British Journal of Nutrition (2023), 129, 1324–1331 doi:10.1017/S000711452200246X

Vitamin B_{12} and gestational diabetes mellitus: a systematic review and meta-analysis

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(Submitted 17 February 2022 – Final revision received 22 June 2022 – Accepted 25 July 2022 – First published online 2 August 2022)

Abstract

The relationship between vitamin B_{12} and gestational diabetes mellitus (GDM) remains controversial. To comprehensively evaluate the relationship between vitamin B_{12} and GDM, and to provide more information on GDM prevention, this study provides a systematic review and meta-analysis of vitamin B_{12} and GDM. As of September 22, 2021, 304 articles were searched in PubMed, Web of Science, EMBASE, and Cochrane databases, of which 15 studies met the inclusion criteria. Results presented there was no association between maternal vitamin B_{12} concentration during the first trimester with GDM, however, low vitamin B_{12} concentration in the second or third trimester of pregnancy was related to an increased risk of GDM. Compared with the non-GDM group, the vitamin B_{12} concentration in the GDM group was remarkably decreased (MD: −10·79; 95%CI: −21·37, −0·21), and vitamin B_{12} deficiency increased the risk for GDM (OR: 1·59; 95%CI: 1·10, 2·29). These effects were more significant among Asians. In addition, an increased ratio of high folate to low vitamin B_{12} in serum also increased the risk of GDM (OR: 1·87; 95% CI: 1·46, 2·41). These results suggest that more vitamin B_{12} may need to be provided during pregnancy.

Keywords: **Gestational diabetes mellitus: Vitamin B_{12}: Folate: Meta-analysis**

Gestational diabetes mellitus (GDM) is a common complication of pregnancy, named 'any degree of glucose intolerance with onset or first recognition during pregnancy'[1]. With the increasing trend during the past two decades, it has become a major public health problem[1]. According to data released by the International Diabetes Federation in 2021, the global prevalence of women with hyperglycaemia during pregnancy is 16·7 %, of which GDM accounts for 80·3 %, and the number of live births affected is as high as 21·1 million[2]. GDM can cause pre-eclampsia and may also increase the incidence of type 2 diabetes mellitus 3–6 years later after pregnancy[3,4]. In addition, it can also lead to adverse pregnancy outcomes (e.g. macrosomia and preterm birth) and increase the risk of fetal adulthood diseases (e.g. obesity and CVD)[5–7]. Therefore, exploring the aetiology of GDM and seeking effective prevention strategies have realistic and long-term significance for improving maternal and infant outcomes.

Vitamin B_{12}, the only water-soluble vitamin that contains metal ions, also known as cobalamin, plays an important role in pregnancy and is essential for DNA synthesis, cell division and amino acid metabolism. Total vitamin B_{12} decreases in concentration during the course of pregnancy, whereas holotranscobalamin (holoTC) remains relatively stable[8,9]. Two studies reported that lower serum total B_{12} concentrations were associated with a higher homeostatic model assessment for insulin resistance (HOMA-IR) index during the third trimester of pregnancy[10], and B_{12}-deficient pregnant women had higher BMI, the sum of skinfold thickness and insulin resistance than non-deficient women[11]. Therefore, the relationship between vitamin B_{12} status during pregnancy and GDM has received widespread attention, but the findings were inconsistent. On the one hand, two studies found that vitamin B_{12} levels were inversely correlated with fasting blood glucose concentrations ($r = -0{\cdot}44$, $P = 0{\cdot}0009$; $r = -0{\cdot}29$, $P = 0{\cdot}004$)[12,13]. Studies reported that vitamin B_{12} levels were significantly lower in GDM groups in the second and third trimesters of pregnancy, especially among Asians[13–17]. Some studies revealed vitamin B_{12} deficiency as a risk factor for GDM[11,13–15,17]. On the other hand, studies showed no association between vitamin B_{12} levels in the second and third trimesters of pregnancy and GDM, and the finding was also supported by others[18–20]. And vitamin B_{12} deficiency was

Abbreviations: **GDM**, **gestational diabetes mellitus**; **MMA**, **methylmalonic acid**.

