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ARTICLE

Epidemiology

Vitamin D status during pregnancy and offspring outcomes: a systematic review and meta-analysis of observational studies

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Abstract

Background/objectives Vitamin D deficiency during pregnancy may influence adverse outcomes in offspring. The aim of this systematic review and meta-analysis of observational studies was to assess the association between low prenatal concentrations of 25(OH)D (by using three different cut-off levels), preterm birth (PTB) and anthropometric and neurodevelopmental outcomes in offspring.

Subjects/methods Studies reporting data on the association between maternal vitamin D concentrations and offspring outcomes identified through a systematic review of scientific literature published in PubMed/MEDLINE, Scopus and the Cochrane Library databases up to April 2017.

Results We included 54 eligible studies. Vitamin D-deficient mothers (<30 nmol/L) had offspring with lower birthweight (MD −87.82 g; 95% CI −119.73, −55.91 g), head circumference (MD −0.19 cm; 95% CI −0.32, −0.06 cm) and a higher risk of small for gestational age (SGA) infants and PTB (OR 1.59; 95% CI 1.24, 2.03) compared to mothers with concentrations ≥30 nmol/L. Vitamin D insufficiency (<50 nmol/L) was associated with a higher risk of SGA and PTB (OR 1.43; 95% CI 1.08, 1.91 and OR 1.28; 95% CI 1.08, 1.52, respectively). Concentrations of 25(OH)D ≥75 nmol/L were not found to be associated with birthweight, SGA or PTB. Offspring of vitamin D-insufficient mothers had lower scores in mental (MD −1.12 points; 95% CI −1.82, −0.42 cm) and language developmental tests (MD −0.35 points; 95% CI −1.00, 0.31 cm).

Conclusion Maternal vitamin D deficiency is associated with offspring adverse anthropometric outcomes and PTB; insufficiency with a higher risk of SGA, PTB and adverse neurodevelopmental outcomes.

Introduction

Vitamin D is a necessary nutrient required for development and vitamin D deficiency has become a major health problem worldwide, affecting over 1 billion people, across all racial, ethnic and age groups [1–3]. In particular, vitamin D deficiency is a highly prevalent condition among pregnant women and has been estimated to affect 20–40% of them [4]. Since foetal and neonatal vitamin D status relies on the mother, vitamin D deficiency during prenatal period has been associated with several negative consequences for offspring health. Accordingly, accumulating research highlights the relationship between low prenatal concentrations of vitamin D and an increased risk of adverse neonatal outcomes, such as low birthweight and length [5–12], small for gestational age (SGA) [5, 6, 8–10, 12–15], preterm birth (PTB) [10, 13, 15], lower head circumference (HC) [7, 8, 11]—a risk factor for neuropsychiatric disorders of developmental origins- [16, 17], asthma, wheeze and

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respiratory tract infections, among others [18–21]. Furthermore, a poorer vitamin D status in pregnancy has been associated with adverse neurodevelopmental outcomes and behavioural problems in some previous studies [17, 22–27].

Despite many studies in this field and the number of systematic reviews and meta-analyses [28–37] trying to summarize the available evidence, there are still numerous conflicting results regarding the relationship between maternal vitamin D concentrations and optimal offspring outcomes, including anthropometric and neurodevelopmental outcomes and behavioural problems.

In addition, very few studies have focussed on the minimum concentrations of 25-hydroxyvitamin D (25(OH)D) from which vitamin D supplementation will be recommended for pregnant women to reduce the risk of adverse outcomes in their children. Given the accumulation of new evidence since the publication of recent reviews, and considering that most meta-analysis have used a single cut-off level for vitamin D deficiency and that, to date, no meta-analysis has quantitatively assessed the effect of low prenatal concentrations of vitamin D on neurodevelopmental outcomes (cognitive, language, and motor development), and there is a need to synthesize research evidence from individual studies. This synthesis would enable health-care providers to agree on the optimal vitamin D status in pregnancy to reduce adverse outcomes in offspring and contribute in our understanding of the effects of both maternal vitamin D deficiency and insufficiency on specific health outcomes.

The aim of this systematic review and meta-analysis of observational studies was to assess the association between low prenatal concentrations of vitamin D (by using three different cut-off values of 25(OH)D concentrations) and anthropometric measures (including birthweight, length, HC, SGA) and other outcomes on their offspring (PTB, mental, language and motor development).

Methods

This study has been recorded in PROSPERO (2017: CDR2017055607), an international database of prospectively registered systematic reviews in health and social care:

https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID = CRD42017055607

This systematic revision and meta-analysis has been carried out following the MOOSE guidelines[38] and specific items from the PRISMA guidelines [39] (items 5, 10 and 14 of the checklist).

Literature search

The studies selected were identified through a systematic review of scientific literature published in PubMed/MEDLINE, Scopus and the Cochrane Library databases to up April, 2018. We searched for the following keywords: ((“Vitamin D”[Mesh]) AND (“Pregnancy”[Mesh] OR “pregnant”) AND (“Infant”[Mesh] OR “Child”[Mesh]) AND (“Birth weight”[Mesh] OR “Body Height”[Mesh] OR “head circumference” OR “cephalic perimeter” OR growth OR “Premature Birth”[Mesh] OR “Infant, Small for Gestational Age”[Mesh] OR “Neurobehavioral Manifestations”[Mesh] OR “Neurodevelopmental Disorders”[Mesh] OR “Cognition”[Mesh] OR “Child Development”[Mesh] OR “Child Behavior”[Mesh] OR “Psychomotor Performance”[Mesh])). No date or language restrictions were applied. Case reports, comments, editorials, letters, reviews, systematic reviews and meta-analyses were excluded. Additional articles were identified after citation tracking and manual search.

Study selection

The studies were first filtered by title and then by the abstract (Fig. 1) and duplicate publications were removed. We reviewed the studies and selected if they met following inclusion criteria: (a) Original study articles that explored the relationship between maternal vitamin D status and offspring outcomes (anthropometric measures or PTB or neurodevelopment); (b) the study population was adult

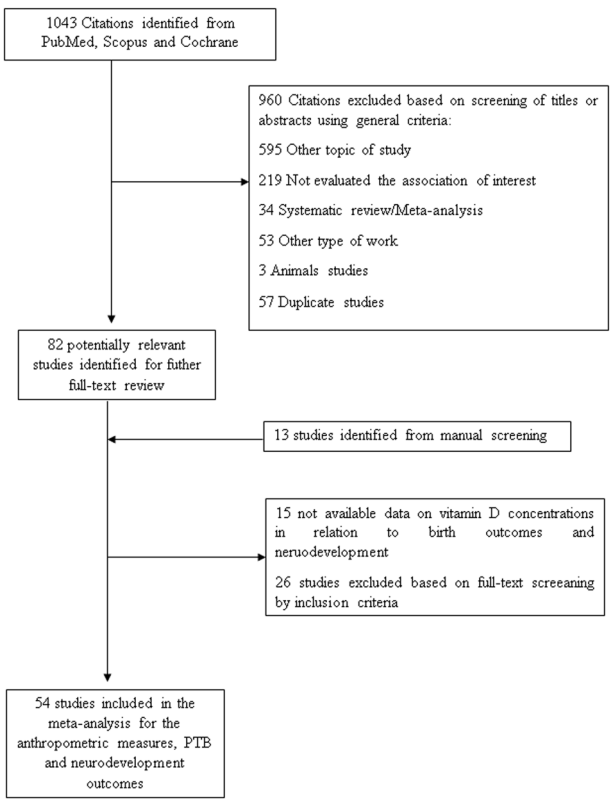

Fig. 1 Flowchart of study search and selection

healthy pregnant women; (c) 25(OH) assays were conducted in maternal or cord blood samples during pregnancy or at delivery; (d) Studies providing information about the newborns, infants or children: anthropometric measurements (birthweight, birth length, birth HC and SGA), PTB and neurodevelopment domains. The excluded criteria were: (a) case reports, comments, editorials and letters; (b) animal studies; (c) duplicated studies; and (d) pregnant women with serious specific diseases. From each study selected, we extracted the relevant information shown in Table 1. The articles were categorized based on the result of interest: birthweight, birth length and birth HC, SGA (below the 10th percentile), PTB (before 37 weeks of gestation), and neurodevelopment domains.

Two reviewers (MV and MT) independently reviewed the literature searches and acquired the full-length articles for all citations meeting the predefined selection criteria. We resolved any disagreements through consensus or arbitration by a third reviewer (VA).

We defined vitamin D deficiency and insufficiency as 25 (OH)D concentrations <30 and <50 nmol/L, respectively, defined by the Institute of Medicine [40] and suboptimal concentration (<75 nmol/L) proposed by the American Society of Endocrinology [41]. Therefore the analyses were made in three subgroups depending on the cut-off used (<30 vs ≥30 nmol/L; <50 vs ≥50 nmol/L and <75 vs ≥75 nmol/L). If studies reported 25(OH)D concentrations in ng/mL, we multiply by 2.5 to convert into nmol/L (nmol/L = 2.5 × ng/mL) [42].

