Vitamin D concentrations during pregnancy and in cord blood: a systematic review and meta-analysis

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Abstract (163 words)

Context: Effect size estimates for the association between vitamin D concentrations during pregnancy and in cord blood vary widely across studies.

Objective: To estimate the pooled effect size for the association between circulating 25-hydroxyvitamin D (25(OH)D) concentrations, a marker of vitamin D status, during pregnancy and in cord blood.

Data sources: Searches were performed in PubMed, EMBASE, and Web of Science databases from their inception to February 2021.

Data extraction: Correlation coefficient (r) values for association between 25(OH)D concentrations during pregnancy and in cord blood were extracted.

Data analysis: The r values were pooled using random-effects meta-analyses. Sensitivity and subgroup analyses were performed to investigate sources of heterogeneity.

Conclusion: A total of 26 articles were included, comprising 30 studies of 6212 mother-infant dyads. The pooled r for all studies was 0.72 (95%CI: 0.64-0.79), indicating high heterogeneity (I^2=95%, p<0.01). After removing the influential and outlier studies, the pooled r for 9 studies was 0.70 (95%CI: 0.66-0.74) with a substantial reduction in heterogeneity (I^2=41%, p=0.10).

Keywords: vitamin D, pregnancy, cord blood, supplementation, mother-offspring dyad

Introduction

Vitamin D is a fat-soluble steroid hormone that plays an important regulatory role in many functions of human body including bone mineralisation, calcium absorption, and immune responses activation [1]. Optimal vitamin D concentrations during pregnancy were associated with a reduced risk of gestational diabetes mellitus[2] and adverse pregnancy outcomes[3] and improved infant growth [4]. In view of its health benefits, maintaining sufficient vitamin D levels is recommended for individuals of all ages including infants and young children [5]. An increasing body of evidence supports the lifelong health implications of cord blood vitamin D concentrations. Several epidemiological studies reported that cord blood vitamin D concentrations had an inverse association with the risk of respiratory infection in childhood and childhood-onset allergic diseases [6,7].

While vitamin D concentrations in older children and adults are largely influenced by environmental exposures such as sun exposure and dietary intake [8-12], cord blood vitamin D concentrations are mainly influenced by maternal vitamin D status [13,14]. Although the association of vitamin D concentrations during pregnancy and in cord blood is evident, the reported estimates of this association vary across studies. Furthermore, it is uncertain whether the estimate would fluctuate or remain steady across pregnancy stages. Methodological factors such as sample size, vitamin D measurement techniques, and other sampling issues can result in the variability between the sample estimates. For example, some studies measured maternal vitamin D concentrations during early to mid-pregnancy [3,15], whereas other studies measured maternal vitamin D concentrations during late pregnancy [16,17]. As the half-life of 25-hydroxyvitamin D (25(OH)D) is approximately 2 to 3 weeks [18], it is possible that the vitamin D stored in the mother's body during late pregnancy, compared to the earlier stages of pregnancy, might have stronger protective effects against adverse birth outcomes

such as low birthweight and preterm birth [19,20], which require comparability of studies for substantiation.

To date, there has been no comprehensive systematic review with a meta-analysis to quantify a pooled measure of effect size reported in studies on vitamin D concentrations during pregnancy and in cord blood. Thus, the focus of this review was to provide quantitative evidence by pooling results across the relevant studies, inclusive of all trimesters, to obtain a more precise estimate of the association between vitamin D concentrations in maternal blood during pregnancy and umbilical cord blood at delivery. Another focus was to analyse the reported effect sizes between study subgroups stratified by sample characteristics and other methodological factors.

Methods

Study protocol

This systematic review and meta-analysis were planned, conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. This study is registered with the PROSPERO registration number CRD42021273348; the full protocol is available on the PROSPERO website.

Search strategy

We searched PubMed, EMBASE, and Web of Science databases for articles published from the inception of the databases to 10th February 2021. The search strategy included the following terms: ("vitamin D level" OR "vitamin D status" OR "25(OH)D") AND ("maternal" OR "pregnancy") AND ("neonatal" OR "infant" OR "cord blood"). Our

search was restricted to human studies and published in English. In addition, the reference lists of all retrieved articles were also checked to identify additional relevant studies.

Selection of articles

Articles were selected for inclusion if they met the following criteria: (a) investigation of the relationship between vitamin D concentrations during pregnancy and in umbilical cord blood; (b) collection of maternal blood during the gestation period and foetal blood at delivery (cord blood); (c) measurement and reporting of 25(OH)D which is the sum of $25(OH)D_2$ and $25(OH)D_3$ concentrations in the collected samples; and (d) publication as a full paper in a peer-reviewed scientific journal. The following studies were excluded: (a) studies reporting no quantitative estimates of the strength of the association of interest; (b) studies on vitamin D concentrations in maternal blood after pregnancy or their offspring blood in the postpartum period; (c) studies reporting values of either $25(OD)D_2$ or $25(OH)D_3$ but not both; (d) experimental research including clinical trials and intervention studies, and (e) review articles, letters, comments, case reports, and unpublished articles such as thesis and conference abstracts. When multiple reports were published on the same study population, the publication that included the most details would be chosen.

Data extraction

Two reviewers (RTM and RSW) screened the titles and abstracts, reviewed the full texts of all potentially relevant articles, and extracted and entered data from the included studies into a structured characteristic table. The extracted data included the name of the first author, publication year, age of pregnant women, features of study design, sample characteristics, blood sample collection time, and other information as required. Disagreements were resolved by consensus or discussion with a third reviewer (KTT).

Quality assessment

We assessed the methodological quality of the included studies using a modified version of the Joanna Briggs Institute (JBI) Critical Appraisal Checklist designed for studies reporting prevalence data [22], which consists of nine items covering the following four domains: study design, sample selection, measurement method, and statistical analysis. With a maximum score of nine, the quality assessment grading scheme was 0-3 as poor quality, 4-7 as fair quality, and 8-9 as good quality. Each study was assessed by two independent reviewers (RTM and RSW), and any discrepancies between the ratings were resolved by discussion with a third reviewer (KTT).

