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RESEARCH ARTICLE

Maternal and cord blood betatrophin (angiopoietin-like protein 8) in pregnant women with gestational diabetes and normoglycemic controls: A systematic review, meta-analysis, and meta-regression

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Abstract

Aims: This systematic review and meta-analysis examined maternal and cord blood betatrophin levels in pregnant women with gestational diabetes mellitus (GDM) and normoglycemic controls.

Material and Methods: PubMed, Cochrane Library, Embase, LILACS, WangFang, and China National Knowledge Infrastructure were searched for literature from inception until May 2022. The primary outcomes were maternal and cord blood betatrophin levels. A random-effect meta-analysis was used to estimate the pooled results. The mean differences (MDs) or standardised MDs (SMD) and their 95% confidence intervals (CIs) were calculated. I^2 tests were used to evaluate the heterogeneity. The quality of studies was evaluated using the Newcastle–Ottawa Scale.

Results: Betatrophin levels were reported in 22 studies with a total of 3034 pregnant women, and in seven studies including cord blood from 456 infants. Women with GDM display higher betatrophin levels than the normoglycemic controls (SMD = 0.85, 95% CI: 0.38–1.31) during the second half of the pregnancy. The sensitivity analysis indicated that no single study had significantly influenced the betatrophin overall outcomes. There was heterogeneity between the studies as evidenced by high I^2 values. Meta-regression analysis indicated a significant regression coefficient for maternal betatrophin and glycosilated haemoglobin. There was no significant difference in cord blood betatrophin in infants from women with and without GDM (SMD = 0.34, 95% CI: −0.15–0.83). Women with GDM also had significantly higher insulin, glucose, glycosylated haemoglobin, HOMA-IR, LDL-cholesterol, HDL-cholesterol, triglycerides, and body mass index compared with the normoglycemic controls.

Conclusions: Maternal betatrophin levels were higher in women with GDM than in the normoglycemic controls. There was no difference in cord blood betatrophin.

Faustino R. Pérez-López, Junhua Yuan and Manuel Sánchez-Prieto contributed equally to the work as first author.

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KEYWORDS
angiopoietin-like protein 8, betatrophin, gestational diabetes mellitus, glucose, glycosilated haemoglobin

1 | INTRODUCTION

Angiopoietin-like proteins are a group of compounds with a similar structure to angiopoietins and with multibiological functions, including participation in glucose and lipid metabolism, insulin resistance, inflammation, and carcinogenesis.[1–4] Those proteins are considered orphan ligands since they do not bind to the receptors of angiopoietins.[5] Angiopoietin-like protein 8 is also known as betatrophin, lipasin, recombinant β-cell trophic factor, refeeding induced fat and liver, hepatocellular carcinoma-associated protein TD26, or hepatocellular carcinoma-associated gene TD. It is a 198 amino acid adipokine mainly secreted by the liver and adipose tissue that controls pancreatic beta-cell proliferation.[6] It favours insulin resistance,[7] and is an independent predictor of the development of type 2 diabetes mellitus (T2DM),[6] and reduces triglyceride clearance.[8] The risk of developing diabetes has a stepwise increase across betatrophin quartiles, having people in the highest hormone quartile at more than a threefold higher risk of incident diabetes than the subjects in the lowest quartile, although there is no significant relation between serum betatrophin and indices of insulin resistance.[9]

GDM is a frequent medical complication of pregnancy and the placenta is exposed to the concomitant hormones, cytokines, and metabolic changes that affect both the mother and the foetus. Many markers and hormones have been proposed to evaluate the endocrine and metabolic changes associated with GDM, including betatrophin.[10] Maternal circulating betatrophin seems to be increased during the third trimester in women with GDM.[11] However, there is a scarce information during the first half of the pregnancy, results are heterogeneous during the second half of the pregnancy, and the infant betatrophin information is limited. In addition, betatrophin participation in glucose tolerance and lipid metabolism remains unclear.[3,4,6] This systematic review and meta-analysis evaluated maternal betatrophin in early and late gestational phases and glucose- and lipid-related changes in pregnant women with and without GDM as screened with recommended oral glucose tolerance tests (OGTTs).

2 | METHODS

2.1 | Data sources and search strategy

This systematic review and meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analysis Guidelines.[12] The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD42022311372). Studies published up to May 2022 in English, Chinese, French, Portuguese, German, and Spanish were considered for inclusion in this review, without any restriction. The authors translated the Chinese language articles into English. A comprehensive search syntax using MeSH and free text terms was developed for PubMed and adapted as appropriate for the other searched databases, including Embase, Cochrane Library, LILACS (*Literatura Latino Americana e do Caribe em Ciências da Saúde*), China National Knowledge Infrastructure, and Wang Fang (Table S1). There were no restrictions during the search and no filters were applied. The search MeSH terms included 'betatrophin', 'angiopoietin-like protein 8', 'lipasin', 'recombinant β-cell trophic factor', 'refeeding induced fat and liver', 'hepatocellular carcinoma-associated protein TD26', or 'hepatocellular carcinoma-associated gene TD', combined with 'gestational diabetes mellitus', 'GDM', or 'diabetes pregnancy'. A description of the search terms and strategy is available in Table S1. We also performed a manual search of the 'grey literature' (e.g., medRxiv and Grey Literature Report) to detect other potentially eligible investigations.

2.2 | Eligibility criteria

The protocol specified to include prospective or retrospective observational studies if they reported betatrophin (or synonymous names) levels in maternal blood or cord blood immediately after delivery. Studies were included if: (1) reported data on the maternal and/or cord betatrophin in pregnant women with and without GDM and/or their infants; (2) the studied population was screened for GDM during the second half of the pregnancy with a validated procedure; (3) betatrophin levels were measured using enzyme-linked immunosorbent assay (ELISA), radioimmunoassay, or other acceptable methods; (4) the full-text was available and provided enough information. We excluded studies focussing on women with other concomitant gestational pathologies, review articles, and studies not giving information about the GDM screening procedures.

2.3 | Data collection and quality assessment

The Population, Exposure, Comparators, Outcomes, Study Design (PECOS) criteria were developed a priori to guide the scope of the review, along with the procedures, selection, and synthesis of the literature search. Studies were eligible if they met the following inclusion criteria: *Population:* pregnant women without pregestational or obstetric pathology not receiving any treatment. *Exposure:* GDM diagnoses reached by validated international scientific criteria or other internationally recognised scientific organisations.[13–19]

Comparator: participants without GDM and any other obstetric pathology. *Outcomes*: The primary outcome was circulating maternal and/or cord blood betatrophin levels. Secondary outcomes were insulin-, glucose-, and lipid-related outcomes. *Study design*: observational studies including pregnant women with and without GDM and without any other obstetric pathology. Cord blood betatrophin levels were considered representative of infant values.

A pre-designed data extraction form was used to extract information on the following variables: country, sample size, age, clinical characteristics of pregnancy, gestational age (GA) at betatrophin measurement, methods used to assess the presence and absence of GDM, and measured outcomes. For the meta-analyses, we collected mean and error measures. When these were not provided or when mean and error measures were presented only in figures, we contacted the corresponding author to obtain specific information. Results reported as graphics were digitalised to obtain numerical data.[20,21]

When the median and interquartile range (IQR) were provided, the mean was estimated using the formula $x = (a + 2m + b)/4$ using the values of the median (m), P25 and P75 (a and b, respectively) and the standard deviation (SD) was estimated using SD = IQR/1.35. When the median and range were provided, the mean was estimated using the formula $x = (a + 2m + b)/4$ using the values of the median (m), the smallest value, and the largest value (a and b, respectively), and the SD was estimated using the formula SD = range/4 if the sample size was <70, and SD = range/6 if the sample size was >70.[22]

Methodological quality of studies was assessed using the nine-star Newcastle–Ottawa Scale (NOS), which uses pre-defined criteria namely: selection (population representativeness), comparability (adjustment for confounders), and ascertainment of outcome.[23] The NOS assigns a maximum of four points for selection, two points for comparability, and three points for exposure or outcome. NOS scores of ≥7 were considered as high-quality studies and NOS scores of 5–6 were considered moderate quality. Any discrepancies were addressed by a re-evaluation of the original article to reach a consensus.

2.4 | Statistical analyses

Because studies might have potential differences in phenotype baseline characteristics, recruitment procedures, lifestyle differences (including nutrition and physical activity), and laboratory measurement differences, we followed the DerSimonian and Laird random-effects model.[24] Continuous outcomes were planned as mean (mean difference [MD] or standardised MD differences [SMDs]) with their corresponding 95% confidence intervals (CI). The effect size presented as MD or SMD with a p value of <0.05 was considered statistically significant. The Hedges' g method was used to measure effect sizes, interpreting the magnitude of SMDs as small (0.20), moderate (0.50), or large (0.80).[25]

We evaluated statistical heterogeneity using the Chi^2, the I^2 statistic, and the between-study variance using the Tau^2. An I^2 value of 0%–30% defined low heterogeneity, 30%–65% moderate heterogeneity, and >65% substantial heterogeneity.[26] A $p < 0.1$ for the Chi^2 defined the presence of heterogeneity, and a $Tau^2 > 1$ defined the presence of substantial statistical heterogeneity. One-study leave-out sensitivity analysis was performed to test the robustness of the overall betatrophin result.[27] We also performed meta-regression analyses[28] to explore the sources of heterogeneity expected in meta-analyses of maternal betatrophin studies.

2.5 | Sub-group analyses and publication bias

We predefined subgroup analyses to explore betatrophin heterogeneity by (i) GA (first and second half of the pregnancy), (ii) ethnicity/lifestyles (western women vs. Chinese women), (iii) small HOMA-IR difference between women with GDM and normoglycemic controls (<0.8 vs. >0.8), and (iv) high glycosilated haemoglobin levels versus low glycosilated haemoglobin levels (cut-off 5.4% or 36 mmol/ml).[29] Calculated betatrophin means were considered for sub-analyses if at least three studies were in each subgroup factor.

Potential publication bias was estimated by the Begg's funnel plot and the Egger's linear regression test.[30] Statistical analyses were conducted using Review Manager (RevMan 5.3; Cochrane Collaboration) and Open Meta software (GPR, FRPL, and SRV).

