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Association between maternal vitamin D levels and risk of adverse pregnancy outcomes: a systematic review and dose–response meta-analysis†

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Epidemiological studies have investigated the associations between vitamin D and the risk of adverse pregnancy outcomes; however, the results are conflicting and dose–response relationships remain to be confirmed. This study aimed to summarize previous studies on the associations of vitamin D levels with the risk of gestational diabetes mellitus (GDM), pre-eclampsia (PE), gestational hypertension (GH), and caesarean section (C-section), and to clarify the dose–response trends. PubMed, Embase, Scopus, and Web of Science were searched to identify eligible articles. A total of 69 prospective observational studies including cohort studies, case-cohort studies, or nested case-control studies were included in the current systematic review, of which 68 studies were available for meta-analysis. Compared with the lowest level, the highest level of 25(OH)D was significantly associated with a lower risk of GDM (RR: 0.76; 95% CI: 0.66–0.87), PE (RR: 0.74; 95% CI: 0.60–0.90;), and GH (RR: 0.87; 95% CI: 0.79–0.97); however, no significant relationship was found for C-section (RR: 1.00; 95% CI: 0.90–1.12). There was significant between-study heterogeneity for GDM (I^2 = 69.2%; $P_{heterogeneity}$ < 0.001), PE (I^2 = 52.0%; $P_{heterogeneity}$ = 0.001), and C-section (I^2 = 59.1%; $P_{heterogeneity}$ < 0.001), while no heterogeneity was found for GH (I^2 = 0.0%; $P_{heterogeneity}$ = 0.676). For each 25 nmol L^{-1} increase in 25(OH)D, the pooled RR was 0.92 (95% CI: 0.86–0.97) for GDM and 0.89 (95% CI: 0.84–0.94) for PE, respectively. Notably, the dose–response analysis showed a non-linear relationship between maternal 25(OH)D levels and the risk of PE ($P_{non\text{-}linearity}$ = 0.009). Our meta-analysis provides further scientific evidence of the inverse association between 25(OH)D levels and the risk of GDM, PE, and GH, which may be useful for the prevention of pregnancy complications. However, more evidence from prospective studies is needed regarding the dietary intake of vitamin D during pregnancy.

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Introduction

Gestational diabetes mellitus (GDM), pre-eclampsia (PE), gestational hypertension (GH), and caesarean section (C-section) are serious adverse pregnancy outcomes that increase the risk of maternal and fetal/neonatal death and long-term health risks for the mother and offspring, such as diabetes mellitus, obesity, and cardiovascular disease.[1–4] Vitamin D is an essential fat-soluble steroid hormone mainly produced through dietary intake and skin exposure to ultraviolet B rays from sunlight.[5] However, increased air pollution, lifestyle changes, and the use of sunscreen products have further affected the synthesis of vitamin D, leading to a widespread prevalence of vitamin D deficiency, especially in pregnant women.[6–8] In addition to the well-documented effect in regulating calcium and phosphorus balance and maintaining bone health, numerous studies have identified that vitamin D has anti-inflammatory and immunomodulatory functions,[9,10] which take on pivotal roles in pregnancy.

Observational studies have extensively investigated the associations of maternal vitamin D deficiency with the risk of adverse pregnancy outcomes, but the results are inconsistent.[11–16] Some cohort studies have found that vitamin D deficiency is associated with a reduced risk of GDM[16] and PE.[11] However, the results of some other studies showed no significant association between vitamin D deficiency and the risk of GDM, PE, GH, or C-section.[12–15] Since 2011, many meta-analyses of observational studies have been published, showing that maternal vitamin D status is inversely associated with the risk of GDM[17,18] and PE,[19] but not with C-section.[20] However, previous studies had some limitations in their

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design and therefore no clear conclusions could be drawn. For example, some research included studies with cross-sectional designs or case-control studies, which may affect the reliability of the results. To the best of our knowledge, no meta-analysis has examined the relationship between vitamin D levels and the risk of GH, and only one study in 2013 assessed the relationship between vitamin D levels and the risk of C-section. In addition, most of the studies did not explore the dose–response relationship of vitamin D levels with the risk of adverse pregnancy outcomes.

Due to the lack of a comprehensive meta-analysis of prospective studies on pregnancy complications, we performed this meta-analysis to provide updated evidence on the association of maternal blood and dietary levels of vitamin D with the risk of adverse pregnancy outcomes.

Methods

Search strategy

This meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (ESI Table S1†),[21] and our protocol has been registered in PROSPERO (CRD42021244431). We conducted a systematic search of electronic databases including PubMed, Embase, Scopus, and Web of Science from the inception to January 19, 2021. In short, we searched for the following keywords: ("Vitamin D" OR "25-hydroxyvitamin D" OR "25 (OH)D" OR "Cholecalciferol" OR "Ergocalciferol") AND ("Gestational diabetes mellitus" OR "Pre-eclampsia" OR "Hypertension, pregnancy-induced" OR "Caesarean section" OR "Pregnancy outcome"). Details of the search strategy are provided in ESI Table S2.† Additionally, the bibliographies of relevant meta-analyses were manually searched to identify eligible literature.

Study selection

We included studies that met the following criteria: (1) studies with prospective design (cohort, case-cohort, or nested case-control studies); (2) reported the intake of vitamin D or 25(OH) D level as exposure; (3) reported the incidence of pregnancy outcomes such as GDM, GH, PE, and C-section as the outcome variables; (4) reported risk estimates and 95% confidence intervals (CIs), or provided sufficient data to calculate these values; and (5) for dose–response analysis, studies should report at least three exposure categories and provide the number of cases and participants in each category. We excluded letters, commentaries, reviews, meta-analyses, conference abstracts, studies without original data, and non-English articles.

Data extraction and quality assessment

Two investigators (RZ and LZ) independently extracted the following information from each eligible study using a standardized data collection form: first author's name, year of publication, country, study design, mean age or age range of participants, sample size, vitamin D assessment methods, type of outcomes, and adjustment factors. The study quality of selected studies was assessed using the Newcastle Ottawa Quality Assessment Scale (NOS).[22] Studies scoring more than six stars are regarded as high in quality.

Statistical methods

RRs and corresponding 95% CIs were used as the risk estimates for studies, and HRs and ORs were considered approximately equal to the RRs. A random-effects model was used to pool RRs and 95% CIs for the comparison of the highest *versus* lowest category of exposure.[23] We used risk estimates from the multivariate models. Heterogeneity between studies was evaluated by Cochran's Q test ($P < 0.10$) and the I^2 statistic test.[24] I^2 values of 25%, 50%, and 75% were considered as low, moderate, and high heterogeneity, respectively.[25] We conducted the subgroup analyses to identify sources of heterogeneity by potential influencing factors such as study type, geographic location, study quality, sample size, 25(OH)D assay methods, blood sample type, trimester of sample collection, and whether adjusting for important factors. Meta-regression was performed to explore the heterogeneity between subgroups.[26] Funnel plots and Egger's regression test[27] were used to assess the publication bias. We also performed sensitivity analyses with a random-effects model to assess the effect of excluding each study on the overall estimates.

For the dose–response meta-analysis, 25(OH)D concentrations of ng mL^{-1} were converted to nmol L^{-1} by multiplying the values by 2.5. In studies that provided at least three categories of vitamin D levels, we extracted the mean or median vitamin D level in each category. When studies reported range values, we calculated the midpoint between the lower and upper limits of the category. If the highest category was open-ended, the width of the adjacent interval was used to calculate the upper bound. For studies that did not use the lowest category as the reference, we recalculated risk estimates using the method described by Hamling *et al.*[28]

A linear dose–response analysis of a random-effects model was performed using the generalized least squares regression to estimate the RRs for every 25 nmol L^{-1} increments in 25 (OH)D levels.[29] In addition, we examined the possible non-linear dose–response relationships by modeling the 25(OH)D levels through restricted cubic splines with 3 knots at the 10th, 50th, and 90th percentiles of the distribution.[30,31] The non-linear P value ($P_{\text{non-linearity}}$) was calculated by a likelihood ratio test.[30,32] We used STATA version 15.1 (StataCorp, College Station, TX) for all analyses. Statistical tests were performed using a two-tailed method with a significance level of $P < 0.05$.

Results

Literature search and study characteristics

Our search retrieved 7427 records, of which 7212 were excluded by the initial screening according to titles and abstracts. After the full-text screening, 145 articles were further excluded (ESI Table S3†), and we finally included 69 articles

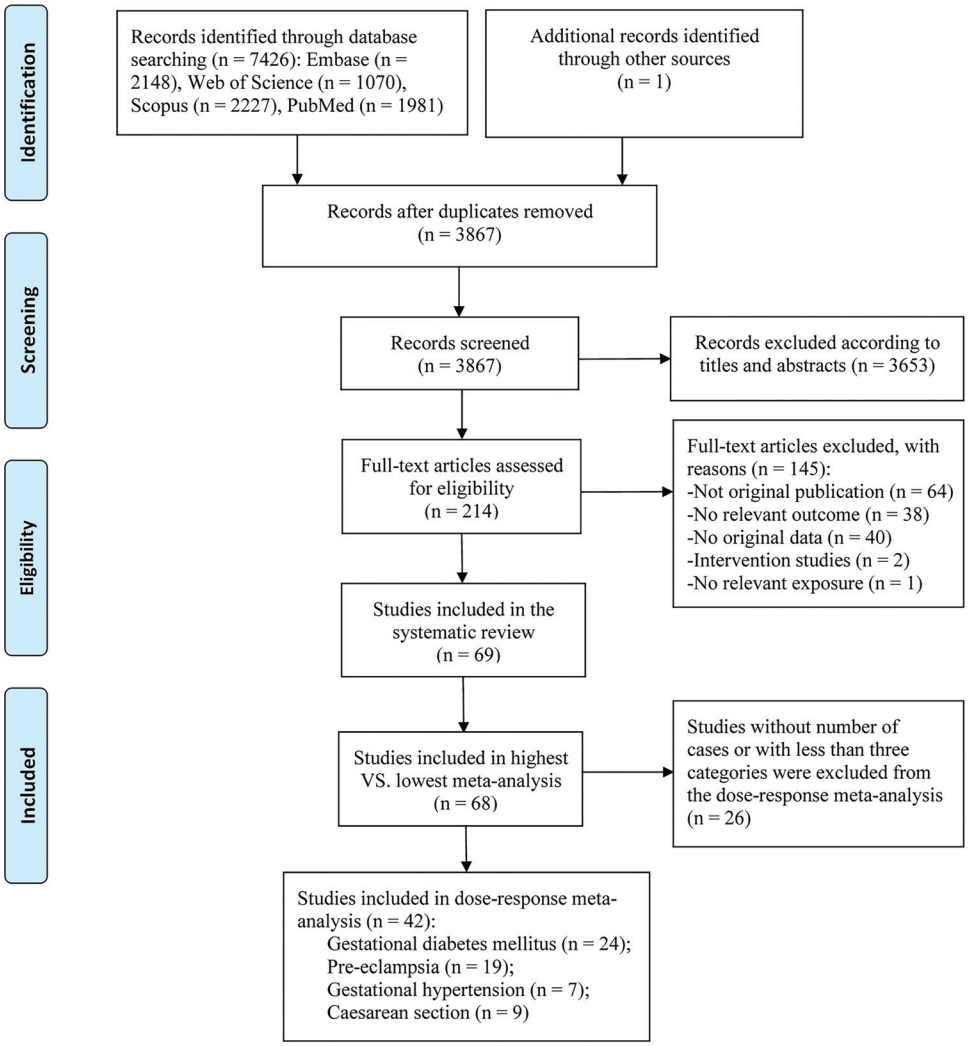

Fig. 1 Flow chart of study selection.

published from 2007 to 2021 (Fig. 1). Only one study reported the effect of vitamin D intake,[33] the other 68 were studies on 25(OH)D levels, of which 36 studies were included in the meta-analysis for GDM,[14–16,34–66] 26 for PE,[11,14,37,40,41,46,47,53,58,63,66–81] 11 for GH,[14,37,42,46,53,63,74,77,78,82,83] and 24 for C-section.[12,16,37,38,41,42,46,47,53,56,66,84–96] For 25(OH)D levels, 17 articles detected 25(OH)D by LC-MS,[12,36,37,39,40,44,49,50,52,59,61,69,70,74,75,80,89] 10 by CLIA,[11,14,41–43,55,64,79,81,91] eight by ECLIA,[34,35,46,51,54,63,66,67] eight by ELISA,[38,47,72,84,87,90,92,96] seven by RIA,[15,45,57,60,71,77,82] six by HPLC,[56,68,76,86,88,93] and three by EIA.[65,78,95] Vitamin D intake was assessed using the food frequency questionnaire.[33] Among all included articles, there were 46 cohort studies,[12,14–16,33,34,37,38,40,42,44–51,53,54,56,59,62–64,66,67,74,76–79,81,83–94,96] 21 nested case-control studies,[11,35,39,41,43,52,55,57,58,60,61,65,68,70–73,75,80,82,95] and two case-cohort studies.[36,69] Twenty articles were conducted in Asia,[15,16,34,38,44,49,51,54,59,60,62–64,66,81,85,87,89,95,96] 23 in North America,[11,12,36,39,43,47,50,53,55,61,65,68–70,72,75–77,79,80,82,93,94] 19 in Europe,[33,37,41,45,46,52,56,57,67,71,73,74,78,83,84,88,90–92] five in Australia and New Zealand,[14,40,42,48,58] and two in Africa.[35,86] Forty-two studies were of high quality (ESI Tables S4 and S5†). The characteristics of included studies are shown in Table 1.

Maternal vitamin D levels and the risk of gestational diabetes mellitus

Thirty-six studies, including 101 116 individuals and 11 127 cases, indicated that the highest level of 25(OH)D was significantly associated with a 24% reduction in the risk of GDM compared to the lowest level (RR: 0.76; 95% CI: 0.66–0.87); however, significant heterogeneity was found between studies (I^2 = 69.2%, $P_{\text{heterogeneity}}$ < 0.001) (Fig. 2 and Table 2). In most subgroups, a significant negative association between 25(OH)D levels and risk of GDM was still observed, particularly in nested case-control studies, participants from North America, and studies controlling for maternal age, BMI, and season in their analysis (Table 3).