Data synthesis and analysis

We provided a narrative synthesis of the results of the included studies and pooled the Pearson's correlation coefficient (r), served as effect size indices, for the overall association between vitamin D concentrations in maternal serum and umbilical cord blood using inverse-variance weighted random-effects analyses with the Hartung-Knapp adjustment of the Restricted Maximum Likelihood estimator, which can account for the degree of heterogeneity across studies due to differences in study populations and procedures. The pooled correlation coefficient and corresponding 95% confidence intervals (CI) were computed by transforming the r from each study into Fisher's z score and weighted with the inverse of the variance of the r coefficients. For ease of interpretation and presentation of effect size estimates in the forest plots, all values were then back transformed to the correlation coefficients [23]. Following Cohen's guidelines [24], correlation coefficients were considered small when $r \geq 0.10$ to <0.30, medium when $r \geq 0.30$ to <0.50, and large when $r \geq 0.50$ to <1.00.

The heterogeneity of the included studies was tested using the Cochrane's Q test and quantified with I^2 statistic, which describes the percentage of variation in the effect size estimates across studies. A value of $p < 0.05$ for Cochrane's Q indicated the presence of heterogeneity, whereas I^2 statistic with values of 25%, 50%, and 75% indicated low, moderate, and high degrees of heterogeneity [25]. If high heterogeneity was detected, a sensitivity analysis [26] would be performed to examine changes in the pooled effect size estimate after excluding the influential studies with extreme effect sizes identified through the Graphic Display of Heterogeneity (GOSH) plots analysis [27]. Due to the very small number of included studies in each country, we categorized the studies based on race rather than nationality, resulting in two racial groups, namely Asians and Caucasians. Between-group sources of heterogeneity were explored using subgroup analyses based on timing of maternal vitamin D measurement (third trimester or before third trimester), race (Asian or Caucasian), sample size (<100 or 100-300 or >300), and vitamin D measurement techniques (electrochemiluminescence immunoassay (ECLIA) or radioimmunoassay (RIA) or chemiluminescence immunoassay (CLIA) or liquid chromatography-tandem mass spectrometry (LC-MS-MS)/ high performance liquid chromatography (HPLC) or enzyme immunoassay (EIA)/enzyme-linked immunosorbent assay (ELISA)). Meta-regression was also performed to examine the effect of publication year (continuous) on the heterogeneity of the included studies. Funnel plots and Egger's test results were generated to assess potential publication bias. All analyses were performed using R statistical software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and the R package "meta" version 4.18-1 (Schwarzer, Freiburg, Germany). A two-tailed $p < 0.05$ was considered statistically significant.

Results

Study selection

A total of 1270 articles were initially identified using the search strategies. After removing the duplicates and reviewing the titles and abstracts, 94 articles were eligible for full-text review. Of these articles, 26 articles [13,16,17,28-50] met the inclusion criteria. As four articles [13,28,37,40] reported results of two different cohorts, a total of 30 studies were included in the current systematic review and meta-analysis. A flow chart showing the study search and selection process is summarized in Figure 1.

Methodological quality

All articles except one [47] had clearly defined criteria for subject inclusion and exclusion. Four articles [13,31,34,41] did not define the subject recruitment period. Nine articles [13,33,39,40,42,45,46,48,50] further defined the gestational week at which maternal blood samples were collected. 12 articles [30,31,33,34,37,39,41-44,47,48] were considered to have sampled study participants in an appropriate way, but only five articles [29,33,37,43,46] had adequate sample size. All articles except one [31] reported vitamin D measurement techniques. The mean methodological quality score of the included articles was 5.5/9, with three articles [33,37,39] rated as good quality and two articles [31,38] rated as poor quality. Details of the methodological assessment rating of the 26 included articles are shown in S1 Table.

Study characteristics

Table 1 describes the key characteristics of the 26 included articles, resulting in a total of 30 studies involving 6488 mothers and 6212 infants. The sample size ranged between 37 and 862 with considerable diversities of maternal physical health characteristics. The studies were published between 2005 and 2020 and included participants from Europe, the United States, New Zealand, and Asia. 14 studies recruited Asian samples [17,31,32,34-36,38,42,43,45-49]; 11

studies recruited Caucasian samples [13,28,30,33,39-41,44,50]; 5 studies included mixed/other racial samples [13,16,29,37]. Among these included studies, three studies [38,39,50] did not report age of the mothers, while 16 studies [13,28-33,35,36,38,40,42,43,45,48,50] did not provide information on infant sex. 21 studies [13,16,17,29-31,33-36,38-40,43,44,46-50] collected maternal blood in the third trimester; five studies [37,40,42,45] collected maternal blood before the third trimester; and the remaining four studies [28,32,41] did not specify the sample collection timeframe. Overall, seven assay techniques were used to measure vitamin D concentrations, with six studies using ECLIA [17,28,33,34,41,49], four studies using CLIA [30,37,42,47], two studies using EIA [38,45], two studies using ELISA [36,43], one study using HPLC [13], eight studies using LC-MS-MS/HPLC [13,32,37,39,40,44], six studies [16,29,35,46,48,50] using RIA, and the remaining study [31] providing no information on the assay technique. Furthermore, no studies except one (3.85%) [42] reported that their laboratories had participated in external laboratory proficiency testing programs, such as the Vitamin D Standardization Program (VDSP) or the Vitamin D External Quality Assessment Scheme (DEQAS).

Qualitative synthesis

Three studies reported very small ($r < 0.10$) [31,40] or small-to-medium ($r < 0.30$) [43] correlation coefficients. They had small sample size (<100) consisting of participants from Asia (Pakistan and Iran) and New Zealand. Among these three studies, Wheeler et al. collected maternal blood at <20 gestational weeks [40], whereas the study conducted by Karim, Nusrat, and Aziz did not report their vitamin D assay technique [31]. On the other hand, two studies [32,38] reported very large ($r > 0.90$) correlation coefficients. Their sample size was also small (<100) and consisted of participants from Asia (Korea and China). Specifically, Wang et al. did not report age of recruited pregnant women [38], whereas 56% of the mothers in the

study conducted by Kim et al. [32] were diagnosed with gestation diabetes mellitus. All these studies with extreme effect sizes did not report infant sex.