3 | RESULTS

3.1 | Characteristics of included studies

The electronic search from the databases yielded 115 records after removing duplicated publications (83 in English and 32 in Chinese, Table S1). The review after screening by title yielded 73 items, and after evaluation of abstract content, 47 items were assessed for eligibility, and 33 remained for full-text review. Ten articles did not provide appropriate groups of study or had other limitations and were excluded. The excluded studies along with the reason for their exclusion are shown in Figure 1. Twenty-three articles provided information about maternal and/or cord blood betatrophin in pregnancies with and without GDM and were included for qualitative and quantitative synthesis.[31–53] In 22 studies, betatrophin was measured using ELISA and in one study by radioimmunoassay.[33] There was no grey literature concerning the research topic. The authors were contacted for clarification of the reported results.[32]

Studies of maternal betatrophin were carried out 15 in China,[33,34,38,40,42,43,45,46,48–53] four in Turkey,[32,36,37,39] one in Austria,[44] one in Egypt,[31] one in Germany,[35] one in Poland,[47] and one in Spain.[41] Table 1 displays information on the period of study, number of participants, age, GA at maternal betatrophin and other biochemical measurements, OGTT and GA at GDM screening, and aims of studies. Table S2 summarises the exclusion criteria and main results of the 23 meta-analysed studies.[31–53] All pregnant women were screened for GDM at 24–32 weeks of pregnancy using 75-g OGTT,[31–33,35–40,42–53] except for one study using an OGTT with

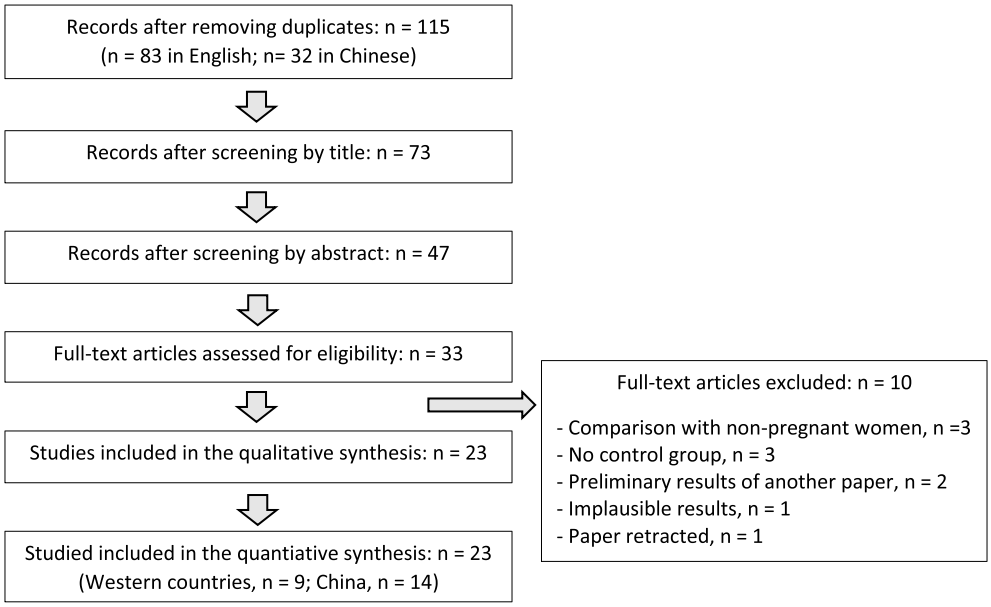


FIGURE 1 Flowchart of study selection.

100-g glucose,[41] and in another study, the glucose dose was not specified[34] (Table 1).

Twenty-two studies reported maternal betatrophin levels among 1316 women with GDM and 1718 normoglycemic controls (Table 1, Figure 2A),[31–48,50–53] published between 2015[34–36,44,47] and 2022.[39,51] Seven studies reported cord blood betatrophin in pregnancies with GDM (n = 232) and normoglycemic controls (n = 224)[41,45,47,49–51,53] (Table 1, Figure 2B). Studies reporting maternal betatrophin GDM sample sizes across studies ranged from 20[39,47] to 119,[43] and in normoglycemic controls ranged from 17[44] to 270.[42] Betatrophin measurements were performed during the first half of the pregnancy,[34,38,39,43,52] second half of the pregnancy,[31–37,40–42,44–49,52,53] and in one study during cesarean deliveries[50] (Table 1).

3.2 | Risk of bias assessment

Using the NOS scale, 21 studies were identified as high quality,[31–33,35–48,50–53] and the other two were of moderate quality[34,49] (Table S3). All publications identified the study population and described screening procedures to detect GDM and normoglycemic controls, and betatrophin measurement methods. They were representative of average GDM cases, and controls were derived from the same population as non-cases.

3.3 | Meta-analyses of maternal and neonate outcomes

In 22 studies (n = 3304 participants),[31–48,50–53] there was not a significant difference in maternal betatrophin levels during the first half pregnancy in women with GDM compared to normoglycemic controls, while during the second half of the pregnancy betatrophin levels were higher in women with GDM than in those in normoglycemic controls (Figure 2A). Pre-pregnancy body mass index (BMI) was significantly higher in women with GDM as compared to normoglycemic controls (Figure 2B). BMI during the current pregnancy was also significantly higher in women with GDM as compared to the control group (Figure 2C). In seven studies,[41,45,47,49–51,53] there was no significant difference in cord blood betatrophin (Figure 2D). In seven studies, birthweight was significantly higher in neonates from GDM cases as compared to those from normoglycemic controls (Figure 2E). All these outcomes displayed high heterogeneity (Table 2).

Maternal fasting glucose (Figure 3A), insulin (Figure 3B), HOMA-IR (Figure 3C), glycosilated haemoglobin (Figure 3D), and triglycerides (Figure 3E) results were significantly higher in women with GDM than in those with normoglycemic controls, while HDL-cholesterol levels were significantly lower in women with GDM than in normoglycemic controls (Figure 3F) with Hedges values >0.2. The SMDs were high for total and LDL-cholesterol in women with GDM (Figure 3G,H). There was high heterogeneity in all comparisons (Table 2).

3.4 | Betatrophin sub-group analyses, meta-regression, and sensitivity analysis

Pregnant women with GDM had increased betatrophin levels when GDM cases were compared to normoglycemic controls by both HOMA-IR difference between <0.8 and when the difference was >0.8 (Figure 4A). The test for subgroup difference was significant (Table 3). Pregnant women with high and normal glycosilated haemoglobin levels displayed similar increased betatrophin levels without significant subgroup difference (Figure 4B, Table 3).

Pregnant women from western countries did not show a significant difference in betatrophin levels when compared with GDM cases and normoglycemic controls. On the contrary, Chinese women

TABLE 1 Characteristics of 23 meta-analysed studies on maternal or cord blood betatrophin in pregnancies with GDM or NGT: PoS, sample size, ToS, age, GA at the maternal or cord betatrophin study, glucose dose at OGTT and GA at testing, and study aims.

Authors	Location and PoS	Sample size. Type of study	Age	GA at maternal or cord blood betatrophin study	Glucose dose and gestational age at OGTT	Study aims
Abdeltawab A et al.[31]	Mansoura, Egypt. PoS: January 2019 to December 2019	GDM: $n = 109$. Control group: $n = 103$. ToS: CC matched by age, BMI, and gestational age at GDM screening	GDM: 29.9 ± 6.28 years; control group: 29.7 ± 5.85	24–28 weeks	A 75-g OGTT at 24–28 weeks of pregnancy	To study blood betatrophin levels and miRNA-223 in women with and without GDM
Bulmus FG et al.[32]	Elazığ, Turkey. PoS: January 2017 to January 2018	GDM: $n = 30$. Control: $n = 30$. ToS: BMI and gestational age-matched case-control study	GDM: 34.5 ± 5.05 years. Control group: 32.93 ± 5.34 years	24–28 weeks	A 75-g OGTT at 24–28 weeks of pregnancy	To study betatrophin in women with GDM and its association with lipid and carbohydrate metabolism
Chen L et al.[33]	Hanchuan, Hubei, China. PoS: August 2015 to March 2018	GDM: $n = 119$. Control group: $n = 100$. ToS: CC study with similar age, gestational age, parity, and BMI	GDM: Age 28.49 ± 7.17 years. Control group: Age 28.38 ± 7.42 years	24–26 weeks	A 75g OGTT at 24–26 weeks of pregnancy	To study betatrophin in women with GDM, and its relationship with glucose and lipid metabolism
Chen XJ et al.[34]	Shenzhen, China. PoS: December 2018 to December 2019	GDM: $n = 35$. Control group: $n = 35$. ToS: Cross-sectional	GDM: Age 27.36 ± 4.18 years. Control group: 26.98 ± 3.25 years	7–13 weeks of pregnancy	OGTT (dose not detailed) at 24–28 weeks of pregnancy	To study betatrophin, glucose, and lipid metabolism in women with GDM
Ebert T et al.[35]	Leipzig, Germany. PoS: 2006 to 2011	GDM: $n = 74$. Control group: $n = 74$. ToS: Cross-sectional gestational age-matched study	GDM: Age median 31 [7.5] years. Control group: Median 28.9 [4.5]	GDM group: At 28.9 [4.7] weeks. Control group at 28.4 [5.7] weeks	A 75-g OGTT at 24–28 weeks of pregnancy	To study betatrophin, glucose and lipid metabolism, inflammation, and renal function in GDM
Erol O et al.[36]	Antalya, Turkey. PoS: January 2013 to June 2013	GDM: $n = 45$. Control group: $n = 45$. ToS: Prospective case-control matched for gestational age and BMI	GDM 29 ± 6.1 years. Control group: Age 27.3 ± 5.5 years	24–28 weeks	A 75-g OGTT at 24–28 weeks of pregnancy	To investigate maternal betatrophin levels and metabolic parameters in women with GDM
Ersoy GS et al.[37]	Istanbul, Turkey. PoS: January 2015 to April 2015	GDM: $n = 62$ women. Control group: 73 women. ToS: Case control matched for age, BMI and gestational age	GDM: Age 32.52 ± 3.92 years. Control group: 31.48 ± 3.58	25–29 weeks	A 75-g OGTT at 25–29 weeks of pregnancy	To study Wnt1-inducible signalling pathway protein-1, betatrophin, and metabolic parameters in pregnant women with GDM
Huang Y et al.[38]	Jiangsu, China. PoS: August 2015 to January 2016	GDM: $n = 88$. Control group: $n = 386$. ToS: Cross-sectional study	GDM: 29.7 ± 3.9. Control group: 28.1 ± 3.7 years	Betatrophin measured at 12–16 weeks	A 75-g OGTT at 24–28 weeks of pregnancy	To study betatrophin and other risk factors in early pregnancy to predict subsequent GDM
Kirlangic MM et al.[39]	Istanbul, Turkey. PoS: Not stated	GDM: $n = 20$. Control group: $n = 125$. ToS: Case-control study	GDM: Age: 32.00 ± 4.56 ± 6.09 years. Control group: 27.06 ± 4.94 years	11.65–1.31 weeks (GDM), and 11.82 ± 1.79 weeks (control group)	A 75-g OGTT at 24–28 weeks of pregnancy	To compare maternal betatrophin during the first trimester of pregnancy in women with GDM and healthy pregnant controls

(Continues)

TABLE 1 (Continued)