We extracted the means and standard deviations of the anthropometric measurements (birthweight, birth length and birth HC), the neurodevelopmental tests and the number of PTB infants and SGA infants (raw data). We contacted some authors to obtain additional data from the studies.

The quality of the publications was assessed using the STROBE [43] criterion for observational studies. The articles were categorized as follows: "high" quality if the score was ≥17 items (≥80% of the checklist), "moderate" quality if the score was 13–16 items (60–79% of checklist) and "low" quality if the score was ≤12 items (<50% of the checklist). Low-quality articles were not included in the analysis.

Statistical analysis

The associations between maternal vitamin D status and the offspring outcomes were measured by difference in means (95% confidence intervals (CIs)) and SGA and PTB were expressed by odds ratio (OR) (95% CIs) using random effects. A forest plot was used to visually evaluate the pooled effect. Heterogeneity was calculated by using Cochrane X^2 statistical test and the degree of heterogeneity was quantified by I^2 test. An $I^2 > 50\%$ ($p < 0.1$) was considered as a measure of high heterogeneity [44]. Sensitivity analyses were used to investigate the origin of heterogeneity by assessing the effect of studies on outcomes by performing the analyses after excluding one or more studies. In addition, univariate meta-regression analysis were performed to assess whether the heterogeneity observed may be further explained by differences in ethnic diversity for birthweight and SGA, outcomes with more than three studies in each subgroup. Publication bias was first assessed with the Egger's test [45] (STATA software, version 12.0) and then tested with the funnel plot to confirm the presence or absence of bias, because a result in the non-significant Egger's test does not indicate an asymmetry, and it is recommended to complement the analysis with the vision of the distribution of the studies emitted by the funnel plot [46]. Data analysis was made using the Review Manager Software (version 5.3, Cochrane Collaboration) [47].

Results

A flowchart of the study selection process is depicted in Fig. 1. A total of 54 studies were included in the meta-analysis. There were a total of 67,484 participants and the age of women ranged from 18 to 45 years. The characteristics of the studies included in this meta-analysis are shown in Table 1.

The overall score on the STROBE checklist ranged from 15 to 18, with a mean score of 17 out of 22 points; as a result, 34 studies were of "high" quality (≥17 items) and 20 were rated as "moderate" quality (Supplemental Table 1).

Maternal status of vitamin D and anthropometric measures at birth

Mothers with vitamin D concentrations <30 vs ≥30 nmol/L had newborns with a lower weight and lower HC, whereas no differences were found in infants' length (Fig. 2). There was significant heterogeneity ($I^2 = 58$, 69 and 66%, respectively). Regarding birthweight and HC, as shown in Supplemental Fig. 6, the study of Dalgärd et al. caused asymmetry in the funnel plot. The heterogeneity decreased significantly when this study was excluded ($I^2 = 38$ and 18%, respectively), maintaining the estimated effect (birthweight: mean difference (MD) −98.33 g, 95% CI −125.74 to −70.92 g) (HC: MD −0.27 cm, 95% CI −0.35 to −0.20 cm) (Supplemental Fig. 1).

Meta-regression analysis showed that the heterogeneity observed cannot be explained by differences in the ethic group of the studies included, although we observed a trend to lower effects of maternal vitamin deficiency on birthweight in the Asian ethnic group (Supplemental Table 2).

Regarding birth length, the study of Reichetzeder et al. caused asymmetry in the funnel plot and the heterogeneity

Table 1 Characteristics of studies included in meta-analysis

Study	Country/ethnicity	Study design	Sample	Specimen, gestational age at time of sampling (weeks), assay method and 25(OH)D cut-off used (nmol/L)	Child outcomes
Studies included in anthropometric measures and preterm birth					
Arija et al. [72]	Spain	Cohort study	428	Maternal blood, <12 weeks of gestation ELISA Deficiency <50 nmol/L	SGA and PTB
Ates et al. [49]	Turkey	Cohort study	229	Maternal blood, 11–13 weeks of gestation LC-MS/MS Severe deficiency 25 nmol/L; moderate deficiency 25–47.5 nmol/L; mild deficiency 50–74.5 nmol/L; desirable reference limit >75 nmol/L	Birthweight
Aydogmus et al. [5]	Turkey	Cohort study	180	Maternal blood, >28 weeks of gestation ELISA Deficiency <37.5 nmol/L; insufficiency 37.5–74 nmol/L; sufficient >75 nmol/L.	Birthweight, SGA
Baker et al. [93]	United States Black White	Nested case–control	160	Maternal blood, 14 weeks of gestation LC-MS Deficiency <50 nmol/L; insuffciency 50–74.9 nmol/L; sufficiency ≥75 nmol/L	PTB
Bärebring et al. [94]	Sweden	Cohort study	2052	Maternal blood, 8–12 weeks of gestation LC-MS/MS High status ≥75 or 100 nmol/L, sufficiency ≥50 nmol/L, insufficiency 30–50 nmol/L	SGA and PTB
Bodnar et al. [62]	United States	Case–control	413	Maternal blood, <22 weeks of gestation ELISA Deficiency <37.5 nmol/l; insufficiency 37.5–75 nmol/l; sufficiency >75 nmol/l	SGA
Bodnar et al. [80]	United States	Nested case–control	2327	Maternal blood, <20 weeks of gestation LC-MS/MS Deficiency <50 nmol/L; insuffciency 50–74.9 nmol/L; sufficiency ≥75 nmol/L	PTB
Bowyer et al. [90]	Australia	Cohort study	971	Maternal blood, 30–32 weeks of gestation CLIA Deficiency <50 nmol/L; sufficiency ≥25 nmol/L	Birthweight
Boyle et al. [13]	New Zealand, Europe/ other ethnicities	Cohort study	1710	Maternal blood, 15 weeks of gestation LC-MS Severe deficiency <25 nmol/L; deficiency <50 nmol/L; insufficiency <75 nmol/L	SGA
Burris et al. [6]	United States White Black	Cohort study	1303	Maternal blood, 26–28 weeks of gestation CLIA and RIA Severe deficiency <25 nmol/L; deficiency 25–<50 nmol/L; insufficiency 50–<75 nmol/L; sufficiency ≥75 nmol/L	Birthweight, SGA
Chen et al. [61]	China	Cohort study	3658	Maternal blood, any stage of pregnancy RIA Deficient <50 nmol/L; insufficient 50–75 nmol/L; sufficient ≥75 nmol/L	SGA
Chi et al. [23]	China	Cohort study	160	Maternal blood, 28 weeks of gestation EIA Deficiency <50 nmol/L	Birthweight, birth Length and HC
Choi et al. [81]	Korea	Cohort study	282	Maternal blood, any trimester their of pregnancy LC-MS/MS Deficiency <50 nmol/L; suboptimal 50–75 nmol/L; sufficient ≥75 nmol/L	SGA and PTB
Dalgärd et al. [50]	Denmark	Cohort study	1038	Cord blood, delivery LC-MS/MS <12 nmol/L; 12–<25 nmol/L; 25–<50 nmol/L; ≥50 nmol/L	Birthweight, birth HC
Ertl et al. [95]	United Kingdom	Case–control	1150	Maternal blood, 11–13 weeks of gestation LC-MS/MS Deficiency <50 nmol/L and insufficiency <75 nmol/L	SGA
Eckhardt et al. [7]	United States White, Black	Cohort study	2473	Maternal blood, ≥26 weeks of gestation LC-MS/MS Deficiency <30 nmol/L	Birthweight, birth length and HC
Eggemoen et al. [51]	Norway	Cohort study	719	Maternal blood, 15 and 37 weeks RIA <37 nmol/L; ≥37 nmol/L	Birthweight
Farrant et al. [52]	India	Cohort study	559		Birthweight

Table 1 (continued)