Quantitative evaluation

In the meta-analysis of 30 studies, obtained from 26 included articles, with a total of 6212 mother-infant dyads, random effect model revealed a statistically significant, positive, and large correlation between maternal vitamin D concentrations during pregnancy and foetal vitamin D concentrations at delivery (pooled r=0.72, 95%CI=0.64-0.79, $p < 0.001$) with high heterogeneity (I^2=95%, $p_{heterogeneity}$<0.01) (Figure 2).

Moderator analysis

Meta-regression and subgroup analyses were performed to explore the sources of high heterogeneity. The meta-regression analysis found no effect of publication year on the heterogeneity of the included studies (estimate = -0.001, p=0.792). In subgroup analyses (Table 2), the pooled correlation between vitamin D concentrations during pregnancy and in cord blood was smaller among studies collecting maternal blood before the third trimester (pooled r=0.44, p=0.012), compared with studies collecting maternal blood during the third trimester (pooled r=0.75, p<0.001) (p for subgroup difference <0.001). No significant differences in the pooled correlation estimates were observed between study subgroups stratified by race, sample size, or vitamin D measurement techniques. Details of the subgroup characteristics of the 30 included studies are shown in Table S2.

Sensitivity analysis and publication bias

The GOSH plots analysis identified 21 studies from 17 articles [29,31-33,35-40,42-47,50] as influential studies (i.e., those having a very large influence on the overall results). After

removing these influential studies, the degree of between-study heterogeneity substantially decreased from 95% ($p<0.01$) to 41% ($p=0.10$), but the overall adjusted estimate remained large and statistically significant (pooled $r=0.70$, $p<0.001$) (S1 Figure). Figure 3 illustrates a symmetric funnel plot of correlations for the included studies. Results of the Egger's test showed no significant publication bias (bias=3.01, $p=0.143$).

Discussion

This meta-analysis, based on 30 studies (corresponding to 26 articles), found a statistically significant, positive, and large correlation between vitamin D concentrations during pregnancy and in cord blood. Notably, maternal vitamin D concentrations in the third trimester, compared to the concentrations in the earlier stages of pregnancy, had a stronger link with umbilical cord blood vitamin D concentrations, but the strength of the association did not vary by other studied factors, namely participants' race, sample size, and vitamin D measurement techniques. Our meta-analytic results provide pooled evidence on the strength of the association between vitamin D concentrations during pregnancy and in cord blood. The findings reinforce the current recommendations and guidelines for pregnant women to obtain more vitamin D through supplementation or consumption of a healthy balance diet, which is beneficial for their offspring vitamin D concentrations after birth.

Although the analysis of funnel plot and Egger's test showed no obvious publication bias, the results of sensitivity analyses indicated that 21 studies from 17 articles included in the present review had a very large effect on the overall results [29,31-33,35-40,42-47,50]. Furthermore, the included studies were mostly of fair quality and had high heterogeneity. As revealed by the subgroup analysis, the high heterogeneity was caused by the between-study differences in maternal vitamin D measurement time. Other factors such as maternal age, health conditions,

sun exposure, and diets are likely sources of heterogeneity, but cannot be analysed in this meta-analysis due to limited information from the original studies. Future studies should clarify the effect of these factors on the link between maternal and foetal vitamin D concentrations.

Although the association of vitamin D concentrations during pregnancy and in cord blood is well recognized, there has been no consensus regarding the strength of the association due to high variability between effect size estimates across studies. Our meta-analytic results can add to the existing body of literature that the overall strength of the association, after pooling the results of the relevant studies, was r = 0.70, which is a large effect size according to Cohen's guidelines [24]. After further removal of influential studies with extreme effect sizes, the pooled estimate remained largely unchanged, and the 95% confidence interval of 0.60 to 0.78 suggested a moderately good estimate precision. Although vitamin D concentrations during pregnancy and in cord blood are highly correlated with each other, the mechanisms of vitamin D acquisition for pregnant women and foetuses are completely different. In general, adults obtain vitamin D primarily from exposing their skin under ultraviolet-B (UVB) radiation and secondarily from dietary sources or supplements [51,52]. The amount of vitamin D synthesized by the skin would depend on environmental exposure and endogenous factors, such as length of sun exposure, seasonality, coverage of skin by clothing or sunscreen, and skin pigmentation [51]. Dietary sources of vitamin D for pregnant women include oily fish, fish liver oil, egg yolk, vitamin D fortified grain and dairy products, or vitamin D supplements [51-56]. The vitamin D3 obtained through skin synthesises and dietary intake are then converted to its major circulation form, 25(OH)D, by the liver, and eventually to its biologically active form, 1-25-OH_2-D, by the kidneys [52]. On the other hand, foetuses mainly acquire vitamin D from their mothers in the form of 25(OH)D which can freely cross

the placenta during pregnancy [57-59], particularly when maternal serum 1-25-OH_2-D concentration is high [58]. In addition, the placenta can also produce and secret 1,25-OH_2-D [60]. Previous studies have reported that mothers without adequate intake of vitamin D are more likely to have neonates with insufficient vitamin D concentrations at delivery [57,61].

Another notable finding is the high I^2 value (95%). Subgroup analyses showed no significant differences in the effect size estimate between studies stratified by participants' race and study sample size. Although the pooled effect sizes were largely consistent between vitamin D measurement techniques, the subgroup analysis of the studies using EIA/ELISA found no significant association between vitamin D concentrations during pregnancy and in cord blood plus wide confidence intervals, suggesting that the estimates reported in these studies were imprecise. Recent evidence suggests that the use of EIA/ELISA could result in overestimation of vitamin D concentrations due to its high susceptibility to cross-reactivity and interferences from other metabolites. For example, EIA/ELISA cannot detect and differentiate C3-epimers from vitamin D metabolites [62-64]. Apart from vitamin D3 and D2 which are the two primary metabolites of vitamin D, C3-epimers may also be derived by the liver and kidney during the conversion process to 25(OH)D [65]. Notably, the concentrations of C3-epimers were found to be elevated during pregnancy and infancy [66,67]. These C3-epimers are structurally similar to the vitamin D metabolites, but their biological activities and functions are different due to poor interactions with vitamin D receptors [65,68]. Other measurement techniques such as LC-MS/MS would be able to determine the concentrations of individual vitamin D metabolites including 25(OH)D2, 25(OH)D3, and C3-epimers, which can increase the precision of the estimation of maternal and cord blood vitamin D concentrations, respectively.