Authors	Location and PoS	Sample size. Type of study	Age	GA at maternal or cord blood betatrophin study	Glucose dose and gestational age at OGTT	Study aims
Lu B et al.[40]	Kunshan City, Jiangsu Province, China. PoS: October 2015 to August 2016	GDM: n = 53. Control: n = 57. ToS: Case-control study	GDM: 30.17 ± 4.93 years. Control group: 29.02 ± 3.79	23.51 ± 6.23 (GDM), and 25.32 ± 4.08 weeks (control group)	A 75-g OGTT at 23–29 weeks of pregnancy	To investigate the association between betatrophin and GDM
Martinez Perez B et al.[41]	Tarragona, Spain. PoS: Not stated	GDM: n = 46. Control group: n = 37. ToS: Cross-sectional study	GDM: 32.11 ± 4.92 years. Control group 31.49 ± 5.44 years	At the time of OGTT (before the 30th week of pregnancy), and from cord blood	A 100-g OGTT before the 30th week of pregnancy	To study betatrophin and its relationship with newborn adiposity
Pan R et al.[42]	Jiangsu, Zhenjiang, China. PoS: Not stated	GDM: n = 96. Control group: n = 270. ToS: Cross-sectional study	GDM: 32.34 ± 2.25 years. Control group: 28.62 ± 1.47 years	Within 1 month of the OGTT	A 75-g OGTT at 24–28 weeks of pregnancy	To study betatrophin and the risk of GDM as well as to predict postpartum T2DM
Si F et al.[43]	Chengde, Hebei, China. PoS: May 2019 to August 2020	GDM: n = 119. Control group: n = 60. ToS: Case-control study	GDM: 28.42 ± 5.91 years. Control group: 28.56 ± 5.76 years	13.04 ± 0.84 weeks (GDM) and 13.15 ± 0.83 weeks (control group)	A 75-g OGTT at 24–26 weeks of pregnancy	To study betatrophin and omentin-1 levels in women with GDM, and their correlation with glycolipid metabolism and insulin resistance
Trebotic LK et al.[44]	Austria. PoS: Not stated	GDM: n = 21. Control group: n = 19. ToS: Cross-sectional study. BMI matched	GDM: 30.95 ± 5.15 years. Control group: 34.53 ± 4.23 years	24–28 weeks of pregnancy	A 75-g OGTT at 24–28 weeks of pregnancy	To investigate the role of betatrophin in women with GDM and its association with lipid and glucose metabolism
Wang GH et al.[45]	Lianyungang, China. PoS: June 2013 to June 2015	GDM: n = 30. Control group: n = 30. ToS: Case-control study	GDM: 29.03 ± 3.56 years. Control group: 30.43 ± 3.87 years	38.85 ± 0.83 weeks (GDM) and 38.81 ± 0.94 weeks (control group). Betatrophin also measured in cord blood	A 75-g OGTT at 24–28 weeks of pregnancy	To study maternal cord blood betatrophin levels and other biochemical indexes in pregnant women with GDM
Wang P et al.[46]	Anhui, Heifei, China. PoS: March 2016 to August 2016	GDM: n = 30 normal weight and 30 overwight women. Control group n = 30 normal weight and n = 30 overwight. ToS: Case-control study	GDM: Normal weight 30.86 ± 4.66 years; overweight: 33.82 ± 5.16 years. Control group: Normal weight, 29.82 ± 4.29 years; overweight: 31.89 ± 4.88 years	24–32 weeks	A 75-g OGTT at 24–32 weeks of pregnancy	To study betatrophin levels in pregnant women with normal weight and overweight with GDM
Wawrusiewicz Kurylonek N et al.[47]	Bialystock, Poland. PoS: Not stated	GDM: n = 20. Control group: n = 20. ToS: Case control study	GDM: 32 [27.5–36.0]. Control group: 31 [29.5–33.0] years	GDM: 39.5 [39–40] weeks. Control group: 39 [38–40] weeks, and from cord blood	A 75-g oral OGTT at 24–30 weeks of pregnancy	To study maternal and infant betatrophin and its mRNA expression in adipose and placental tissues in women with GDM

TABLE 1 (Continued)

Authors	Location and PoS	Sample size. Type of study	Age	GA at maternal or cord blood betatrophin study	Glucose dose and gestational age at OGTT	Study aims
Wu LJ et al.[48]	Xianning and Thongshan, Hubei Province, China. PoS: November 2018 to November 2019	GDM: $n = 60$. Control group: $n = 60$. ToS: Case-control study	GDM: 28.23 ± 2.79 years. Control group: 28.71 ± 2.54 years	24–28 weeks	A 75-g-OGTT at 24–28 weeks of pregnancy	To study plasma betatrophin, visfatin, and nuclear factor-κB in patients with GDM
Xie X et al.[49]	Wuhan, China. PoS: August 2013 to October 2013	GDM: $n = 23$. Control group: $n = 31$. ToS: Cross sectional study	GDM: 32 (28–34). Control group: 30 (26–32) years	Only in cord blood	A 75-g OGTT at 24–28 weeks of pregnancy	To study cord blood betatrophin in offsprings from GDM mothers, and glucose and other maternal metabolic parameters
Yang F et al.[50]	Lianyungang, Jiangsu, China. PoS: June 2017 to June 2018	GDM: $n = 40$. Control group: $n = 37$ who delivered by cesarean section. ToS: Cross-sectional	GDM: 30.41 ± 3.91 years. Control group: 28.83 ± 4.32 years	In at term cesarean section before placental delivery at 38.66 ± 1.01 weeks; control group 38.92 ± 1.05 weeks, and in cord blood	A 75-g OGTT at 24–28 weeks of pregnancy	To study vitamin D and betatrophin levels in GDM patients in blood collected after delivery of the foetus but before the delivery of the placenta
Yuan J et al.[51]	Qingdao, China. PoS: December 2018 to May 2019	GDM: $n = 23$. Control group: $n = 19$. ToS: Case-control study	GDM: 30 (28–34) years. Control group: 28 (28–30) years	Days of pregnancy 252 (217–252; GDM), and 252 (217–252) days control group. Cord blood after delivery	A 75-g OGTT at 24–28 weeks of pregnancy	To study placenta and maternal betatrophin metabolism as potential biomarker for GDM
Zhou C et al.[52]	Yichang City, Hubei Province, China. PoS: May 2016 to May 2017	GDM: $n = 43$. Control group: $n = 51$. ToS: Case-control study	GDM: 27.3 ± 6.1 years. Control group: 28.0 ± 6.9 years	GDM: 12.2 ± 0.6 weeks. Control group: 12.4 ± 0.8 weeks	A 75-g OGTT at 24–28 weeks of pregnancy	To study the first trimester serum betatrophin, interleukin-33, adiponectin and glycolipid metabolism in women with GDM
Zhu Z et al.[53]	Quingdao, China. PoS: December 2016 to January 2019	GDM: $n = 50$. Control group: $n = 50$. ToS: Case-control study	GDM: 31.34 ± 5.01 years. Control group: 31.4 ± 4.18 years	At the time of GDM screening and from cord blood after delivery	A 75-g OGTT at 24–27 weeks +6 days of pregnancy	To study maternal and cord blood betatrophin, glucose and lipid metabolism in women with GDM

Note: Values are reported as mean ± standard deviation, median [interquartile range], or median (range).

Abbreviations: BMI, body mass index; GA, gestational age; GDM, gestational diabetes mellitus; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PoS, period of study; ToS, type of study.

with GDM displayed higher betatrophin levels than normoglycemic controls. However, the test for sub-group difference was not significant (Figure 4C, Table 3).

The results of meta-regression analysis indicated a statistically significant regression coefficient only for glycosilated haemoglobin. Pre-pregnancy BMI, current pregnancy BMI, insulin, glucose, HOMA-IR, total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides variability across the included studies could not be the source of heterogenitiy (Figure S1).

The results of a one-study-leave-out sensitive analysis for maternal betatrophin levels during the second half of the pregnancy seemed to be robust (Figure S2). The funnel plot analysis with Begg's correlation ($p = 0.79$) and Egger's regression tests ($p = 0.96$) indicated no significant publication bias (Figure S3).

4 | DISCUSSION

4.1 | Main findings and interpretation

In this systematic review and meta-analysis of 22 studies of high or moderate quality, maternal betatrophin levels were significantly higher in pregnant women with GDM than in normoglycemic controls, and in seven studies neonates did not have a difference in their cord blood betatrophin levels. Also, women with GDM had significantly higher levels of glucose, insulin, HOMA-IR, glycosylated haemoglobin, total cholesterol, LDL-cholesterol, and triglycerides, and lower HDL-cholesterol levels than normoglycemic controls. Meta-regression analysis of maternal betatrophin indicated a statistically significant coefficient for glycosylated haemoglobin.

Betatrophin is a protein mainly originating from the liver and a small fraction from adipose tissue that is involved in glucose and lipid metabolism,[6,54,55] insulin resistance,[56] T2DM,[57–59] and atherogenesis.[60] A previous meta-analysis in the general population reported a correlation between betatrophin and insulin resistance, and associations were still significant when participants were separated as diabetes mellitus, GDM, and non-diabetics.[2] Excessive body weight and obesity have been related to elevated betatrophin levels and the risk of developing metabolic syndrome in non-pregnant women, although moderate and intense physical activity may reduce betatrophin levels.[61] In pregnant women, GDM and excessive body weight are risk factors for both the mother and the offspring due to the associated reduced available foetal oxygen secondary to the insulin stimulation of the foetal metabolism.[62,63] However,