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not associated with GDM[18]. Even more, a Chinese cohort study demonstrated higher vitamin B_{12} concentrations in the first-trimester GDM group than in the control group (421·00 *v.* 364·00 pg/ml, $P < 0·002$)[21].

The aim of this study is to conduct a systematic review and meta-analysis on the association of vitamin B_{12} with GDM and to clarify whether vitamin B_{12} deficiency is associated with GDM. Recent studies have shown that high concentrations of folate interfere with GDM, and the article further explores the relationship between high folate:low vitamin B_{12} ratio and GDM.

Methods

Search strategy

The study was conducted by the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines recommendations and searches performed in PubMed, Web of Science, EMBASE and Cochrane to identify all relevant publications updated before 22 September 2021. This review evaluated the effect of vitamin B_{12} concentration during pregnancy on GDM. Databases were searched by terms: vitamin B_{12}; B_{12}, Vitamin; Vitamin B_{12}; B_{12}, Vitamin; Cyanocobalamin; Cobalamins; Cobalamin; Eritron; Diabetes, Gestational; Diabetes, Pregnancy-Induced; Diabetes, Pregnancy Induced; Pregnancy-Induced Diabetes; Gestational Diabetes; Diabetes Mellitus, Gestational; Gestational Diabetes Mellitus. The full search strategy for the PubMed database is listed (online Supplementary Table S1).

Inclusion criteria

For this paper, the association of vitamin B_{12} and GDM was eligible for inclusion as follows: (1) studies showed the comparison of vitamin B_{12} concentrations in GDM and the non-GDM (control group) women; or (2) studies reported the incidence or prevalence of GDM based on the concentration of vitamin B_{12} or its deficiency levels, or the folic acid:vitamin B_{12} ratio.

Exclusion criteria

The following studies were excluded: (1) title/abstract/full text due to non-relevance; or (2) reviews, meta-analyses, conferences, letters, guidelines or English Literature; or (3) unable to get the full text; or (4) no *in vitro* or *in vivo* experiments; or (5) no relevant value for vitamin B_{12} or study variables.

Study selection process

Two independent authors (Xue Chen and Yushan Du) first independently screened the titles and abstracts, then identified that the relevant variables of the full-text articles were eligible. Finally, this paper included fifteen studies that fulfilled the inclusion criteria (Fig. 1).

Data extraction and quality assessment

Two reviewers independently extracted data from the study according to the pre-designed Excel tables. The data include the first author, publication year, participant nationality, study design, GDM diagnostic criteria, period of oral glucose tolerance test and vitamin B_{12} test, and the sample size. The quality assessment used the Newcastle–Ottawa Scale. The third reviewer will be joined the assessment if there are disagreements on the trial's risk of bias.

Data synthesis and analysis

Meta-analysis was performed using R 4.1.0 software. Results are presented as mean differences (MD) for continuous variables (concentrations of vitamin B_{12}) and the differences in risk ratios (adjustment of vitamin B_{12} deficiency) between GDM and non-GDM. Given that different periods for vitamin B_{12} and oral glucose tolerance tests are evaluated, we expect a large amount of heterogeneity in the results. The I^2 statistic is used to assess the heterogeneity between studies. I^2 values >50 % are considered to indicate a large heterogeneity, and further subgroup analyses explored the cause. Funnel charts with Egger's tests were used to measure publication bias.

Result

Study characteristics

A total of 304 studies were identified, and fifteen studies were finally included. Details of the included studies are shown in Table 1. Of the fifteen studies, nine of them were from Europe (including the UK, Poland, Italy and Turkey) and six of them were from Asia (including China, Singapore, Pakistan and India). In all fifteen studies, the periods of oral glucose tolerance test, that is, the diagnosis time of GDM was between 24 and 32 weeks of pregnancy. However, the periods for vitamin B_{12} are inconsistent: four of the fifteen studies were detected during the first trimester (<13 weeks), ten were during the second or third trimester (>13 weeks), and one was not listed.