Table 1 Characteristics of included studies on maternal vitamin D levels and adverse pregnancy outcomes

Author, year	Country, study type	Study period	Sample size	Age range or mean age (years)	Mean ± SD or median (IQR) vitamin D concentration	Exposure assessment method	Gestational week for vitamin D measurement	Categories of vitamin D level	Outcomes	NOS score	Adjusted variables
Chen *et al.* 2020[16]	China, Retrospective cohort	2017–2018	2814	30.5 ± 4.98	53.1 ± 9.9 nmol L^{-1}	Colloidal gold immunochromatography	16.3 ± 2.3	<50 nmol L^{-1} ≥50 nmol L^{-1}	GDM, C-section	8	(1), (2), (3), (9)
Xu *et al.* 2018[62]	China, Prospective cohort	2015–2016	827	Case: 29 (26–34), Control: 25 (22–28)	15.3 (10.4–21.7) ng mL^{-1}	NR	At the first prenatal visit	<10.4 ng mL^{-1} 10.4–15.3 ng mL^{-1} 15.4–21.7 ng mL^{-1} >21.7 ng mL^{-1}	GDM	7	(1), (2), (5), (6), (8), (9), (10), (11), (14), (15), (16), (17), (19), (20), (21), (22), (23)
Zhu *et al.* 2019[15]	China, Prospective cohort	2013–2014	3110	26 7 ± 3 7	18.2 ± 8.4 ng mL^{-1}	RIA	<14	<20 ng mL^{-1} 20–30 ng mL^{-1} >30 ng mL^{-1}	GDM	9	(1), (2), (3), (4), (6), (7), (9), (10), (14)
Yang *et al.* 2018[63]	China, Prospective cohort	2013–2017	23 100	32 ± 4.2	NR	ECLIA	16	<30 nmol L^{-1} 30–50 nmol L^{-1} >50 nmol L^{-1}	GDM, PE, GH	5	None
Al-Ajlan *et al.* 2018[34]	Saudi Arabia, Prospective cohort	NR	419	28.7 ± 6.1	19.1 ± 15.1 nmol L^{-1}	ECLIA	11.2 ± 3.4	<50 nmol L^{-1} ≥50 nmol L^{-1}	GDM	7	(1), (2), (3), (9), (10), (11), (21), (29), (30), (31)
Chen *et al.* 2020[85]	China, Retrospective cohort	2015–2017	261	30.1 ± 4.0	22.2 ± 9.0 ng mL^{-1}	NR	24–28	<20 ng mL^{-1} ≥20 ng mL^{-1}	C-section	4	None
Gernand *et al.* 2015[12]	U.S., Prospective cohort	1959–1966	2798	NR	50.3 ± 27.8 nmol L^{-1}	LC-MS	≤26	<30 nmol L^{-1} 30–49 nmol L^{-1} 50–74 nmol L^{-1} ≥75 nmol L^{-1}	C-section	7	(2), (5), (13)

Table 1 *(Contd.)*

Author, year	Country, study type	Study period	Sample size	Age range or mean age (years)	Mean ± SD or median (IQR) vitamin D concentration	Exposure assessment method	Gestational week for vitamin D measurement	Categories of vitamin D level	Outcomes	NOS score	Adjusted variables
Hemmingway *et al.* 2018[74]	Ireland, Prospective cohort	2008–2011	1754	30.5 ± 4.5	22.7 ± 10.3 ng mL^{-1}	LC-MS	15	<30 nmol L^{-1} 30–<75 nmol L^{-1} ≥75 nmol L^{-1}	GH, PE	7	GH: (2), (6), (11). PE: (2), (4), (17). SGA: (4), (11), (14)
Yuan *et al.* 2017[96]	China, Prospective cohort	2012–2015	1924	Case: 30.2 ± 3.8, Control: 28.9 ± 3.0	43.4 (35.2–56.9) nmol L^{-1}	ELISA	T2	<25 nmol L^{-1} 25–37.4 nmol L^{-1} 37.5–49.9 nmol L^{-1} 50–74.9 nmol L^{-1} >75 nmol L^{-1}	C-section	8	(1), (2), (3), (9), (10), (13), (16), (32), (33)
Al-Shafei *et al.* 2020[35]	Sudan, Nested case-control	2017.1–2017.11	Case: 60 Control: 60	Case: 29.2 ± 6.0, Control: 28.0 ± 5.7	Case: 7.3 (5.7–8.8) ng mL^{-1}, Control: 8.4 (6.6–11.9) ng mL^{-1}	ECLIA	≤14	<6 ng mL^{-1} ≥6 ng mL^{-1}	GDM	6	None
Yue *et al.* 2020[64]	China, Retrospective cohort	2018–2020	8468	NR	NR	CLIA	≤20	<20 ng mL^{-1} 20–30 ng mL^{-1} ≥30 ng mL^{-1}	GDM	8	(1), (2), (3), (19), (21)
Abd Aziz *et al.* 2020[38]	Malaysia, Prospective cohort	NR	60	34.8 ± 3.9	34.5 ± 14.1 nmol L^{-1}	ELISA	12–14	≤50 nmol L^{-1} >50 nmol L^{-1}	GDM, C-section	6	None
Dwarkanath *et al.* 2019[44]	India, Prospective cohort	2008–2014	392	23.9 ± 3.8	34.4 (23.8–45.8) nmol L^{-1}	LC-MS	12	<30 nmol L^{-1} <50 nmol L^{-1} <75 nmol L^{-1}	GDM	9	(1), (2), (3), (4), (9), (11)
Li *et al.* 2020[51]	China, Retrospective cohort	2014–2017	34 417	30.6 ± 3.5	42.9 (32.9–51.9) nmol L^{-1}	ECLIA	16	<50 nmol L^{-1} ≥50 nmol L^{-1}	GDM	7	(1)

Table 1 *(Contd.)*

Author, year	Country, study type	Study period	Sample size	Age range or mean age (years)	Mean ± SD or median (IQR) vitamin D concentration	Exposure assessment method	Gestational week for vitamin D measurement	Categories of vitamin D level	Outcomes	NOS score	Adjusted variables
Xia *et al.* 2018[61]	U.S., Nested case-control	2009–2013	Cases: 107, Control: 214	Case:30.5 ± 5.7, Control:30.4 ± 5.4	NR	LC-MS	10–14	<50 nmol L^{-1}	GDM	8	(1), (2), (3), (5), (8), (9), (10), (11), (13)
Thiele *et al.* 2019[94]	U.S., Retrospective cohort	2009–2013	357	30.6 ± 4.5	29.9 ± 10.9 ng mL^{-1}	NR	15–26	≥50 nmol L^{-1}	C-section	5	None
							<36	≤20.9 ng mL^{-1}			
Shao *et al.* 2020[59]	China, Prospective cohort	2011–2018	2789	28.7 ± 3.8	18.6 ± 8.6 ng mL^{-1}	LC-MS	8–14	21.0–29.9 ng mL^{-1}	GDM	9	(1), (2), (3), (4), (8), (9), (11), (14), (29)
								>30 ng mL^{-1}			
								<20 ng mL^{-1}			
Salakos *et al.* 2021[57]	French and Belgium, Nested case-control	2012–2014	Case: 250, Control: 941	Case: 32.8 ± 5.3, Control: 32.3 ± 5.0	Case: 21.1 ± 10 ng mL^{-1}, Control: 22.7 ± 10 ng mL^{-1}	RIA	10–14	≥20 ng mL^{-1}	GDM	6	None
								<10 ng mL^{-1}			
								10–30 ng mL^{-1}			
								≥30 ng mL^{-1}			
Öcal *et al.* 2019[90]	Turkey, Prospective cohort	2012–2014	600	Case: 18.4 ± 1.3, Control: 28.7 ± 5.4	Case: 15.4 ± 7.9 ng mL^{-1}, Control: 14.9 ± 4.7 ng mL^{-1}	ELISA	During pregnancy	<10.9 ng mL^{-1}	C-section	4	None
								≥10.9 ng mL^{-1}			
Kısa *et al.* 2020[88]	Turkey, Prospective cohort	2017	86	18–40	13.6 ± 6.6 ng mL^{-1}	HPLC	11–13	≤10 ng mL^{-1}	C-section	6	None
								>10 ng mL^{-1}			
Iqbal *et al.* 2020[49]	India, Prospective cohort	2019	290	24.9 ± 2.7	Case: 33.5 ± 16.3 nmol L^{-1}, Control: 38.2 ± 18.5 nmol L^{-1}	LC-MS	T1	<30 nmol L^{-1}	GDM	8	(1), (2), (3), (4), (9), (11)
								30–50 nmol L^{-1}			
								50–75 nmol L^{-1}			
								50–75 nmol L^{-1}			
								≥75 nmol L^{-1}			
Bomba-Opon *et al.* 2014[83]	Poland, Prospective cohort	NR	280	NR	NR	NR	11–13	<20 ng mL^{-1}	GH	5	None
								≥20 ng mL^{-1}			
Bozdag *et al.* 2020[41]	Turkey, Nested case-control	NR	283	NR	9.5 ng mL^{-1}	CLIA	T1	<10 ng mL^{-1}	GDM, PE, C-section	5	None
								≥10 ng mL^{-1}			

Table 1 *(Contd.)*

Author, year	Country, study type	Study period	Sample size	Age range or mean age (years)	Mean ± SD or median (IQR) vitamin D concentration	Exposure assessment method	Gestational week for vitamin D measurement	Categories of vitamin D level	Outcomes	NOS score	Adjusted variables
Hajianfar *et al.* 2019[87]	Iran, Prospective cohort	NR	812	NR	NR	ELISA	8–16	<10 ng mL^{-1}	C-section	6	None
							32–34	10–29 ng mL^{-1} >30 ng mL^{-1}			
Griew *et al.* 2019[48]	Australia, Prospective cohort	2011–2013	742	29.1 ± 4.9	43.5 ± 21.9 nmol L^{-1}	NR	6–18	<12.5 nmol L^{-1}	GDM	6	None
								12.5–29.9 nmol L^{-1} 30–49.9 nmol L^{-1} ≥50 nmol L^{-1}			
Benachi *et al.* 2019[71]	French and Belgium, Nested case-control	2012–2014	Case: 83, Control: 319	Case: 32.2 ± 5.9, Control: 31.7 ± 5.0	Case: 20.1 ± 9.3 ng mL^{-1}, Control: 22.3 ± 11.1 ng mL^{-1}	RIA	10–14	<10 ng mL^{-1}	PE	5	None
								10–30 ng mL^{-1} ≥30 ng mL^{-1}			
Wilson *et al.* 2018[14]	Australia and New Zealand, Prospective cohort	2004–2008	2800	28 ± 6	68.1 ±27.1 nmol L^{-1}	CLIA	14–16	<44 nmol L^{-1}	PE, GH, GDM	9	(1), (2), (5), (6), (7), (11), (13)
								44–63 nmol L^{-1} 63–81 nmol L^{-1} >81 nmol L^{-1}			
Eggemoen *et al.* 2018[45]	Norway, Prospective cohort	2008–2010	745	29.8 (29.5–30.2)	50.2 (48.3–52.1) nmol L^{-1}	RIA	15	<50 nmol L^{-1}	GDM	8	(1), (3), (4), (5), (9), (13)
								≥50 nmol L^{-1}			
Wen *et al.* 2017[95]	China, Nested case-control	2012–2015	4718	NR	43.7 (35.5–57.9) nmol L^{-1}	EIA	Mid-late pregnancy	<25.0 nmol L^{-1}	C-section	8	(1), (2), (3), (8), (9), (10), (13), (16), (32), (33)
								25.0–37.4 nmol L^{-1} 37.5–49.9 nmol L^{-1} 50.0–74.9 nmol L^{-1} >75.0 nmol L^{-1}			
Gbadegesin *et al.* 2017[86]	Nigeria, Prospective cohort	2012–2013	461	31.26	NR	HPLC	10–28	0–20 ng mL^{-1}	C-section	5	None
								21–30 ng mL^{-1} >30 ng mL^{-1}			

Table 1 *(Contd.)*

Author, year	Country, study type	Study period	Sample size	Age range or mean age (years)	Mean ± SD or median (IQR) vitamin D concentration	Exposure assessment method	Gestational week for vitamin D measurement	Categories of vitamin D level	Outcomes	NOS score	Adjusted variables
Van Weert *et al.* 2016[78]	The Netherlands, Prospective cohort	2003–2004	2074	30.2 ± 4.6	60.0 ±29.8 nmol L^{-1}	EIA	<17	<20 nmol L^{-1} 20–29.9 nmol L^{-1} 30–49.9 nmol L^{-1} ≥50 nmol L^{-1}	PE, GH	8	(1), (2), (4), (5), (6)
Dodds *et al.* 2016[43]	Canada, Nested case-control	2002–2010	Case: 395, Control: 1925	NR	Case: 45.5 (35.9–56.7) nmol L^{-1}, Control: 51.9 (40.6–62.4) nmol L^{-1}	CLIA	<20	<30 nmol L^{-1} 30–<50 nmol L^{-1} ≥50 nmol L^{-1}	GDM	8	(1), (2), (8), (9), (13)
Boyle *et al.* 2016[40]	New Zealand, Prospective cohort	2005–2008	1710	30.3 ± 4.7	72.9 ± 27.0 nmol L^{-1}	LC-MS	15	<25 nmol L^{-1} 25–49.9 nmol L^{-1} 50–74.9 nmol L^{-1} >75 nmol L^{-1}	PE, GDM	8	(2), (5)
Baca *et al.* 2016[69]	U.S., Case-cohort	1999–2010	Cases: 650 Sub-cohort: 2327	NR	Case: 57.8 (57.3–58.3) nmol L^{-1}, Sub-cohort: 64.6 (64.4–64.8) nmol L^{-1}	LC-MS	<20	<25 nmol L^{-1} 25–50 nmol L^{-1} 50–75 nmol L^{-1} ≥75 nmol L^{-1}	PE	8	(1), (2), (3), (4), (5), (6), (8), (9), (14), (35)
Ates *et al.* 2016[37]	Turkey, Prospective cohort	2012–2014	229	29.5 ± 4.9	13 ± 9.4 ng mL^{-1}	LC-MS	11–14	<10 ng mL^{-1} ≥10 ng mL^{-1}	GDM, GH, PE, C-section	7	None
Rodriguez *et al.* 2015[56]	Spain, Prospective cohort	2003–2008	2382	32.0 ± 4.2	29.4 (21.8–37.2) ng mL^{-1}	HPLC	13.5 ± 2	<20 ng mL^{-1} 20–29.99 ng mL^{-1} ≥30 ng mL^{-1}	GDM, C-section	9	(1), (2), (3), (4), (6), (7), (13), (14), (18)