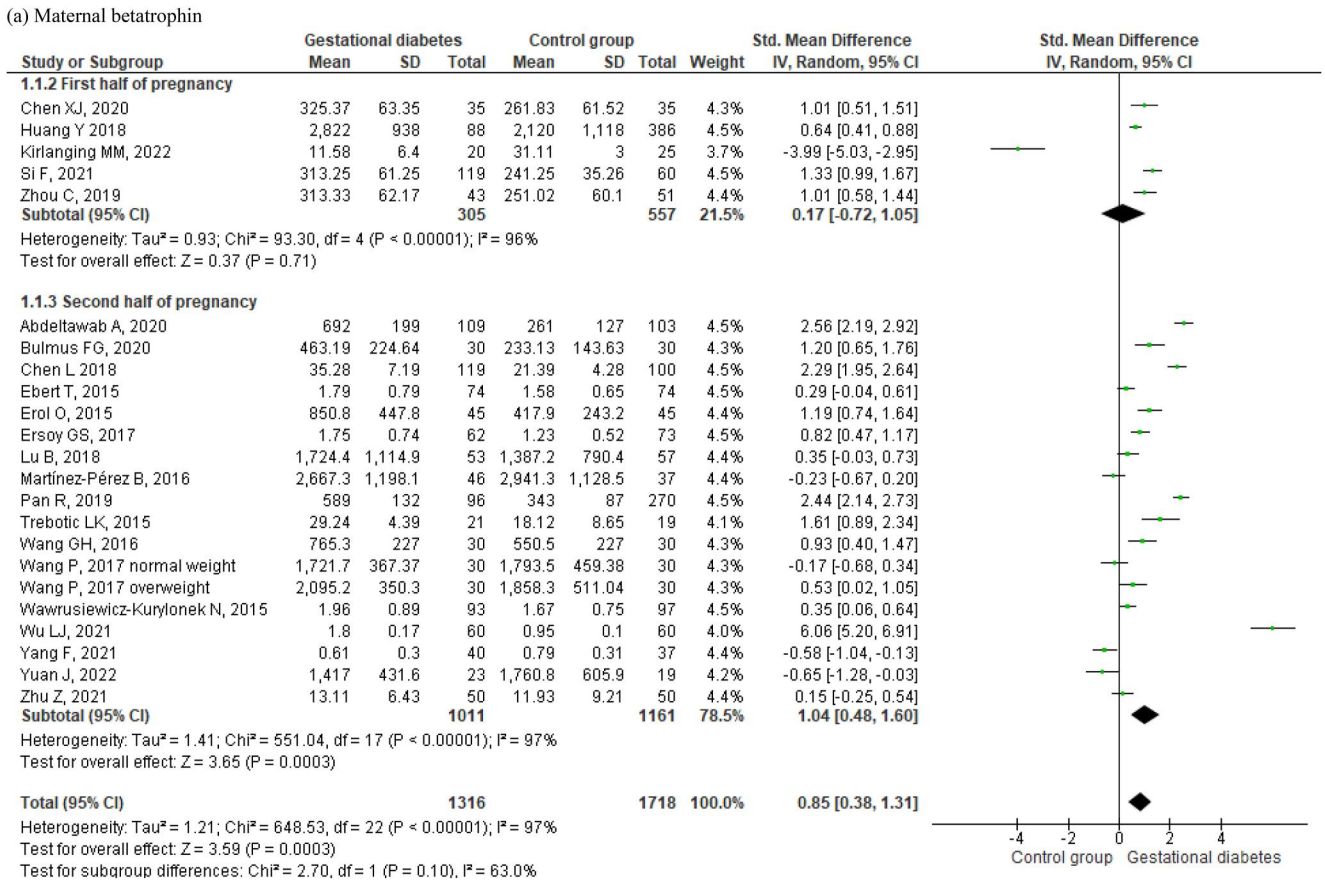
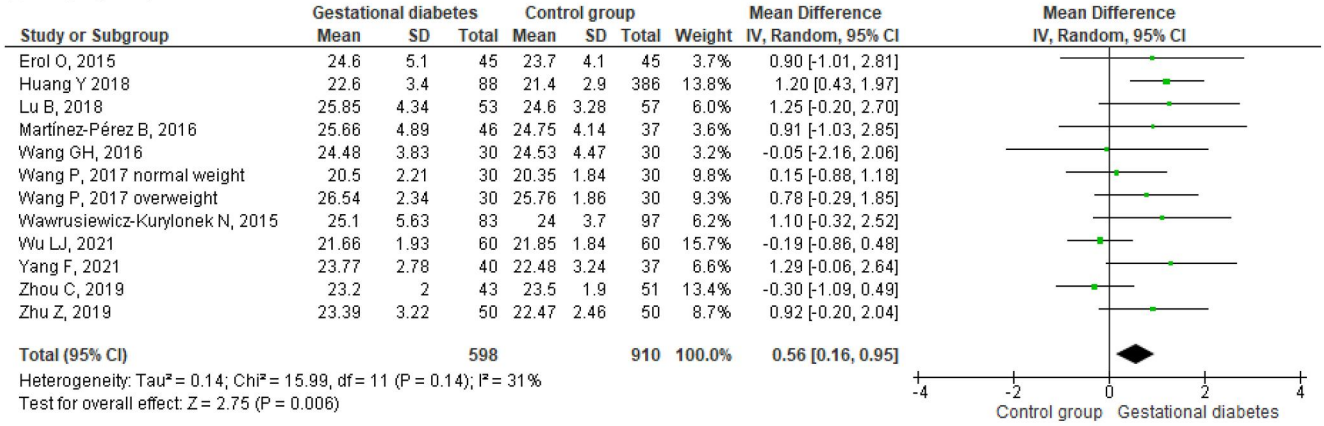


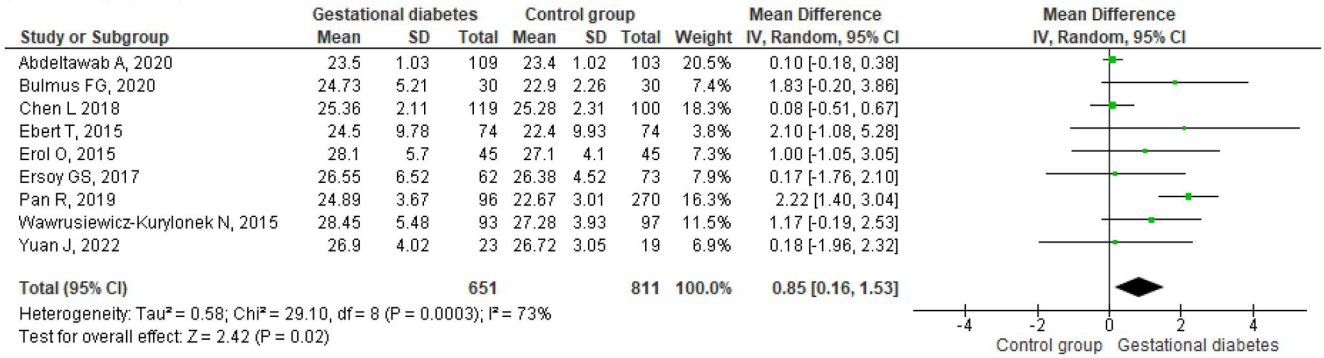
FIGURE 2 Forest plots of studies comparing (A) Maternal betatrophin, (B) Pre-pregnancy BMI, (C) Current pregnancy BMI, (D) Cord blood betatrophin, and (E) Birthweight (grams) in pregnant women with and without gestational diabetes mellitus. BMI, body mass index.

(b) Pre-pregnancy BMI



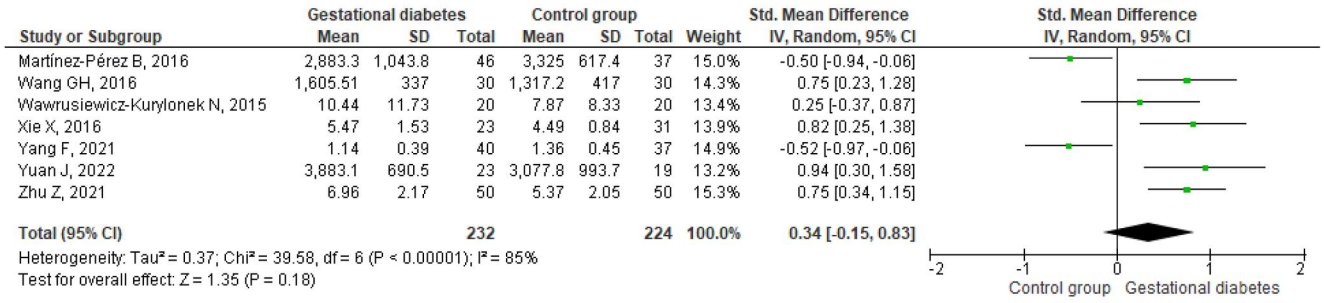
Heterogeneity: Tau² = 0.14; Chi² = 15.99, df = 11 (P = 0.14); I² = 31%
Test for overall effect: Z = 2.75 (P = 0.006)

(c) Current pregnancy BMI



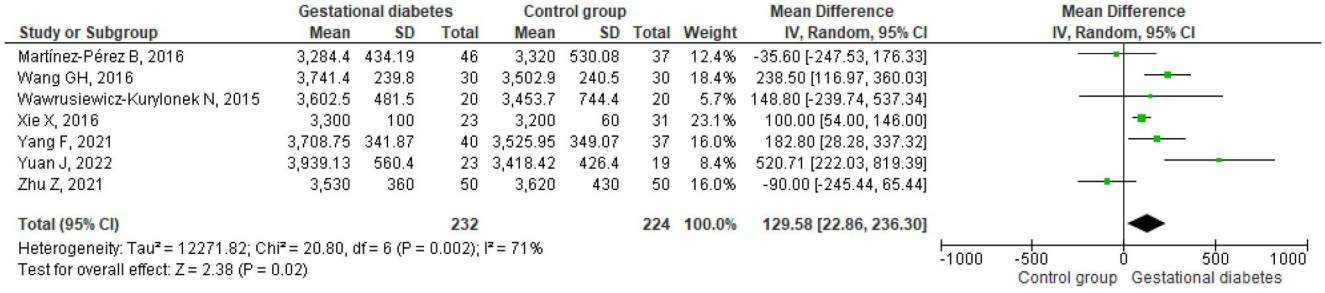
Heterogeneity: Tau² = 0.58; Chi² = 29.10, df = 8 (P = 0.0003); I² = 73%
Test for overall effect: Z = 2.42 (P = 0.02)

(d) Cord blood betatrophin



Heterogeneity: Tau² = 0.37; Chi² = 39.58, df = 6 (P < 0.00001); I² = 85%
Test for overall effect: Z = 1.35 (P = 0.18)

(e) Birthweight (grams)



Heterogeneity: Tau² = 12271.82; Chi² = 20.80, df = 6 (P = 0.002); I² = 71%
Test for overall effect: Z = 2.38 (P = 0.02)

FIGURE 2 (Continued)

experimental studies support a neutralising betatrophin effect on insulin resistance,[64,65] reducing tissue inflammation and weight gain, and improving glucose tolerance.[66]

The meta-analysed women with GDM had higher pre-pregnancy and pregnancy BMI than the control group. They also had higher maternal betatrophin levels and glucose metabolism

TABLE 2 Pooled effects as MD or SMDs and 95% CI using random effect models and heterogeneity (I^2) in pregnant women with GDM and those with NGT.

