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Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis

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Summary

Vitamin D has well-defined classical functions related to calcium metabolism and bone health but also has non-classical effects that may influence other aspects of health. There has been considerable recent interest in the role of vitamin D on outcomes related to pregnancy and young child health but few efforts have been made to systematically consolidate this evidence to inform the research and policy agenda for low income countries.

A systematic review was undertaken to identify intervention and observational studies of vitamin D supplementation, intake, or status (25-hydroxy-vitamin D) during pregnancy on perinatal and infant health outcomes. Data from trials and observational studies isolating the effect of vitamin D supplementation and intake were extracted and study quality was evaluated. Meta-analysis was used to pool effect estimates.

We identified 5 randomized trials with outcomes of relevance to our review. All had small sample size and dosage amount, duration, and frequency varied as did the ability to correct deficiency. Pooled analysis of trials using fixed effects models suggested protective effects of supplementation on low birthweight (3 trials, Risk ratio (RR)=0.40 [95% confidence interval (CI), 0.23, 0.71]) and non-significant but suggestive effects of daily supplementation on small-for-gestational age (SGA) (2 trials, RR=0.67, [0.40, 1.11]. No effect on preterm delivery (<37 weeks) was evident (2 trials, RR=0.77 [0.35, 1.66]).

Little evidence from trials exists to evaluate the effect of vitamin D supplementation during pregnancy on maternal, perinatal or infant health outcomes. Based on both trials and observational studies, we recommend that future research explore SGA, preterm delivery, pre-eclampsia, and maternal and childhood infections, as outcomes of interest. Trials should focus on populations with a high prevalence of vitamin D deficiency, explore the relevance of timing of supplementation, and the dosage used in such trials should be sufficient to correct deficiency.

Introduction

There is evidence of early interest in the relationship between vitamin D status and perinatal health outcomes. "Rachitic pelvis" was noted as a common obstetric complication in the early 20th century, and may have contributed to the development of caesarian section birthing procedures.¹ In the 1930's, Green and Mellanby speculated that vitamin D had little

“anti-infective” activity but “might prove of significance in connexion with other obstetric difficulties, such as uterine inertia.”² Associations between childhood rickets, sunlight, or cod-liver oil and risk of respiratory infections such as TB and pneumonia were recognized a century ago, although it has only been in recent years that the effects of vitamin D on immunity have been revisited and the underlying mechanisms behind its putative effects have started to become more clear.³

Vitamin D can be synthesized in the skin through exposure to ultraviolet (UV) light or can be obtained through dietary intake. Sunlight exposure is often the major influence on vitamin D status and is influenced by skin color, latitude, season, as well as lifestyle and cultural practices. In comparison, diet is often thought to exert a minor influence on vitamin D status although consumption of supplements can strongly influence status.^{4, 5}

Globally, it has been estimated that a billion people may be affected by vitamin D deficiency or insufficiency.⁶ Generally, populations from countries near the equator (particularly agrarian and nomadic populations) are thought to have sufficient exposure to UV wavelengths required for optimal vitamin D status, and this has indeed been the case in some surveys.^{4, 7} Yet, childhood rickets, a condition caused vitamin D and/or calcium deficiency, has long been noted in certain equatorial populations, particularly those in which head covering or spending time indoors is common.⁴ Recent studies in Ethiopia and India have also found that more than 80% and 66% of pregnant women suffered from vitamin D deficiency using a cutoff of <50nmol/L 25(OH)D, indicating the need for more research on potential adverse effects and benefits of supplementation in developing country contexts.^{8, 9}

Metabolism of vitamin D during pregnancy and maternal-fetal links

Once ingested or produced by the body, vitamin D₃ is transported to the liver for hydroxylation to 25(OH)D, the main circulating form of vitamin D and best measure of vitamin D status, and then to the kidney where the active hormonal form of vitamin D, 1,25(OH)₂D, is produced. Maternal 25(OH)D is thought to freely cross the human placenta as it does in rats.¹⁰ The placenta expresses vitamin D receptors (VDR) and also produces the enzyme CYP27B1 to convert 25(OH)D to its active form.¹¹