Table 1 *(Contd.)*

Author, year	Country, study type	Study period	Sample size	Age range or mean age (years)	Mean ± SD or median (IQR) vitamin D concentration	Exposure assessment method	Gestational week for vitamin D measurement	Categories of vitamin D level	Outcomes	NOS score	Adjusted variables
Nobles *et al.* 2015[53]	U.S., Prospective cohort	2007–2012	237	NR	30.4 ± 12.0 ng mL^{-1}	NR	15.2 ± 4.7	<30 ng mL^{-1} ≥30 ng mL^{-1}	GDM, GH, PE, C-section	9	(1), (2), (5), (8), (9), (29)
Loy *et al.* 2015[89]	Singapore, Prospective cohort	2009–2010	940	30.5 ± 5.1	81.0 ± 27.2 nmol L^{-1}	LC-MS	26–28	≤75 nmol L^{-1} >75 nmol L^{-1}	C-section	8	(1), (2), (3), (4), (5), (6), (11), (16), (18)
Jain *et al.* 2015[60]	India, Nested case-control	NR	Case: 32, Control: 178	<45	Case:11.9 ± 3.4 nmol L^{-1}, Control: 22.3 ± 15.3 nmol L^{-1}	RIA	<20	<20 ng mL^{-1} 20–29 ng mL^{-1} >30 ng mL^{-1}	GDM	6	None
Gidlöf *et al.* 2015[73]	Sweden, Nested case-control	1994–1995	Case: 39, Control: 120	Case: 29.2 ± 5.4, Control: 29.2 ± 4.6	Case: 52.2 ± 20.5 nmol L^{-1}, Control: 48.6 ± 20.5 nmol L^{-1}	NR	12	<50 nmol L^{-1} ≥50 nmol L^{-1}	PE	6	None
Flood-Nichols *et al.* 2015[47]	U.S., Retrospective cohort	2014	235	24.3 ± 4.4	27.6 (13–71.6) ng mL^{-1}	ELISA	8–12	<50 nmol L^{-1} 50–75 nmol L^{-1} >75 nmol L^{-1}	GDM, PE, C-section	7	(2), (5), (6), (9)
Davies-Tuck *et al.* 2015[42]	Australia, Prospective cohort	2009–2010	1550	30.0 ± 5.4	47.0 (12–178) nmol L^{-1}	CLIA	13.7 ± 3.3	<50 nmol L^{-1} 50–74 nmol L^{-1} >74 nmol L^{-1}	GDM, GH, C-section	7	(1), (2), (3), (13)
Aydogmus *et al.* 2015[84]	Turkey, Prospective cohort	2013–2014	148	Groups I: 23.9 ± 4.6, Groups II: 24.9 ± 5.9	Groups I: 10.8 ± 3.8 ng mL^{-1}, Groups II: 23.8 ± 13.3 ng mL^{-1}	ELISA	>28	<15 ng mL^{-1} ≥15 ng mL^{-1}	C-section	5	None
Arnold *et al.* 2015[36]	U.S., Case-cohort	1996–2008	Case: 135, Control: 517	Case: 33.5 ± 4.6, Control: 32.6 ± 4.4	Case: 27.3 ± 8.7 ng mL^{-1}, Control: 29.3 ± 8.3 ng mL^{-1}	LC-MS	16	<20 ng mL^{-1} 20–29 ng mL^{-1} ≥30 ng mL^{-1}	GDM	8	(1), (2), (5), (9), (10)
Anderson *et al.* 2015[82]	U.S., Nested case-control	NR	Case: 37, Control: 11	Case: 25.3 ± 0.7, Control: 24.2 ± 0.6	NR	RIA	T1	<20 ng mL^{-1} 21–29 ng mL^{-1} >30 ng mL^{-1}	GH	6	None

Table 1 *(Contd.)*

Author, year	Country, study type	Study period	Sample size	Age range or mean age (years)	Mean ± SD or median (IQR) vitamin D concentration	Exposure assessment method	Gestational week for vitamin D measurement	Categories of vitamin D level	Outcomes	NOS score	Adjusted variables
Alvarez-Fernandez *et al.* 2015[67]	Spain, Retrospective cohort	2010–2013	257	NR	Case: 35.8 (27.6–46.0) nmol L^{-1}, Control: 33.9 (23.8–44.9) nmol L^{-1}	ECLIA	9–12	<50 nmol L^{-1}	PE	7	None
Achkar *et al.* 2015[11]	Canada, Nested case-control	2002–2010	Case: 169, Control: 1975	NR	Case: 47.2 ±17.7 nmol L^{-1}, Control: 52.3 ±17.2 nmol L^{-1}	CLIA	<20	≥50 nmol L^{-1} <30 nmol L^{-1} 30–<50 nmol L^{-1} ≥50 nmol L^{-1}	PE	8	(1), (2), (3), (6), (8), (9), (13)
Zhou *et al.* 2014[66]	China, Prospective cohort	2010–2012	1953	Group A: 29.2 ± 3.5, Group B: 29.5 ± 3.6, Group C: 30.3 ± 3.9	27.03 ± 7.92 ng mL^{-1}	ECLIA	16–20	≤20 ng mL^{-1} 21–29 ng mL^{-1} ≥30 ng mL^{-1}	GDM, PE, C-section	6	None
Wetta *et al.* 2014[80]	U.S., Nested case-control	2007–2008	Case: 89, Control: 177	Case: 26.1 ± 5.5, Control: 25.2 ± 6	Case: 27.4 ± 14.4 ng mL^{-1}, Control: 28.6 ± 12.6 ng mL^{-1}	LC-MS	15–21	<15 ng mL^{-1} <30 ng mL^{-1} ≥30 ng mL^{-1}	PE	9	(1), (2), (3), (5), (6), (8), (9), (16)
Park *et al.* 2014[54]	Korea, Prospective cohort	2011–2012	523	Case: 34.8 ± 3.6, Control: 33.6 ± 3.7	Case: 35.3 ± 16.5 nmol L^{-1}, Control: 32 ± 14.5 nmol L^{-1}	ECLIA	12–14	<25.0 nmol L^{-1} 25.0–49.9 nmol L^{-1} ≥50.0 nmol L^{-1}	GDM	8	(1), (2), (8), (9), (16), (17)
Schneuer *et al.* 2014[58]	Australia, Nested case-control	2006–2007	5109	NR	56.4 (43.3–69.8) nmol L^{-1}	NR	10–14	<37.5 nmol L^{-1} 37.5–49.9 nmol L^{-1} 50–75 nmol L^{-1} >75 nmol L^{-1}	PE, GDM	8	(1), (2), (3), (6), (9), (16), (13), (14)
Reichetzeder *et al.* 2014[92]	Germany, Prospective cohort	2007–2008	547	30.9 ± 6.1	18 ± 19 nmol L^{-1}	ELISA	Prior to delivery	<1 nmol L^{-1} 1–25 nmol L^{-1} ≥25 nmol L^{-1}	C-section	5	None

Table 1 *(Contd.)*

Author, year	Country, study type	Study period	Sample size	Age range or mean age (years)	Mean ± SD or median (IQR) vitamin D concentration	Exposure assessment method	Gestational week for vitamin D measurement	Categories of vitamin D level	Outcomes	NOS score	Adjusted variables
Lacroix *et al.* 2014[50]	Canada, Prospective cohort	NR	655	28.4 ± 4.5	63.0 ± 18.8 nmol L^{-1}	LC-MS	6–13	<50 nmol L^{-1} 50–74.9 nmol L^{-1} ≥75 nmol L^{-1}	GDM	6	None
Scholl *et al.* 2013[76]	U.S., Prospective cohort	2001–2007	1141	22.8 ± 5.4	NR	HPLC	13.7 ± 5.7	<12 ng mL^{-1} 12–15.9 ng mL^{-1} 16.0–19.9 ng mL^{-1} ≥20.0 ng mL^{-1}	PE	8	(1), (2), (3), (5), (6), (15)
Wei *et al.* 2012[79]	Canada, Prospective cohort	2004–2006	697	Case: 30.9 ± 5.3, Control: 30.3 ± 4.8	Case: 51.1 ± 14.8 nmol L^{-1}, Control: 56.0 ± 19.1 nmol L^{-1}	CLIA	12–18	<50 nmol L^{-1} ≥50 nmol L^{-1}	PE	7	(1), (2), (6), (9)
Scholl *et al.* 2012[93]	U.S., Prospective cohort	2001–2007	1153	NR	NR	HPLC	13.7 ± 5.6	<30 nmol L^{-1} 30–49.9 nmol L^{-1} 50–125.0 nmol L^{-1} >125 nmol L^{-1}	C-section	8	(1), (2), (3), (5), (6), (9), (15)
Perez-Ferre *et al.* 2012[91]	Spain, Prospective cohort	2010	266	33 (29–36)	18.9 (11.5–24.7) ng mL^{-1}	CLIA	24–28	<20 ng mL^{-1} ≥20 ng mL^{-1}	C-section	6	(1), (2), (5), (6), (16)
Parlea *et al.* 2012[55]	Canada, Nested case-control	2008–2009	Case: 116, Control: 219	Case: 34.3 ± 4.3, Control: 34.3 ± 4.1	Case: 56.3± 19.4 nmol L^{-1}, Control: 62.0 ± 21.6 nmol L^{-1}	CLIA	15–18	<46.9 nmol L^{-1} 46.9–60.4 nmol L^{-1} 60.4–73.5 nmol L^{-1} ≥73.5 nmol L^{-1}	GDM	5	(2), (8)
Fernandez-Alonso *et al.* 2012[46]	Spain, Prospective cohort	2009–2010	466	NR	27.6 ±9.9 ng mL^{-1}	ECLIA	11–14	<20 ng mL^{-1} 20–29.99 ng mL^{-1} ≥30 ng mL^{-1}	GDM, PE, GH, C-section	7	None

Table 1 *(Contd.)*

Author, year	Country, study type	Study period	Sample size	Age range or mean age (years)	Mean ± SD or median (IQR) vitamin D concentration	Exposure assessment method	Gestational week for vitamin D measurement	Categories of vitamin D level	Outcomes	NOS score	Adjusted variables
Baker *et al.* 2012[39]	U.S., Nested case-control	2004–2009	Case: 60, Control: 120	Case: 35 (31–37), Control: 33 (30–36)	89 (73–106) nmol L^{-1}	LC-MS	11–14	<50 nmol L^{-1} 50–74.9 nmol L^{-1} ≥75 nmol L^{-1}	GDM	8	(1), (2), (8), (9), (14)
Makgoba *et al.* 2011[52]	UK, Nested case-control	NR	Case: 90, Control: 158	Case: 34.2 ± 4.9, Control: 33.1±4.7	Case: 18.9 ± 10.7 ng mL^{-1}, Control: 19.0 ± 10.7 ng mL^{-1}	LC-MS	T1	<25 nmol L^{-1} 25–50 nmol L^{-1} ≥50 nmol L^{-1}	GDM	6	None
Azar *et al.* 2011[68]	U.S., Nested case-control	NR	Case: 23, Control: 24	Case: 28.5 ± 5.6, Control: 29.9 ± 3.8	NR	HPLC	12.2 ± 1.9	<15 ng mL^{-1} 15–20 ng mL^{-1} 20–30 ng mL^{-1} ≥30 ng mL^{-1}	PE	5	None
Shand *et al.* 2010[77]	Canada, Prospective cohort	2004–2008	221	NR	47.7 (34.2–67.9) nmol L^{-1}	RIA	10–20	<37.5 nmol L^{-1} 37.5–49.9 nmol L^{-1} 50–75 nmol L^{-1} >75 nmol L^{-1}	PE, GH	6	None
Powe *et al.* 2010[75]	U.S., Nested case-control	1998–2006	Case: 39, Control: 131	Case: 28.9 ± 6.4, Control: 30.4 ± 6	Case: 27.4 ± 1.9 ng mL^{-1}, Control: 28.8 ± 0.8 ng mL^{-1}	LC-MS	T1	Q1–Q4	PE	7	(2), (5), (9), (28)
Baker *et al.* 2010[70]	U.S., Nested case-control	2004–2008	Cases:43 Controls: 198	Case: 30 (25–34), Control: 28 (23–32)	Case: 75 (47–107) nmol L^{-1}, Control: 98 (68–113) nmol L^{-1}	LC-MS	15–20	<50 nmol L^{-1} 50–74.9 nmol L^{-1} ≥75 nmol L^{-1}	PE	8	(1), (2), (3), (8), (9)
Haugen *et al.* 2009[33]	Norway, Prospective cohort	2007	23 423	NR	Case: 7.7 (1.5-30.0) μg d^{-1}, Control: 8.4 (1.7-31.4) μg d^{-1}	FFQ	During the first 4–5 months of pregnancy	<5.0 μg d^{-1} 5.0–9.9 μg d^{-1} 10.0–14.9 μg d^{-1} 15.0–20.0 μg d^{-1} >20.0 μg d^{-1}	PE	7	(1), (2), (4), (6), (9), (12)

Table 1 *(Contd.)*

Author, year	Country, study type	Study period	Sample size	Age range or mean age (years)	Mean ± SD or median (IQR) vitamin D concentration	Exposure assessment method	Gestational week for vitamin D measurement	Categories of vitamin D level	Outcomes	NOS score	Adjusted variables
Zhang *et al.* 2008[65]	U.S., Nested case-control	2002–2004	Case: 57 Control: 114	Case: 34.3 ± 4.8, Control: 33.1 ± 3.9	Case: 24.2 ± 8.5 ng mL^{-1}, Control: 30.1 ± 9.7 ng mL^{-1}	EIA	16	<20 ng mL^{-1} 20–29 ng mL^{-1} ≥30 ng mL^{-1}	GDM	8	(1), (2), (5), (10)
Bodnar *et al.* 2007[72]	U.S., Nested case-control	1997–2001	Case: 49 Control: 216	NR	Case: 45.4 (38.6-53.4) nmol L^{-1}, Control: 53.1 (47.1–59.9) nmol L^{-1}	ELISA	<22	<37.5 nmol L^{-1} 37.5–75 nmol L^{-1} >75 nmol L^{-1}	PE	6	(2), (4), (5), (8), (9), (17)
Yue *et al.* 2021[81]	China, Retrospective cohort	2017–2019	7976	NR	NR	CLIA	<20	<10 ng mL^{-1} 10–20 ng mL^{-1} 20–30 ng mL^{-1} ≥30 ng mL^{-1}	PE	8	(1), (2), (3), (19), (21), (37), (40), (41)

Abbreviations: CI, confidence interval; CLIA, chemiluminescent Immunoassay; C-section, caesarean section; ECLIA, electrochemical luminescence immunoassay; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; FFQ, food frequency questionnaire; GDM, gestational diabetes mellitus; GH, gestational hypertension; HPLC, high-performance liquid chromatography; LC-MS, liquid chromatography-mass spectrometry; NOS, Newcastle Ottawa scale; NR, not reported; PE, pre-eclampsia; RIA, radioimmunoassay; RR, relative risk; T1, first trimester; T2, second trimester. Adjusted variables: (1) maternal age, (2) pre-pregnancy BMI/weight, (3) parity, (4) education, (5) race/ethnicity, (6) smoking, (7) alcohol consumption, (8) gestational age of blood sampling, (9) sampling season, (10) family history, (11) physical activity, (12) maternal height, (13)study site, (14) socioeconomic status,(15) gestational weeks at admission, (16) abnormal pregnancy history, (17) supplementation, (18) infant sex, (19) cholesterol, (20) high density lipoprotein, (21) triglyceride, (22) fasting plasma glucose, (23) CRP, (24) anaemia status, (25) CD4 cell count, (26) HIV RNA level, (27) ARV regimen, (28) skin color, (29) gestational weight gain, (30) sun exposure, (31) HbA1c, (32) menarche age, (33) menstrual cycle, (34) birth weight, (35) marital status, (36)religion, (37) blood pressure, (38) parathyroid hormone status, (39)gravidity, (40) homocysteine, (41) folate.