Outcome (Figures)	Included studies (*k*)	Participants GDM/NGT	SMD or MD and 95% CI	I^2 (%)	*p*
Maternal betatrophin (Figure 2A)	22	1316/1718	SMD 0.85 [0.38, 1.31]	97	<0.00001
First half of the pregnancy	5	305/557	SMD 0.17 [−0.72, 1.05]	96	<0.00001
Second half of the pregnancy	17	1011/1161	SMD 1.04 [0.48, 1.60]	97	<0.00001
Pre-pregnancy BMI (Figure 2B)	12	598/910	MD 0.56 [0.16, 0.95]	31	0.006
Current pregnancy BMI (Figure 2C)	9	651/811	MD 0.85 [0.16, 1.53]	73	0.02
Cord blood betatrophin (Figure 2D)	7	232/224	SMD 0.34 [−0.15, 0.83]	85	0.18
Birthweight (Figure 2E)	7	232/224	MD 129.58 [22.86, 236.30]	71	0.02
Maternal glucose (Figure 3A)	19	1088/1511	SMD 1.42 [1.07, 1.77]	93	<0.00001
First half of the pregnancy	5	305/557	SMD 1.32 [0.79, 1.85]	88	<0.00001
Second half of the pregnancy	14	783/954	SMD 1.46 [1.01, 1.91]	94	<0.00001
Maternal insulin (Figure 3B)	18	973/738	SMD 1.20 [0.66, 1.74]	94	<0.00001
First half of the pregnancy	4	217/171	SMD 0.64 [0.31, 0.98]	57	0.002
Second half of the pregnancy	14	756/738	SMD 1.20 [0.66, 1.74]	95	<0.00001
HOMA-IR (Figure 3C)	19	1069/1177	MD 0.85 [0.56, 1.14]	90	<0.00001
First half of the pregnancy	4	217/171	MD 0.92 [0.24, 1.59]	89	<0.00001
Second half of the pregnancy	15	852/1006	MD 0.83 [0.50, 1.16]	90	<0.00001
Glycosilated haemoglobin (Figure 3D)	13	858/963	SMD 0.97 [0.48, 1.47]	95	<0.00001
First half of the pregnancy	2	139/85	SMD 0.68 [0.29, 1.07]	34	0.0006
Second half of the pregnancy	11	719/878	SMD 1.04 [0.47, 1.62]	96	0.0004
Total cholesterol (Figure 3E)	18	1050/1276	SMD 0.25 [0.04, 0.47]	83	0.009
First half of the pregnancy	4	285/532	SMD 0.21 [−0.01, 0.43]	41	0.07
Second half of the pregnancy	13	765/744	SMD 0.25 [−0.03, 0.54]	86	0.08
LDL-cholesterol (Figure 2F)	16	989/1103	SMD 0.48 [0.12, 0.84]	93	0.09
First half of the pregnancy	3	197/146	SMD 0.99 [0.71, 1.27]	29	0.25
Second half of the pregnancy	13	792/957	SMD 0.37 [−0.04, 0.78]	94	0.08
HDL-cholesterol (Figure 2G)	16	1035/1140	SMD −0.35 [−0.50, −0.19]	67	<0.00001
First half of the pregnancy	3	197/146	SMD −0.99 [−0.71, −0.27]	29	<0.00001
Second half of the pregnancy	13	792/957	SMD −0.37 [−0.04, −0.78]	94	<0.00001
Triglycerides (Figure 2H)	16	939/877	SMD 0.68 [0.44, 0.92]	83	<0.00001
First half of the pregnancy	3	197/146	SMD 0.47 [0.24, 0.69]	0	0.53
Second half of the pregnancy	13	742/731	SMD 0.72 [0.44, 1.01]	85	<0.00001

Abbreviations: BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; MD, mean differences; NGT, normal glucose tolerance; SMDs, standardised MDs.

alterations demonstrated by increased glucose, insulin, HOMA-IR, and glycosylated haemoglobin as compared to normoglycemic controls. These differences are probably related to hyperinsulinemia in pregnant women with GDM and seems analogous to those reported in the general population.[2] Also, insulin resistance is well-known as a contributor to the metabolic disturbances of GDM,[67] and the HOMA-IR is an early marker and a predictive surrogate index of GDM.[68] In this meta-analysis, insulin, glucose, and the HOMA-IR were increased in GDM cases as compared to normoglycemic controls during the early and second half of the pregnancy. In the meta-regression analysis, we found that glycosilated haemoglobin was associated with increased betatrophin. Glycosilated haemoglobin is the result of non-enzymatic binding of glucose to haemoglobin and other plasma proteins that represents glucose levels during the previous 4–8 weeks with good reliability and low intelaboratory variation,[69] and is not influenced by circadian factors, meals, fasting stress, and treatments that alter glucose metabolism.[29,70,71]

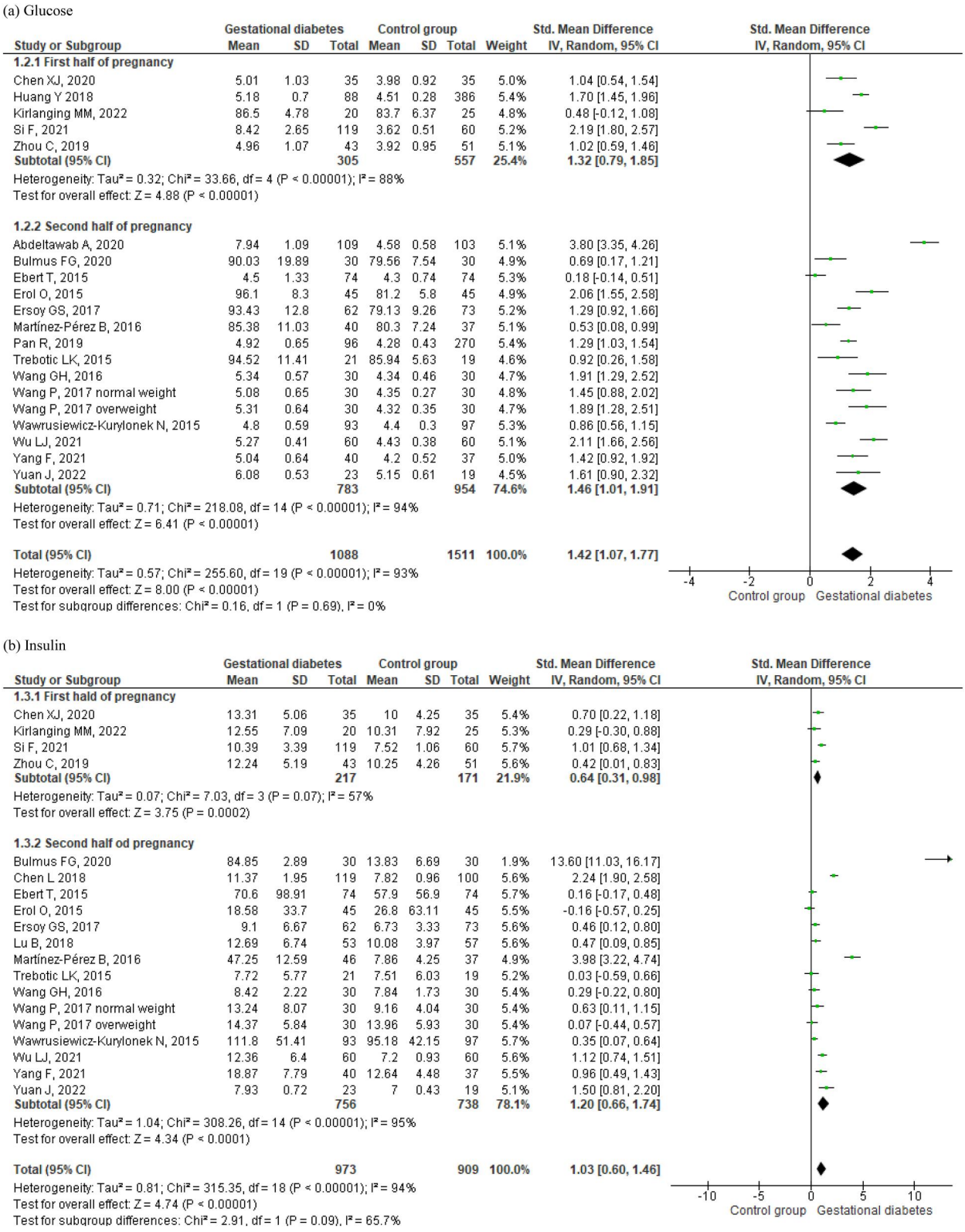
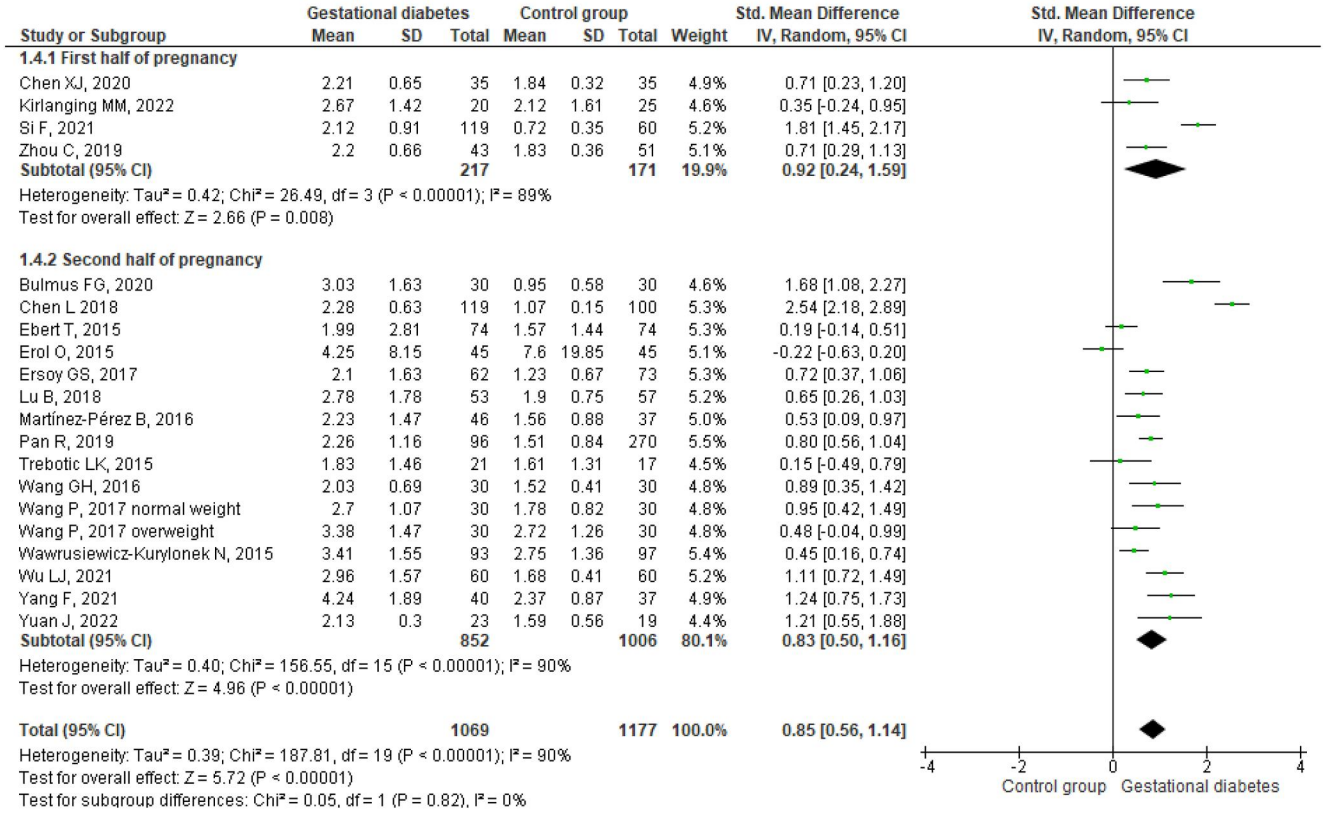


FIGURE 3 Forest plots of studies comparing maternal (A) fasting glucose, (B) insulin, (C) HOMA-IR, (D) glycosilated haemoglobin, (E) total cholesterol, (F) LDL-cholesterol, (G) HDL-cholesterol, and (H) triglycerides in pregnant women with and without gestational diabetes mellitus.