Study	Country/ethnicity	Study design	Sample	Specimen, gestational age at time of sampling (weeks), assay method and 25(OH)D cut-off used (nmol/L)	Child outcomes
				Maternal blood, ≥37 weeks of gestation RIA Hypovitaminosis <50 nmol/L	
Fernandez Alonso et al. [89]	Spain	Cohort study	466	Maternal blood, 11–14 weeks of gestation CLIA Deficient <50 nmol/L; insufficient 50–74.5 nmol/L; sufficient ≥75 nmol/L	PTB
Flood-Nichols et al. [82]	United States	Cohort study	235	Maternal blood, 5 and 12 weeks ELISA Severe deficiency 50 nmol/L; 51–74 nmol/L; sufficiency 75 nmol/L	PTB
Gale et al. [53]	United Kingdom Caucasian	Cohort study	466	Maternal blood, 32.6 weeks of gestation RIA Deficiency <27.5 nmol/L; insufficiency 27.5–50 nmol/L; sufficiency >50 nmol/L	Birthweight, birth length and HC
Gernand et al. [8]	United States White Black	Cohort study	2146	Maternal blood, <26 weeks of gestation LC-MS/MS <37.5 nmol/L; ≥37.5 nmol/L	Birthweight and SGA
Gernand et al. [83]	United States White Black	Cohort study	792	Maternal blood, ≥26 weeks of gestation LC-MS/MS Deficiency <30 nmol/L; inadequacy 50 nmol/L;	SGA
Gould et al. [17]	Australia	Data from RCTs	334	Cord blood, delivery LC-MS/MS Deficiency <25 nmol/L; insufficiency 25–50 nmol/L; sufficiency >50 nmol/L	Birthweight, birth length, HC and SGA
Hanieh et al. [25]	Vietnam	Cohort study	960	Maternal blood, 32 weeks of gestation LC-MS/MS Deficiency <37.5 nmol/L, insufficiency ≤37.5 and <75 nmol/L, ≥75 nmol/L	Birthweight, birth length, HC
Leffelaar et al. [9]	Netherlands	Cohort study	3730	Maternal blood, 13.5 weeks of gestation EIA Deficiency ≤29 nmol/L; insufficiency 30–49.9 nmol/L; sufficiency ≥50 nmol/L	Birthweight, SGA
Miliku et al. [10]	Netherlands	Cohort Study	7098	Maternal blood, 20.3 weeks of gestation LC-MS/MS Severely deficient <25 nmol/L; deficient 25–49.9 nmol/L; sufficient 50–74.9 nmol/L; optimal ≥75 nmol/L	Birthweight, birth length and HC, SGA
Morgan et al. [84]	Canada	Nested case–control	1656	Cord blood, delivery CLIA <50 nmol/L; 50–75 nmol/L; ≥75 nmol/L	SGA and PTB
Morley et al. [54]	Australia	Cohort study	374	Maternal blood, 28–32 weeks of gestation RIA Low <28 nmol/L and high ≥28 nmol/L	Birthweight and birth HC
Mcdonnell et al. [91]	United States	Cohort study	1064	Maternal blood, 24–28 weeks LC/MS <50 nmol; 50–75 nmol/L; 75–100 nmol/L	PTB
Ong et al. [55]	Singapore	Cohort study	910	Maternal blood, 26–28 weeks of gestation LC-MS/MS Deficiency ≤29 nmol/L; insufficiency 30–49.9 nmol/L; sufficiency ≥50 nmol/L	Birthweight, length, HC at birth and at 3, 6, 9, 12, 15, 18, 24 months; SGA and PTB
Perez Ferre et al. [14]	Spain	Cohort Study	266	Maternal blood, 26–28 weeks CLIA Deficiency <50 nmol/L	Birthweight, SGA, PTB
Reichetzeder et al [92]	Germany	Cohort Study	547	Maternal blood, NA ELISA <1, severe deficiency ≥1 and 25 nmol/L, moderate deficiency ≥25 nmol/L	Birthweight, birth length and HC
Rodriguez et al. [56]	Spain	Cohort Study	2382	Maternal blood, 13.5 weeks of gestation HLPC Deficiency <50 nmol/L; insufficiency 50–74 nmol/L; sufficiency >75 nmol/L	Birthweight, birth length and HC, SGA
Seto et al. [96]	United States	Cohort study	438	Cord blood, delivery CLIA Sufficient ≥50 nmol/L and deficient <50 nmol/L	SGA
Song et al. [11]	China	Cross-sectional	70	Maternal blood, delivery ELISA Severe deficiency <25 nmol/L; deficiency 20 and	Birthweight, birth length and HC

Table 1 (continued)

Study	Country/ethnicity	Study design	Sample	Specimen, gestational age at time of sampling (weeks), assay method and 25(OH)D cut-off used (nmol/L)	Child outcomes
				50 nmol/L; insufficiency 50 and 75 nmol/L; 75 nmol/L normal	
Shand et al. [85]	Canada	Cohort study	227	Maternal blood, 10–20 weeks of gestation RIA <37.5 nmol/L; <50 nmol/L; >75 nmol/L	PTB
Schneuer et al. [15]	Australia	Nested case–control	5109	Maternal blood, 10–14 weeks of gestation CLIA <15; <25; <37.5; <50; <75 nmol/L	SGA and PTB
Tabatabaei et al. [97]	Canada	Case–control		Maternal blood, 8–14 weeks of gestation LC-MS <50, 50–75 and >75 nmol/L	PTB
Thorp et al. [86]	United States	Nested case–control	265	Maternal blood, 16–22 weeks of gestation LC-MS <50 nmol/L; >50 nmol/L	PTB
Viljakainen et al. [59]	Finland	Cohort study	98	Maternal blood, 37–42 weeks of gestation EIA Deficiency <50 nmol/L; insufficiency 51–74 nmol/L; sufficiency >75 nmol/L	Birthweight, birth length and HC
Wang et al. [48]	China	Cohort study	747	Maternal blood, 1 trimester ECLIA Deficiency <50 nmol/L; insufficiency 50–74 nmol/L; sufficiency >75 nmol/L	Birthweight, birth HC and SGA
Wagner et al. [87]	United States	Data from RCTs	50	Maternal blood, delivery RIA ≤50 nmol/L; <50–100 nmol/L; ≥ 100 nmol/L	PTB
Weinert et al. [57]	Brazil	Cohort study	184	Maternal blood, third trimester of pregnancy CLIA <50 nmol/L and >50 nmol/L	Birthweight and SGA
Wetta et al. [98]	United States	Nested case–control	200	Maternal blood, 15–21 weeks of gestation LC-MS Deficiency <37.5 nmol/L and insufficiency <75 nmol/L	PTB
Yang et al. [88]	China	Cohort study	138	Maternal blood, NA HLPC <50 nmol/L, ≥50 nmol/L; and 25, 50, 30, ≥30 nmol/L	PTB
Zhou et al. [99]	China	Cohort study	2960	Maternal blood, 16–20 weeks of gestation CLIA Low level ≤50 nmol/L; medium level 52.5–74.5 nmol/L; high level ≥75 nmol/L	Birthweight, birth length and SGA
Zhu et al. [12]	China	Cohort study	1491	Cord blood, delivery RIA Deciles 1–10; 11–20; 21–30; 31–40; 41–50; 51–60; 61–70; 71–80; 81–90; 91–100 nmol/L	Birthweight and SGA
Zhu et al. [100]	China	Cohort study	821	Maternal blood, before delivery ELISA Severe deficiency ≤25 nmol/L, mild deficiency 25–50 nmol/L, insufficiency 50–75 nmol/L	PTB
Studies included in neurodevelopmental outcomes					
Arija et al. [72]	Spain	Cohort study	428	Maternal blood, <12 weeks for gestation ELISA Deficiency <50 nmol/L	40 days Mental, motor and language development (BSDI III)
Chi et al. 2018 [23]	China	Cohort study	160	Maternal blood, 28 weeks of gestation EIA Deficiency <50 nmol/L	6 months Mental and motor development (BSDI III)
Darling et al. [26]	United Kingdom	Cohort study	7065	Maternal blood, ≥22 weeks of gestation HLPC Deficiency <50 nmol/L	6–42 months and 7, 8, 9 years Fine-motor and gross-motor development (ALSPAC test), behaviour (SDQ test), intelligence quotient (WISC test), reading (NARA test)
Gale et al. [53]	United Kingdom	Cohort study	466	Maternal blood, 32.6 weeks of gestation RIA <27.5, 27.5–50 and >50 nmol/L	9 years Intelligence quotient (WISC test) and behaviour (SDQ test)
Gould et al. [17]	Australia	Data from an RCT	337	Cord blood, delivery LC-MS/MS	18 months and 4 years Mental, motor, social-emotional

Table 1 (continued)

