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META-ANALYSIS

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Vitamin B12 insufficiency is associated with increased risk of gestational diabetes mellitus: a systematic review and meta-analysis

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Abstract

Purpose Vitamin B12 deficiency has been associated with a plethora of metabolic abnormalities, such as hyperhomocysteinaemia, insulin resistance and defective synthesis of neurotransmitters and fatty acids. Inconsistency exists as to whether vitamin B12 deficiency is also associated with increased risk of gestational diabetes mellitus (GDM). The purpose of this study was to systematically review and meta-analyze the existing evidence for this association.

Methods A comprehensive search was conducted in PubMed, Scopus and Cochrane Central up to April 30, 2019. Data are expressed as odds ratio (OR) with 95% confidence interval (CI). The I^2 index was employed for heterogeneity.

Results Six studies ($n = 1810$ pregnant women, 309 GDM cases) fulfilled the eligibility criteria for qualitative and two studies for quantitative analysis. In five studies providing data on vitamin B12 concentrations for both groups, women with GDM had lower vitamin B12 levels when compared with non-GDM women. Women with vitamin B12 deficiency were at higher risk for developing GDM when compared with those who were vitamin B12 sufficient: OR 1.81 (95% CI, 1.25–2.63, I^2: 0%). Due to the small number of studies, the role of potential confounders could not be safely estimated.

Conclusions Vitamin B12 deficiency seems to be associated with increased risk of GDM. More studies are needed to further strengthen this finding and to clarify possible pathogenetic mechanisms.

Keywords Gestational diabetes mellitus · Pregnancy · Diabetes · Vitamin B12 deficiency

Introduction

Gestational diabetes mellitus (GDM) refers to carbohydrate intolerance of variable severity which is diagnosed during pregnancy. The definition is applied regardless of whether insulin or diet modification is used for treatment, or whether this condition persists after pregnancy [1, 2]. GDM is a common condition, with a prevalence of up to 18% depending on the criteria used for its diagnosis [3]. It can lead to adverse pregnancy outcomes, as it affects both mother and fetus, but appropriate treatment may improve perinatal morbidity and mortality and maternal health [4].

Vitamin B12 is a water-soluble vitamin that plays a crucial role in the methylation of DNA and cell metabolism. Activated coenzyme B12 acts as a methyl donor for the methylation processes of DNA and RNA and is also important for the synthesis of proteins and lipids. Its deficiency may lead to disruption of DNA synthesis, cellular inflammation, adiposity dysfunction with increased lipogenesis and homocysteine levels [5]. It has been speculated that elevated homocysteine concentrations and changes in the adipose tissue due to B12 deficiency could lead to insulin resistance and, thus, it has been suggested that B12 deficiency might result in glucose intolerance [5].

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Low vitamin B12 concentrations are common in pregnancy in all trimesters worldwide and may affect maternal and fetal health parameters, such as maternal body mass index (BMI), insulin resistance and affected lipid profile [6–10]. However, conflicting data exist with respect to the association between vitamin B12 deficiency and the risk of GDM [6–11], although studies from the UK and India have demonstrated an increased incidence of GDM in women with vitamin B12 deficiency [12, 13].

The aim of the current study was to systematically review and meta-analyze the existing evidence regarding the association between B12 deficiency and the risk of GDM. We also tried to elucidate the contributory role of potential confounders, such as BMI, homocysteine, folate and triglyceride concentrations, in this association.

Materials and methods

Search strategy

A comprehensive search was conducted up to April 30, 2019. We researched relevant studies in PubMed (Medline), Cochrane Central Register of Controlled Trials and Scopus. The following search string was used in PubMed: ((((((((((gestational diabetes[MesH]) OR pregnancy diabetes[tiab]) OR gestational hyperglycemia[tiab]) OR gestational hyperglycemia[tiab]) OR hyperglycemia pregnancy[tiab]) OR hyperglycemia pregnancy[tiab])) OR glucose pregnancy[tiab])) AND ((vitamin B12[MeSH]) OR hydroxocobalamine[tiab]))).