The most widely appreciated role of vitamin D in the human body is to maintain normal levels of calcium and phosphate in the blood which in turn facilitate other essential processes such as bone mineralization, contraction of muscles, nervous system activities, and cellular function.¹² Adequate vitamin D status is critically important for the neonate, with neonatal hypocalcemia and rickets being major consequences of deficiency.¹⁰ In areas where vitamin D deficiency is endemic, rickets may be diagnosed soon after birth¹⁰. In general, breast-milk is thought to be a relatively poor source of vitamin D, making maternal vitamin D status during pregnancy important for vitamin D status of the child during early infancy.^{10, 13, 14}

There are a number of plausible biological pathways through which vitamin D could influence placental, fetal, and maternal health or growth during pregnancy. Vitamin D has important immune-modulating properties of vitamin D which may help to establish a proper maternal immune response to the placenta.^{15–17} It also regulates key target genes associated with proper implantation of the placenta.¹⁸ Vitamin D has a direct role in the production of antimicrobial peptides such as cathelicidin, which are produced upon activation of up-regulated vitamin D receptors, require 25(OH)D as a substrate for production, and may play an important role in preventing infection during pregnancy or early childhood.^{3, 19–22} In its active form, vitamin D regulates expression of human chorionic gonadotropin (hCG) in syncytiotrophoblasts and stimulates production of sex steroids.^{23, 24} In vitro and animal studies have also suggested that vitamin D has important roles in glucose and insulin

metabolism which may affect availability of energy to the fetus.^{16, 2525, 26} Vitamin D also influences musculoskeletal growth.^{27–30}

Requirements for vitamin D

The recommended daily allowance (RDA) of vitamin D for women in the United States aged 19–50 years, including during pregnancy, was recently established at 600 IU per day.³¹ This recommendation was based on the amount of intake necessary to sustain blood levels of 25(OH)D above 50nmol/L for populations with minimal sunlight exposure and was developed solely based on outcomes related to skeletal health.³¹ This recommendation was contentious as many researchers have argued that insufficiency should be defined at thresholds of 75 nmol/L or even higher which would require a much higher intake to reach.^{32, 33}

A number of recent reviews have covered a rapidly growing body of literature on vitamin D during pregnancy,^{4, 16, 34–37} although few have taken a systematic approach³⁵ and only a couple have focused on the implications for low income country settings.^{4, 38} To address this gap, we undertook a systematic review of the literature on vitamin D during pregnancy and perinatal and infant health outcomes.

Methods

The primary aim of our literature search was to identify epidemiologic studies that isolated the effect of intake of vitamin D from supplements or diet on the outcomes presented in Table 1. Skeletal health related outcomes such as bone mineralization and rickets were not part of this review and have been detailed elsewhere.^{31, 3910} Recognizing in advance that few supplementation trials had been published, we sought to also identify prospective observational studies with intake of vitamin D or maternal blood 25(OH)D levels during pregnancy as exposures. Using the search strings outlined in Table S1 we searched the NLM Pubmed database and Cochrane Library through June 2011 as well as the bibliographies of reviews and relevant studies.

An initial review of titles and abstracts was undertaken by one reviewer followed by an in-depth review of full papers that could not be initially excluded (ATL). We excluded (1) non-human studies (2) studies not in English, French, or Spanish (3) reviews, case reports and commentaries (4) topics unrelated to the review (5) studies that could not isolate the effects of vitamin D supplementation or intake (6) cross sectional and non-prospective case-control studies. A modified version of the Child Health Epidemiology Reference Group's GRADE tool was used to evaluate intervention studies and observational studies of vitamin D intake for risk of bias, and those with a study quality of "Very Low" were excluded. Authors of recent trials presenting clinical outcomes were requested to provide additional data on other outcomes of relevance to the meta-analysis.