Study	Country/ethnicity	Study design	Sample	Specimen, gestational age at time of sampling (weeks), assay method and 25(OH)D cut-off used (nmol/L)	Child outcomes
				Deficiency <25 nmol/L; insufficiency 25–50 nmol/L; sufficiency >50 nmol/L	(BSDI III) and language (BSDI III, DAS II and CELF-P2)
Hanieh et al. [25]	Vietnam	Cohort study	960	Maternal blood, 32 weeks of gestation LC-MS/MS Deficiency <37.5 nmol/L, insufficiency ≤37.5 and <75 nmol/L, ≥ 75 nmol/L	6 months. Mental, motor, social-emotional and language (BSDI III)
Keim et al. [101]	United States	Cohort study	363	Maternal blood, ≤26 weeks of gestation RIA <25, 25–<50, 50–<75 and 75 nmol/L	8 months, 4 and 7 years Mental and motor development (BSDI II) Intelligence quotient (Stanford-Binet Intelligence and WISC tests) Achievement (WRAT test)
Morales et al. [22]	Spain	Cohort study	1820	Maternal blood, 13.5 weeks of gestation HLPC <50, 50–75 and >75 nmol/L	14 months Mental and motor development (BSID II)
Tylasky et al. [27]	United States	Cohort study	1020	Maternal blood, second trimester of gestation EIA <50 nmol/L, 50–74.9 nmol/L and ≥75 nmol/L	24 months Mental and language development (BSDI III)
Zhu et al. [78]	China	Cohort study	363	Cord blood, delivery RIA Quintile 1: 5.56–20.8; Quintile 2: 20.9–30.9; Quintile 3: 31.0–39.8; Quintile 4: 39.9–51.0; Quintile 5: 51.3–111	16 and 18 months Mental and motor development (BSDI II)

25(OH)D 25-hydroxyvitamin, *ELISA* enzyme-linked immunosorbent assay, *CLIA* chemiluminescence immunoassay, *RIA* radioimmunoassay, *LC-MS/MS* liquid chromatography-tandem mass spectrometry, HPLC high performance liquid chromatography, *EIA* enzyme immunoassay, *ECLIA* electro-chemiluminescence inmmunoassay, *NA* not available, *SGA* small for gestational age, *HC* head circumference, *BSDI (II and III)* Bayley scales 2 and 3 edition, *ALSPAC* The Avon Longitudinal Study of Parents and Children Preschool Test, *SDQ* Strengths and Difficulties Questionnaire, *NARA* Neale Analysis of Reading Ability, *WISC* Intelligence Scale for Children, *WRAT* Wide Range Achievement Test, *DAS II* Differential Ability Scales, *CELF-P2* Clinical Evaluation of Language Fundamentals Preschool, *PLS-TL* Preschool Language Scale, *CBCL* Child Behavior Checklist, *K-BIT* Kauffman Brief Intelligence Test, *KABC* Kauffman Assessment Battery for Children

decreased significantly when this study was excluded ($I^2 =$ 46 %), maintaining the estimated effect (MD −0.43 cm, 95% CI −0.75 to −0.10 cm) (Supplemental Fig. 1).

Anthropometric measures according to maternal vitamin D concentrations <50 or ≥50 nmol/L are shown in Fig. 3. There were no significant differences in birthweight, birth length or HC between babies born to vitamin D-insufficient mothers compared to babies born to vitamin D-sufficient mothers. Regarding birthweight, although there was significant heterogeneity ($I^2 = 84$, 63 and 98%, respectively), it decreased when the studies by Leffelaar et al. and Wang et al., which caused asymmetry in the funnel plot (Supplemental Fig. 7), were excluded ($I^2 = 40\%$), maintaining the estimated effect (MD 3.23 g, 95% CI −24.31 to 30.77 g; Supplemental Fig. 2). Regarding birth length, the heterogeneity decreased significantly when the study by Chi et al., which caused asymmetry, was excluded ($I^2 = 57\%$), maintaining the estimated effect (MD −0.06 cm, 95% CI −0.14 to 0.26 cm). Regarding HC, the heterogeneity decreased significantly when the studies by Chi et al. and Wang et al., which caused asymmetry, were excluded ($I^2 = 66\%$), maintaining the estimated effect (MD −0.06 cm, 95% CI −0.25 to 0.13 cm; Supplemental Fig. 2).

Maternal status of vitamin D and SGA and PTB

Mothers with vitamin D concentrations <30 vs >30 nmol/L (Fig. 4) had a 59% probability of having SGA infants, although with high heterogeneity ($I^2 = 71\%$). The heterogeneity decreased significantly when the study by Bodnar et al. (2010), which caused asymmetry in the funnel plot, was excluded ($I^2 = 52\%$), maintaining the estimated effect (OR 1.72, 95% CI 1.41 to 2.10; Supplemental Fig. 3).

No significant association was found between vitamin D deficiency and PTB (Fig. 4), although with high heterogeneity. It decreased significantly when the studies by Fernández Alonso et al. and Shand et al., which caused asymmetry, were excluded ($I^2 = 0\%$), observing a significant relationship between maternal vitamin D deficiency and PTB (OR 1.23, 95% CI 1.05 to 1.43; Supplemental Fig. 3).

As shown in Fig. 5, maternal vitamin D insufficiency was associated with an increased risk of SGA, although with high heterogeneity ($I^2 = 89\%$). The heterogeneity decreased significantly when the studies by Leffelaar et al., Chen et al. (2015) and Choi et al., which caused asymmetry in the funnel plot, were excluded ($I^2 = 47\%$), maintaining

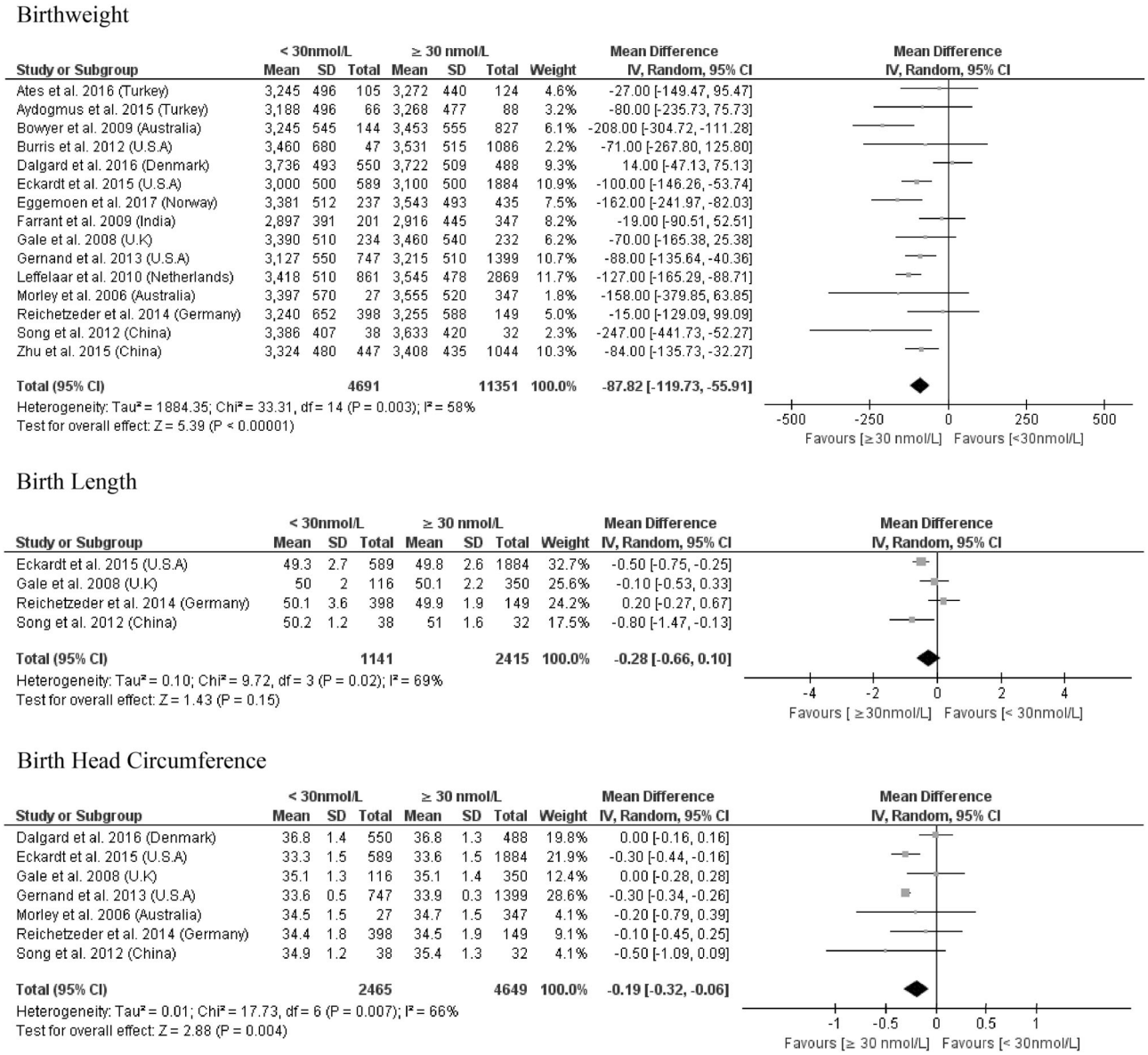

Fig. 2 Forest plots showing the association of maternal vitamin D concentrations (<30 and ≥30 nmol/L) with anthropometric measures at birth

the estimated effect (OR 1.31, 95% CI 1.12 to 1.54; Supplemental Fig. 4).