For Scopus the following search string was used: ((((((((((gestational AND diabetes[title/abstract]) OR pregnancy AND diabetes[title/abstract]) OR gestational AND hyperglycaemia[title/abstract]) OR gestational AND hyperglycemia[title/abstract]) OR hyperglycaemia AND pregnancy[title/abstract]) OR hyperglycemia AND pregnancy[title/abstract])) OR glucose AND pregnancy[title/abstract])) AND ((vitamin AND b12[title/abstract]) OR hydroxocobalamine[title/abstract]))).

Trial selection

Inclusion criteria were: (i) studies providing data about vitamin B12 concentrations during pregnancy and the prevalence or incidence of GDM; (ii) studies providing extractable data; (iii) studies providing the exact number of pregnant women with GDM and vitamin B12 sufficiency and deficiency. Both cohort and case-control studies were eligible. Studies were excluded if: (i) they were referring to other vitamins apart from B12, not directly linked to GDM; (ii) they were conducted in vitro; (iii) the control group (non-GDM women) was missing; (iv) they were written in non-English language; (v) they included women on antidiabetic medications or were diagnosed with DM before pregnancy. The studies excluded and their reasons for exclusion are presented in Supplementary Table 1.

Data extraction

The following data were recorded: (i) first author; (ii) year of publication; (iii) country in which the study was conducted; (iv) study design (case-control/cohort); (v) study duration; (vi) criteria of GDM definition; (vii) total number of pregnant women who participated in the study; (viii) number of GDM women; (ix) ethnicity; (x) pregnancy trimester during which the study was conducted. Parameters such as the age and BMI of women with and without GDM, as well as vitamin B12, folate, homocysteine and triglyceride concentrations were recorded for both groups (GDM and non-GDM women).

Risk of bias and study quality assessment

Newcastle−Ottawa scale (NOS) was used for assessing the quality of each study. This system evaluates studies based on three criteria: (i) participant selection; (ii) comparability of study groups; (iii) assessment of the outcome or exposure. A study can be awarded a maximum of four stars for the selection category, a maximum of two stars for the comparability category and a maximum of three stars for the outcome/exposure category. These results are presented in Supplementary Table 2.

Statistical analysis

The following comparisons were made according to the incidence or prevalence of GDM: (i) Pregnant women with GDM and vitamin B12 sufficiency were compared with those with GDM and vitamin B12 deficiency; (ii) Pregnant women with normal glucose homeostasis and vitamin B12 sufficiency were compared with those of normal glucose homeostasis and vitamin B12 deficiency. Additionally, vitamin B12 concentrations in GDM and non-GDM women were compared. Heterogeneity was tested with the Cochrane chi-square test and the degree of heterogeneity was quantified by the I^2 statistics. An I^2 index of 30–60% was considered as moderate, whereas values >60% were considered as high degree of heterogeneity. Associations were reported as odds ratio (OR) with 95% confidence intervals (CI). A p value of <0.05 was considered as statistically significant. All analyses were performed with the latest version of *STATA* software.