Study data were extracted using a standard spreadsheet. Review Manager 5.1⁴⁰ was used to generate pooled effect estimates for all outcomes with data from more than one eligible study. For studies with continuous outcomes we generated mean differences and for dichotomous outcomes we calculated relative risk or odds ratio estimates, each with 95% confidence intervals. Inverse variance weights were used to generate pooled effect estimates with a fixed effects (FE) model in absence of significant heterogeneity. Heterogeneity was explored through visual inspection of Forest plots as well as through I^2 values and Chi-square tests for heterogeneity. In the presence of significant heterogeneity ($p < 0.10$), we used a random effects (RE) model. For trials testing multiple intervention arms (of daily or bolus doses), we pooled data from intervention arms, calculated the pooled mean and standard

deviation⁴¹ where appropriate, and also presented separate analysis for daily vs. bolus dosage. For observational studies, comparisons were made of extreme categories.

Results

Identification of studies

We identified 944 hits through our database searches and five additional studies through bibliographical searches (Figure 1). Five trials of vitamin D supplementation during pregnancy met our inclusion criteria, one of which did not provide sufficient data for inclusion in quantitative analysis⁴², and one study was excluded that ranked ‘Very low’ on GRADE criteria (Table 2 and Table S2).⁴³ Additional data was received from the authors of two recently published trials (personal communication with Dr. Yu, Nov. 2011 and Drs. Hollis/Wagner, Jan. 2012). Six observational studies of vitamin D intake were identified of which two^{44, 45} ranked ‘Very Low’ on GRADE criteria. (Table S3). We also found 13 studies with prospective assessment of 25(OH)D prior to birth outcomes (Table S4) and four studies in which pre-eclampsia was reported as an outcome (Table S5).

All but one trial⁴⁶ and four observational studies of 25(OH)D were conducted in high-income country settings, and most populations had either a presumed risk or high prevalence of deficiency at baseline (Table 1).^{9, 47–50} Dosing approaches in the trials varied: Two trials contained multiple intervention arms testing both daily supplementation (800 IU and 1000 IU D₂) and high single dose supplementation (200,000 IU) in the third trimester. One recent trial tested both daily 2000 IU D₃ and 4000 IU D₃, the latter at the upper limit of the current U.S. recommendations and a study in India tested the effects of two bolus doses of 600,000 IU.³¹

Vitamin D supplementation appeared to improve maternal 25(OH)D levels in all four trials for which data was available although mean attained levels at term in two trials indicated that the dosage tested was not sufficient to alleviate deficiency in much of the population (Table S6).^{42, 51} In contrast, the results of trials by Hollis and Brooke indicate a substantial improvement in vitamin D status, and there is some speculation that the dose used in the latter trial may have been higher than reported.^{5, 36, 52}

Birthweight, low birthweight, and crown-heel length at birth

The results of all meta-analyses are summarized in Table 3. Pooled analysis of all five trials with information on mean birthweight suggested no significant overall effect (Figure S1), although significant heterogeneity was apparent ($I^2=70\%$, $p=0.0009$) and appeared to originate primarily from the divergent results of studies testing a large bolus dose, one of which showed a significant increase and the other which showed a significant decrease in birthweight. Pooled results of observational studies indicated a significant 52g increase [3.5, 102] comparing the highest vs. lowest categories of intake (Figure S1). An observational study in New Zealand also found a significant 71g birth weight difference across quartiles of intake noting low median intakes of 68 IU/day in the population though data was insufficient for pooling.⁵³

Pooled analysis of three trials revealed that supplementation led to a significant 60% reduction in the risk of low birthweight (Figure 2), and disaggregated analysis of bolus high dose trials also suggested a strong benefit (2 trials, RR=0.25, [0.11, 0.61]) although daily supplementation trials did not show statistically significant benefit (2 trials, RR=0.56, [0.27, 1.13])(Figure S2).