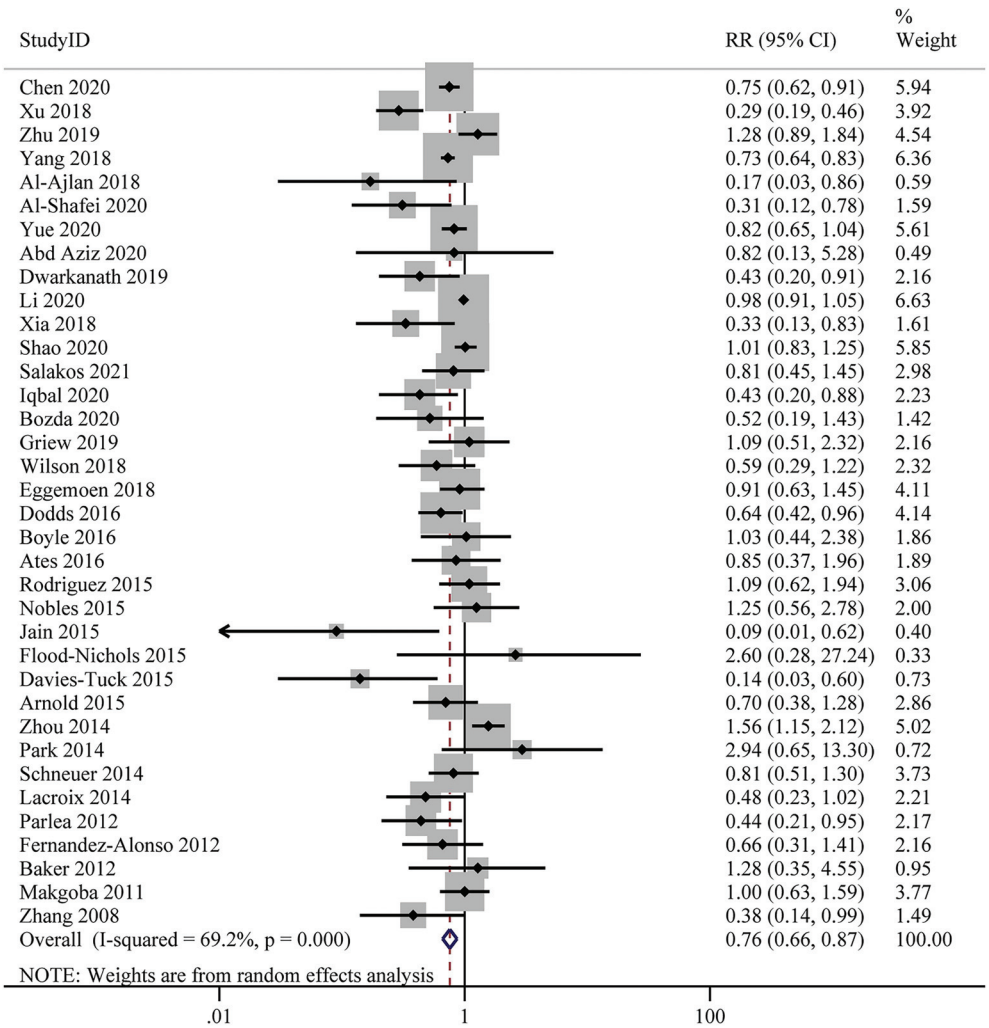

Fig. 2 Maternal 25(Oh)D levels and risk of gestational diabetes mellitus, the highest *versus* lowest category.

Table 2 Maternal 25(OH)D levels and the risk of adverse pregnancy outcomes, the highest *vs.* lowest and dose–response meta-analyses

	Highest *vs.* lowest meta-analyses				Dose–response meta-analyses			
Outcomes	N	RR (95% CI)	I^2 (%)	$P_{heterogenity}$	N	RR (95% CI)	I^2 (%)	$P_{heterogenity}$
GDM	36	0.76 (0.66, 0.87)	69.2	<0.001	24	0.92 (0.86, 0.97)	73.6	<0.001
PE	26	0.74 (0.60, 0.90)	52.0	0.001	19	0.89 (0.84, 0.94)	49.4	0.008
GH	11	0.87 (0.79, 0.97)	0.0	0.676	7	0.98 (0.92, 1.04)	26.6	0.226
C-section	24	1.00 (0.90, 1.12)	59.1	<0.001	9	1.03 (0.99, 1.08)	26.5	0.209

Abbreviations: CI, confidence interval; C-section, caesarean section; GDM, gestational diabetes mellitus; GH, gestational hypertension; PE, pre-eclampsia; RR, relative risk.

Twenty-four publications on the association between 25 (OH)D levels and the risk of GDM were included in the dose–response analysis. No evidence of a non-linear association between 25(OH)D levels and GDM risk was found ($P_{non\text{-}linearity}$ = 0.695) (ESI Fig. S1†). For linear dose–response meta-analysis, we found a significant 8% reduction in the risk of GDM for each 25 nmol L^{-1} increase in 25(OH)D levels (RR: 0.92; 95% CI: 0.86–0.97), with high heterogeneity (I^2 = 73.6%, $P_{heterogeneity}$ < 0.001) (Fig. 3 and Table 2).

Maternal vitamin D levels and risk of pre-eclampsia

Twenty-six studies with a total of 55 203 participants and 4518 cases were included in this analysis. The pooled RR for the risk of PE, comparing the highest with the lowest level of 25 (OH)D, was 0.74 (95% CI: 0.60–0.90), indicating a significant

Table 3 Subgroup analyses of maternal 25(OH)D levels and risk of adverse pregnancy outcomes

		GDM					PE					GH					C-section				
Subgroups		N	RR (95% CI)	I^2 (%)	$P_h{}^1$	$P_h{}^2$	N	RR (95% CI)	I^2 (%)	$P_h{}^1$	$P_h{}^2$	N	RR (95% CI)	I^2 (%)	$P_h{}^1$	$P_h{}^2$	N	RR (95% CI)	I^2 (%)	$P_h{}^1$	$P_h{}^2$
All studies		36	0.76 (0.66, 0.87)	69.2	<0.001		26	0.74 (0.60, 0.90)	52.0	0.001		11	0.87 (0.79, 0.97)	0.0	0.676		24	1.00 (0.90, 1.12)	59.1	<0.001	
Study type																					
Cohort		25	0.81 (0.70, 0.94)	73.1	<0.001	0.15	16	0.75 (0.67, 0.85)	2.4	0.426	0.81	10	0.88 (0.79, 0.97)	0.0	0.662	0.38	22	0.99 (0.88, 1.12)	58.6	<0.001	0.63
Nested case-control		11	0.61 (0.46, 0.81)	38.0	0.096		10	0.68 (0.42, 1.12)	75.5	<0.001		1	0.51 (0.15, 1.73)	—	—		2	1.09 (0.75, 1.57)	81.9	0.019	
Geographic location																					
Europe		5	0.91 (0.72, 1.16)	0.0	0.847	0.54	6	0.87 (0.59, 1.28)	28.8	0.219	0.27	4	1.08 (0.69, 1.69)	11.4	0.336	0.27	4	0.76 (0.48, 1.19)	68.3	0.024	0.01
North America		9	0.62 (0.46, 0.83)	18.7	0.276		12	0.53 (0.39, 0.71)	31.5	0.139		3	0.67 (0.34, 1.32)	0.0	0.867		5	0.76 (0.60, 0.96)	0.0	0.498	
Asia		16	0.79 (0.65, 0.95)	81.6	<0.001		5	0.89 (0.53, 1.52)	70.6	0.009		2	0.85 (0.76, 0.95)	0.0	0.759		13	1.05 (0.94, 1.17)	52.5	0.014	
Others		6	0.64 (0.41, 1.01)	50.3	0.074		3	1.13 (0.78, 1.63)	0.0	0.592		2	1.01 (0.54, 1.91)	0.0	0.549		2	1.40 (0.89, 2.21)	65.2	0.090	
Study quality																					
<7		11	0.73 (0.53, 1.00)	71.4	<0.001	0.99	8	0.88 (0.59, 1.32)	68.6	0.002	0.25	4	0.84 (0.76, 0.94)	0.0	0.536	0.11	12	1.08 (0.92, 1.26)	57.3	0.007	0.10
≥7		25	0.75 (0.64, 0.88)	67.7	<0.001		18	0.67 (0.52, 0.85)	38.7	0.048		7	1.12 (0.84, 1.50)	0.0	0.906		12	0.91 (0.82, 1.01)	24.5	0.203	
Sample size																					
<2000		26	0.64 (0.49, 0.84)	68.2	<0.001	0.14	19	0.79 (0.59, 1.04)	49.8	0.007	0.39	8	1.02 (0.75, 1.38)	0.0	0.562	0.64	20	1.03 (0.91, 1.17)	54.0	0.002	0.26
≥2000		10	0.86 (0.76, 0.98)	68.8	0.001		7	0.64 (0.47, 0.89)	60.9	0.018		3	0.86 (0.77, 0.95)	0.0	0.723		4	0.87 (0.80, 0.95)	0.0	0.742	
Blood sample type																					
Serum		26	0.83 (0.72, 0.95)	63.6	<0.001	0.08	24	0.72 (0.58, 0.89)	54.8	0.001	0.46	11	0.87 (0.79, 0.97)	0.0	0.676	NC	20	1.03 (0.92, 1.16)	61.4	<0.001	0.16
Plasma		9	0.54 (0.34, 0.86)	79.5	<0.001		2	0.97 (0.52, 1.80)	0.0	0.434		0	—	—	—		4	0.84 (0.63, 1.12)	40.3	0.170	
25(OH)D assay methods																					
LC-MS/HPLC		11	0.76 (0.60, 0.98)	42.7	0.065		9	0.58 (0.40, 0.83)	34.7	0.140	0.05	2	1.28 (0.88, 1.87)	0.0	0.680	0.09	7	1.04 (0.75, 1.44)	71.8	0.002	0.62
ELISA/EIA		3	0.63 (0.23, 1.68)	19.8	0.287	0.64	3	0.54 (0.20, 1.43)	66.3	0.051		1	0.93 (0.37, 2.35)	—	—		8	0.98 (0.87, 1.11)	9.3	0.358	
RIA		4	0.90 (0.57, 1.42)	61.0	0.053		2	0.72 (0.40, 1.30)	24.3	0.251		2	0.63 (0.27, 1.45)	0.0	0.641		0	—	—	—	
ECLIA		7	0.88 (0.66, 1.17)	84.5	<0.001		4	0.77 (0.70, 0.86)	0.0	0.594		2	0.85 (0.76, 0.95)	0.0	0.757		2	1.10 (0.99, 1.23)	0.0	0.794	
CLIA		6	0.61 (0.45, 0.84)	40.2	0.138		5	0.77 (0.41, 1.43)	73.9	0.004		2	1.01 (0.54, 1.91)	0.0	0.549		3	0.84 (0.44, 1.62)	84.0	0.002	
Others		5	0.71 (0.45, 1.12)	79.4	0.001		4	1.08 (0.74, 1.56)	49.0	0.117		2	0.58 (0.21, 1.58)	0.0	0.327		4	0.87 (0.79, 0.96)	0.0	0.519	
Trimester of sample collection																					
T1		17	0.72 (0.55, 0.94)	66.9	<0.001	0.60	9	1.29 (0.96, 1.73)	0.3	0.431	0.01	4	0.63 (0.31, 1.27)	0.0	0.643	0.74	7	1.22 (1.04, 1.44)	0.0	0.452	0.49
T2		11	0.83 (0.69, 1.00)	75.1	<0.001		8	0.78 (0.60, 1.01)	37.2	0.132		3	1.02 (0.73, 1.43)	58.5	0.090		6	0.91 (0.74, 1.10)	74.7	0.001	
T3		—	—	—	—		—	—	—	—		—	—	—	—		4	0.92 (0.82, 1.04)	0.0	0.428	
During pregnancy		9	0.65 (0.45, 0.95)	61.1	0.008		9	0.47 (0.37, 0.61)	0.0	0.604		4	0.82 (0.48, 1.39)	0.0	0.990		8	0.99 (0.77, 1.28)	61.5	0.011	
Number of adjusted factors																					
<6		22	0.79 (0.67, 0.93)	65.5	<0.001	0.78	17	0.87 (0.69, 1.10)	44.0	0.027	0.06	9	0.87 (0.78, 0.96)	0.0	0.545	0.76	18	1.05 (0.92, 1.21)	64.8	<0.001	0.16
≥6		14	0.71 (0.53, 0.94)	74.5	<0.001		9	0.55 (0.39, 0.79)	53.5	0.028		2	1.02 (0.53, 1.95)	0.0	0.544		6	0.89 (0.80, 1.00)	0.0	0.539	
Adjusted for confounding factors																					
Age	Yes	21	0.74 (0.62, 0.88)	72.5	<0.001	0.75	11	0.56 (0.41, 0.77)	50.1	0.029	0.03	4	0.94 (0.59, 1.52)	0.0	0.909	0.91	9	0.86 (0.76, 0.98)	37.2	0.121	0.001
	No	15	0.77 (0.59, 1.00)	61.7	0.001		15	0.91 (0.71, 1.17)	44.0	0.035		7	0.90 (0.73, 1.11)	12.6	0.334		15	1.13 (1.01, 1.28)	33.1	0.103	
BMI	Yes	20	0.70 (0.56, 0.87)	68.6	<0.001	0.52	15	0.57 (0.44, 0.74)	37.7	0.070	0.01	5	1.15 (0.85, 1.56)	0.0	0.796	0.10	11	0.85 (0.76, 0.96)	26.0	0.197	0.001
	No	16	0.82 (0.68, 0.98)	67.4	<0.001		11	1.02 (0.76, 1.37)	51.0	0.026		6	0.84 (0.76, 0.94)	0.0	0.795		13	1.16 (1.03, 1.30)	31.4	0.132	
Season	Yes	15	0.70 (0.55, 0.90)	72.1	<0.001	0.65	9	0.58 (0.37, 0.90)	64.6	0.004	0.16	0	—	—	—	NC	5	0.86 (0.78, 0.94)	9.0	0.355	0.03
	No	21	0.80 (0.68, 0.95)	65.6	<0.001		17	0.82 (0.66, 1.02)	38.8	0.052		11	0.87 (0.79, 0.97)	0.0	0.676		19	1.08 (0.96, 1.21)	45.1	0.018	