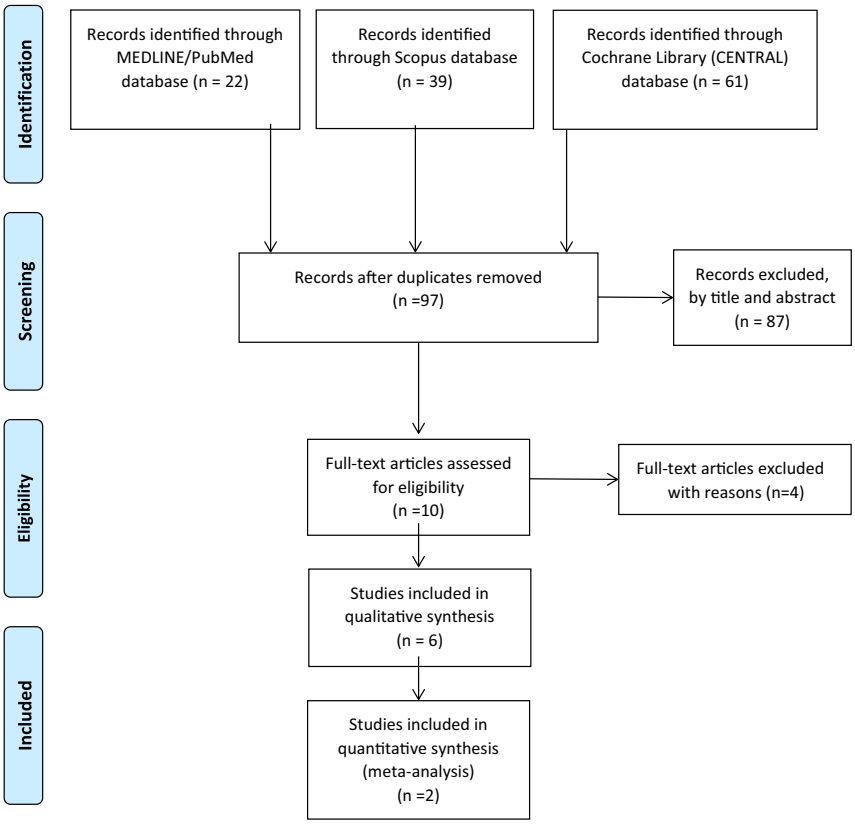

Fig. 1 Flow chart diagram

Results

Descriptive data

Initial screening yielded 122 publications. After removing duplicates, 97 publications were assessed for eligibility, 87 of which were excluded based on their title and/or abstract information. Finally, ten studies were assessed as full texts for eligibility, four of which were excluded due to the following reasons: (i) They were conducted in vitro ($n = 2$); (ii) They did not provide data on GDM women ($n = 1$); (iii) They were written in non-English language ($n = 1$). Six studies were included in the qualitative analysis [12–17], two of which [12, 13], could be meta-analyzed. The remainder [14–17] was excluded due to lack of data on the exact number of GDM according to B12 status. A flow diagram of the systematic review is presented in Fig. 1. The descriptive characteristics of the studies' participants are presented in Table 1. All studies were published between 2003 and 2016. The studies were of prospective ($n = 2$), case-control ($n = 2$) or cross-sectional ($n = 2$) design. The number of participants ranged from 61 to 785, yielding a total number of 1810 pregnant women, with 309 GDM cases. Studies varied from 6 months to 3 years (data available from six studies). The most common criteria used [13–15] for GDM diagnosis were the "Carpenter and Coustan" criteria by which after a 100-g oral glucose load two or more of the following plasma values should be met: fasting ≥ 95 mg/dLl, ≥180 mg/dL at 60 min, ≥155 mg/dL at 120 min and ≥140 mg/dL at 180 min [18], but in some studies [12, 17] the WHO 1999 (fasting glucose ≥6.1 mmol/L (≥110 mg/dL) or 2-h glucose ≥7.8 mmol/L (≥140 mg/dL)) [19] and "American Diabetes Association" (ADA) criteria [20] were applied [16]. According to the latter criteria, the diagnosis of GDM is set after 100-g oral glucose load (≥95 mg/dL fasting, ≥180 mg/dL at 1 h, ≥155 mg/dL at 2 h, and ≥140 mg/dL at 3 h). Two or more of the plasma glucose values must be met or exceeded for a positive diagnosis. Vitamin B12 deficiency was defined with B12 concentrations <200 pg/mL. Apart from indigenous pregnant populations, a cohort from the UK [12] included pregnant women of different origin, with different social and cultural/nutritional habits. Cohorts from Turkey [14, 15] constituted the most homogenous native populations.

Comparison between GDM and non-GDM women according to age and BMI

All but one [13] studies provided information about age and BMI. As expected, women with GDM tended to be older and with higher BMI when compared with those of normal glucose homeostasis. These are presented in detail in Table 2.

Table 1 Descriptive studies' characteristics

ID	First author	Year of publication	Country	Study design	Study duration (years)	GDM criteria	Number of pregnant women	Number of women with GDM (%)	Ethnicity	Weeks of pregnancy
1	Sukumar	2016	UK	Case-control	3	WHO 1999	344	143 (41.6)	European: 86.9% S. Asian: 9.3% Afro-Caribbean: 1.2% Other: 1.2%	26–28
2	Krishnaveni	2009	India	Prospective	2	Carpenter and Coustan	785	49 (6.2)	Hindu: 59.5% Muslim: 33.1% Other: 3.8	30
3	Tarim	2004	Turkey	Prospective	1	Carpenter and Coustan	304	28 (9.2)	Turkish	24–28
4	Guven	2006	Turkey	Cross-sectional	2	Carpenter and Coustan	223	30 (13.4)	Turkish	24–28
5	Seghieri	2003	Italy	Cross-sectional	One semester	American Diabetes Association	93	15 (16.1)	Italian	24–28
6	Idzior-Walus	2008	Poland	Case-control	No data	WHO 1999	61	44 (72.1)	No data	26–32