In addition, we found that the association between vitamin D concentrations during pregnancy and in cord blood can be influenced by the timing of maternal vitamin D measurement. Although the association was significant regardless of measurement time (before third trimester versus during third trimester), the average effect size was much larger for studies measuring maternal vitamin D concentrations in the third trimester than those with measurement in the earlier stages of pregnancy. The result is consistent with a previous animal model study which observed a faster rate of transfer of vitamin D from mother to foetus in the third trimester of pregnancy [69]. Rapid reduction of vitamin D metabolites and physiological changes during pregnancy are some possible reasons for the between-study differences in the strength of the association due to maternal vitamin D measurement time. Based on the pooled evidence from human studies, our review indicates a strong link between maternal vitamin D concentrations in the third trimester and their offspring vitamin D concentrations at birth. The findings would help to illustrate the importance of regular monitoring of vitamin D concentrations for all pregnant women including those in late pregnancy period.

This study has several limitations which should be considered when interpreting our results. First, some moderator analysis subgroups such as the EIA/ELISA techniques contained few studies which could potentially reduce the reliability of the correlation estimate for this vitamin D measurement technique. Furthermore, only one study provided information as to whether their laboratory had participated in an external laboratory proficiency testing program. This may contribute to the high heterogeneity between the included studies. Given the importance of standardization of 25(OH)D for producing robust estimates, future studies should consider reporting this information. Second, many included studies sampled participants with medical conditions, and two studies did not provide details of participants'

physical health conditions [44,45]. Factors such as diet, smoking status, and sunlight exposure are known to affect vitamin D concentrations, but very few included studies reported these details. Consequently, our review could not determine whether medical and lifestyle factors would affect the relationship between vitamin D concentrations during pregnancy and in cord blood. Third, only articles published in English were included in this review, which may have introduced bias. In addition, we were only able to examine the impact of two racial groups on the strength of the association, suggesting the need to conduct more investigations on this topic in other racial groups.

Despite high heterogeneity between the included studies, our meta-analysis provides evidence for the association of vitamin D concentrations in maternal blood during pregnancy and cord blood at delivery. Large-size prospective cohort studies with sufficient details regarding maternal medical conditions, their dietary and lifestyle patterns during pregnancy, and adequate adjustment for confounding factors are needed to validate the present study findings. Overall, our results indicate that maternal vitamin D concentration across pregnancy phases, particularly in the third trimester, has a substantial effect on cord blood vitamin D concentration. Future trials should identify the best timing of supplementation and examine its consequences for both pregnant women and their offspring.

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Table 1. Characteristics of studies included in the current meta-analysis of correlations between vitamin D levels during pregnancy and in cord blood

Article	Publication year	Pregnant women, age (years)	Observation year	Study place	Total sample size	Time for collection of maternal blood sample	Maternal physical health characteristics	Maternal vitamin D level	Infant sex	Cord blood vitamin D level	Vitamin D testing method
Chiu [17]	2015	30.43	October 2007 to September 2010	Taiwan	164	Before delivery (≥34 weeks of gestation)	Atopic disease: 68(41.5%); smoking history: 9(0.05%)	58.0±19.3 nmol/L	M: 97(56 %); F: 72(44 %)	75.7±30.2 nmol/L	ECLIA
Dovnik [28]	2014	September: 29.1; December: 29.3	2013	Slovenia	September: 100; December: 99	Before delivery (full-term pregnancy except 1 in September and 8 in December group)	Gestation diabetes mellitus/hypertension (September): 26(26%); Gestation diabetes mellitus/hypertension (December): 18(18%)	September: 54.3±25.2 nmol/L; December: 33.3±18.6 nmol/L	NR	September: 73.9±33.2 nmol/L; December: 52.7±27.4 nmol/L	ECLIA
Dror [29]	2011	26.4	December 2006 to January 2008	USA	Mothers: 206; Neonates: 199	Before delivery (full-term pregna	Obesity: 88 (48.1%)	29.7±13.6 nmol/L	NR	17.5±9.2 nmol/L	RIA

						ncy)					
Dror [16]	2012	26.85	December 2006 to January 2008	USA	80	Before delivery (37–42 weeks gestation)	Average BMI: 31.55 kg/m^2	75.7 nmol/L	M: 40(50 %); F: 40(50 %)	42.1 nmol/L	RIA
Godang [50]	2014	NR	2001-2008	Norway	202	At gestational weeks 30-32	Obese: 14(7%)	45.0 nmol/L	NR	31.0 nmol/L	RIA
Halicioglu [30]	2012	27.19	March to May 2008	Turkey	258	3 days before delivery (full-term pregnancy)	No known history of evidence of rheumatological, thyroid or adrenal diseases, hepatic or renal failure, gestational diabetes, hypertension, pre-eclampsia/eclampsia or any long-term medical therapy	28.8±13.5 nmol/L	NR	36.6±21.6 nmol/L	CLIA
Karim [31]	2011	28.16	From August 1, 2008	Pakistan	50	Before delivery (full-	No systemic disease; Obese: 3(6%)	60.0 nmol/L	NR	63.6 nmol/L	Unspecified

			onwards			term pregnancy)					
Kim [32]	2017	34.03	May 2014 to March 2015	Korea	87	Before delivery	Gestation diabetes mellitus: 32(56%)	40.2 nmol/L	NR	49.5 nmol/L	LC-MS/MS
Krieger [33]	2018	32.9	August 2014 to June 2016	Switzerland	Mothers: 305; Neonates: 283	Pregnancy weeks 36-42	No known history of HIV, parathyroid, renal or liver disease, chronic malabsorption syndromes or granulomaforming disorders, or suspected drug or alcohol abuse; Smoking history: 116(38%)	median: 46.0 nmol/L	NR	median: 50.0 nmol/L	ECLIA
Liao [34]	2016	29.4	NR	Taiwan	372	During third gestation	NR	median: 38.0 nmol/L	M: 179(49 %); F: 193(52 %)	median: 149.7 nmol/L	ECLIA
Sachan [35]	2005	24	September to November 2002	India	Mothers: 207; Neonates: 117	Before delivery (full-term pregnancy)	No known history of chronic liver disease, renal disease, or treatment with	35.0 nmol/L	NR	26.8 nmol/L	RIA