Abbreviations: CI, confidence interval; CLIA, chemiluminescent Immunoassay; C-section, caesarean section; ECLIA, electrochemical luminescence immunoassay; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; GDM, gestational diabetes mellitus; GH, gestational hypertension; HPLC, high-performance liquid chromatography; LC-MS, liquid chromatography-mass spectrometry; NC, not calculable; NOS, Newcastle Ottawa scale; PE, pre-eclampsia; RIA, radioimmunoassay; RR, relative risk; T1, first trimester; T2, second trimester. $P_h{}^1 = P$ for heterogeneity within each subgroup. $P_h{}^2 = P$ for heterogeneity between subgroups with meta-regression.

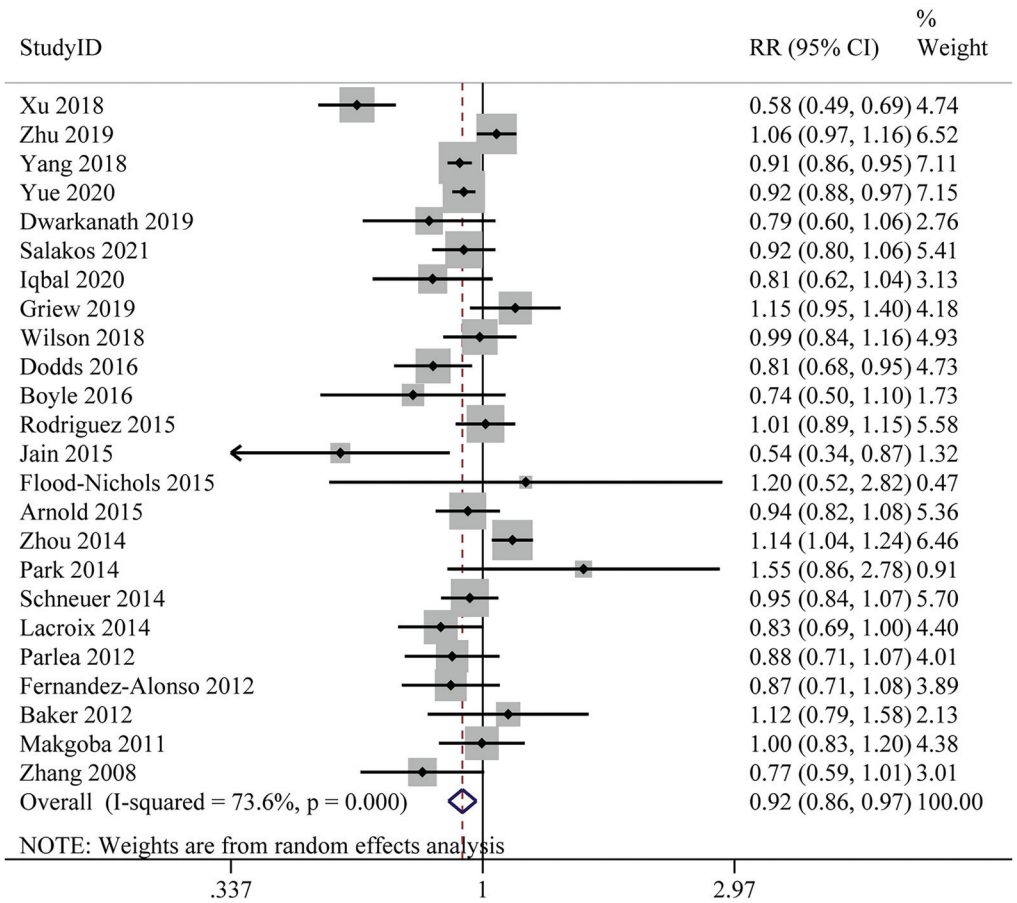

Fig. 3 Linear dose–response meta-analysis of maternal 25(Oh)D levels (per 25 nmol L^{-1} increase) and risk of gestational diabetes mellitus.

inverse association. However, there was evidence of moderate heterogeneity between studies (I^2 = 52.0%, $P_{heterogeneity}$ = 0.001) (Fig. 4 and Table 2). Subgroup analyses showed that the associations between 25(OH)D levels and risk of PE was significant in cohort studies, studies conducted in North America, studies of higher quality, studies using LC-MS/HPLC or ECLIA for 25(OH)D assays, and studies in which samples were collected throughout pregnancy. At the same time, the between-study heterogeneity was significantly reduced in these subgroups (Table 3).

Nineteen articles with sufficient data were identified for inclusion in the dose–response meta-analysis of PE. We found that each 25 nmol L^{-1} increase in 25(OH)D levels was associated with an 11% lower risk of PE (RR: 0.89; 95% CI: 0.84–0.94), with moderate heterogeneity (I^2 = 49.4%, $P_{heterogeneity}$ = 0.008) (ESI Fig. S2† and Table 2). Results of the dose–response meta-analysis showed a non-linear trend between 25(OH)D levels and PE risk ($P_{non\text{-}linearity}$ = 0.009), where the RRs continued to decrease as 25(OH)D levels increased from zero to higher; however, the risk declined more significantly from 40 nmol L^{-1} onwards (Fig. 5).

We only retrieved one study from the Norwegian Mother and Child Cohort Study that examined the association between vitamin D intake and risk of PE. The result showed that the intake of vitamin D from supplements was associated with a reduced risk of PE.[33] However, due to the small number of articles, we did not conduct a further meta-analysis.

Maternal vitamin D levels and the risk of gestational hypertension

A total of 11 studies with 32 657 participants and 2572 cases provided data on the relationship between the highest *versus* the lowest level of 25(OH)D and the risk of GH. Highest level of 25(OH)D in comparison with lowest level decreased risk of GH by 13% (RR: 0.87; 95% CI: 0.79–0.97), with no significant between-study heterogeneity (I^2 = 0%, $P_{heterogeneity}$ = 0.676) (Fig. 6 and Table 2). Subgroup analyses revealed that the associations between 25(OH)D levels and risk of GH was significant in cohort studies, studies from Asia, studies of lower quality, studies with sample sizes ≥2000, studies using ECLIA for 25(OH)D assays, studies with fewer than six adjusting factors, and studies without adjustment for BMI (Table 3).

Seven publications were incorporated into the dose–response meta-analysis for GH. There was no evidence of a non-linear relationship between maternal 25(OH)D levels and the risk of GH ($P_{non\text{-}linearity}$ = 0.209) (ESI Fig. S3†). Moreover, the linear dose–response relationship between each 25 nmol L^{-1} increase in 25(OH)D levels and GH risk was not significant

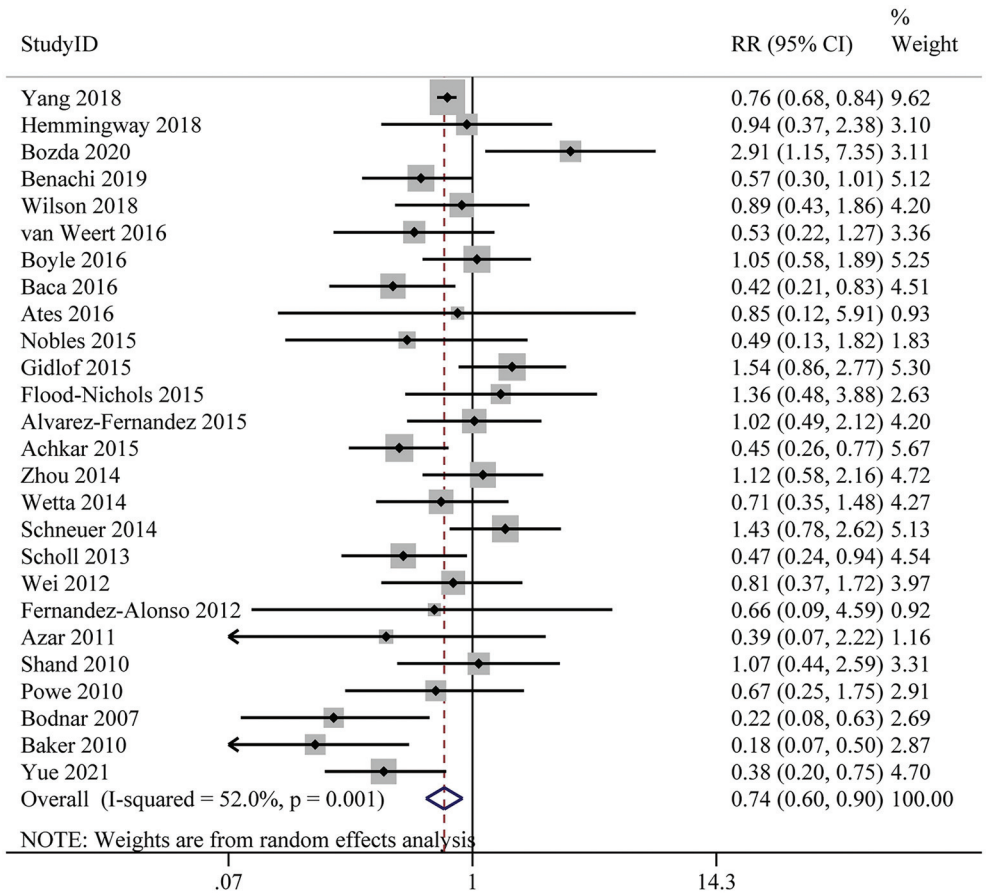

Fig. 4 Maternal 25(Oh)D levels and risk of pre-eclampsia, the highest *versus* lowest category.

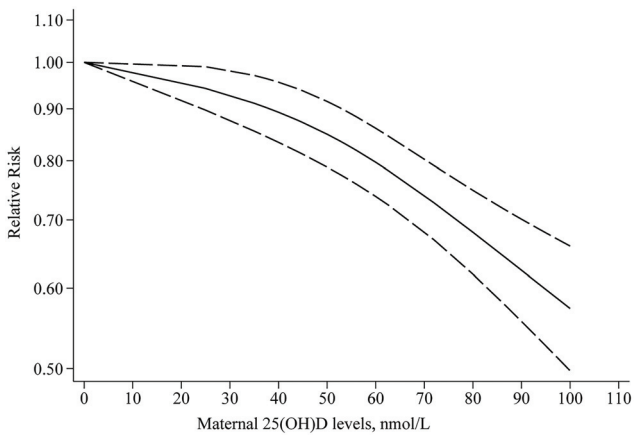

Fig. 5 Non-linear dose–response meta-analysis of maternal 25(Oh)D levels and risk of pre-eclampsia.

(RR: 0.98; 95% CI: 0.92–1.04; I^2 = 26.6%, $P_{\text{heterogeneity}}$ = 0.226) (ESI Fig. S4† and Table 2).

Maternal vitamin D levels and the risk of caesarean section

Twenty-four studies were included in the highest *versus* lowest meta-analysis on the relationship between maternal 25(OH)D levels and the risk of C-section, with a total of 25 107 participants and 7670 cases. We found no significant association between maternal 25(OH)D levels and risk of C-section (RR: 1.00; 95% CI: 0.90–1.12; I^2 = 59.1%, $P_{\text{heterogeneity}}$ < 0.001) (ESI Fig. S5† and Table 2). Subgroup analyses revealed that the inverse association between maternal 25(OH)D levels and risk of C-section was significant in studies conducted in North America, studies with sample sizes ≥2000, and studies adjusted for maternal age, BMI, or season (Table 3).

Out of 24 articles, nine studies were included in the dose–response analysis. In the non-linear dose–response analysis, the maternal 25(OH)D levels were not associated with the risk of C-section ($P_{\text{non-linearity}}$ = 0.773) (ESI Fig. S6†). Estimation of a linear dose–response trend demonstrated that an increase of 25 nmol L^{-1} in 25(OH)D was not associated with a higher risk of C-section (RR: 1.03; 95% CI: 0.99–1.08; I^2 = 26.5%, $P_{\text{heterogeneity}}$ = 0.209) (ESI Fig. S7† and Table 2).