Meta-regression analysis showed that the heterogeneity observed cannot be explained by differences in the ethic group of the studies included, although we observed a trend towards increased effects of maternal vitamin D insufficiency (<50 nmol/L) on SGA in the Asian ethnic group (Supplemental Table 2).

Regarding PTB, a significant relationship was observed, although with high heterogeneity. It decreased significantly when the study by Bodnar et al. (2015) was excluded ($I^2 =$ 24%), maintaining the estimated effect (OR 1.21, 95% CI 1.07 to 1.38; Supplemental Fig. 4).

Maternal status of vitamin D (<75 or ≥75 nmol/L) and anthropometric measures and PTB

Anthropometric measures according to the maternal vitamin D concentrations <75 or ≥75 nmol/L are shown in Fig. 6. No significant differences were found when comparing birthweight, SGA or PTB in offspring born to mothers with vitamin D concentrations <75 nmol/L vs those born to mothers with vitamin D concentrations ≥75 nmol/L. Although there was no significant heterogeneity in birthweight or SGA outcomes ($I^2 = 27$, 39%, respectively), in PTB the heterogeneity was significantly high (72%). It decreased when the study by Bodnar et al. (2015), which

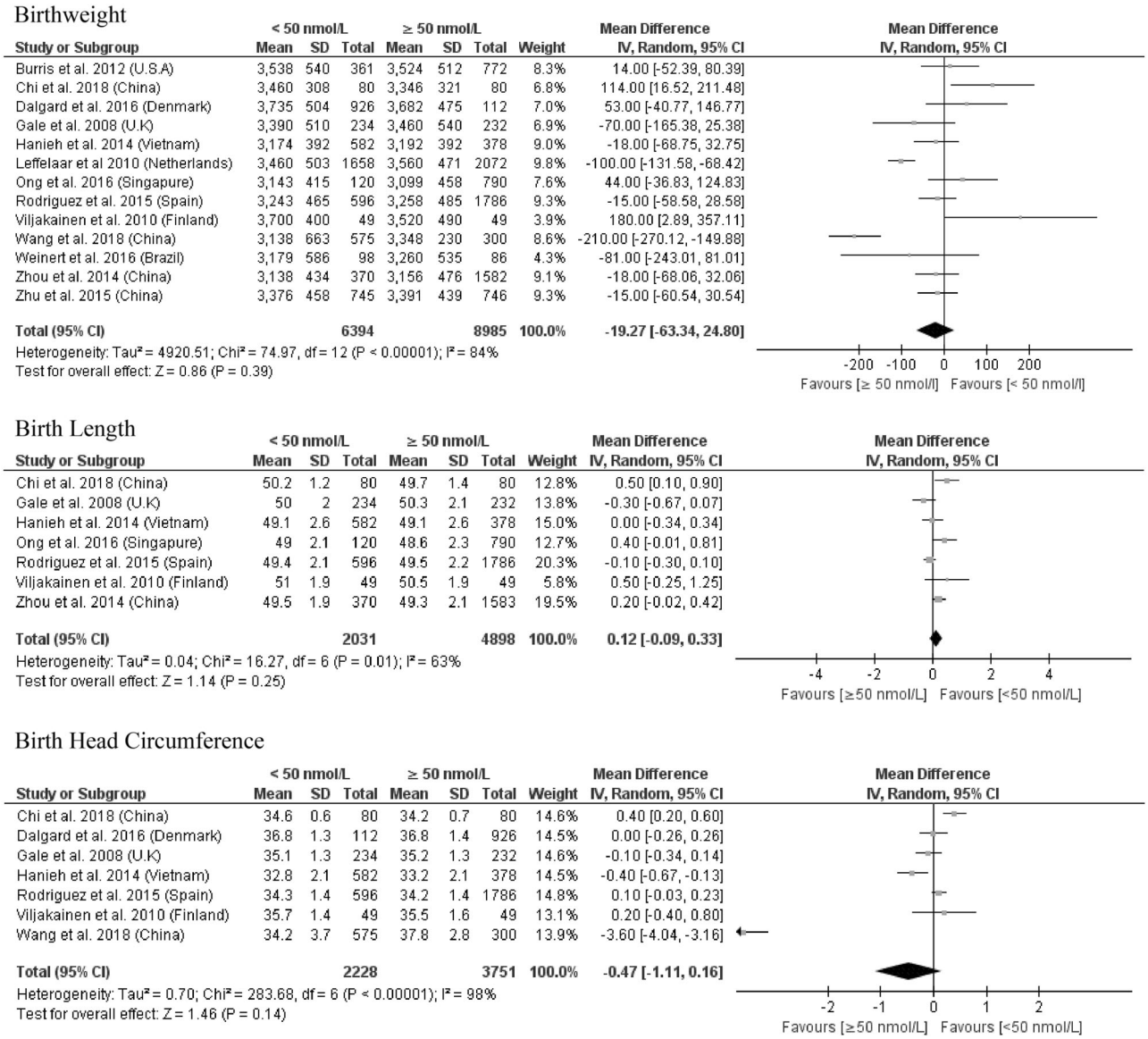

Fig. 3 Forest plots showing the association of maternal vitamin D concentrations (<50 and ≥50 nmol/L) with anthropometric measures at birth

caused asymmetry, was excluded ($I^2 = 52\%$), maintaining the estimated effect (Supplemental Fig. 4).

Maternal status of vitamin D and neurodevelopment

Vitamin D-insufficient mothers had children with lower scores in the mental development test (Fig. 7). Although here there was significant heterogeneity ($I^2 = 70\%$), the heterogeneity decreased significantly when the study by Chi et al., which caused asymmetry, was excluded ($I^2 = 5\%$), maintaining the estimated effect (MD −0.67 points, 95% CI −0.95 to −0.40; Supplemental Fig. 5).

There were no significant differences in language development scores when comparing children of vitamin D-insufficient mothers with vitamin D-sufficient mothers, with significant heterogeneity ($I^2 = 78\%$). The heterogeneity decreased significantly when the study by Darling et al. (6 months), which caused asymmetry, was excluded ($I^2 = 43\%$), observing a significant effect in the association between maternal vitamin D status and language development (MD −1.12 points, 95% CI −1.82 to −0.42; Supplemental Fig. 5).

There were no significant differences in the motor development scores between children born to vitamin D-insufficient mothers and children of vitamin D-sufficient mothers with significant heterogeneity ($I^2 = 65\ \%$). The heterogeneity decreased significantly when the study by Zhu et al. (2015), which caused asymmetry, was excluded ($I^2 = 48\%$), maintaining the estimated effect (MD −0.13 points, 95% CI −0.50 to 0.23; Supplemental Fig. 5).