Sub-group analyses demonstrated that maternal betatrophin levels were increased in pregnant women with GDM with (i) either small or high HOMA-IR differences as compared to the control group, and (ii) in both GDM with both normal and increased glycosilated haemoglobin levels. The sub-group analysis of women compared by ethnicity/nationality indicates that women from western countries did

(c) HOMA-IR



(d) Glycosilated hemoglobin

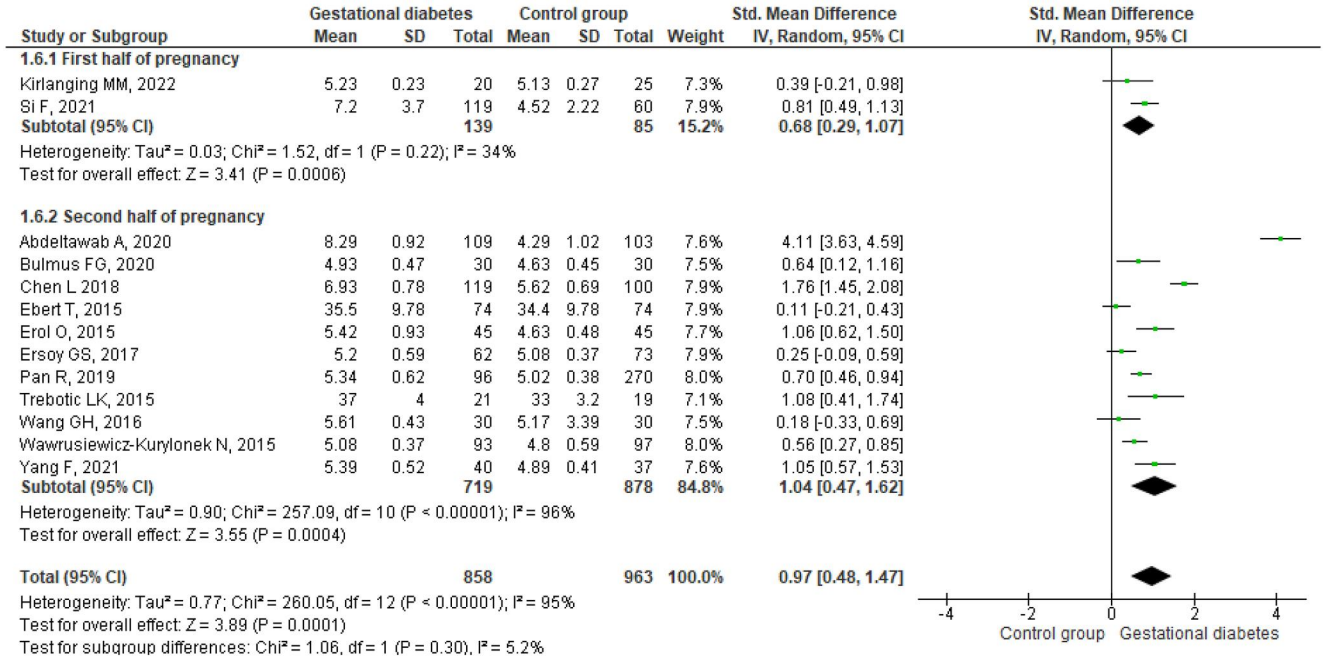
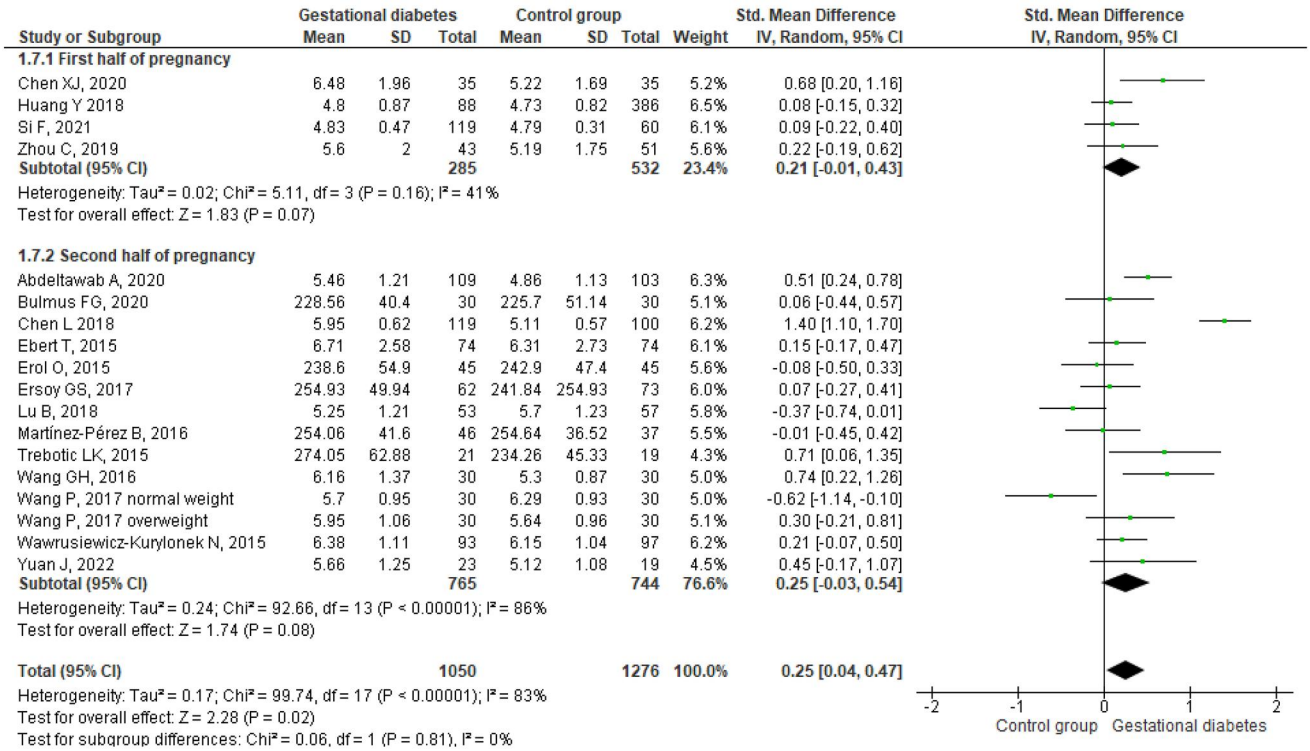


FIGURE 3 (Continued)

not show a difference in betatrophin levels compared with women with and without GDM. However, Chinese women with GDM had significantly higher betatrophin levels than normoglycemic controls, whereas pregnant women from western countries did not display a difference. Ethnicity, country of birth, and body composition determine the GDM risk.[72–74] There are several explanations for those differences, including that pancreatic beta cells are less in Asian women, limiting the possibility of compensating for insulin changes

(e) Total cholesterol



(f) LDL-cholesterol

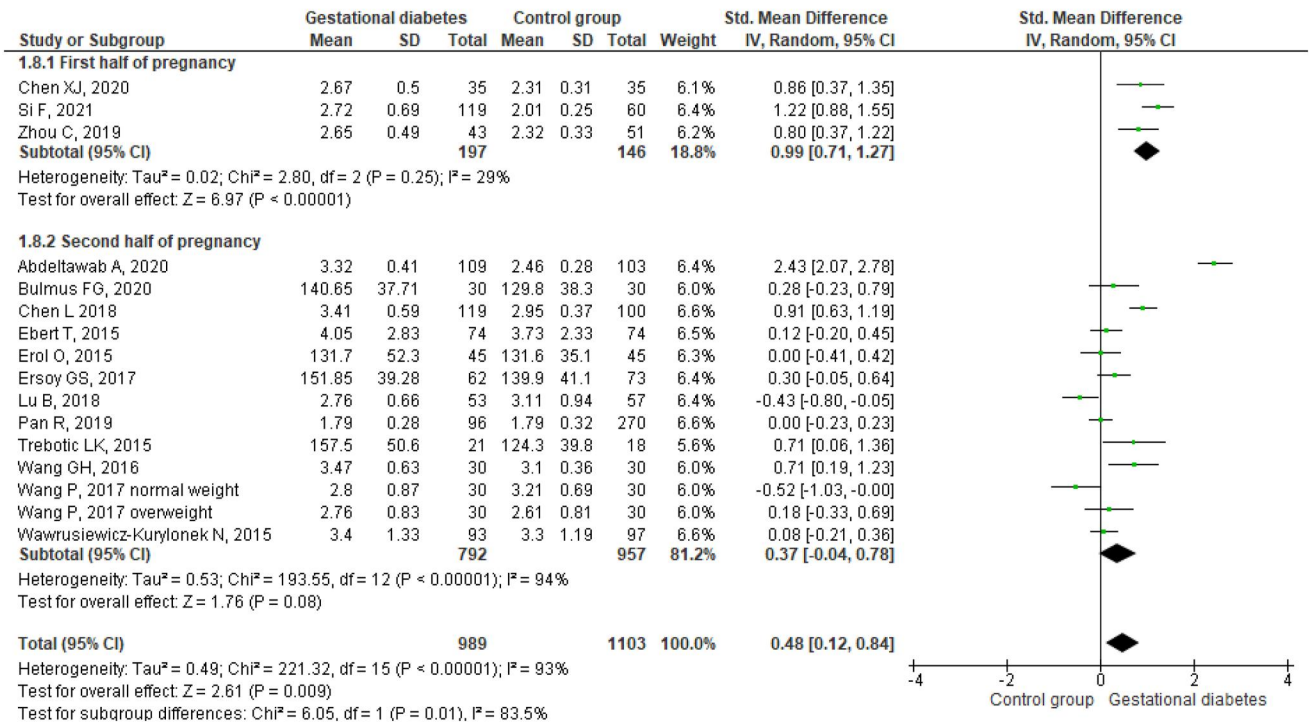
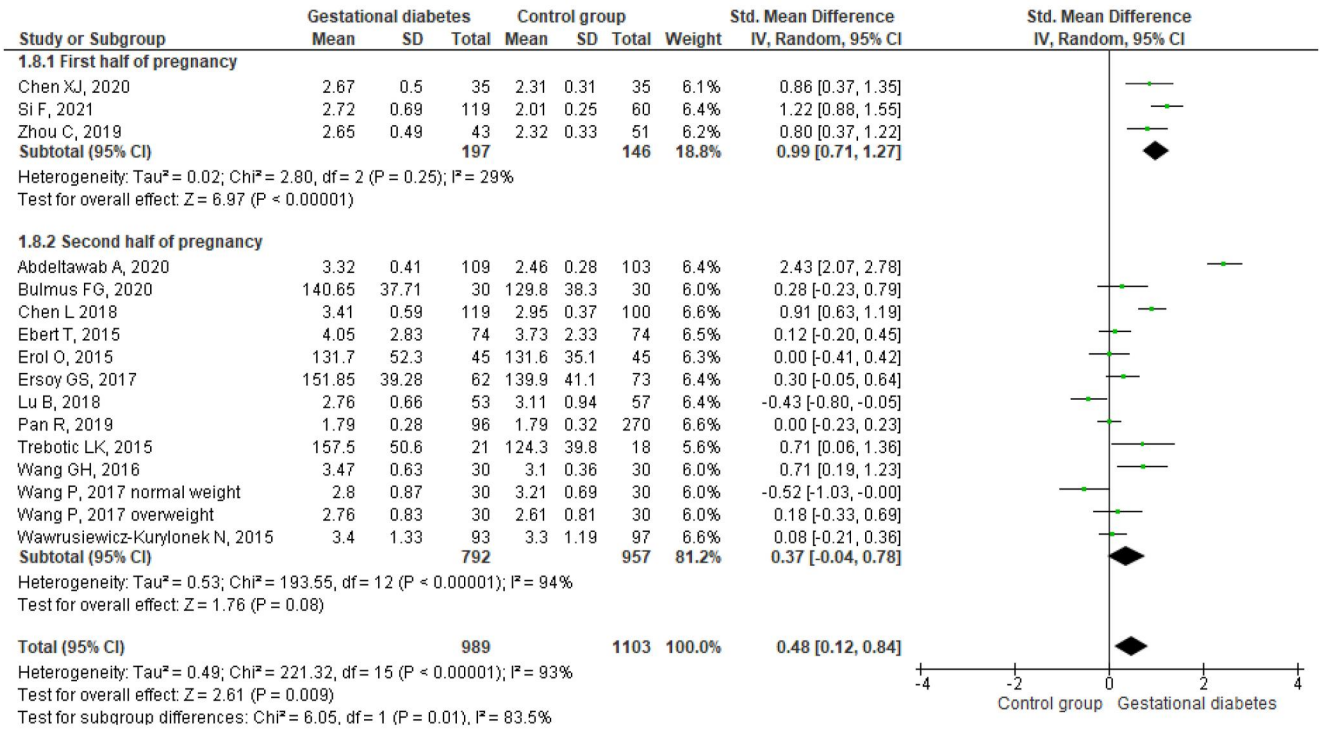