Sensitivity analysis and publication bias

Due to the significant heterogeneity among studies between maternal 25(OH)D levels and the risk of GDM, we performed sensitivity analyses using a random effect model to test whether the pooled RR was significantly influenced by a specific study in the highest *versus* lowest meta-analysis (ESI

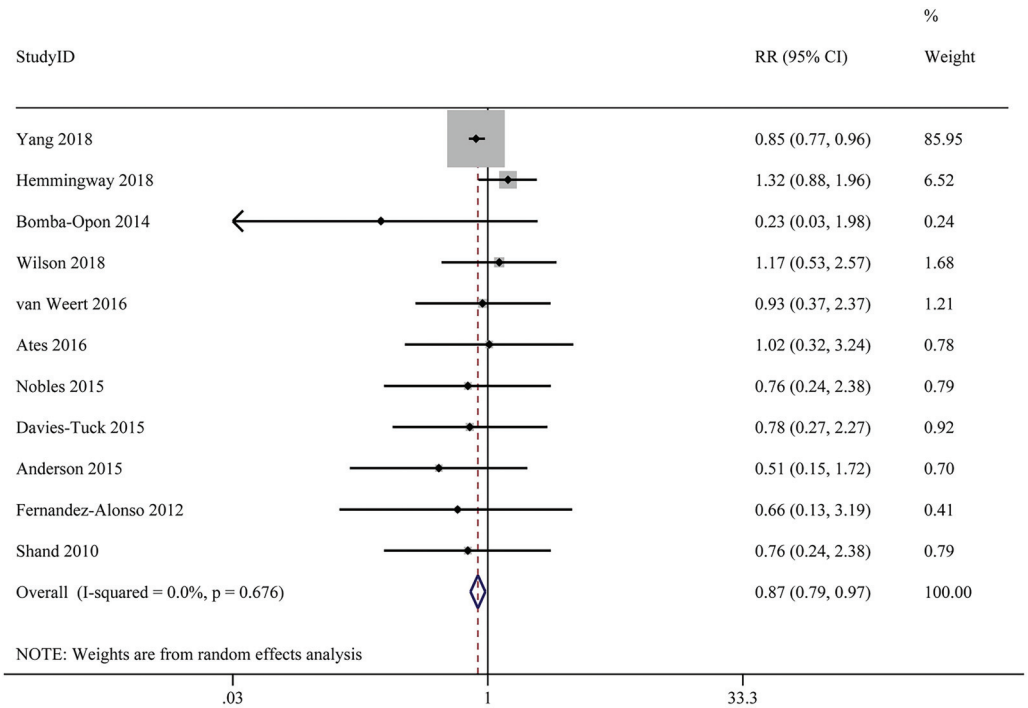

Fig. 6 Maternal 25(Oh)D levels and risk of gestational hypertension, the highest *versus* lowest category.

Table S6†). The results suggested that the overall estimates were not substantially altered by excluding one study at a time, with the pooled RRs ranging from 0.73 to 0.80. None of the excluded studies explained the large degree of heterogeneity in the findings. Similarly, sensitivity analyses demonstrated that none of the individual studies significantly affected the overall results for PE, GH, and C-section. Based on the funnel plot and Egger's regression test, no evidence of publication bias was observed for PE (P = 0.698), GH (P = 0.858), or C-section (P = 0.983). For GDM, the funnel plot was asymmetrical and the Egger's test (P = 0.016) showed a significant publication bias (ESI Fig. S8–S11†).

Discussion

Main findings

This meta-analysis of sixty-eight prospective studies systematically assessed the associations of vitamin D levels with the risk of GDM, PE, GH, and C-section by comparing the highest and lowest levels and performing dose–response analyses. The findings showed that the highest level of 25(OH)D was significantly correlated with reduced risk of GDM, PE, and GH compared to the lowest level. Further, the dose–response analysis suggested that each 25 nmol L^{-1} increase in 25(OH)D was associated with an 8% and 11% reduction in the risk of GDM and PE, respectively. There was evidence of a non-linear trend in the risk of PE, with a more dramatic decline in 25(OH)D from 40 nmol L^{-1}. Moreover, we found no association between vitamin D levels and the risk of C-section.

Strengths and limitations

Our study has several strengths. Firstly, this is the first comprehensive systematic review and dose–response meta-analysis to investigate the linear and non-linear relationships between maternal vitamin D levels and the risk of adverse pregnancy outcomes, including GDM, PE, GH, and C-section. Secondly, we incorporated studies that were truly prospective designed, excluding studies in which the gestational week of vitamin D measurement co-occurred as the endpoint or after the endpoint, to ensure a more plausible inference of causality. Thirdly, the large number of participants and cases provided sufficient statistical power to quantitatively assess the association of 25(OH)D levels with the risk of adverse pregnancy outcomes.

Besides these strengths, this study also has some limitations that should be acknowledged. Firstly, there was significant heterogeneity among studies for GDM, PE, and C-section risk. We performed extensive subgroup analyses and sensitivity analyses to explore the potential source of heterogeneity. The results identified factors including geographic location, 25(OH)D assay methods, trimester of sample collection, and whether adjustment for confounding factors may be a significant source of heterogeneity. Secondly, although the RRs were derived from the multivariate models, our results could not completely rule out the unmeasured confounders. Thirdly, the gestational week vitamin D measured was not explicitly described in some of the included studies, limiting our estimate of the effect of vitamin D levels on outcomes at different trimesters. Moreover, there are few studies on the association between the dietary intake of vitamin D and pregnancy out-

comes, so insufficient data are available to perform a meta-analysis. More studies which combine vitamin D intake with blood biomarkers are necessary for the future. Finally, there was a publication bias in this meta-analysis, which can be partly explained by the fact that some studies reporting negative results for the association of vitamin D levels with GDM risk were not published. In the future, more large sample population studies are needed to verify our results further.

Interpretation

In agreement with our findings, recent studies have found a significant protective effect of higher vitamin D levels on the risk of GDM.[17,18,97] However, controversy still exists regarding the dose–response relationship between vitamin D and the risk of GDM. In a recent systematic review and meta-analysis by Sadeghian *et al.*,[97] each 10 nmol L^{-1} increase in circulating 25(OH)D was associated with a 2% reduction in the risk of GDM. However, findings from another meta-analysis by Milajerdi *et al.*[18] indicated a U-shaped non-linear association between serum vitamin D levels and risk of GDM. Several methodological limitations may restrict the validity of the estimated effect values from these studies. The authors included studies in which 25(OH)D was measured on the same day as or after screening for GDM and could not ensure the prospective property of the studies. Also, they only included studies with serum samples, which resulted in fewer GDM cases being included in the study. In contrast, our study included both serum and plasma samples and further explored differences in subgroup analyses. Overall, it is necessary to conduct well-designed studies to elucidate the dose–response relationship between vitamin D levels and GDM risk.

We found a significant non-linear dose–response association between vitamin D levels and the risk of PE, with the risk decreasing more rapidly when vitamin D levels exceeded 40 nmol L^{-1}. Several meta-analyses on the same topic were previously published, but they did not examine the potential non-linear and linear associations.[19,20,98–100] Similar to our findings, some of these studies found that vitamin D deficiency or insufficiency was related to a higher risk of PE.[19,20,100] However, two other studies showed that PE risk was not influenced by vitamin D levels during pregnancy.[98,99] The discrepancies can be primarily attributed to the different inclusion criteria, with some studies including both cohort and cross-sectional studies, whereas the current meta-analysis included only prospective studies.

In this meta-analysis, maternal vitamin D levels in the highest category were protectively associated with the risk of GH compared with the lowest category. However, we did not find a significant dose–response relationship. To the best of our knowledge, this is the first meta-analysis to quantitatively summarize the association between vitamin D levels during pregnancy and GH. Nevertheless, the above results are based on a small number of studies, and further research is needed to shed light on this issue.

In line with the current study, the results of a systematic review and meta-analysis in 2013 showed no significant association between vitamin D levels and risk of C-section.[20] Although vitamin D was found to reduce the common causes of the occurrence of C-section such as GDM and PE, and most studies did not distinguish whether the outcome was a primary C-section or whether it was an active elective cesarean delivery, which may somewhat influence the results. Future studies on this association need to consider and collect these essential factors associated with outcomes to improve the existing evidence.

The specific mechanisms behind the effects of vitamin D on adverse pregnancy outcomes are not well understood; however, the extra-skeletal effects of vitamin D may play a crucial role. For instance, vitamin D has an integral part in maintaining glucose and insulin homeostasis;[101] therefore, higher vitamin D levels may reduce the risk of GDM. In addition, active vitamin D can inhibit the renin–angiotensin system (RAS),[102] which is an essential pathway in the regulation of PE and GH.[103] Furthermore, vitamin D is considered to have anti-inflammatory properties that may reduce the maternal inflammatory response.[104] Consequently, these mechanisms may explain why higher vitamin D levels may reduce the risk of adverse pregnancy outcomes. However, more animal studies or clinical trials are needed to demonstrate the specific mechanisms.

In addition, our systematic review found that the mean 25(OH)D concentrations in pregnant women were highly varied in different regions, from 18 nmol L^{-1}–98 nmol L^{-1}.[12,70,92] There are several possible influential factors that may contribute to discrepancies in vitamin D status between populations, such as sun exposure, diet, nutritional status, and renal function.[105] Also, differences in the assay methods for blood 25(OH)D concentrations may have contributed to the discrepancy.[105] Furthermore, the bioavailability of vitamin D intake varies among individuals, which may be explained in part by genetic variability in the vitamin D receptor (VDR).[106,107]

Conclusions

In conclusion, our comprehensive meta-analysis provides further evidence that higher 25(OH)D levels during pregnancy are associated with a lower risk of GDM and PE in a dose–response manner. However, the inverse association between maternal 25(OH)D levels and GH was significant in the highest *versus* lowest meta-analysis, but no dose–response relationship was found. Moreover, we found no association between vitamin D levels and the risk of C-section. More randomized controlled trials and animal experiments are needed to further evaluate the associations of vitamin D levels with adverse pregnancy outcomes to prove our findings.

Author contributions

Rui Zhao: conceptualization, methodology, software, formal analysis, and writing – original draft. Leilei Zhou: method-

ology, validation, data curation, and writing – original draft. Shanshan Wang: methodology, resources, and validation. Guoping Xiong: conceptualization, supervision, writing – review and editing, and funding acquisition. Liping Hao: conceptualization, supervision, writing – review and editing, project administration, and funding acquisition. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declared no conflict of interest.

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References

1 P. Wu, R. Haththotuwa, C. S. Kwok, A. Babu, R. A. Kotronias, C. Rushton, A. Zaman, A. A. Fryer, U. Kadam, C. A. Chew-Graham and M. A. Mamas, Preeclampsia and Future Cardiovascular Health: A Systematic Review and Meta-Analysis, *Circ.: Cardiovasc. Qual. Outcomes*, 2017, **10**, e003497.

2 A. Hauspurg, W. Ying, C. A. Hubel, E. D. Michos and P. Ouyang, Adverse pregnancy outcomes and future maternal cardiovascular disease, *Clin. Cardiol.*, 2018, **41**, 239–246.

3 E. C. Johns, F. C. Denison, J. E. Norman and R. M. Reynolds, Gestational Diabetes Mellitus: Mechanisms, Treatment, and Complications, *Trends Endocrinol. Metab.*, 2018, **29**, 743–754.

4 A. Słabuszewska-Jóźwiak, J. K. Szymański, M. Ciebiera, B. Sarecka-Hujar and G. Jakiel, Pediatrics Consequences of Caesarean Section-A Systematic Review and Meta-Analysis, *Int. J. Environ. Res. Public Health*, 2020, **17**, 8031.

5 M. G. Kimlin, Geographic location and vitamin D synthesis, *Mol. Aspects Med.*, 2008, **29**, 453–461.

6 S. Karras, S. A. Paschou, E. Kandaraki, P. Anagnostis, C. Annweiler, B. C. Tarlatzis, B. W. Hollis, W. B. Grant and D. G. Goulis, Hypovitaminosis D in pregnancy in the Mediterranean region: a systematic review, *Eur. J. Clin. Nutr.*, 2016, **70**, 979–986.

7 M. F. Holick, The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention, *Rev. Endocr. Metab. Disord.*, 2017, **18**, 153–165.

8 R. M. Mogire, A. Mutua, W. Kimita, A. Kamau, P. Bejon, J. M. Pettifor, A. Adeyemo, T. N. Williams and S. H. Atkinson, Prevalence of vitamin D deficiency in Africa: a systematic review and meta-analysis, *Lancet Global Health*, 2020, **8**, e134–e142.

9 N. Q. Liu, A. T. Kaplan, V. Lagishetty, Y. B. Ouyang, Y. Ouyang, C. F. Simmons, O. Equils and M. Hewison, Vitamin D and the regulation of placental inflammation, *J. Immunol.*, 2011, **186**, 5968–5974.

10 B. Schröder-Heurich, C. J. P. Springer and F. von Versen-Höynck, Vitamin D Effects on the Immune System from Periconception through Pregnancy, *Nutrients*, 2020, **12**, 1432.

11 M. Achkar, L. Dodds, Y. Giguère, J. C. Forest, B. A. Armson, C. Woolcott, S. Agellon, A. Spencer and H. A. Weiler, Vitamin D status in early pregnancy and risk of preeclampsia, *Am. J. Obstet. Gynecol.*, 2015, **212**, 511e511–511e517.

12 A. D. Gernand, M. A. Klebanoff, H. N. Simhan and L. M. Bodnar, Maternal vitamin D status, prolonged labor, cesarean delivery and instrumental delivery in an era with a low cesarean rate, *J. Perinatol.*, 2015, **35**, 23–28.

13 A. D. Gernand, H. N. Simhan, K. M. Baca, S. Caritis and L. M. Bodnar, Vitamin D, pre-eclampsia, and preterm birth among pregnancies at high risk for pre-eclampsia: an analysis of data from a low-dose aspirin trial, *BJOG*, 2017, **124**, 1874–1882.

14 R. L. Wilson, A. J. Leviton, S. Y. Leemaqz, P. H. Anderson, J. A. Grieger, L. E. Grzeskowiak, P. E. Verburg, L. McCowan, G. A. Dekker, T. Bianco-Miotto and C. T. Roberts, Vitamin D levels in an Australian and New Zealand cohort and the association with pregnancy outcome, *BMC Pregnancy Childbirth*, 2018, **18**, 251.

15 B. Zhu, K. Huang, S. Yan, J. Hao, P. Zhu, Y. Chen, A. Ye and F. Tao, VDR variants rather than early pregnancy Vitamin D concentrations are associated with the risk of gestational diabetes: The Ma'anshan Birth Cohort (MABC) Study, *J. Diabetes Res.*, 2019, **2019**, 8313901.

16 G. D. Chen, T. T. Pang, P. S. Li, Z. X. Zhou, D. X. Lin, D. Z. Fan, X. L. Guo and Z. P. Liu, Early pregnancy vitamin D and the risk of adverse maternal and infant outcomes: A retrospective cohort study, *BMC Pregnancy Childbirth*, 2020, **20**, 465.