Effects of vitamin B_{12} and gestational diabetes mellitus

The effect of vitamin B_{12} concentration (pmol/l) during pregnancy on GDM is shown in Fig. 2. Compared with the non-GDM group, the vitamin B_{12} concentration in the GDM group was lower (MD = −6·83; 95 % CI (−17·56, 3·89)), although there is no significant statistical difference.

In subgroup analysis (Fig. 2), there was no association between maternal vitamin B_{12} concentration with GDM during the first trimester (MD = 15·75; 95 % CI (-20·05, 51·54)). However, the vitamin B_{12} concentration in the GDM group was remarkably lower than that in the non-GDM group (MD = -10·79; 95 % CI (-21·37, -0·21)) during the second or third trimester. We further analysed ethnicity as there is large heterogeneity (I^2 = 78 %, $P < 0·01$). The results illustrated that the vitamin B_{12} concentration of Asians dropped dramatically in the GDM group during the second or third trimester (MD = -25·78; 95 % CI (-38·56, -12·99)) (Fig. 3). There is no publication bias in the analysis (online Supplementary Fig. S1), and Egger's tests were not significant ($P = 0·52$).

Effects of vitamin B_{12} deficiency and gestational diabetes mellitus

Six of the fifteen included studies examined the effect of vitamin B_{12} deficiency in the second or third trimester on GDM. The

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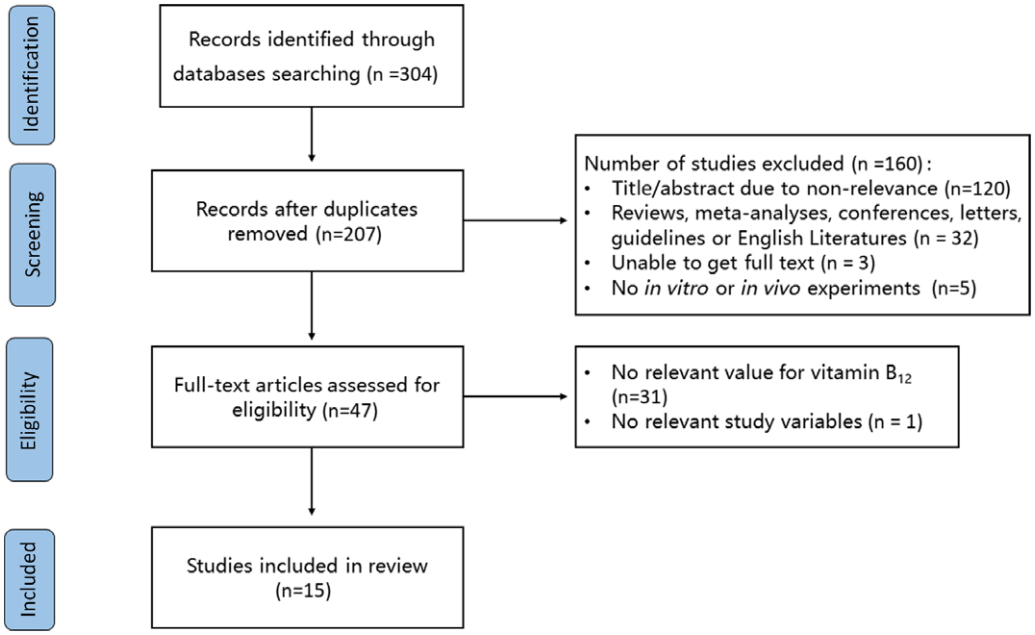

Fig. 1. PRISMA flow diagram for reviews of selection process. PRISMA, Preferred Reporting Items of Systematic Reviews and Meta-Analyses.

results suggested that vitamin B_{12} deficiency was associated with 1·59 times higher risk of GDM than the non-GDM group (OR: 1·59; 95 % CI (1·10, 2·29)) (Fig. 4). Further steps were taken to analyse these results due to heterogeneity (I^2 = 77 %, P < 0·01). There was a higher risk of vitamin B_{12} deficiency in GDM in Asians (OR: 2·08; 95 % CI (1·47, 2·96)), but no effects were observed among Europeans (Fig. 4). The publication bias was acceptable (online Supplementary Fig. S2), and Egger's tests were not significant (P = 0·09).