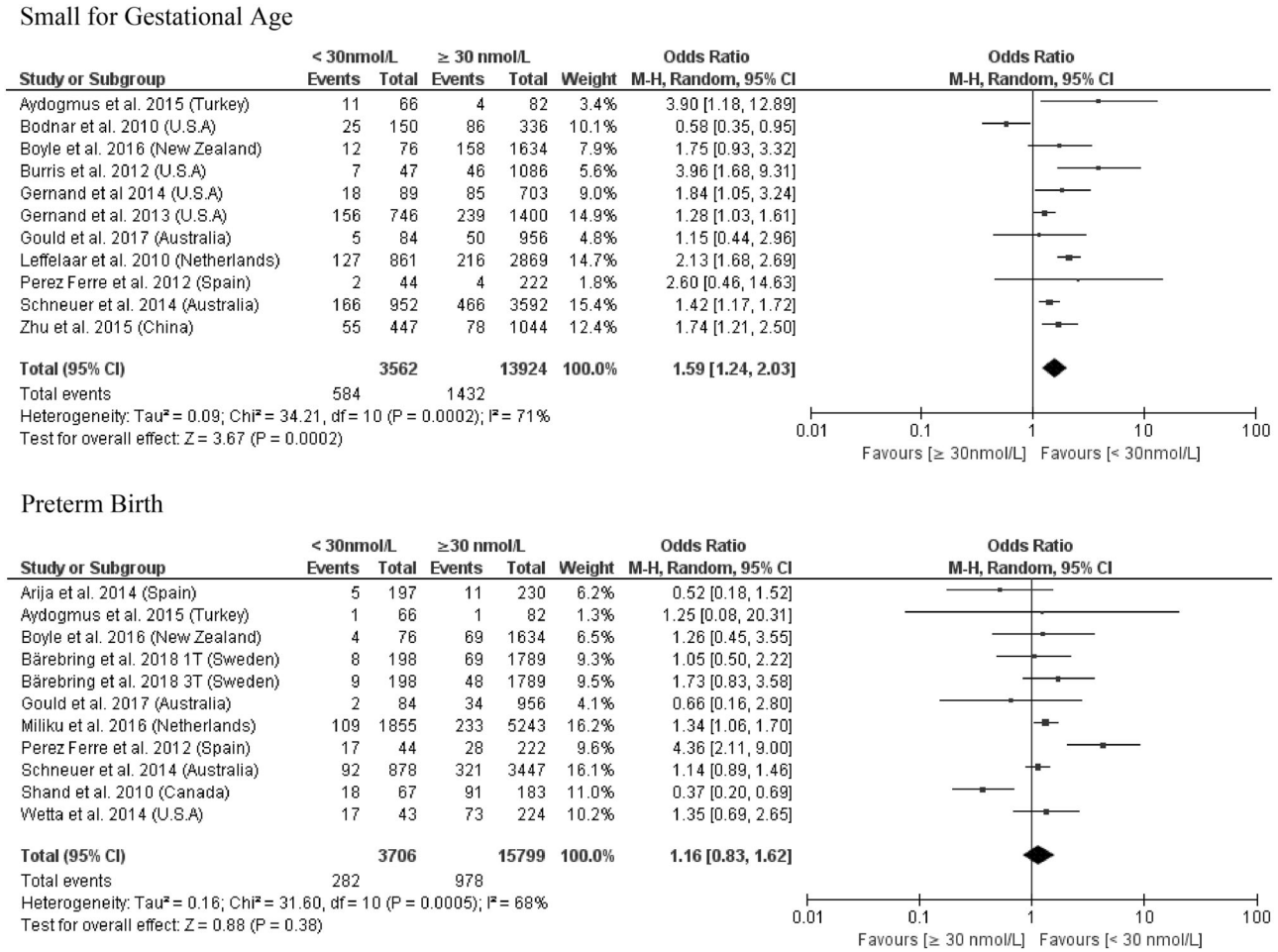

Fig. 4 Forest plots showing the association of maternal vitamin D concentrations (<30 and ≥30 nmol/L) with small for gestational age (SGA) and preterm birth (PTB)

Discussion

The findings of the present meta-analysis indicate that the adverse neonatal outcomes of low 25(OH)D concentrations during pregnancy depends on the level of deficiency. Maternal vitamin D deficiency (<30 nmol/L) has an effect on offspring anthropometric parameters, being associated with lower birthweight and HC in their offspring (compared to mothers with concentrations ≥30 nmol/L); both vitamin D deficiency and insufficiency (<50 nmol/L) are related to a higher risk of SGA and PTB. Maternal 25(OH)D concentrations ≥75 nmol/L were not observed to be associated neither with birthweight, nor SGA nor PTB. Meanwhile, in this meta-analysis we have observed that maternal vitamin D insufficiency is related to poorer neurodevelopmental outcomes in their offspring.

Regarding birthweight and HC, maternal vitamin D deficiency was associated with a reduction of 87.82 g (−119.73 to −55.91) of infant birthweight and with a reduction of 0.19 cm (−0.32 to −0.06) of HC, respectively. No difference was observed neither in birthweight nor in HC of newborns whose mothers were vitamin D insufficient and those with 25(OH)D concentrations ≥50 nmol/L during pregnancy. Our results support the conclusions of some previous research [31, 32, 34, 36, 48], although this association has not been found in other previous studies [17, 25, 36, 37, 49–58]. Certainly, differences in the specific criteria used to define the cut-off point for vitamin D deficiency could contribute to the differences observed. Particularly, in our study we have used three cut-off points according to the recommendations of the IOM and the Society of Endocrinology [40].

Regarding HC, to date, very few studies have linked maternal vitamin D status to child HC, with mixed findings [7, 8, 11, 32, 50, 52, 54, 56, 59]. Although to date there is no cut-off point associated with lower HC in offspring, recent studies confirm that vitamin D supplementation during pregnancy increases both infant length and HC at birth (MD: 0.43, 95% CI: 0.03 to 0.83) [60]. To date, the mechanisms implied in the role of vitamin D in birthweight have been proposed and previous work evidences that

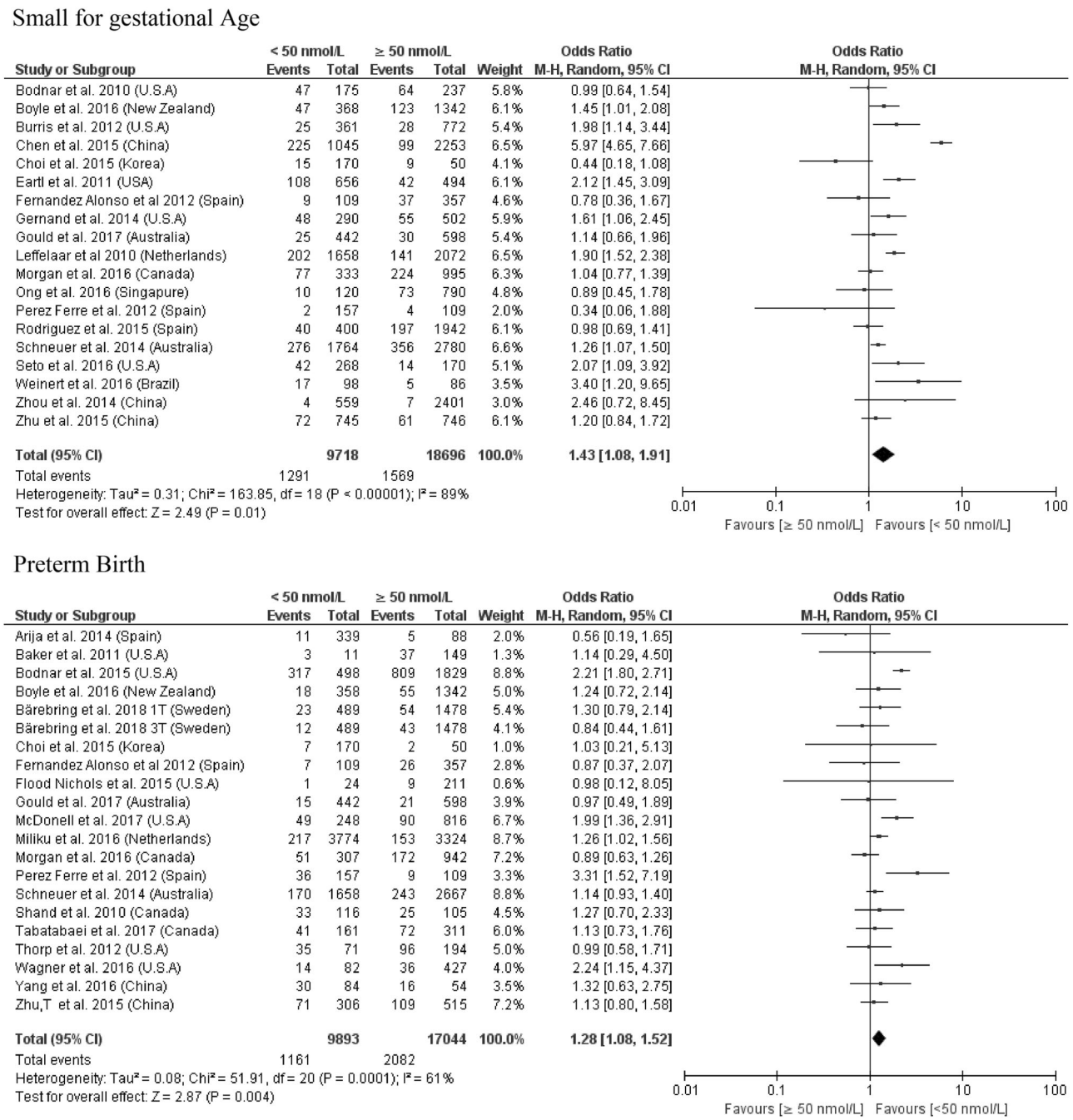

Fig. 5 Forest plots showing the association of maternal vitamin D concentrations (<50 and ≥50 nmol/L) with small for gestational age (SGA) and preterm birth (PTB)

vitamin D has a crucial role in the foetal bone development [61]. Placental vitamin D receptor (VDR) plays a pivotal role during pregnancy and maternal VDR gene polymorphisms have been demonstrated to influence birthweight with differential effects accruing across racial groups [62, 63]. Recently, it has been proposed that maternal vitamin D concentrations during pregnancy is determinant of offspring telomere length, which is correlated positively with newborn body weight [64]. Further studies are warranted to clarify the mechanisms behind it.

In this meta-analysis, no effect was observed in birth length (by using two different cut-off levels). These results are in line with two previous systematic review and meta-analysis of observational studies that did not find associations [32, 37, 65], suggesting that maternal vitamin D status has no effect on birth length.