17 L. Wang, C. Zhang, Y. Song and Z. Zhang, Serum vitamin D deficiency and risk of gestational diabetes mellitus: a meta-analysis, *Arch. Med. Sci.*, 2020, **16**, 742–751.

18 A. Milajerdi, F. Abbasi, S. M. Mousavi and A. Esmaillzadeh, Maternal vitamin D status and risk of gestational diabetes mellitus: A systematic review and meta-analysis of prospective cohort studies, *Clin. Nutr.*, 2021, **40**, 2576–2586.

19 S. Akbari, B. Khodadadi, S. A. Y. Ahmadi, S. Abbaszadeh and F. Shahsavar, Association of vitamin D level and vitamin D deficiency with risk of preeclampsia: A systematic review and updated meta-analysis, *Taiwan. J. Obstet. Gynecol.*, 2018, **57**, 241–247.

20 F. Aghajafari, T. Nagulesapillai, P. E. Ronksley, S. C. Tough, M. O'Beirne and D. M. Rabi, Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies, *Br. Med. J.*, 2013, **346**, f1169.
21 D. Moher, A. Liberati, J. Tetzlaff, D. G. Altman and P. Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, *PLoS Med.*, 2009, **6**, e1000097.
22 A. Stang, Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses, *Eur. J. Epidemiol.*, 2010, **25**, 603–605.
23 R. DerSimonian and N. Laird, Meta-analysis in clinical trials revisited, *Contemp. Clin. Trials*, 2015, **45**, 139–145.
24 J. P. Higgins and S. G. Thompson, Quantifying heterogeneity in a meta-analysis, *Stat. Med.*, 2002, **21**, 1539–1558.
25 J. P. Higgins, S. G. Thompson, J. J. Deeks and D. G. Altman, Measuring inconsistency in meta-analyses, *Br. Med. J.*, 2003, **327**, 557–560.
26 S. G. Thompson and J. P. Higgins, How should meta-regression analyses be undertaken and interpreted?, *Stat. Med.*, 2002, **21**, 1559–1573.
27 M. Egger, G. Davey Smith, M. Schneider and C. Minder, Bias in meta-analysis detected by a simple, graphical test, *Br. Med. J.*, 1997, **315**, 629–634.
28 J. Hamling, P. Lee, R. Weitkunat and M. Ambühl, Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category, *Stat. Med.*, 2008, **27**, 954–970.
29 S. Greenland and M. P. Longnecker, Methods for trend estimation from summarized dose-response data, with applications to meta-analysis, *Am. J. Epidemiol.*, 1992, **135**, 1301–1309.
30 L. Desquilbet and F. Mariotti, Dose-response analyses using restricted cubic spline functions in public health research, *Stat. Med.*, 2010, **29**, 1037–1057.
31 N. Orsini, R. Li, A. Wolk, P. Khudyakov and D. Spiegelman, Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software, *Am. J. Epidemiol.*, 2012, **175**, 66–73.
32 V. Bagnardi, A. Zambon, P. Quatto and G. Corrao, Flexible meta-regression functions for modeling aggregate dose-response data, with an application to alcohol and mortality, *Am. J. Epidemiol.*, 2004, **159**, 1077–1086.
33 M. Haugen, A. L. Brantsaeter, L. Trogstad, J. Alexander, C. Roth, P. Magnus and H. M. Meltzer, Vitamin D supplementation and reduced risk of preeclampsia in nulliparous women, *Epidemiology*, 2009, **20**, 720–726.
34 A. Al-Ajlan, S. Al-Musharaf, M. A. Fouda, S. Krishnaswamy, K. Wani, N. J. Aljohani, A. Al-Serehi, E. Sheshah, N. M. Alshingetti, I. Z. Turkistani, A. Afrah Alharbi, B. A. Alraqebah, A. M. Ali, G. Al-Saeed and N. M. Al-Daghri, Lower vitamin D levels in Saudi pregnant women are associated with higher risk of developing GDM, *BMC Pregnancy Childbirth*, 2018, **18**, 86.
35 A. I. Al-Shafei, D. A. Rayis, A. H. Mohieldein, O. A. El-Gendy and I. Adam, Maternal early pregnancy serum level of 25-Hydroxyvitamin D and risk of gestational diabetes mellitus, *Int. J. Gynecol. Obstet.*, 2020, **152**, 382–385.
36 D. L. Arnold, D. A. Enquobahrie, C. Qiu, J. Huang, N. Grote, A. VanderStoep and M. A. Williams, Early Pregnancy Maternal Vitamin D Concentrations and Risk of Gestational Diabetes Mellitus, *Paediatr. Perinat. Epidemiol.*, 2015, **29**, 196–199.
37 S. Ates, O. Sevket, P. Ozcan, F. Ozkal, M. O. Kaya and B. Dane, Vitamin D status in the first-trimester: Effects of vitamin D deficiency on pregnancy outcomes, *Afr. Health Sci.*, 2016, **16**, 36–43.
38 N. H. A. Aziz, N. A. Yazid, R. A. Rahman, N. A. Rashid, S. K. Wong, N. V. Mohamad, P. S. Lim and K. Y. Chin, Is first trimester maternal 25-hydroxyvitamin d level related to adverse maternal and neonatal pregnancy outcomes? A prospective cohort study among Malaysian women, *Int. J. Environ. Res. Public Health*, 2020, **17**, 3291.
39 A. M. Baker, S. Haeri, C. A. Camargo, A. M. Stuebe and K. A. Boggess, First-trimester maternal vitamin D status and risk for gestational diabetes (GDM) a nested case-control study, *Diabetes/Metab. Res. Rev.*, 2012, **28**, 164–168.
40 V. T. Boyle, E. B. Thorstensen, D. Mourath, M. B. Jones, L. M. E. McCowan, L. C. Kenny and P. N. Baker, The relationship between 25-hydroxyvitamin D concentration in early pregnancy and pregnancy outcomes in a large, prospective cohort, *Br. J. Nutr.*, 2016, **116**, 1409–1415.
41 H. Bozdag and E. Akdeniz, Does severe vitamin D deficiency impact obstetric outcomes in pregnant women with thyroid autoimmunity?, *J. Matern. – Fetal Neonat. Med.*, 2020, **33**, 1359–1369.
42 M. Davies-Tuck, C. Yim, M. Knight, R. Hodges, J. C. G. Doery and E. Wallace, Vitamin D testing in pregnancy: Does one size fit all?, *Aust. N. Z. J. Obstet. Gynaecol.*, 2015, **55**, 149–155.
43 L. Dodds, C. G. Woolcott, H. Weiler, A. Spencer, J. C. Forest, B. A. Armson and Y. Giguère, Vitamin D Status and Gestational Diabetes: Effect of Smoking Status during Pregnancy, *Paediatr. Perinat. Epidemiol.*, 2016, **30**, 229–237.
44 P. Dwarkanath, P. Vinotha, T. Thomas, S. Joseph, A. Thomas, G. Shirley, C. N. Sheela, S. Mehta and A. V. Kurpad, Relationship of Early Vitamin D Concentrations and Gestational Diabetes Mellitus in Indian Pregnant Women, *Front. Nutr.*, 2019, **6**, 116.
45 Å. Eggemoen, C. W. Waage, L. Sletner, H. L. Gulseth, K. I. Birkeland and A. K. Jenum, Vitamin D, Gestational Diabetes, and Measures of Glucose Metabolism in a Population-Based Multiethnic Cohort, *J. Diabetes Res.*, 2018, **2018**, 8939235.
46 A. M. Fernandez-Alonso, E. C. Dionis-Sanchez, P. Chedraui, M. D. Gonzalez-Salmeron and F. R. Perez-

Lopez, First-trimester maternal serum 25-hydroxyvitamin D-3 status and pregnancy outcome, *Int. J. Gynecol. Obstet.*, 2012, **116**, 6–9.

47 S. K. Flood-Nichols, D. Tinnemore, R. R. Huang, P. G. Napolitano and D. L. Ippolito, Vitamin D deficiency in early pregnancy, *PLoS One*, 2015, **10**, e0123763.

48 K. Griew, R. Nunn, G. Fairbrother and S. Tewari, Early pregnancy vitamin D deficiency and gestational diabetes: Exploring the link, *Aust. J. Gen. Pract.*, 2019, **48**, 797–802.

49 S. Iqbal, M. Malik and G. Bano, Serum Vitamin D levels and gestational diabetes mellitus: analysis of early pregnancy cohort from a teaching hospital of Kashmir Valley, *J. Fam. Med. Prim. Care*, 2020, **9**, 4323–4328.

50 M. Lacroix, M. C. Battista, M. Doyon, G. Houde, J. Ménard, J. L. Ardilouze, M. F. Hivert and P. Perron, Lower vitamin D levels at first trimester are associated with higher risk of developing gestational diabetes mellitus, *Acta Diabetol.*, 2014, **51**, 609–616.

51 H. Li, J. Ma, R. Huang, Y. Wen, G. Liu, M. Xuan, L. Yang, J. Yang and L. Song, Prevalence of vitamin D deficiency in the pregnant women: an observational study in Shanghai, China, *Arch. Public Health*, 2020, **78**, 31.

52 M. Makgoba, S. M. Nelson, M. Savvidou, C. M. Messow, K. Nicolaides and N. Sattar, First-trimester circulating 25-hydroxyvitamin D levels and development of gestational diabetes mellitus, *Diabetes Care*, 2011, **34**, 1091–1093.

53 C. J. Nobles, G. Markenson and L. Chasan-Taber, Early pregnancy Vitamin D status and risk for adverse maternal and infant outcomes in a bi-ethnic cohort: The Behaviors Affecting Baby and You (B.A.B.Y.) Study, *Br. J. Nutr.*, 2015, **114**, 2116–2128.

54 S. Park, H. K. Yoon, H. M. Ryu, Y. J. Han, S. W. Lee, B. K. Park, S. Y. Park, C. H. Yim and S. H. Kim, Maternal vitamin D deficiency in early pregnancy is not associated with gestational diabetes mellitus development or pregnancy outcomes in Korean pregnant women in a prospective study, *J. Nutr. Sci. Vitaminol.*, 2014, **60**, 269–275.

55 L. Parlea, I. L. Bromberg, D. S. Feig, R. Vieth, E. Merman and L. L. Lipscombe, Association between serum 25-hydroxyvitaminD in early pregnancy and risk of gestational diabetes mellitus, *Diabetic Med.*, 2012, **29**, e25–e32.

56 A. Rodriguez, R. García-Esteban, M. Basterretxea, A. Lertxundi, C. Rodríguez-Bernal, C. Iñiguez, C. Rodriguez-Dehli, A. Tardõn, M. Espada, J. Sunyer and E. Morales, Associations of maternal circulating 25-hydroxyvitamin D3 concentration with pregnancy and birth outcomes, *BJOG*, 2015, **122**, 1695–1704.

57 E. Salakos, T. Rabeony, M. Courbebaisse, J. Taieb, V. Tsatsaris, J. Guibourdenche, M. V. Senat, H. Haidar, J. C. Jani, D. Barglazan, E. Maisonneuve, M. C. Haguet, N. Winer, D. Masson, C. Elie, J. C. Souberbielle and A. Benachi, Relationship between vitamin D status in the first trimester of pregnancy and gestational diabetes mellitus - A nested case-control study, *Clin. Nutr.*, 2021, **40**, 79–86.

58 F. J. Schneuer, C. L. Roberts, C. Guilbert, J. M. Simpson, C. S. Algert, A. Z. Khambalia, V. Tasevski, A. W. Ashton, J. M. Morris and N. Nassar, Effects of maternal serum 25-hydroxyvitamin D concentrations in the first trimester on subsequent pregnancy outcomes in an Australian population, *Am. J. Clin. Nutr.*, 2014, **99**, 287–295.

59 B. Shao, M. Mo, X. Xin, W. Jiang, J. Wu, M. Huang, S. Wang, X. Muyiduli, S. Si, Y. Shen, Z. Chen and Y. Yu, The interaction between prepregnancy BMI and gestational vitamin D deficiency on the risk of gestational diabetes mellitus subtypes with elevated fasting blood glucose, *Clin. Nutr.*, 2020, **39**, 2265–2273.

60 M. Jain, S. Kapry, S. Jain, S. K. Singh and T. B. Singh, Maternal Vitamin D Deficiency: A Risk Factor for Gestational Diabetes Mellitus in North India, *Gynecol. Obstet.*, 2015, **5**, 1000264.

61 J. Xia, Y. Song, S. Rawal, J. Wu, S. Hinkle, M. Y. Tsai and C. Zhang, Vitamin d status during pregnancy and the risk of gestational diabetes mellitus-a longitudinal study in a multiracial cohort, *Diabetes*, 2018, **67**, A385.

62 C. Xu, H. H. Ma and Y. Wang, Maternal Early Pregnancy Plasma Concentration of 25-Hydroxyvitamin D and Risk of Gestational Diabetes Mellitus, *Calcif. Tissue Int.*, 2018, **102**, 280–286.

63 L. Yang, L. Song, X. Xu, Y. Liu, H. Li and L. Tang, Prevalence of Vitamin D Deficiency during Second Trimester of Pregnancy in Shanghai China, Risk Factors and Effects on Pregnancy Outcomes, *Iran. J. Public Health*, 2018, **47**, 1145–1150.

64 C. Y. Yue and C. M. Ying, Sufficience serum vitamin D before 20 weeks of pregnancy reduces the risk of gestational diabetes mellitus, *Nutr. Metab.*, 2020, **17**, 89.

65 C. Zhang, C. Qiu, F. B. Hu, R. M. David, R. M. van Dam, A. Bralley and M. A. Williams, Maternal plasma 25-hydroxyvitamin D concentrations and the risk for gestational diabetes mellitus, *PLoS One*, 2008, **3**, e3753.

66 J. Zhou, L. Su, M. Liu, Y. Liu, X. Cao, Z. Wang and H. Xiao, Associations between 25-hydroxyvitamin D levels and pregnancy outcomes: A prospective observational study in southern China, *Eur. J. Clin. Nutr.*, 2014, **68**, 925–930.