Ratio of folate and vitamin B_{12} on gestational diabetes mellitus

Five of the fifteen studies assessed the risk of GDM with high folate:low vitamin B_{12} ratio (Fig. 5). An increased maternal high folate:low vitamin B_{12} ratio during the second or third trimester was associated with an 87 % increased risk of GDM compared with non-GDM (OR: 1·87; 95 % CI (1·46, 2·41)). The publication bias was acceptable (online Supplementary Fig. S3), and Egger's test was not significant (P = 0·70).

Discussion

This meta-analysis showed that vitamin B_{12} concentrations were lower in the GDM group, particularly in the second or third trimester, which was more remarkable for Asians. Some biochemical studies have shown decrease in circulating cobalamin levels during pregnancy[8,9,22]. This was associated with a physiological decline in maternal vitamin B_{12}. The level of vitamin B_{12} was influenced by the concentration of the two plasma-binding proteins, transcobalamin and haptocorrin. Some studies had reported that total vitamin B_{12} levels in the mother gradually decreased during pregnancy with the decrease in holohaptocorrin (holo HC), and total B_{12}-binding capacities had less saturation, although the levels of holotranscobalamin (holoTC) remain relatively stable[8,9,23]. Thus, in addition to vitamin B_{12} transferred to the fetus and hemodilution, physiological fall in maternal B_{12} was also associated with changes in B_{12}-binding proteins and biomarkers[8,24,25]. Since there were only two studies on ethnic groups of Asian[21,26], the results may need further studies to verify.

Intracellularly, there were two vitamin B_{12}-dependent enzymatic reactions. And vitamin B_{12} deficiency led to impaired methylation and impaired metabolism of methylmalonate. In the absence of vitamin B_{12}, 5-methyltetrahydrofolate cannot be used for the formation of methionine and tetrahydrofolate, resulting in a state of pseudo-folate deficiency (methyl-trap). DNA synthesis based on methyl-traps was impaired, and alterations in mitochondrial content or function may progressively lead to the development of insulin resistance[27,28]. High homocysteine (Hcy) can induce cellular stress, apoptosis, and endothelial and DNA damage, which associate with CVD, preeclampsia and type 2 diabetes mellitus [29,30]. Additionally, vitamin B_{12} deficiency leads to an elevated methylmalonic acid (MMA) concentration, a product of hydrolysis of the excessive concentration of methylmalonyl-CoA. MMA-CoA accumulation can inhibit fatty acids oxidation and hence increase adipogenesis and IR[28]. This paper meta-analysed the risk of vitamin B_{12} deficiency during pregnancy on GDM and found that the risk of vitamin B_{12} deficiency during pregnancy in the GDM group was 1·59 times higher than that in the non-GDM group (OR: 1·59; 95 % CI (1·10, 2·29)), and the risk for Asians could reach 2·08 times (OR: 2·08; 95 % CI (1·47, 2·96)). Therefore, we speculated that vitamin B_{12} deficiency during pregnancy may induce GDM through IR. Unfortunately, four of the six studies defined vitamin B_{12} deficiency concentrations as <150 pmol/l, while the other two were well below this standard. This was unlikely to provide a GDM risk threshold based on vitamin B_{12} deficiency levels in the second or third trimester.

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Table 1. Characteristics of the inclusion study (*n* 15)