WHO World Health Organization, *GDM* gestational diabetes mellitus

Table 2 Age and BMI of the participants

ID	First author	Mean age the e of the entire cohort (years)	Mean age of GDM women (years)	Mean age of non-GDM women (year)	p value[a]	Mean BMI of the entire cohort (kg/m$^{2)}$	Mean BMI of GDM women (kg/m$^{2)}$	Mean BMI of non-GDM women (kg/m$^{2)}$	p value[b]
1	Sukumar	30.3 ± 5.8	31.4 ± 5.8	29.6 ± 5.9	$p = 0.0053$	28.8 ± 7.4	31.7 ± 7.0	26.7 ± 7.1	$p < 0.0001$
2	Krishnaveni	23 ± 3	N/A	N/A	—	23.1(20.8–25.9)	N/A	N/A	—
3	Tarim	N/A	32 ± 4.0	26.8 ± 4.4	$p < 0.0001$	N/A	27.1 ± 2.1	25.24 ± 1.9	$p < 0.0001$
4	Guven	N/A	30.0 ± 4.3	28.6 ± 3.4	$p = 0.0446$	N/A	29.1 ± 4.1	27.88 ± 2.8	$p = 0.0297$
5	Seghieri	N/A	34.6 ± 3.1	32.3 ± 3.7	$p = 0.0264$	N/A	26.7 ± 3.2	26.3 ± 3.7	$p = 0.6966$
6	Idzior-Walus	N/A	30.5 ± 6.6	26.2 ± 4	$p = 0.0150$	N/A	27.8 ± 5.2	25.6 ± 3.4	$p = 0.1123$

Data are presented as mean ± SD or range

BMI body mass index, *GDM* gestational diabetes mellitus, *N/A* not available

[a]Comparison of the age between the groups of GDM and non-GDM women

[b]Comparison of the BMI between the groups of GDM and non-GDM women

Table 3 GDM cases according to maternal vitamin B12 status

ID	First author	Vitamin B12 deficiency (entire cohort)		GDM cases with vitamin B12 deficiency (%)	GDM cases with vitamin B12 sufficiency (%)
		Yes (%)	No (%)		
1	Sukumar	90 (26.2)	254 (73.8)	46 (51.1)	97 (38.2)
2	Krishnaveni	334 (43.2)	439 (56.7)	29(8.7)	20 (4.6)
3	Tarim	N/A	N/A	N/A	N/A
4	Guven	N/A	N/A	N/A	N/A
5	Seghieri	N/A	N/A	N/A	N/A
6	Idzior-Walus	N/A	N/A	N/A	N/A

Data are presented as mean or median

N/A not available

Table 4 Comparison between GDM and non-GDM women according to vitamin B12 concentrations

ID	First author	Vitamin B12 concentrations (pg/mL)		*p* value
		Normal glucose tolerance	GDM	
1	Sukumar	195.6 (157.9–244.6)	169.0 (140.2–217.7)	$p < 0.01$
2	Krishnaveni	N/A	N/A	N/A
3	Tarim	161.8 ± 55.3	150.8 ± 45.5	$p = 0.1066$
4	Guven	234.5 ± 295.9	160.4 ± 31.1	$p = 0.0008$
5	Seghieri	229.9 ± 44.32	242.9 ± 39.2	$p = 0.2513$
6	Idzior-Walus	287.0 ± 37.5	262 ± 82.6	$p = 0.1079$

Data are presented as mean (± SD) or median (interquartile range)

GDM gestational diabetes mellitus, *N/A* not available

Comparison between GDM and non-GDM women according to vitamin B12 concentrations

Five studies provided data on vitamin B12 concentrations in both groups of pregnant women (GDM and non-GDM) [12, 14–17]. A higher proportion of women with GDM had B12 insufficiency compared with non-GDM in all the eligible studies (Table 3). Moreover, women with GDM demonstrated lower vitamin B12 levels in two studies [12, 14] compared with non-GDM women, whereas in three studies [15–17] the difference did not reach statistical significance (Table 4).

