 to 0.51 | 81%  |
| WHO                     | 4       | 235 | 428     | 0.76  | 0.46 to 1.05 | 60%  |
| Carpenter & Coustan     | 2       | 183 | 371     | 0.06  | −0.12 to 0.24 | 31%  |
| NDDG                    | 2       | 55  | 55      | 1.20  | 0.72 to 1.67 | 25%  |
| Countries               |          |     |         |       |            |      |
| Asia                    | 6       | 391 | 583     | 0.78  | 0.30 to 1.26 | 89%  |
| Europe                  | 5       | 248 | 411     | 0.42  | −0.06 to 0.89 | 85%  |
| North America           | 3       | 245 | 257     | 0.08  | −0.38 to 0.54 | 75%  |
| Maternal age            |          |     |         |       |            |      |
| Matched                 | 10      | 517 | 859     | 0.67  | 0.37 to 0.97 | 80%  |
| Higher in GDM           | 4       | 367 | 392     | 0.08  | −0.48 to 0.64 | 92%  |
| Maternal BMI            |          |     |         |       |            |      |
| Matched                 | 8       | 286 | 258     | 0.80  | 0.50 to 1.10 | 60%  |
| Higher in GDM           | 6       | 598 | 993     | 0.16  | −0.18 to 0.50 | 89%  |
| Gestational weeks of RBP4 measurement | 13 | 824 | 1011 | 0.49 | 0.21 to 0.77 | 86%  |

GDM: gestational diabetes mellitus; RBP4: retinol-binding protein-4; BMI: body Mass Index; ADA: American Diabetes Association; WHO: World Health Organization; NDDG: National Diabetes Data Group; SMD: standardized mean difference.

Bold values indicate SMD is significant between GDM and the controls (p < 0.05).
higher circulating RBP4 levels than the normglycemic pregnant women. Our meta-analysis had some strengths. First of all, both case-control and cohort studies were included to explore the relationships between RBP4 concentrations and risk of GDM, and the significant associations were not influenced by the study designs. Second, our findings could avoid some important potential bias, since results of stratification according to confounders such as maternal age and BMI still demonstrated significantly higher RBP4 concentrations in women with GDM.

However, several limitations should also be addressed. First, there were limited studies on the maternal circulating levels of RBP4 in the first trimesters of pregnancy. Thus, we could not address adequately the time course of the alteration in circulating RBP4 levels. Second, heterogeneity among the studies was significant, this could be partly explained by the various assay used for the measurement of RBP4 concentrations in different studies. Third, women with GDM had a higher incidence of developing a series of adverse pregnancy outcomes such as preeclampsia, preterm labor, stillbirth as well as dystocia due to macrosomia [56,57]. However, none of the studies in the current meta-analysis explored whether elevated circulating RBP4 levels were associated with adverse pregnancy outcomes in these population.

In conclusion, our findings suggested that Asian women with GDM had increased circulating RBP4 levels in their second/third trimester of pregnancy. In future, prospective cohorts with standardized assay measurement beginning from the first trimester of pregnancy are needed to ascertain the causality between changes in RBP4 concentrations and subsequent increased risk of GDM.

Declaration of interest
The authors have no competing interests to declare. This work was supported by the President Grant from Nanfang Hospital (2012C026) to Dr. Qi Tao, Huang. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Ethical approval
The study was approved by the local Institutional Review Board.

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Supplementary material available online
Supplementary Figure S1 and Table S1