The majority of studies examining relationships between maternal vitamin D status and mean or low birthweight found no association.^{9, 30, 47, 49, 54, 55} However, two large studies,

one from the Netherlands and the other from Australia both found significantly lower birthweight among infants born to women with vitamin D deficiency (using thresholds of <25 and 29 nmol/L).^{56, 57} Another study from Australia found no overall effect of low maternal 25(OH)D levels (<28 nmol/L) on mean birth weight, yet effect modification was found by infant vitamin D receptor (*FokI*) genotype: offspring born to women in the with higher 25(OH)D levels were significantly heavier within the FF or Ff but not the ff genotypes.⁵⁸

Pooled analysis of two supplementation trials showed no significant difference in mean crown-heel length associated with supplementation (Figure S3). None of the observational studies we identified reported a significant association between maternal 25(OH)D status and crown-heel length at birth.^{9, 30, 47, 54, 55, 59, 60}

Small-for-gestational age and gestational weight gain

Pooled analyses indicated significantly greater average daily weight gain in the third trimester among women supplemented with vitamin D (2 trials, 11.8g/day [3.4, 20.2]) (Figure S4), and a non-statistically significant 33% decrease in the risk of SGA (Figure 2). However, an observational cohort study from Boston reported no difference in birth weight for gestational age by quartile of vitamin D intake in unadjusted analysis.⁶¹

Prospective observational studies of vitamin D status and SGA have had mixed findings (Table S4). Two studies, one of HIV-positive women in Tanzania and another among pregnant adolescents in the UK did not find statistically significant associations between maternal 25(OH)D levels and SGA.^{49, 62} However, the largest study to date, from the Netherlands, found that the risk of SGA among vitamin D deficient women (25(OH)D<30nmol/L), was nearly twice that of women with adequate status in multivariate adjusted models (AOR 1.9 [95% CI: 1.4, 2.7])⁶⁰. A recent nested case-control study from Pittsburgh found evidence of a U-shaped relationship between vitamin D status and SGA among white women in the study: those with serum 25(OH)D levels less than 37.5 nmol/L had a 7.5-fold [95%: 1.8, 31.9] higher risk of SGA compared to those with levels between 37.5 and 75 nmol and those with levels exceeding 75nmol/L had a 2.1 times higher risk [1.2, 3.8].⁶³ Effect modification by race was also evident as no statistically significant relationships between serum 25(OH)D levels and SGA risk were observed among black women included in the study.

Preterm birth

No significant association was evident between vitamin D supplementation and preterm delivery (<37 weeks) or mean duration of gestation in pooled analyses (Figure 3, Figure S5), or in two observational studies of intake of vitamin D and mean duration of gestation (Figure S6).^{5, 42, 64}

Two studies examined relationships with blood levels of 25(OH)D during pregnancy and preterm birth. In Tanzania, no difference in risk of preterm birth (<37 weeks, RR=0.84 [0.55–1.28] or severe preterm birth (<34 weeks, RR=0.77 [0.50, 1.18]) was observed among HIV-positive women using a cutoff of 80 nmol/L. Similarly, no difference in 3rd trimester 25(OH)D levels was found for adolescents in the UK delivering preterm vs. normal gestational length babies⁶².

Observational studies with serum 25(OH)D levels as an exposure did suggest longer gestational duration associated with higher 25(OH)D levels. In The Netherlands, women with serum levels >50nmol/L had a slightly longer gestational length of 40.2 weeks vs. 40.0 weeks vs. women in two categories of lower intake (P<0.001).⁵⁷ An Australian study noted a significant 0.7 week shorter gestation [−1.3, −0.1] among women with blood 25(OH)D

levels <28nmol/L compared to those with higher levels.³⁰ A hospital-based study from Japan also found lower mean 25(OH)D levels among mothers with threatened premature delivery.⁶⁵

Fetal loss

One trial reported a case of stillbirth in the non-intervention arm, but we found no other trials or observational studies of vitamin D intake with data on fetal loss.⁴² One study among HIV+ women from Tanzania found no significant difference in fetal loss among women with deficiency vs. those with sufficient status (RR=1.05; 95% CI (0.63, 1.74)).⁴⁹

Pre-eclampsia, Caesarian section, and maternal mortality

We did not find any published data from trials on the effects of vitamin D supplementation on risk of pre-eclampsia. Preliminary data shared with us by investigators from the trial in South Carolina indicates monotonic reductions in risk with increasing supplement dosage (400 IU, 2000 IU, 4000 IU) for a composite pre-eclampsia/eclampsia/gestational hypertension outcome which although not significant in intent-to-treat analysis, became significant after controlling for race (Hollis et al, *in press*).