Comparison between GDM and non-GDM women according to folate, homocysteine, and triglyceride concentrations

Folate concentrations were comparable between GDM and non-GDM women. In contrast, homocysteine concentrations were higher in GDM than in non-GDM women in four studies [14–17], as well as triglyceride concentrations in three studies [14, 16, 17]. These data are presented in detail in Table 5.

Meta-analysis

Only two of the six included studies could be meta-analyzed [12, 13]. As mentioned above, the remainder did not provide data on the exact number of pregnant women with GDM according to vitamin B12 status.

Pregnant women with vitamin B12 deficiency demonstrated a higher risk of GDM compared with those with vitamin B12 sufficiency [OR: 1.81 (95% CI 1.25–2.63), I^2: 0%] (Fig. 2).

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis on the association between vitamin B12 deficiency and GDM. Pregnant women with vitamin B12 deficiency (defined as concentrations <200 pg/mL) are at an increased risk of GDM compared with those with vitamin B12 sufficiency.

Regarding the primary endpoint, two studies provided available data. The first study, showing that women with vitamin B12 deficiency were at higher risk of GDM, was a prospective cohort from India published in 2009, showing a 2.14 (95% CI: 1.11–4.13) higher risk of GDM in vitamin B12 deficient compared with vitamin B12 sufficient pregnant women [13]. The authors also found a link between vitamin B12 deficiency, adiposity and its related disorders and proposed the term "diabesity" to describe all these together. The possible interpretations of their findings were that B12 deficiency may promote adiposity and that, conversely, adiposity itself may lower B12 concentrations, especially during pregnancy. The proposed mechanisms are the greater hemodilution, increased glomerular filtration rate and urinary losses as well as increased transfer of nutrients

Table 5 Folate, homocysteine and triglyceride concentrations in GDM and non-GDM women

ID	First author	Folate in non-GDM women (nmol/L)	Folate in GDM women (nmol/L)	Homocysteine in non-GDM women (μmol/L)	Homocysteine in GDM women (μmol/L)	Triglycerides non-GDM women (mg/dL)	Triglycerides GDM women (mg/dL)
1	Sukumar	20.8 (14.5–34.4)	21.5 (13.5–34.5)	N/A	N/A	N/A	N/A
2	Krishnaveni	N/A	N/A	N/A	N/A	N/A	N/A
3	Tarim	25.1 ± 10.9	14.36 ± 5.0	4.8 ± 0.9	5.7 ± 0.9	180.0 ± 40.9	249.0 ± 43.5
4	Guven	15.1 ± 7.2	14.36 ± 5.0	7.4 ± 1.6	9.0 ± 3.1	N/A	N/A
5	Seghieri	31.3 ± 16.5	33.3 ± 17.9	4.45 ± 1.5	5.8 ± 2.2	212.3 ± 70.7	247.7 ± 115.0
6	Idzior-Walus	25.1 ± 13.3	25.3 ± 13.5	7.4 ± 1.1	8 ± 2	168.0 ± 44.2	238.0 ± 79.6

Data are presented as mean ± SD or median

N/A not available

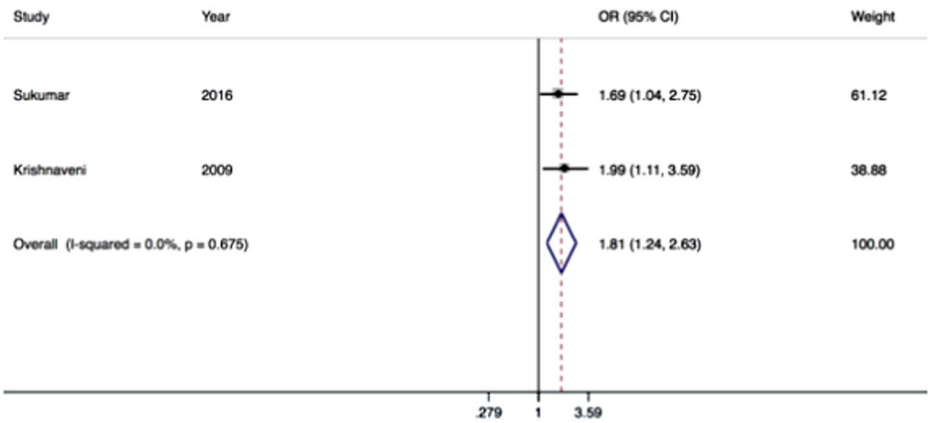

Fig. 2 Forest plot of the comparison between pregnant women with vitamin B12 sufficiency and deficiency, with regard to GDM risk

to the fetus. In this sense, insulin resistance is promoted as well.