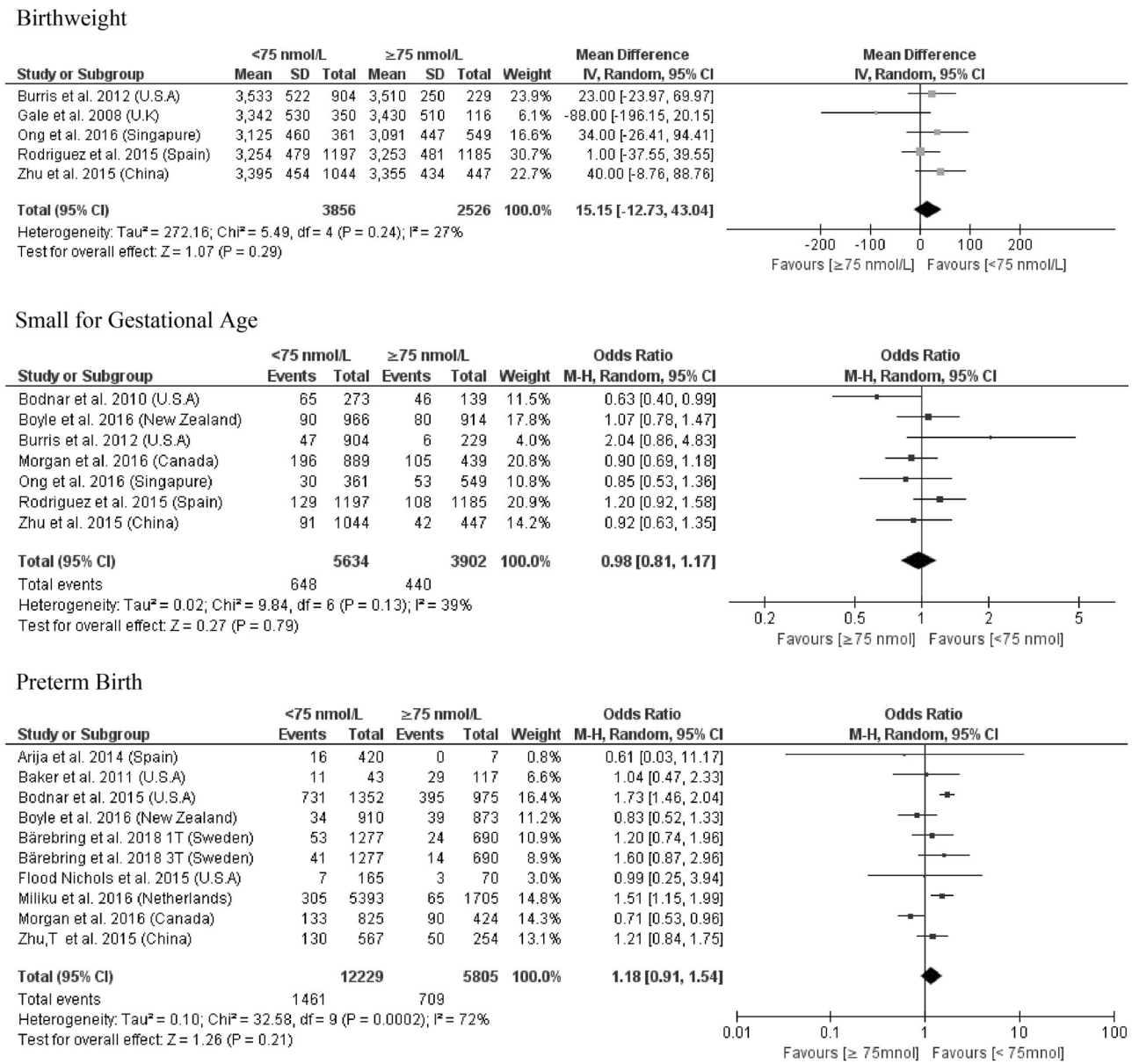

Fig. 6 Forest plots showing the association of maternal vitamin D concentrations (<75 and ≥75 nmol/L) with birthweight, small for gestational age (SGA) and preterm birth (PTB)

In our systematic review, we found an increased risk of SGA in offspring born to women with both maternal vitamin D deficiency and insufficiency during pregnancy, showing that having serum 25(OH)D concentrations <50 nmol/L in pregnancy are sufficient to increase the risk of SGA infants. It is noteworthy that four out of five previous meta-analysis that focussed on vitamin D status during pregnancy and SGA [32, 34, 36, 37, 60] confirm our results and that the only one that found no significant effect of vitamin D supplementation on the risk of SGA included analyses that were heterogeneous in terms of dose, type, duration and the 25(OH)D concentrations assessed at delivery and varied from 7.5 to 147 nmol/L [31].

The discrepancies observed in anthropometric parameters could be in part explained by inconsistencies across published studies in definition of cut-offs for 25(OH)D deficiency (i.e. <10 [49], <20 [57], <37.5 [25] and <50 [52, 55]), time of sampling (i.e. early [56] or late pregnancy [53, 54]), specimens used to assess 25(OH)D concentrations (most of them in maternal blood [25, 36, 49, 51–58] and some of them in cord blood [17, 50]), heterogeneous populations involved (i.e. African [49], Caucasian [17, 36, 53, 54, 56, 57], Indian [52] or Vietnamese [25] women) seasonal differences (summer vs winter), the number of subjects and significant heterogeneity found in previous meta-analysis [37]. Meta-regression analyses were

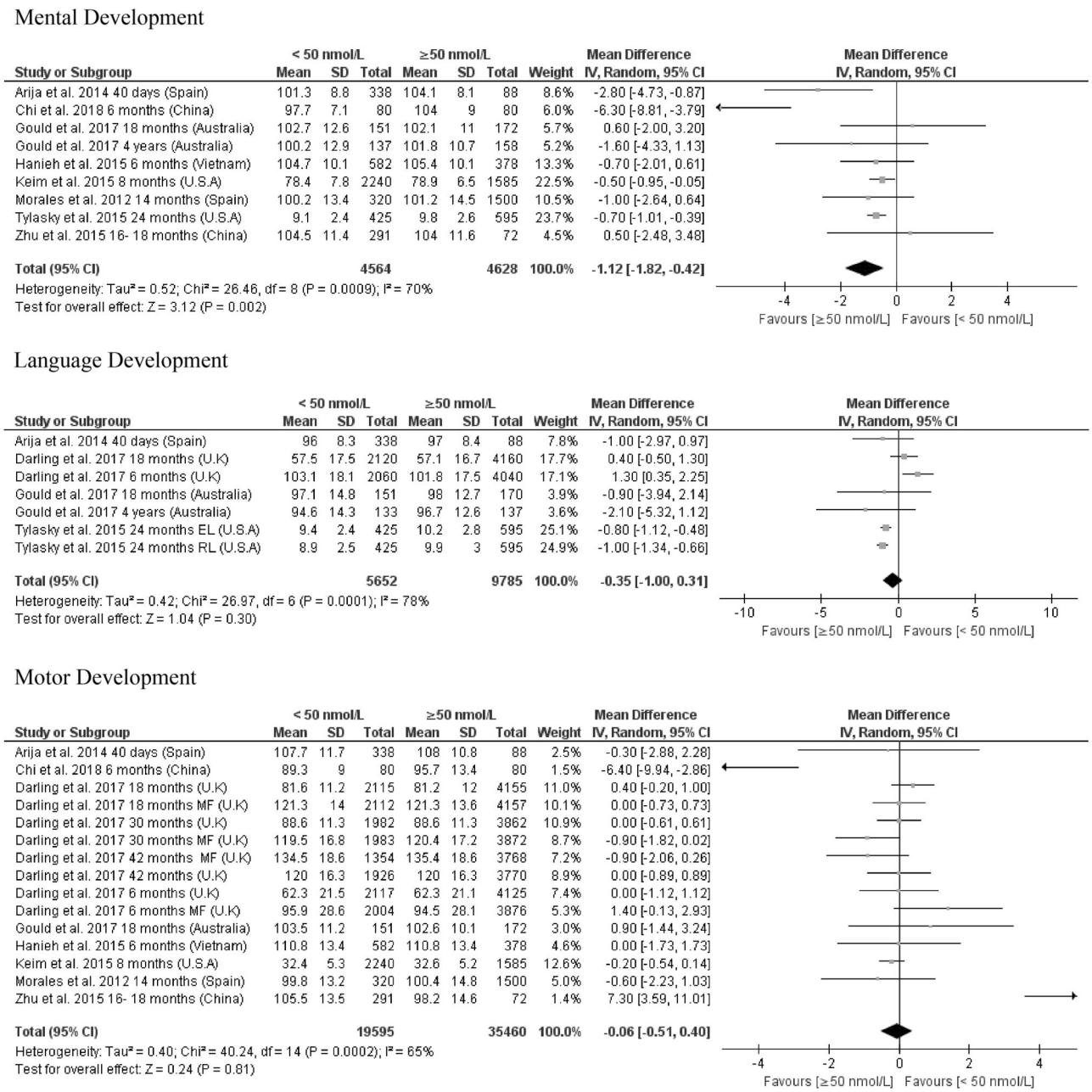

Fig. 7 Forest plots showing the association of maternal vitamin D concentrations (<50 and ≥50 nmol/L) with children's neurodevelopmental scores (mental, language and motor)