							antitubercular or antiepileptic drugs in the previous 3 months				
Song [36]	2013	29.9	April to May 2010	China	Mothers: 70; Neonates: 58	Before delivery (full-term pregnancy)	No known history of renal, bone and gastrointestinal disorders and medications influencing calcium or vitamin D metabolism	28.6 nmol/L	NR	27.9 nmol/L	ELISA
Switkowski [37]	2019	<30 years (Project Viva: 32%; Gen3G: 69%)	Project Viva: 1999 to 2002; Gen3G: 2010 to 2013	Canada	Project Viva: 862; Gen3G: 660	Project Viva: Second trimester; Gen3G: First trimester	Smoking during pregnancy (Project Viva: 13%; Gen3G: 9%); Obese (Project Viva: 15%; Gen3G: 19%)	Project Viva: 59.0 nmol/L; Gen3G: 64.0 nmol/L	Project Viva (M: 53%; F: 47%); Gen3G (M: 52%; F: 48%)	Project Viva: 46.0 nmol/L; Gen3G: 53.0 nmol/L	CLIA
Wang [38]	2010	NR	September 2007	China	77	Before delivery (full-term pregnancy)	No known history of chronic liver disease, renal disease, or treatment with antitubercular or antiepileptic drugs in the previous 3	36.0±19.7 nmol/L	NR	41.0±18.9 nmol/L	EIA

							months				
Weisse [39]	2013	NR	May 2006 to December 2008	Germany	378	34th week of pregnancy	No known history of immune or infectious diseases during pregnancy	median: 55.5 nmol/L	M: 196(52 %); F: 182(48 %)	median: 34.8 nmol/L	LC-MS/MS
Wheeler [40]	2018	32.8	September 2011 to June 2013	New Zealand	32-38 weeks: 80; <20 week gestation: 80; neonates: 122	32-38 weeks of pregnancy; <20-week gestation	No history of disorders known to affect calcium and/or vitamin D metabolism	32-38 weeks: 76.0±34.0 nmol/L; <20 week: 70.0±25.0 nmol/L	NR	41.0±21.0 nmol/L	LC-MS/MS
Zasimovich [41]	2017	Median: 31	NR	Poland	37	NR	no medical history concerning systemic diseases, nor with negative obstetrics and gynecological history (pregnancy-induced hypertension and preeclampsia, gestational	1st trimester: 53.2±23.5 nmol/L; 2nd trimester: 54.0±26.8 nmol/L; 3rd trimester: 55.2±28.4 nmol/L; Delivery: 55.1±22.6 nmol/L	M: 20(54 %); F: 17(46 %)	65.6±25.0 nmol/L	ECLIA

							diabetes, intrahepatic cholestasis of pregnancy, and preterm delivery); non-smoking				
Fouda [42]	2017	28.4	February 2011 to June 2012	Saudi Arabia	Mothers: 280; Neonates: 142	At the first antenatal care visit	14 (5.1%) had hypothyroidism; 12 were hypertensive (4.3%); 7 (2.5%) had bronchial asthma; 15 (10.4%) had preexisting diabetes mellitus; and 21 (14.6%) were diagnosed with gestational diabetes mellitus	18.3±10.3 nmol/L	NR	NR	CLIA
Kazemi [43]	2009	28.5	March and September 2005	Iran	Mothers: 68; Neonates: 61	Before delivery (full-term pregnancy)	No known history of rheumatoid arthritis; thyroid, parathyroid, or adrenal diseases;	19.4±3.9 nmol/L	NR	16.7±2.9 nmol/L	ELISA

							hepatic or renal failure; metabolic bone disease; type 1 diabetes mellitus; or malabsorption				
Matejek [44]	2020	<25, 13(15.1 %); 26–30, 33(37.4 %); 31–35, 20(23.3 %); >35, 20(23.3 %);	Januray 2015 to December 2016	Czech Republic	94 (very low birth weight infants)	Before delivery (27-30 weeks)	NR	Median: 32.0 nmol/L	M: 53(56 %); F: 47(44 %)	Median: 21.0 nmol/L	LC-MS/MS
Nandal [45]	2016	30.83	November 2013 to May 2014	India	60 (vitamin D supplemented)	20±2 weeks of gestation	NR	Median: 30.0 nmol/L	NR	Median: 116.1 nmol/L	EIA
Niwa [46]	2016	31.5	June 2011 to September 2012	Japan	612	34 gestational weeks	No major complications such as gestational diabetes mellitus or toxemia of pregnancy, no need emergent caesarean section	Median: 47.5 nmol/L	M: 314(51 %); F: 298(49 %)	Median: 31.8 nmol/L	RIA

Shor [47]	2015	28.3	March to June 2011	Israel	208	Before delivery (full-term pregnancy)	Healthy, low-risk	37.5±129.1 nmol/L	M: 44%	36.3±21.0 nmol/L	CLIA
Sogawa [48]	2019	32.9	2012 to 2015	Japan	256	At 35-36 gestational weeks	No known history of hypertensive disorders in pregnancy, gestational diabetes mellitus, or use of corticosteroids or heparin	47.0±17.5 nmol/L	NR	29.9±10.5 nmol/L	RIA
Wegienka [13]	2016	30.3	Since 2007	USA	Black: 175(73%); White: 66(27%)	Third trimester	Obese: 46.4%	Black: 50.3 nmol/L; White: 82.3 nmol/L	NR	Black: 28.9 nmol/L; White: 49.6 nmol/L	HPLC
Yu [49]	2020	29.5	June 2017 to October 2018	China	295	Before delivery (full-term pergnancy)	No known history of infection during pregnancy and early membrane rupture, chorioamnionitis, preeclampsia, hypertension, gestational	51.2 nmol/L	M: 147(50%); F: 148(50%)	69.1 nmol/L	ECLIA

				diabetes, chronic diarrhea, liver diseases, kidney diseases, parathyroid diseases, and other calcium-modifying conditions	