The second study investigating the association between maternal vitamin B12 levels during pregnancy and the risk of GDM was published in 2016 [12]. This was retrospective in design, including data from the UK population showing not only an association of low vitamin B12 status during pregnancy with increased risk for GDM, but also an independent predictive role of high BMI during the first semester, for B12 deficiency. However, this study did not prove causation or the direction of the relationship between these factors.

On a pathogenetic basis, vitamin B12 seems to play a fundamental role in the synthesis of DNA, proteins and lipids. Along with folate, it participates in a series of cellular reactions by acting as essential co-factors for the synthesis of methionine from homocysteine [21]. Moreover, at the mitochondrial level, vitamin B12 acts as coenzyme for the conversion of methylmalonyl-CoA to succinyl-CoA, during the process of fatty acid oxidation. In the absence of vitamin B12, this process is inhibited and lipogenesis is promoted [22]. Vitamin B12 deficiency in human adipocytes changes tissue-specific microRNAs (mirRs) and circulating miRs (which are epigenetic modulators) leading to adverse metabolic phenotype and excessive lipid accumulation [23]. Therefore, pregnant women with vitamin B12 deficiency are more prone to obesity, insulin resistance and, concomitantly, GDM.

Regarding our study's secondary endpoint, both homocysteine and triglyceride concentrations were higher in women with GDM compared to those with non-GDM. Folate concentrations were similar between groups. Hyperhomocysteinemia is a marker of both folate and vitamin B12 deficiency and has been studied and identified as a risk factor for diabetes mellitus, insulin resistance and cardio-vascular disease [24–26]. The positive association between homocysteine and elevated insulin resistance might be caused by the insulin-mediated reduction in the activity of key enzymes which govern the remethylation pathway or control the transsulfuration pathway [27]. Differences in oral folate supplementation or in serum albumin have been identified as modulators of homocysteine concentrations during pregnancy [28]. Three studies [14–16] have shown higher homocysteine concentrations in GDM compared with non-GDM women. However, Idzior-Walus et al. [17] did not observe any difference in homocysteine levels between the these two groups. Therefore, more studies are needed to confirm this association. On the other hand,

hypertriglyceridaemia is a common feature in insulin-resistant patients [29]. Triglycerides may increase oxidative stress and impair insulin action [30]. With respect to vitamin B12, Idzior-Walus et al. [17]. demonstrated a negative association between vitamin B12 and serum triglyceride concentration in GDM women ($r = -0.42$, $p < 0.01$). Conflicting data with regard to triglyceride concentrations in GDM and non-GDM women have been reported [14, 16]. With respect to BMI, the results were not conclusive when pregnant women with GDM were compared with non-GDM women [12, 14–17].

Our study has certain limitations. First, due to lack of available studies, a relatively small number of studies were included in this meta-analysis, which does not allow to draw safe conclusions. Second, the diagnosis of GDM was set with different criteria. Third, the association between the aforementioned confounders and vitamin B12 concentrations was not investigated by all studies; therefore, it was impossible to perform a meta-regression analysis. Fourth, in the studies included in the present systematic review, it was not specified if women with GDM were receiving metformin, which could have modified B12 concentrations. Fifth, the nutritional habits of the participants were mentioned only in one of the studies. Last but not least, it is not specified, apart from one study, if the women that participated in the studies were under vitamin supplementation.

Conclusions

In summary, this systematic review and meta-analysis shows that pregnant women with vitamin B12 deficiency are at almost twofold higher risk to develop GDM, when compared with those with vitamin B12 sufficiency. This should be taken into account when building prognostic models for detection of GDM, especially in high-risk women. Well-designed prospective, cohort and interventional studies are needed to elucidate this association and to investigate whether supplementation with B12 before or during pregnancy could reduce this risk.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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