performed to assess whether the heterogeneity observed may be further explained by differences in ethnic diversity. However, we only were able to study this relationship in two anthropometric outcomes. Particularly, we found that ethnic differences did not influence the association between maternal vitamin D concentrations and birthweight or risk of SGA infants, although a trend to lower effects of maternal vitamin D deficiency on birthweight in the Asian ethnic group and a trend to lower effects of maternal vitamin D insufficiency on SGA in the white ethnic group was observed. We hypothesize that other variables, such as poverty, food deprivation, etc., may affect vitamin D-deficient groups more than vitamin D-sufficient groups and that may affect birth anthropometric outcomes more than vitamin D. Since there are many ongoing or planned trials of prenatal vitamin D taking into account confounding factors and different cut-offs, these data will help us to improve the available evidence about this issue.

Overall, in this particular meta-analysis, both maternal vitamin D insufficiency and deficiency were found to be

associated with an increased risk of PTB. Despite the fact that three previous meta-analysis of randomized controlled trials RCTs found that the incidence of PTB was not influenced by vitamin D supplementation during pregnancy [31, 34, 36], none of them assessed maternal vitamin D concentrations before and after supplementation. PTB is believed to result from an inflammatory response for approximately 30% of PTB cases. In fact, labour is an inflammatory process and a balance between innate and adaptive immune cells is required to sustain pregnancy and an alteration of this balance may lead to PTB [66]. It has already been said that vitamin D deficiency may activate inflammatory pathways and alter spontaneous PTB risk [67, 68]. Increased production of inflammatory cytokines has been reported in pregnant women with vitamin D deficiency [69]. It would have been interesting to assess concentrations of pro-inflammatory cytokines or C-reactive protein in these women to test this hypothesis. Although dietary intake of vitamin D has been associated with the normal function of the immune system, the mechanisms that lead to PTB/labour are poorly understood and more studies are needed to determine benefits of vitamin D to immune function during pregnancy. Recently, both maternal and foetal VDR polymorphisms have been related to PTB [70].

To date, few studies have assessed the impact of vitamin D deficiency at preconception period on neurodevelopmental outcomes in their offspring. In our meta-analysis, we only found that children born to vitamin D-insufficient mothers showed a poorer mental and language development. Associations between 25(OH)D deficiency during pregnancy and cognitive and language development have been also previously reported in previous studies involving women from China, Australia, Vietnam, USA and Spain [17, 22–25, 27]. Although other studies found no significant associations between maternal 25(OH)D concentrations and behaviour or verbal intelligence quotient (IQ) in children [26, 53], maternal vitamin D concentrations were assessed at different time points. In line with this, previous studies have identified poorer outcomes on offspring of pregnancies in which the first and second trimesters were in winter or spring [71]. Indeed, regarding both mental and language developmental outcomes, there was a trend to larger effect sizes in the studies that measured maternal 25(OH)D concentrations early in pregnancy, coinciding with prenatal brain development when cell differentiation and the formation of nervous system structures occur [22, 72]. Furthermore, inconsistent results may also be explained by different time points of neurodevelopmental assessments. Indeed, the interactions between the prefrontal cortex and hippocampus play an important role in various cognitive and language functions [73] and the frontal lobe has been demonstrated to show a peak rate growth rate from 9 to 12 months of age [74]. Therefore, we suggest that the adverse effects of maternal vitamin D status during pregnancy on neurocognitive development could more likely affect early child development and even some of them would persist into childhood, and other postnatal factors (including breastfeeding duration, socioeconomic status (SES), maternal mental health, IQ, nutrition, gut microbiota, etc.) could exert beneficial effects on the developing brain [75–77], minimizing the impact of prenatal vitamin D insufficiency on offspring outcomes. Although in our meta-analysis-stratified analysis in mental development did not confirm this hypothesis, sample size was limited (<6 studies) and we were not able to control for this factor.

Regarding motor development, we did not find associations between maternal 25(OH)D concentrations and motor development. Our findings are consistent with two previous studies [13, 78], conducted in Australia and China, respectively, which found that cord blood 25(OH)D concentrations were not correlated with motor development assessed at 18 months of age. On the contrary, two previous studies suggested that prenatal vitamin D deficiency could be related to poorer motor development [27, 30]. One potential explanation could be differences in time of neurodevelopmental assessments (40 days, 6, 8, 14, 18, 30 and 42 months of age). For some authors, the development of motor functions in children is related to a greater degree of neural maturation and synaptic plasticity [79] and myelination has been used as a criteria to assess the level of brain maturation. Despite the fact that myelination begins during early life, at birth only some areas are myelinated and the different regions of the cerebral cortex are myelinated at different stages. In particular, the gross-motor development has been correlated with a good myelination of the pyramidal tract (50% myelinated by 1 year), whereas the fine-motor development of children that develops later has been related with the myelination of the association areas.

Our study suffers from several limitations in large part due to the nature of the studies and the data available. Some studies have adjusted for possible confounding factors [6, 10, 12–15, 17, 48, 50, 51, 54–56, 61, 62, 80–88], while others have not [5, 49, 53, 59, 89]. It is well known that poverty, ethnicity and other deprivation affect vitamin D-deficient groups more than vitamin D-sufficient groups and these social factors may affect birth outcomes more than vitamin D does. Differences in women's adiposity may also contribute to 25(OH)D concentrations and could in part explain the high heterogeneity of pooled data for some variables studied. However, most of the studies included in our meta-analysis showed that the association between maternal 25(OH)D concentrations and child's outcomes remains statistically significant after adjusting for confounding variables [6, 8–10, 14, 15, 51, 57, 61, 62, 80, 83, 87, 90–92]. Different assay techniques were used to measure maternal vitamin D concentrations. Some of our

analyses included few studies. Although there is no minimal number of studies to be used in a meta-analysis, we provide results using <6 in order to observe those results, and even <6 is too low to draw conclusions from. It would be interesting to study the association between maternal 25 (OH)D concentrations ≥30 and ≥75 nmol/L during pregnancy and neurodevelopmental outcomes in the offspring. However, we were unable to find more than three studies in the literature that fit our criteria. Future studies should consider different cut-off levels of vitamin D in predicting the risk for adverse neurodevelopmental outcomes in the offspring. Accordingly, previous data suggest an inverted-U-shaped relation between neonatal vitamin D status and neurocognitive development in toddlers [78]. Future research is needed to understand the implications of these associations in neurodevelopmental outcomes.

There are several methodological strengths of the present study. To our knowledge, this is the first meta-analysis that assessed the effect of maternal vitamin D insufficiency on neurodevelopmental outcomes and, in particular, in mental, language and motor domains. The number of studies included in this review ($n = 54$), including data on >67,484 women–child pairs, the diversity of cultures, ethnic groups, latitudes, seasons and women's age, could make these results generalizable to a wider population. The data were pooled based on three different cut-off values for 25(OH)D concentrations (30, 50 and 75 nmol/L). From the funnel plots in this study, we conclude that there was no obvious publication bias. Study quality assessed using the STROBE criterion was high in 2/3 of the studies. We controlled for heterogeneity among studies included in our meta-analysis.

In conclusion, the present work highlights the intergenerational impact of vitamin D deficiency, insufficiency and suboptimal vitamin D status during pregnancy and indicates that the adverse neonatal outcomes of low 25(OH)D concentrations during pregnancy depends on the level of deficiency. In particular, we found that maternal 25(OH)D deficiency during pregnancy is associated with lower birthweight, HC (not being affected by concentrations ≤50 nmol/L), SGA and PTB; insufficiency is related with a higher probability of having infants with SGA and PTB and suboptimal levels (≥75 nmol/L) are not related with birthweight, SGA and PTB. Furthermore, this meta-analysis shows for the first time that maternal vitamin D insufficiency is associated with a poorer cognitive and language development in the offspring. Further investigation at different stages of pregnancy and development, by using different cut-off levels, etc., is needed to confirm these results.

Assessing vitamin D status in pregnant women and identifying the factors responsible for vitamin D deficiency during pregnancy (SES, ethnicity, inadequate sunlight exposure, environmental pollution, low dietary consumption of vitamin D, etc.) are essential for both maternal and offspring health.

Compliance with ethical standards

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

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