ECLIA=electrochemiluminescence immunoassay; RIA=radioimmunoassay; CLIA=Chemiluminescence ImmunoAssay; LC-MS/MS=Liquid Chromatography - Tandem Mass Spectrometry; HPLC=high performance liquid chromatography; ELISA=enzyme immunoassay (EIA)/enzyme-linked immunosorbent assay ; NR =not reported

Table 2. Effect estimates for each study subgroup

	k	*COR*	**95%CI**	*p*	I^2	**95%CI**	$P_{subgroup}$
Collection of maternal blood sample							<0.001
Third trimester	21	0.75	0.66-0.82	<0.001	0.93	0.90-0.95	
Before third trimester	5	0.44	0.17-0.64	0.012	0.91	0.83-0.96	
Race							0.940
Asian	14	0.73	0.58-0.83	<0.001	0.94	0.92-0.96	
Caucasian	11	0.74	0.59-0.84	<0.001	0.94	0.91-0.96	
Sample size							0.625
<100	13	0.75	0.52-0.88	<0.001	0.95	0.92-0.96	
100-300	10	0.73	0.60-0.82	<0.001	0.93	0.90-0.95	
>300	7	0.67	0.50-0.79	<0.001	0.97	0.96-0.98	
Vitamin D measurement techniques							0.949
ECLIA	7	0.74	0.68-0.79	<0.001	0.71	0.36-0.87	
RIA	6	0.73	0.58-0.83	<0.001	0.91	0.83-0.95	
CLIA	4	0.68	0.34-0.86	0.011	0.95	0.91-0.98	
LC-MS/MS / HPLC	8	0.75	0.49-0.89	0.001	0.98	0.97-0.98	
EIA/ELISA	4	0.76	-0.10-0.97	0.063	0.97	0.94-0.98	

ECLIA=electrochemiluminescence immunoassay; RIA=radioimmunoassay; CLIA=Chemiluminescence ImmunoAssay; LC-MS-MS=Liquid Chromatography - Tandem Mass Spectrometry; HPLC=high performance liquid chromatography; ELISA=enzyme immunoassay (EIA)/enzyme-linked immunosorbent assay; k = number of studies; COR=correlation; CI=confidence interval

Figure 1. Flowchart showing the process of study selection

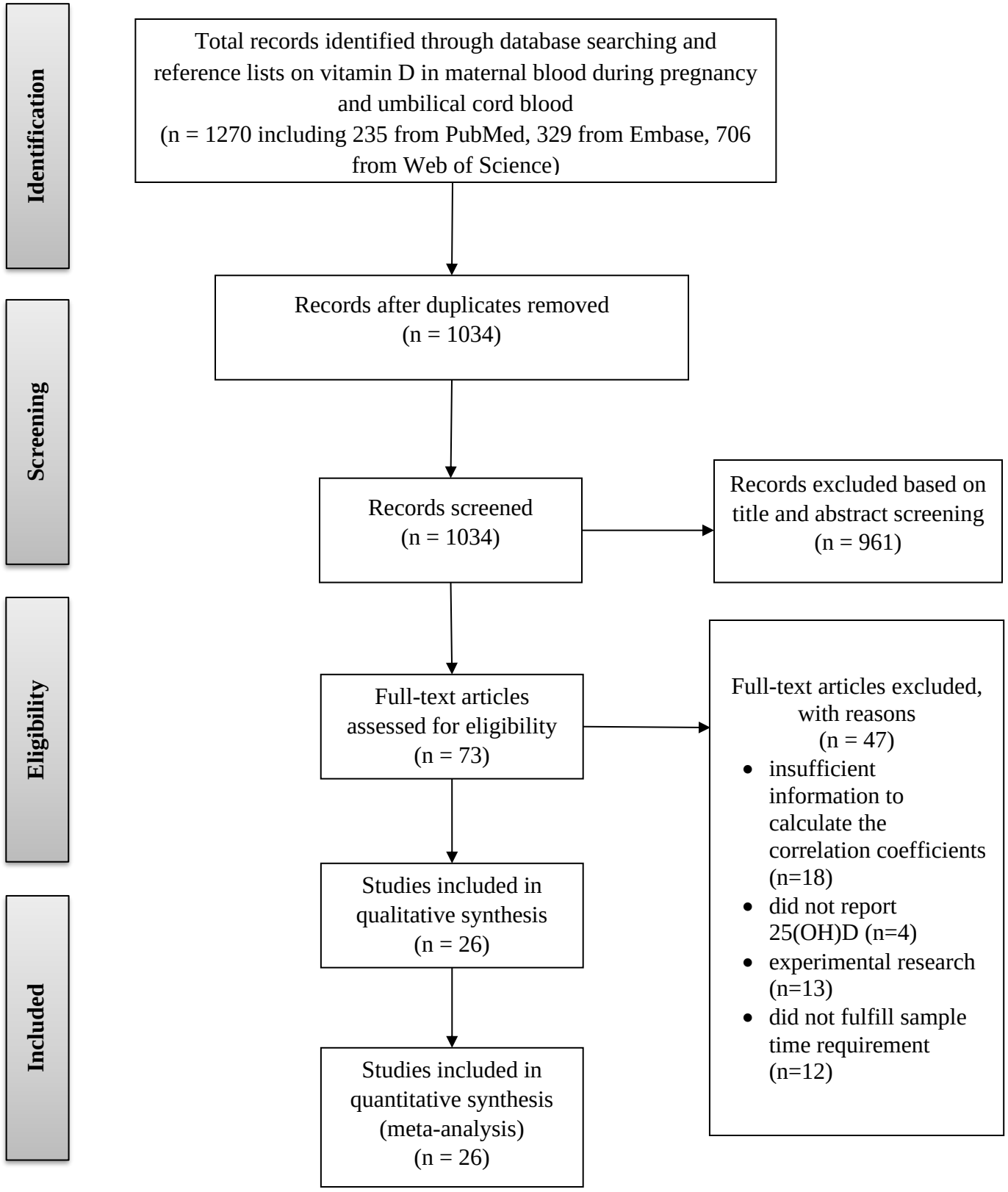


Figure 2. A forest plot showing the correlation between vitamin D levels during pregnancy and in umbilical cord blood