First author	Publication year	Country	Study design	GDM criteria	GDM/non-GDM	OGTT test (week)	The average age of GDM (year)		Folate supplementation	Vitamin B_{12} supplementation	Vitamin B_{12} test (week)
van Weelden	2021	UK	Randomised controlled trial	IADPSG	271/675	23–30	31·8	4·8	Not mentioned	Not mentioned	23–30
Saravanan	2021	UK	Prospective	NICE IADPSG	538/4208 633/4113	26–28	31·9	5·16	yes	no	<16
Jankovic-Karasoulos	2021	Australia, New Zealand, Ireland, UK	Prospective	WHO 2016	33/111	26	28·9	5·2	yes	no	15
Chen	2021	China	Prospective	IADPSG	180/878	24–28	No data		yes	no	9–13
Liu	2020	China	prospective	IADPSG And WHO	67/299	24–28	30·5	4·0	yes	no	<12
Radzicka	2019	Poland	Case–control	IADPSG	60/19	24–28	32·27	4·5	Not mentioned	Not mentioned	24–28
Li	2019	China	Cross-sectional	IADPSG	90/316	24–28	No data		Not mentioned	Not mentioned	24–28
Lai	2018	Singapore	Cross-sectional	WHO 1999	164/749	26	No data		Not mentioned	Not mentioned	26
Butt	2017	Pakistan	Cross-sectional	ADA	59/41	Second or third trimester	26·37	4·33	Not mentioned	Not mentioned	No data
Sukumar	2016	UK	Case–control	WHO 1999	143/201	26–28	31·4	5·8	yes	no	Second or third trimesters
Krishnaveni	2009	India	Retrospective cohort	WHO1999	49/724	30	No data		Not mentioned	Not mentioned	30
Idzior-Waluś	2008	Poland	Case–control	WHO	44/17	26–32	30·5	6·6	yes	no	26–32
Guven	2006	Turkey	Cross-sectional	C&C	30/147	24–28	30·0	4·3	no	no	24–28
Tarim	2004	Turkey	Prospective	C&C	28/210	24–28	32	4·03	Not mentioned	Not mentioned	24–28
Seghieri	2003	Italy	Case–control	ADA	15/78	24–28	34·6	3·1	no	no	24–28

GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; IADPSG, International Association of the Diabetes and Pregnancy Study Groups; NICE, National Institute for Health and Clinical Excellence; ADA, American Diabetes Association; C&C, Carpenter and Coustan.

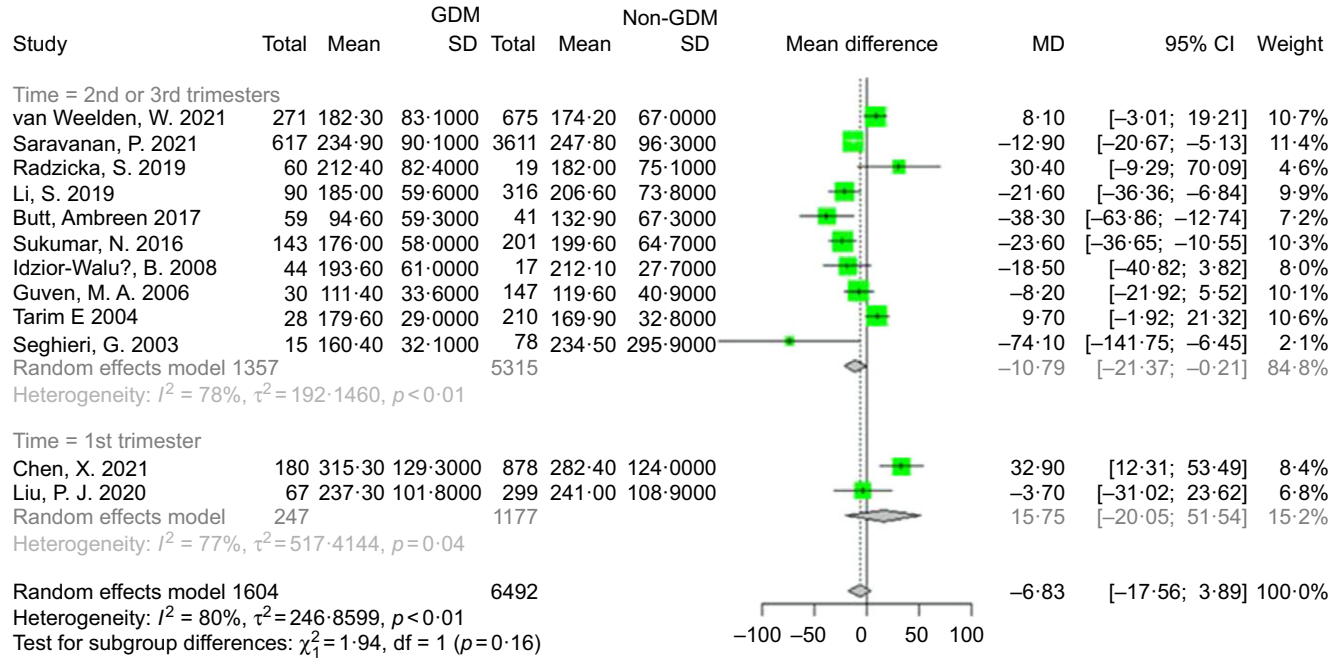

Fig. 2. Effect of vitamin B_{12} concentration (pmol/l) during pregnancy on GDM. GDM, gestational diabetes mellitus.