Pooled analysis of a very large (n=23,423) study from Norway and a large (n=1,718) study from Massachusetts (Figure S7) revealed no significant difference in risk of pre-eclampsia between top and bottom categories of total vitamin D intake (OR=0.95; [95% CI: 0.86, 1.06]). While the comparison between >800 IU with <200 IU of total vitamin D intake in the Norwegian study was not statistically significant (OR=0.89 [0.75, 1.06]), it is important to note that women with intake between 688 and 800 IU had significantly reduced risk of pre-eclampsia (Adjusted OR 0.77 [0.61–0.96]) compared with those consuming <200 IU/day. Interestingly, a heightened risk of gestational hypertension was associated with increased vitamin D intake in the study from Massachusetts (Adjusted OR=1.11 [1.01, 1.21]).

Observational studies of vitamin D status during pregnancy and risk of pre-eclampsia have not shown consistent associations (Table S5) Investigators of a study from Pittsburgh observed an inverse monotonic dose response relationship between 25(OH)D levels in early pregnancy and pre-eclampsia: for every 50 nmol/L decline in 25(OH)D levels, the risk of pre-eclampsia more than doubled (adjusted OR 2.4 [1.1, 5.4]).⁶⁶ Similarly, a nested case control study from North Carolina reported that women with 25(OH)D levels <50 nmol/L had nearly a fourfold greater risk of severe preeclampsia compared with those with levels >75nmol/L.⁶⁷ In contrast, a recent nested case control study conducted in Massachusetts found no statistically significant difference in risk of pre-eclampsia for women with 25(OH)D levels <37.5 nmol/L (AOR 1.35 [0.40, 4.50]).⁶⁸ Another prospective cohort study of pregnancies at high risk for pre-eclampsia in Canada found no effect of 25(OH)D during early pregnancy on pre-eclampsia risk.⁶⁹

In a recently published trial from South Carolina, no statistically significant differences in mode of delivery (Caesarian section vs. vaginal delivery) were noted by vitamin D supplementation group, although adjustment for race reportedly led to a statistical significant trend of increasing protection with higher dosage (Hollis et al, *in press*).⁵ An observational study undertaken in Boston found that women with vitamin D levels 25(OH)D<37.5 nmol/L during pregnancy were found to have nearly a four times greater risk of caesarian delivery (AOR 3.84 [1.71, 8.62]).¹ Similarly no association between maternal vitamin D status and mode of delivery was found in an Australian observational study.⁵⁶

No trials or observational studies of vitamin D supplementation/intake and maternal mortality or morbidity during pregnancy were identified. However, a study from Tanzania found that pregnant women with 25(OH)D levels <80nmol/L had increased risk of HIV

disease progression and that risk of all-cause mortality was significantly lower in the highest quintile of 25(OH)D compared with the lowest (Incidence RR=0.58 [0.40, 0.84]).⁴⁸

Neonatal and infant growth

One supplementation trial in the UK reported significantly greater weight gain among infants born to women supplemented with vitamin D compared with the placebo group 3, 6, 9, and 12 months (12 month comparison: 6.39 kg vs. 5.92 kg in the control group ($p<0.01$)).⁷⁰ Up to 6 months of age, there were no differences in attained height between groups, but by 1 year of age, those in the vitamin D group had grown 27.9 cm vs. 24.6 cm in the placebo group ($p<0.001$).