FIGURE 3 (Continued)

during pregnancy compared with Western pregnant women. A second possibility is that Asian pregnant women have more fat mass.[75,76] In addition, they also have a more visceral fat mass with similar BMI and are more prone to insulin resistance.[77] Further studies should clarify whether ethnicity, lifestyle, or nationality could determine beta-trophin levels in pregnant women with GDM.

(g) HDL-cholesterol



(h) Triglycerides

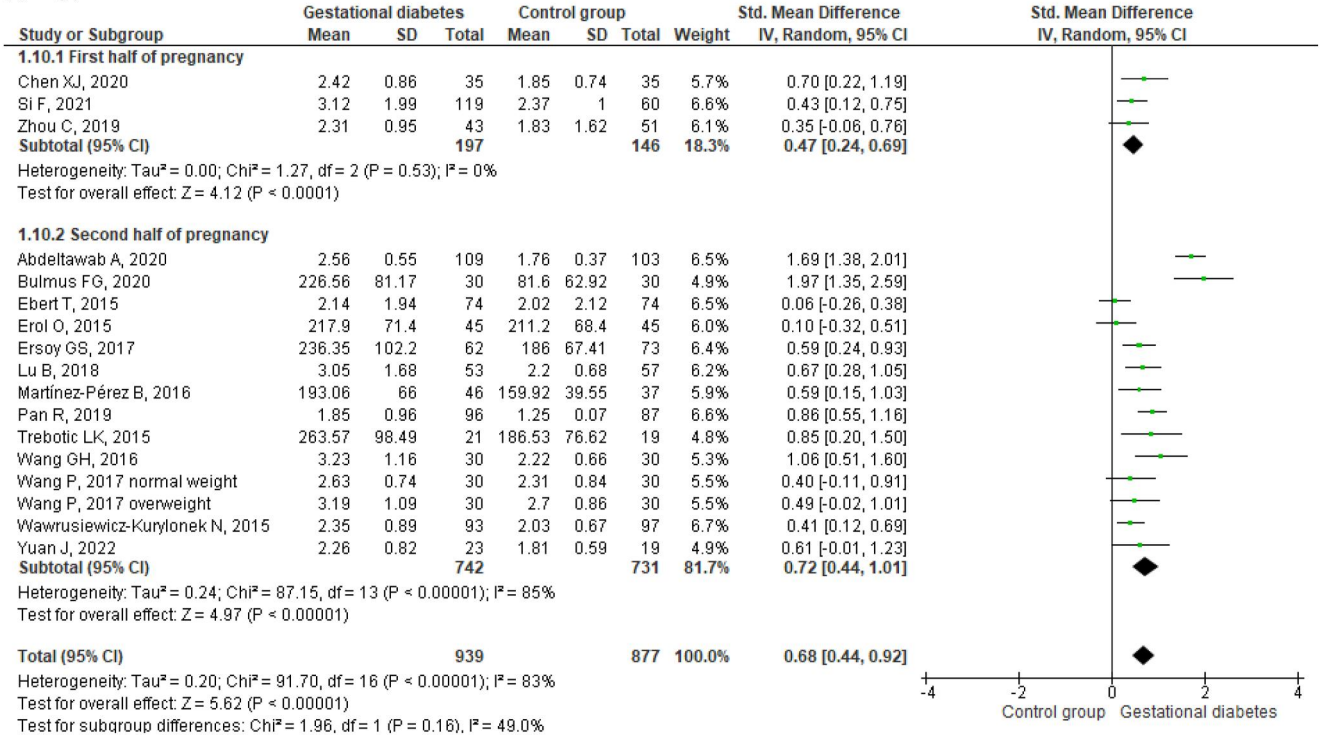
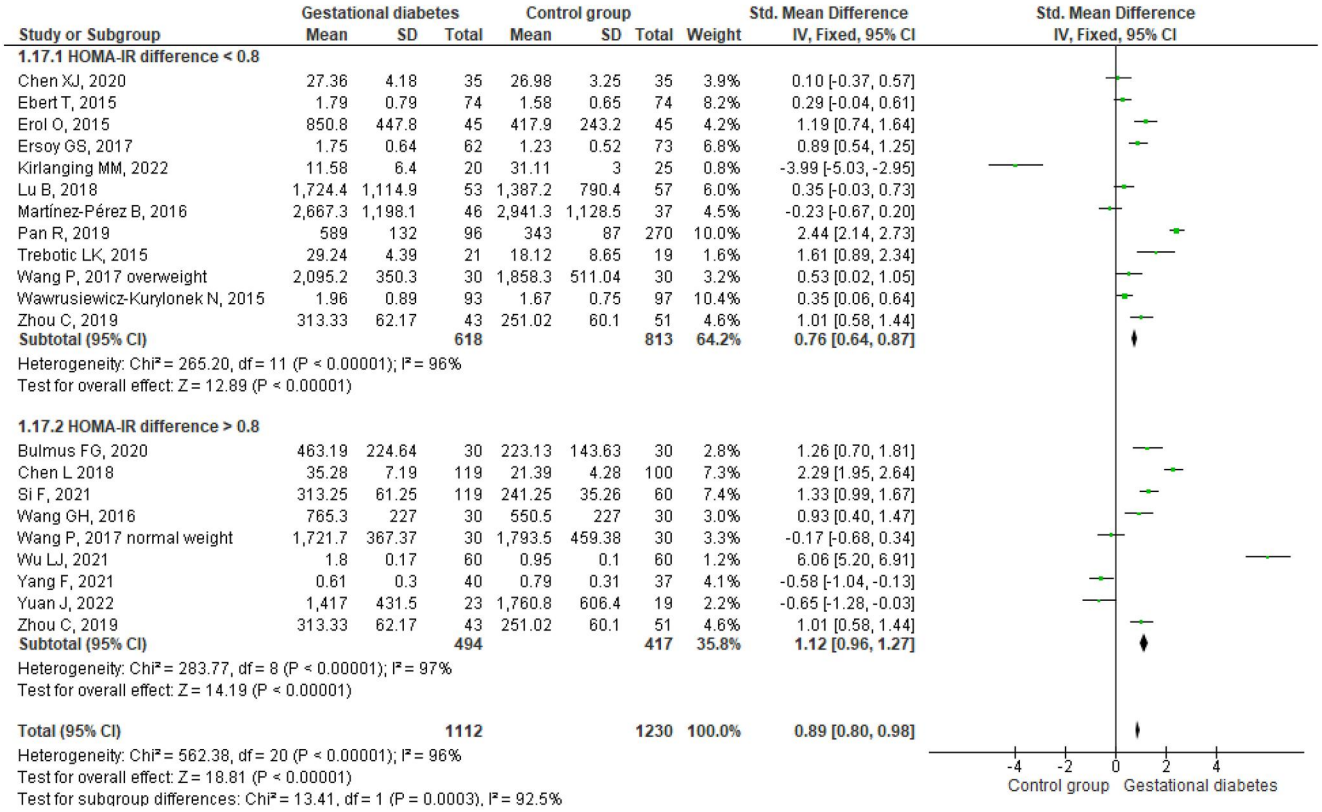


FIGURE 3 (Continued)

In seven studies, cord blood betatrophin did not display a significant difference between newborns from GDM cases and normoglycemic controls, and there was a significantly higher weight in neonates from women with GDM. Both outcomes deserve to be analysed in better studies, since insulin resistance, increased HOMA-IR, and macrosomia are frequent among women with GDM.[62,78]