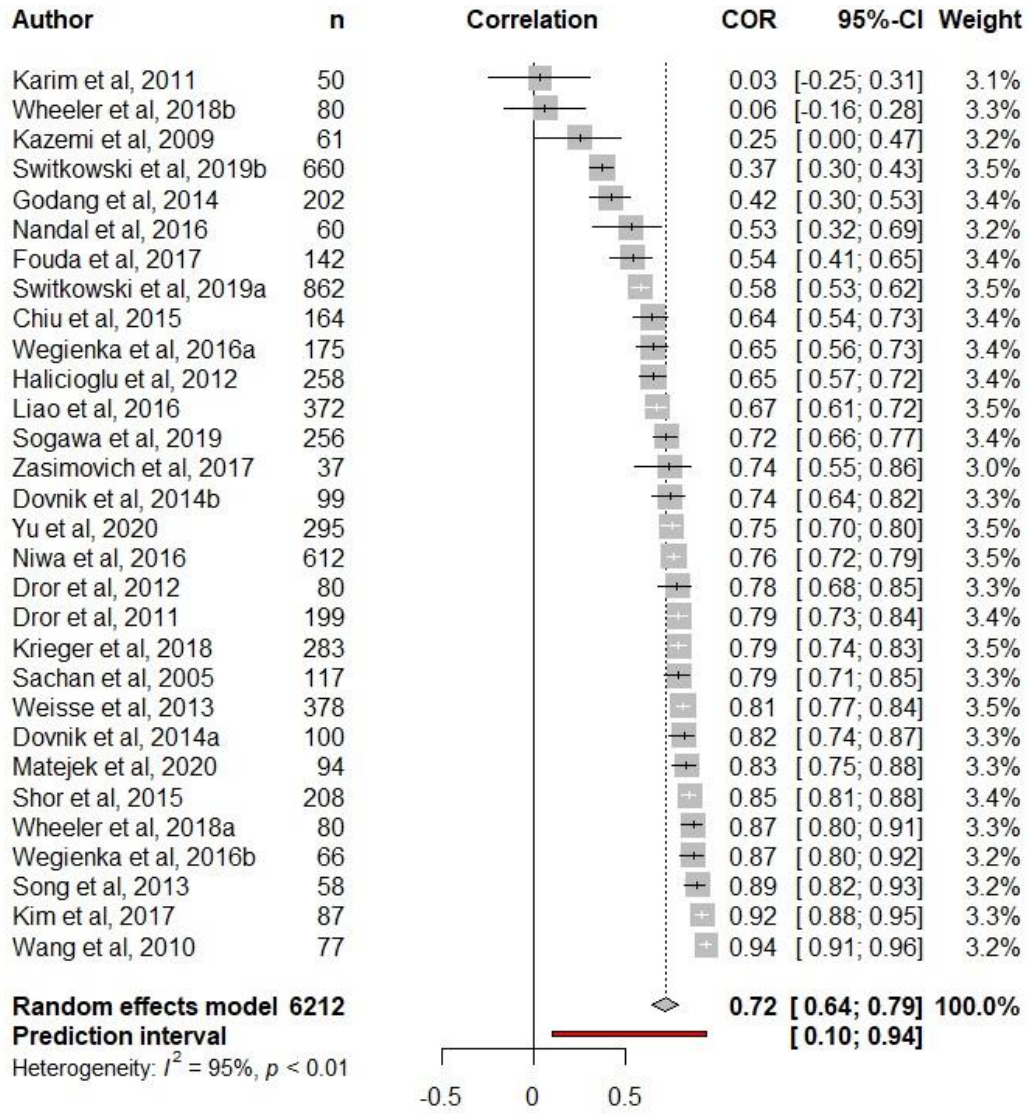
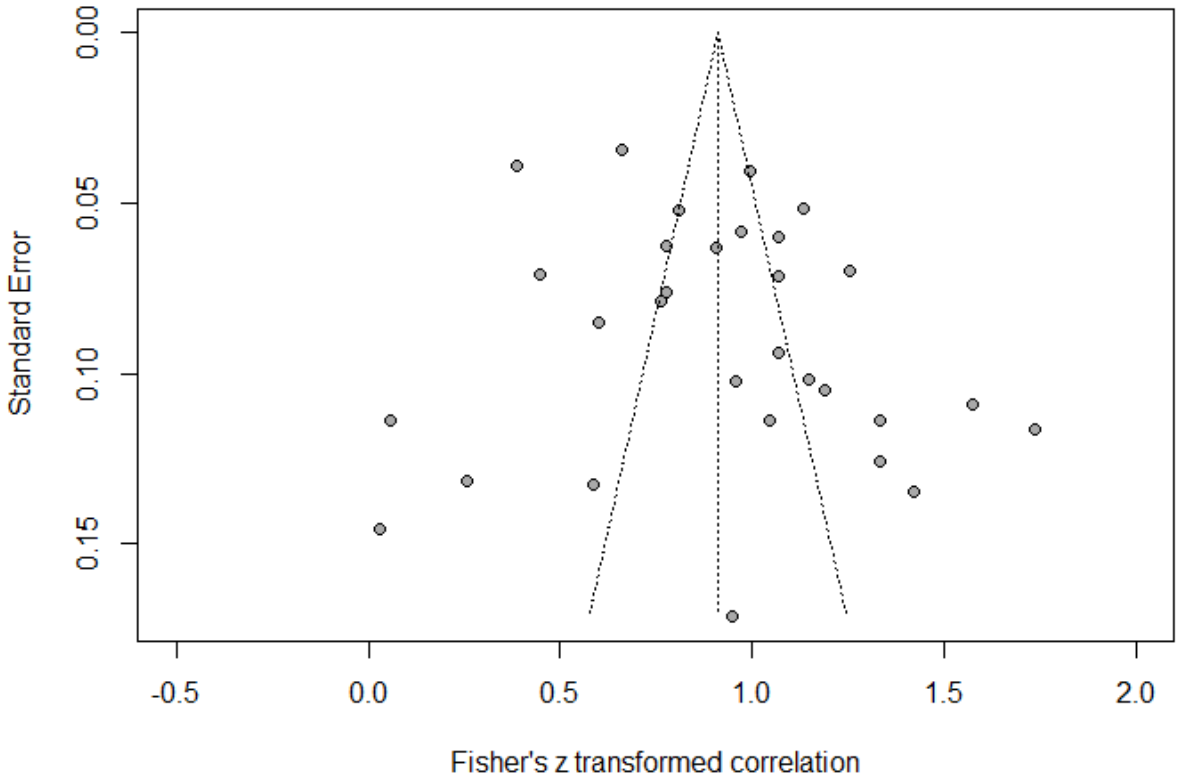