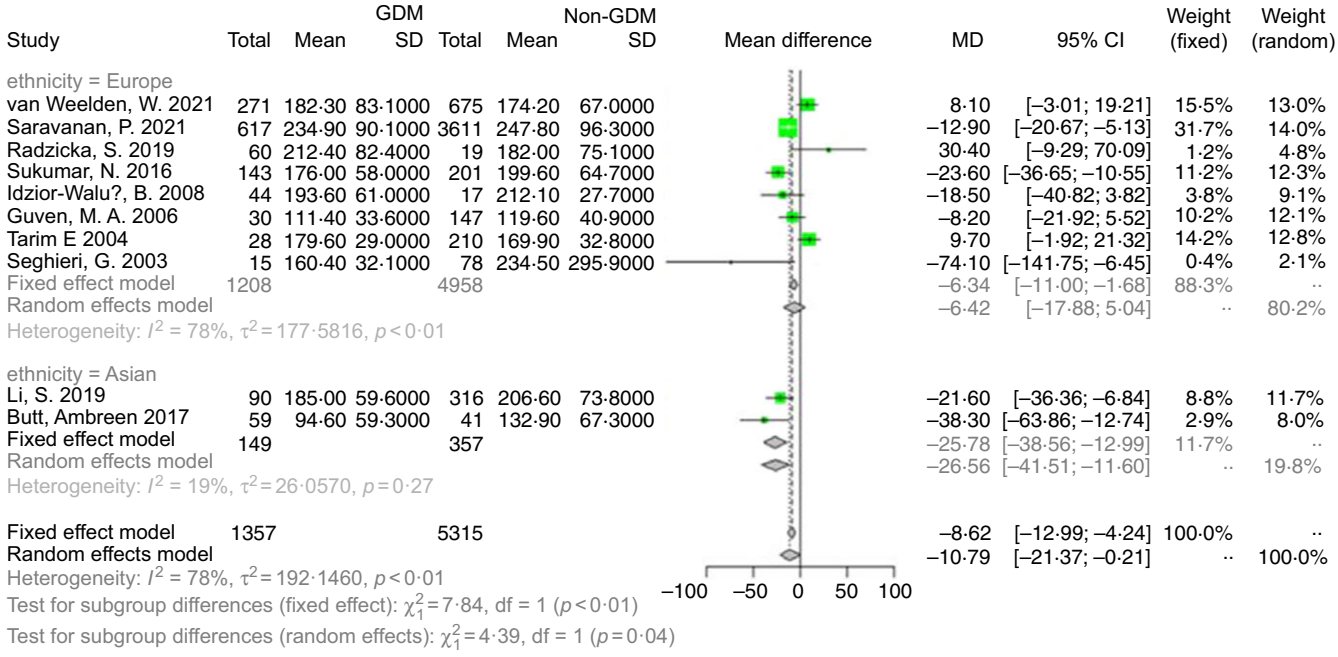

Fig. 3. Effect of vitamin B_{12} concentration (pmol/l) on GDM in the second or third trimester. GDM, gestational diabetes mellitus.

It was known that folate played an important role in the prevention of neural tube defects, and it was recommended for women of childbearing age to take folic acid supplements during the first trimester[31,32]. Some studies had shown that adequate folate intake before pregnancy could reduce the risk of GDM[33]; however, some had also shown that high folate intake and low levels of vitamin B_{12} significantly increased the risk of GDM[21,34]. Therefore, this study tried to clarify the correlation between the high folate to low B_{12} and GDM and showed that in the second or third trimester, higher folate:vitamin B_{12} ratios increased the risk of GDM by 87 % compared with non-GDM (OR: 1·87; 95 % CI (1·46, 2·41)).