67 I. Alvarez-Fernandez, B. Prieto, V. Rodriguez, Y. Ruano, A. I. Escudero and F. V. Alvarez, Role of vitamin D and sFlt-1/PlGF ratio in the development of early-and late-onset preeclampsia, *Clin. Chem. Lab. Med.*, 2015, **53**, 1033–1040.

68 M. Azar, A. Basu, A. J. Jenkins, A. J. Nankervis, K. F. Hanssen, H. Scholz, T. Henriksen, S. K. Garg, S. M. Hammad, J. A. Scardo, C. E. Aston and T. J. Lyons, Serum carotenoids and fat-soluble vitamins in women with type 1 diabetes and preeclampsia: A longitudinal study, *Diabetes Care*, 2011, **34**, 1258–1264.

69 K. M. Baca, H. N. Simhan, R. W. Platt and L. M. Bodnar, Low maternal 25-hydroxyvitamin D concentration increases the risk of severe and mild preeclampsia, *Ann. Epidemiol.*, 2016, **26**, 853–857.e1.

70 A. M. Baker, S. Haeri, C. A. Camargo Jr., J. A. Espinola and A. M. Stuebe, A nested case-control study of midgestation vitamin D deficiency and risk of severe preeclampsia, *J. Clin. Endocrinol. Metab.*, 2010, **95**, 5105–5109.

71 A. Benachi, A. Baptiste, J. Taieb, V. Tsatsaris, J. Guibourdenche, M. V. Senat, H. Haidar, J. Jani, M. Guizani, J. M. Jouannic, M. C. Haguet, N. Winer, D. Masson, M. Courbebaisse, C. Elie and J. C. Souberbielle, Relationship between vitamin D status in pregnancy and the risk for preeclampsia: A nested case-control study, *Clin. Nutr.*, 2019, **39**, 440–446.

72 L. M. Bodnar, J. M. Catov, H. N. Simhan, M. F. Holick, R. W. Powers and J. M. Roberts, Maternal vitamin D deficiency increases the risk of preeclampsia, *J. Clin. Endocrinol. Metab.*, 2007, **92**, 3517–3522.

73 S. Gidlöf, A. T. Silva, S. Gustafsson and P. G. Lindqvist, Vitamin D and the risk of preeclampsia-A nested case-control study, *Acta Obstet. Gynecol. Scand.*, 2015, **94**, 904–908.

74 A. Hemmingway, L. C. Kenny, L. Malvisi and M. E. Kiely, Exploring the concept of functional Vitamin D deficiency in pregnancy: Impact of the interaction between 25-hydroxyVitamin D and parathyroid hormone on perinatal outcomes, *Am. J. Clin. Nutr.*, 2018, **108**, 821–829.

75 C. E. Powe, E. W. Seely, S. Rana, I. Bhan, J. Ecker, S. A. Karumanchi and R. Thadhani, First trimester vitamin D, vitamin D binding protein, and subsequent preeclampsia, *Hypertension*, 2010, **56**, 758–763.

76 T. O. Scholl, X. Chen and T. P. Stein, Vitamin D, secondary hyperparathyroidism, and preeclampsia, *Am. J. Clin. Nutr.*, 2013, **98**, 787–793.

77 A. W. Shand, N. Nassar, P. Von Dadelszen, S. M. Innis and T. J. Green, Maternal vitamin D status in pregnancy and adverse pregnancy outcomes in a group at high risk for pre-eclampsia, *BJOG*, 2010, **117**, 1593–1598.

78 B. van Weert, D. van den Berg, E. J. Hrudey, A. J. Oostvogels, E. de Miranda and T. G. Vrijkotte, Is first trimester vitamin D status in nulliparous women associated with pregnancy related hypertensive disorders?, *Midwifery*, 2016, **34**, 117–122.

79 S. Q. Wei, F. Audibert, N. Hidiroglou, K. Sarafin, P. Julien, Y. Wu, Z. C. Luo and W. D. Fraser, Longitudinal vitamin D status in pregnancy and the risk of pre-eclampsia, *BJOG*, 2012, **119**, 832–839.

80 L. A. Wetta, J. R. Biggio, S. Cliver, A. Abramovici, S. Barnes and A. T. N. Tita, Is midtrimester vitamin D status associated with spontaneous preterm birth and preeclampsia?, *Am. J. Perinatol.*, 2014, **31**, 541–546.

81 C. Y. Yue, J. P. Gao, C. Y. Zhang and C. M. Ying, Is serum vitamin D deficiency before gestational 20 weeks a risk factor for preeclampsia?, *Clin. Nutr.*, 2021, **40**, 4430–4435.

82 C. M. Anderson, J. L. Ralph, L. Johnson, A. Scheett, M. L. Wright, J. Y. Taylor, J. E. Ohm and E. Uthus, First trimester vitamin D status and placental epigenomics in preeclampsia among Northern Plains primiparas, *Life Sci.*, 2015, **129**, 10–15.

83 D. A. Bomba-Opon, R. Brawura-Biskupski-Samaha, S. Kozlowski, P. Kosinski, Z. Bartoszewicz, T. Bednarczuk and M. Wielgos, First trimester maternal serum vitamin D and markers of preeclampsia, *J. Matern.-Fetal Neonat. Med.*, 2014, **27**, 1078–1079.

84 S. Aydogmus, S. Kelekci, H. Aydogmus, S. Eriş, R. Desdicioḡlu, B. Yilmaz and G. Saḷlam, High prevalence of vitamin D deficiency among pregnant women in a Turkish population and impact on perinatal outcomes, *J. Matern.-Fetal Neonat. Med.*, 2015, **28**, 1828–1832.

85 W. Chen, Y. Li, B. Gao, J. Li, M. Zheng and X. Chen, Serum 25-hydroxyvitamin D levels in relation to lipids and clinical outcomes in pregnant women with gestational diabetes mellitus: An observational cohort study, *BMJ Open*, 2020, **10**, e039905.

86 A. Gbadegesin, A. Sobande, O. Adedeji, E. Disu, O. Korede, A. Dosunmu and A. Shakunle, Maternal serum vitamin D levels and pregnancy outcomes: from Lagos, Nigeria, *J. Obstet. Gynaecol.*, 2017, **37**, 25–28.

87 H. Hajianfar, A. Esmailzadeh, A. Feizi, Z. Shahshahan and L. Azadbakht, Association of Maternal Serum Vitamin D Level with Risk of Pregnancy-Related Complications and Neonatal Anthropometric Measures: A Prospective Observational Study, *Int. J. Prev. Med.*, 2019, **10**, 208.

88 B. Kısa, H. Kansu-Celik, T. Candar, E. M. Erol Koc, U. Y. Sert and O. Uzunlar, Severe 25-OH vitamin D deficiency as a reason for adverse pregnancy outcomes, *J. Matern.-Fetal Neonat. Med.*, 2020, **33**, 2422–2426.

89 S. L. Loy, N. Lek, F. Yap, S. E. Soh, N. Padmapriya, K. H. Tan, A. Biswas, G. S. H. Yeo, K. Kwek, P. D. Gluckman, K. M. Godfrey, S. M. Saw, F. Müller-Riemenschneider, Y. S. Chong, M. F. F. Chong, J. K. Y. Chan, A. Sheppard, A. Chinnadurai, A. E. N. Goh, A. Rifkin-Graboi, A. Qiu, B. W. Lee, B. F. P. Broekman, B. L. Quah, B. Shuter, C. K. Chng, C. Ngo, S. C. Y. Hsu, C. L. Bong, C. J. Henry, C. Y. I. Chee, D. Fok, H. Inskip, H. Chen, H. P. S. Van Bever, I. Magiati, I. B. Y. Wong, I. Y. M. Lau, J. Kapur, J. L. Richmond, J. D. Holbrook, J. J. Gooley, K. Niduvaje, L. Singh, L. L. Su, M. Daniel, L. P. C. Shek, M. V. Fortier, M. Hanson, M. Rauff, M. C. Chua, M. Meaney, M. T. Tint, O. H. Teoh, P. C. Wong, P. Agarwal, R. M. Van Dam, S. A. Rebello, S. C. Chong, S. Cai, S. B. Lim, V. S. Rajadurai, W. Stunkel, W. M. Han, W. W. Pang, Y. T. D. Goh, Y. B. Cheung, Y. H. Chan and Y. S. Lee, Association of maternal Vitamin D status with glucose tolerance and caesarean section in a multi-ethnic Asian cohort: The growing up in Singapore towards healthy outcomes study, *PLoS One*, 2015, **10**, e0142239.

90 D. F. Öcal, Z. Aycan, G. Dağdeviren, N. Kanbur, T. Küçüközkan and O. Derman, Vitamin D deficiency in adolescent pregnancy and obstetric outcomes, *Taiwan. J. Obstet. Gynecol.*, 2019, **58**, 778–783.

91 N. Perez-Ferre, M. J. Torrejon, M. Fuentes, M. D. Fernandez, A. Ramos, E. Bordiu, L. Del Valle, M. A. Rubio, A. R. Bedia, C. Montañez and A. L. Calle-

Pascual, Association of low serum 25-hydroxyvitamin D levels in pregnancy with glucose homeostasis and obstetric and newborn outcomes, *Endocrinol. Pract.*, 2012, **18**, 676–684.

92 C. Reichetzeder, H. Chen, M. Föller, T. Slowinski, J. Li, Y. P. Chen, F. Lang and B. Hocher, Maternal vitamin D deficiency and fetal programming - Lessons learned from humans and mice, *Kidney Blood Pressure Res.*, 2014, **39**, 315–329.

93 T. O. Scholl, X. Chen and P. Stein, Maternal vitamin D status and delivery by cesarean, *Nutrients*, 2012, **4**, 319–330.

94 D. K. Thiele, E. N. Erickson and J. M. Snowden, High Prevalence of Maternal Serum 25-Hydroxyvitamin D Deficiency Is Not Associated With Poor Birth Outcomes Among Healthy White Women in the Pacific Northwest, *J. Obstet. Gynecol. Neonatal Nurs.*, 2019, **48**, 163–175.

95 J. Wen, Q. Hong, L. Zhu, P. Xu, Z. Fu, X. Cui, L. You, X. Wang, T. Wu, H. Ding, Y. Dai, C. Ji and X. Guo, Association of maternal serum 25-hydroxyvitamin D concentrations in second and third trimester with risk of gestational diabetes and other pregnancy outcomes, *Int. J. Obes.*, 2017, **41**, 489–496.

96 Y. Yuan, H. Liu, C. Ji, X. Guo, L. Hu, J. Wen and M. Cai, Association of Maternal Serum 25-hydroxyvitamin D Concentrations in Second Trimester with Delivery Mode in A Chinese Population, *Int. J. Med. Sci.*, 2017, **14**, 1008–1014.

97 M. Sadeghian, M. Asadi, S. Rahmani, M. Akhavan Zanjani, O. Sadeghi, S. A. Hosseini and A. Zare Javid, Circulating vitamin D and the risk of gestational diabetes: a systematic review and dose-response meta-analysis, *Endocrine*, 2020, **70**, 36–47.

98 M. J. Aguilar-Cordero, A. Lasserrot-Cuadrado, N. Mur-Villar, X. A. León-Ríos, T. Rivero-Blanco and I. M. Pérez-Castillo, Vitamin D, preeclampsia and prematurity: A systematic review and meta-analysis of observational and interventional studies, *Midwifery*, 2020, **87**, 102707.

99 S. J. Martínez-Domínguez, M. Tajada, P. Chedraui and F. R. Pérez-López, Systematic review and meta-analysis of Spanish studies regarding the association between maternal 25-hydroxyvitamin D levels and perinatal outcomes, *Gynecol. Endocrinol.*, 2018, **34**, 987–994.

100 M. Tabesh, A. Salehi-Abargouei, M. Tabesh and A. Esmaillzadeh, Maternal vitamin D status and risk of pre-eclampsia: a systematic review and meta-analysis, *J. Clin. Endocrinol. Metab.*, 2013, **98**, 3165–3173.

101 S. G. Garbossa and F. Folli, Vitamin D, sub-inflammation and insulin resistance. A window on a potential role for the interaction between bone and glucose metabolism, *Rev. Endocr. Metab. Disord.*, 2017, **18**, 243–258.

102 Y. C. Li, J. Kong, M. Wei, Z.-F. Chen, S. Q. Liu and L.-P. Cao, 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system, *J. Clin. Invest.*, 2002, **110**, 229–238.

103 H. D. Mistry, M. V. H. Ogalde, F. Broughton Pipkin, G. Escher and L. O. Kurlak, Maternal, Fetal, and Placental Selectins in Women With Pre-eclampsia; Association With the Renin-Angiotensin-System, *Front. Med.*, 2020, **7**, 270.

104 C. C. Akoh, E. K. Pressman, E. Cooper, R. A. Queenan, J. Pillittere and K. O. O'Brien, Low Vitamin D is Associated With Infections and Proinflammatory Cytokines During Pregnancy, *Reprod. Sci.*, 2018, **25**, 414–423.

105 K. D. Cashman, K. G. Dowling, Z. Škrabáková, M. Gonzalez-Gross, J. Valtueña, S. De Henauw, L. Moreno, C. T. Damsgaard, K. F. Michaelsen, C. Mølgaard, R. Jorde, G. Grimnes, G. Moschonis, C. Mavrogianni, Y. Manios, M. Thamm, G. B. Mensink, M. Rabenberg, M. A. Busch, L. Cox, S. Meadows, G. Goldberg, A. Prentice, J. M. Dekker, G. Nijpels, S. Pilz, K. M. Swart, N. M. van Schoor, P. Lips, G. Eiriksdottir, V. Gudnason, M. F. Cotch, S. Koskinen, C. Lamberg-Allardt, R. A. Durazo-Arvizu, C. T. Sempos and M. Kiely, Vitamin D deficiency in Europe: pandemic?, *Am. J. Clin. Nutr.*, 2016, **103**, 1033–1044.

106 E. A. Torres Dominguez, A. Meza Peñafiel, A. Gómez Pedraza and E. E. Martínez Leo, Molecular mechanisms from insulin-mimetic effect of vitamin D: treatment alternative in Type 2 diabetes mellitus, *Food Funct.*, 2021, **12**, 6682–6690.

107 S. Shab-Bidar, T. R. Neyestani and A. Djazayery, The interactive effect of improvement of vitamin D status and VDR FokI variants on oxidative stress in type 2 diabetic subjects: a randomized controlled trial, *Eur. J. Clin. Nutr.*, 2015, **69**, 216–222.