(a) HOMA-IR < 0.8 versus HOMA-IR > 0.8



(b) Glycosilated hemoglobin

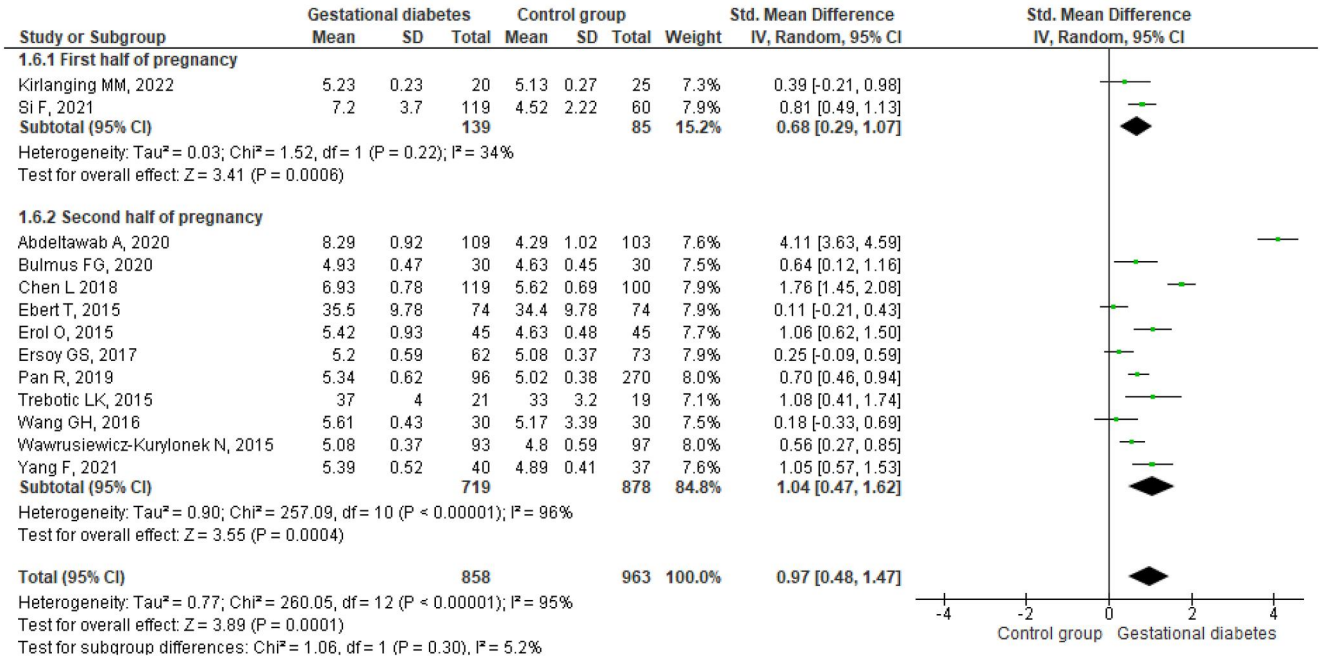


FIGURE 4 Sub-group analyses comparing betatrophin in pregnant women with and without gestational diabetes mellitus: (A) by HOMA-IR values <0.8 versus >0.8, (B) by normal glycosilated haemoglobin (<5.4% or 36 mmol) or increased glycosilated haemoglobin (>5.4% or 36 mmol), and (C) by ethnicity/world region (Western countries vs. Chinese women).

(c) Maternal betatrophin by world region countries (Western women versus Chinese women).

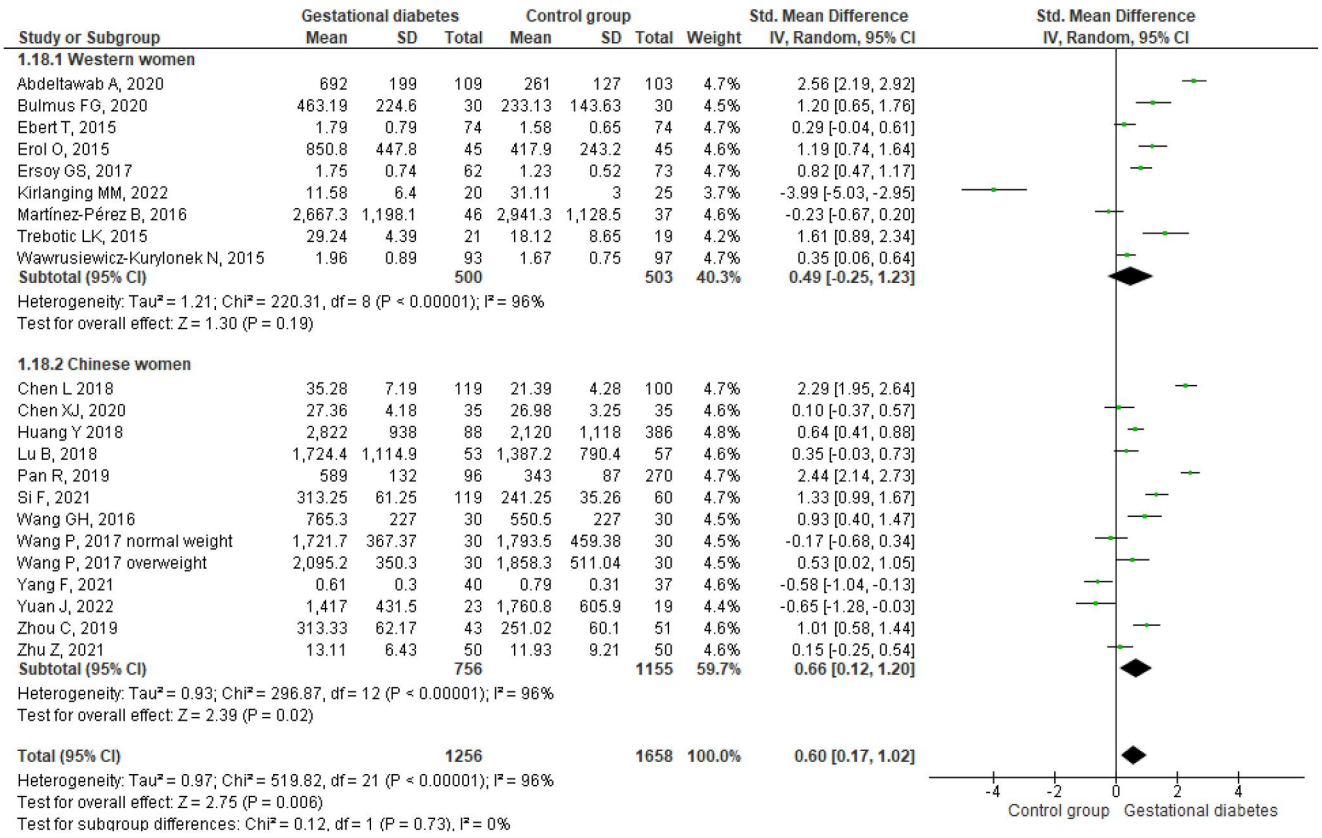


FIGURE 4 (Continued)

TABLE 3 Betatrophin sub-analyses in women with and without GDM by HOMA-IR difference, glycosated haemoglobin (increased or normal), and ethnicity/world regions (Western women vs. Chinese women).

Betatrophin sub-analyses	Included studies (*k*)	Participants GDM/NGT	SMD and 95% CI	I^2 (%)	*p*
Betatrophin sub-analysis HOMA-IR (Figure 4A)					
HOMA-IR difference <0.8	12	618/813	SMD 0.76 [0.64, 0.87]	96	<0.00001
HOMA-IR difference >0.8	9	494/417	SMD 1.12 [0.96, 1.27]	97	<0.00001
Betatrophin sub-analyses by glycated haemoglobin levels (Figure 4B)					
Normal glycosilated haemoglobin	4	259/274	SMD 0.62 [0.26, 0.98]	75	0.008
Increased glycated haemoglobin	7	460/604	SMD 1.42 [0.56, 2.28]	97	<0.00001
Betatrophin sub-analysis (Figure 4C)					
Western women	9	500/503	SMD 0.49 [−0.25, 1.23]	96	<0.00001
Chinese women	12	756/1155	SMD 0.66 [0.12, 1.20]	96	0.02

Abbreviations: CI, confidence interval; GDM, gestational diabetes mellitus; NGT, normal glucose tolerance; SMDs, standardised MDs.

Further studies should clarify the associations of betatrophin with neonatal variables.

In healthy subjects, there is an association of betatrophin and triglycerides.[79] In non-pregnant premenopausal women, betatrophin is correlated with both triglycerides and triglyceride/HDL-cholesterol index[80] and regulates the activity of lipoprotein lipase.[64] Patients with GDM usually display increased levels of triglyceride, total cholesterol, and LDL-cholesterol and lower HDL-cholesterol during pregnancy, and high BMI.[81] Our current results suggest a positive association between betatrophin and both triglycerides and LDL-cholesterol and an inverse association with HDL-cholesterol. On the other hand, it has been reported that insulin increases the expression of betatrophin in white adipose tissue[82], which might explain the increased betatrophin reported in this meta-analysis.

4.2 | Limitations and strength

Our findings should be interpreted with caution to some limitations of observational studies, including the heterogeneity in study designs, selection bias, small samples, different scientific objectives, and exageration of associations. Although studies included in our meta-analysis could be considered as having a low or moderate rate of bias, there are confounding factors such as ethnicity, lifestyle, socioeconomic status, and provided healthcare. For some associations, the number of studies included in a meta-analysis was small (e.g., women during early pregnancy, cord blood outcomes). Overall limitations and heterogeneity were quantified by the high I^2 values.

Strengths of this study include (i) a clear and detailed clinical and molecular classification of GDM and normoglycemic controls based on international recommendations; (ii) a random-effect model used for cumulative meta-analyses; and (iii) the sensitivity analysis indicated the robustness of the overall maternal betatrophin outcome. Moreover, no significant publication bias was detected. Heterogeneity was addressed through sub-group analyses showing that betatrophin results were not influenced by the HOMA-IR and the proposed glycosylated haemoglobin cut-off. On the contrary, we found that ethnicity/lifestyle (Chinese vs. western countries' women) is associated with different maternal betatrophin results.

Further studies are needed (i) to confirm the association of increased maternal betatrophin in Chinese women living outside China and in other Western ethnic groups, and (ii) to study cord blood betatrophin and other neonatal metabolic outcomes.

5 | CONCLUSION

Maternal betatrophin levels were increased in pregnant women with GDM compared with normoglycemic controls, and there was no difference in cord blood betatrophin. Women with GDM had increased pregestational and gestational BMI, insulin, glucose, HOMA-IR, glycosylated haemoglobin and triglyceride levels, and reduced HDL-cholesterol. Increased betatrophin levels in women with GDM were demonstrated in Chinese women and not in those living in western countries. Cord blood betatrophin did not display a statistical difference between neonates from women with and without GDM.

AUTHOR CONTRIBUTIONS

Faustino R. Pérez-López, María T. López-Baena, Junhua Yuan, and Gonzalo R. Pérez-Roncero determined the search strategy and screened the selected studies. Manuel Sánchez-Prieto, Gonzalo R. Pérez-Roncero, and Junhua Yuan extracted the data. Gonzalo R. Pérez-Roncero, Faustino R. Pérez-López, and Seshadri Reddy Varikasuvu performed the statistical analysis. All authors participated in the writing and revision of this paper. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article.

ETHICS STATEMENT

This study did not involve human participants or animal research. This work was based on already produced and published data.

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PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/dmrr.3612.

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