Figure 3. A funnel plot showing the correlation between vitamin D levels during pregnancy and in umbilical cord blood



S1 Table. Quality assessment of the included studies

Article	Clearly defined criteria for inclusion and exclusion in the sample	Clearly defined subject recruitment time	Clearly defined gestational week at which maternal blood were collected	Study participants sampled in an appropriate way	Adequate sample size[#]	Study subjects and setting described in detail	Adequate description of vitamin D assessment	Adequate description of the data	Adequate description of statistical methods	Total score
Chiu [17]	✓	✓				✓	✓	✓	✓	6
Dovnik [28]	✓	✓					✓	✓		4
Dror [29]	✓	✓			✓		✓	✓	✓	6
Dror [16]	✓	✓				✓	✓	✓	✓	6
Godang [50]	✓	✓	✓				✓	✓	✓	6
Halicioglu [30]	✓	✓		✓			✓	✓	✓	6
Karim [31]	✓			✓				✓		3
Kim [32]	✓	✓					✓	✓		4
Krieger [33]	✓	✓	✓	✓	✓		✓	✓	✓	8
Liao [34]	✓			✓		✓	✓		✓	5
Sachan [35]	✓	✓					✓	✓		4
Song [36]	✓	✓					✓	✓		4
Switkowski [37]	✓	✓		✓	✓	✓	✓	✓	✓	8
Wang [38]	✓	✓					✓			3
Weisse [39]	✓	✓	✓	✓		✓	✓	✓	✓	8
Wheeler [40]	✓	✓	✓				✓	✓	✓	6
Zasimovich [41]	✓			✓		✓	✓	✓		5
Fouda [42]	✓	✓	✓	✓			✓	✓		6
Kazemi [43]	✓	✓		✓	✓		✓	✓		6
Matejek [44]	✓	✓		✓		✓	✓	✓		6
Nandal [45]	✓	✓	✓				✓		✓	5
Niwa [46]	✓	✓	✓		✓	✓	✓			6
Shor [47]		✓		✓		✓	✓	✓		5

Sogawa [48]	✓	✓	✓	✓		✓	✓	✓	7
Wegienka [13]	✓		✓			✓	✓	✓	5
Yu [49]	✓	✓			✓	✓	✓	✓	6

Note: [#] Adequate sample size refers to the situation where the reported sample size adequately achieved the desired power as determined through a pre-study power analysis.

S2 Table. Study subgroup characteristics

Study	Race	Collection of maternal blood sample	Sample size	Vitamin D measurement techniques
Chiu et al, 2015	Asian	Third trimester	100-300	ECLIA
Dovnik et al, 2014a	Caucasian	Unspecified/mixed	100-300	ECLIA
Dovnik et al, 2014b	Caucasian	Unspecified/mixed	<100	ECLIA
Dror et al, 2011	Mixed/other	Third trimester	100-300	RIA
Dror et al, 2012	Mixed/other	Third trimester	<100	RIA
Godang et al, 2014	Caucasian	Third trimester	100-300	RIA
Halicioglu et al, 2012	Caucasian	Third trimester	100-300	CLIA
Karim et al, 2011	Asian	Third trimester	<100	Unspecified
Kim et al, 2017	Asian	Unspecified/mixed	<100	LC-MS-MS/HPLC
Krieger et al, 2018	Caucasian	Third trimester	100-300	ECLIA
Liao et al, 2016	Asian	Third trimester	>300	ECLIA
Sachan et al, 2005	Asian	Third trimester	>300	RIA
Song et al, 2013	Asian	Third trimester	100-300	EIA/ELISA
Switkowski et al, 2019a	Mixed/other	Before third trimester	>300	CLIA
Switkowski et al, 2019b	Mixed/other	Before third trimester	>300	LC-MS-MS/HPLC
Wang et al, 2010	Asian	Third trimester	<100	EIA/ELISA
Weisse et al, 2013	Caucasian	Third trimester	>300	LC-MS-MS/HPLC
Wheeler et al, 2018a	Caucasian	Third trimester	100-300	LC-MS-MS/HPLC
Wheeler et al, 2018b	Caucasian	Before third trimester	100-300	LC-MS-MS/HPLC
Zasimovich et al, 2017	Caucasian	Unspecified/mixed	<100	ECLIA
Fouda et al, 2017	Asian	Before third trimester	>300	CLIA
Kazemi et al, 2009	Asian	Third trimester	<100	EIA/ELISA
Matejek et al, 2020	Caucasian	Third trimester	<100	LC-MS-MS/HPLC

Nandal et al, 2016	Asian	Before third trimester	<100	EIA/ELISA
Niwa et al, 2016	Asian	Third trimester	>300	RIA
Shor et al, 2015	Asian	Third trimester	100-300	CLIA
Sogawa et al, 2019	Asian	Third trimester	100-300	RIA
Wegienka et al, 2016a	Mixed/other	Third trimester	100-300	LC-MS-MS/HPLC
Wegienka et al, 2016b	Caucasian	Third trimester	<100	LC-MS-MS/HPLC
Yu et al, 2020	Asian	Third trimester	100-300	ECLIA

S1 Figure. A forest plot showing the correlation between vitamin D levels during pregnancy and in umbilical cord blood after excluding the influential studies with extreme effect sizes