A recent systematic review of the relationship between vitamin B_{12} status, pregnancy outcomes and offspring outcomes in India showed that the prevalence of vitamin B_{12} deficiency in Indian women during pregnancy had 40–70 %, and low maternal B_{12} and low vitamin B_{12}:high folate ratio were associated with a higher risk for GDM[22]. Unlike it, this study targets a wider

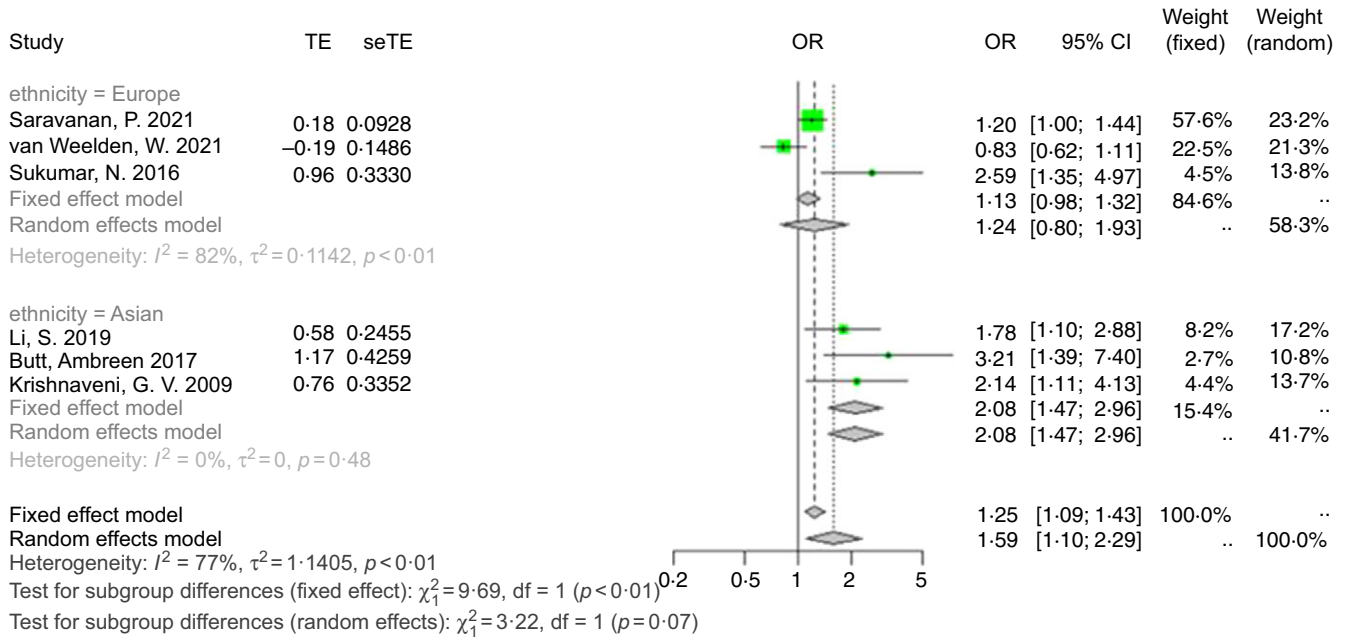

Fig. 4. Effect of vitamin B_{12} deficiency on GDM in the second or third trimester. GDM, gestational diabetes mellitus.

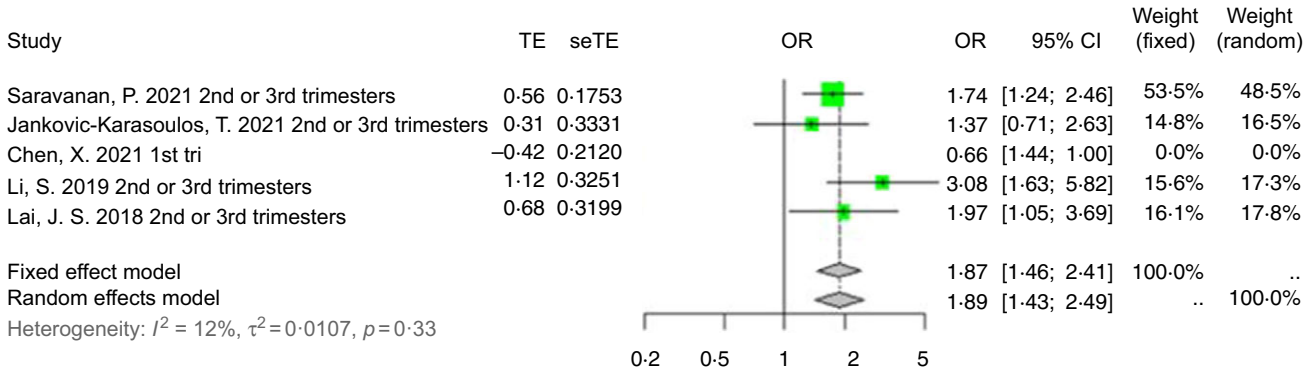

Fig. 5. Effect of the high folate:low vitamin B_{12} ratio on GDM. GDM, gestational diabetes mellitus.

population and is a multi-ethnic analysis of all countries, not just the Indian population, so the findings of the study are more comprehensive. In addition, this study also discussed the status of vitamin B_{12} at different stages of pregnancy, and the risk of vitamin B_{12} deficiency on GDM, which provided a basis for further analysis of the reasonable timing of vitamin B_{12} supplementation during pregnancy and a more accurate exploration of its mechanism.

We should be considered the limitations of the study. First, the lack of vitamin B_{12} biomarkers makes the assessment of GDM relatively simple. Some studies suggested that holoTC might be a better marker of vitamin B_{12} status during pregnancy than total vitamin B_{12} as it was less affected by hormonal changes and by the decrease in the levels of haptocorrin during pregnancy[35,36]. Hcy and MMA levels increased in the third trimester compared with the first trimester, which might be indicative of a degree of metabolic intracellular vitamin B_{12} depletion, even though both Hcy and MMA were lower than the established cut-off levels defining deficiency in non-pregnant women[8,37]. Most markers of vitamin B_{12} status (circulating levels of total vitamin B_{12}, holoTC, MMA and Hcy) are physiologically affected at low levels during pregnancy, complicating the assessment of vitamin B_{12}. Whether the reference values for vitamin B_{12} status in non-pregnant women apply to pregnant women is also debatable. Second, the limited number of studies available for meta-analysis, particularly the lack of data on maternal vitamin B_{12} concentrations in the first trimester (only two studies were inconsistent), hindered accurate assessment of the association between vitamin B_{12} and GDM throughout pregnancy. Third, there were differences in the adjustment confounding factors of GDM risk in the report, so it is uncertain whether the above results will still occur in the second or third trimester.

Conclusions

Taken together, this study revealed that vitamin B_{12} concentrations were lower in the GDM group in the second or third trimester, and vitamin B_{12} deficiency increased the risk of GDM, which

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was more significant in Asians. An increased maternal high folate:low vitamin B_{12} ratio during the second or third trimester also increased the risk of GDM. These results suggest that more vitamin B_{12} needs to be provided during pregnancy. To better promote the results and consider whether vitamin B_{12} supplementation is needed during pregnancy, we need more studies on folate and vitamin B_{12} associated with GDM or glycolipid metabolism. It can provide a theoretical clue for the prevention strategy of GDM and further study on the mechanism of vitamin B_{12} and GDM.

Acknowledgements

This research was supported by the Chinese Nutrition Society-Zhen Dong Tizhi and Health Fund (CNS-ZD2020-115). We also would like to express our sincere gratitude to the editor Matthew Woodcock (Dr.) and three anonymous reviewers for their valuable comments, which have greatly improved this paper.

X. C.: conceptualisation, data curation, formal analysis, methodology, software and writing original draft preparation. Y. D.: data curation. S. X.: methodology and writing – review. Z. L.: writing – review. J. L.: methodology, supervision, writing – review and editing.

The authors declare no conflict of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S000711452200246X

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