A large observational study in the Netherlands found no differences in multivariate adjusted mean weight-for-age z-scores by category of maternal vitamin D status during pregnancy at any measure taken during the first year of life. While infants born to mothers with 25(OH)D levels $<30\text{nmol/L}$ had significantly lower mean length for age z scores at 1 month compared with those born to women adequate status ($>50\text{nmol/L}$), paradoxically they had higher z scores by 12 months with no differences observed at 3, 6, or 9 months.⁵⁷ In another study conducted in the Gambia among a population with high vitamin D status, no significant relationships or trends were found by maternal 25(OH)D status taken at either week 20 or 36 of pregnancy and weight or height-for-age z scores at 2, 13, or 52 weeks.⁴⁷ A cohort study of the effects of maternal vitamin D status during pregnancy on subsequent outcomes in Southampton, UK, found no differences in attained weight or length at 9 months of follow-up across quartiles of 25(OH)D status measured in late pregnancy (with cut-points at <30 , 50, 75, and $>75\text{nmol/l}$).⁵⁴ However, in a linear regression model examining predictors of height at 9 months that included height measured at birth, a significant association with maternal 25(OH)D was observed ($p=0.02$).^{54, 71} A study in India found no difference in attained height at age 5 years between children of mothers with 25(OH)D levels above vs. below 50 nmol/L during pregnancy.⁵⁰

Neonatal and infant morbidity and mortality

We did not identify any trials of vitamin D supplementation during pregnancy with outcomes related to infant or child mortality, though a death was noted in one trial.⁴² In a cohort study of 1,194 children from Massachusetts, no significant trend was found across quintiles of maternal vitamin D intake during pregnancy on risk of reported diagnosis by a health professional of respiratory infections up to 3 years of age in multivariate adjusted analysis.⁶¹ A study of 922 infants in New Zealand found significantly greater risk of respiratory infection (a composite variable of colds, cough, whooping cough, chest infections, and ear infections) by 3 months of age among infants with cord blood levels of 25(OH)D less than 25 nmol/L in adjusted analysis compared with levels at or above 75 nmol/L, OR=2.04 [1.13, 3.17].⁷² In contrast to these findings, a cohort study from Southampton, England which followed up children at age 9 months found that mothers in the top quartile of 25(OH)D status in late pregnancy were significantly more likely to report their children having been diagnosed with pneumonia or bronchiolitis, compared with those in the bottom quartile (unadjusted OR 4.80, [1.01, 22.73]), although no differences in risk for respiratory infections overall or for chest infections or bronchitis were observed.⁵⁴ The same study unexpectedly also found that children of mothers in the highest quartile of vitamin D status were more likely to have reported having one or more bouts of diarrhea vs. those in the bottom quartile (OR=1.87 [1.01, 3.46]). In a study of infants born to HIV+ mothers in Tanzania, vitamin D insufficiency during pregnancy ($<80\text{nmol/L}$) was associated with heightened risk of a composite endpoint of infant mortality/HIV infection (RR=1.49 [1.07, 2.09]).⁴⁹

Discussion

Scientific understanding of the importance of vitamin D during pregnancy for perinatal and child health outcomes is growing rapidly, and our review consolidates a great deal of new information from trials and observational studies not incorporated in a prior meta-analysis on the topic.³⁵ In addition to its classic functions related to calcium homeostasis and bone development, emerging evidence suggests that adequate maternal vitamin D status could play important roles in ensuring proper fetal and placental development and proper immune response and function during pregnancy, although the relative importance of its different putative effects on pathways leading to clinical outcomes is not well understood.^{16, 22, 66}

It is important to interpret the findings of our pooled analyses with caution, particularly given the small number and small sample size of existing trials and the heterogeneity observed across a number of outcomes. Many trials to date were conducted among populations with evidence of high prevalence of deficiency, and provided supplementation during the third trimester at levels that were not sufficient to fully correct deficiency in the population (Table S6). We also note that most studies to date have been conducted in populations located in northern climates with suspected high prevalence of vitamin D deficiency. Caution is therefore also needed when considering the generalizability of these findings to populations with greater potential exposure to sunlight, although it is also important to consider the role that cultural practices of head covering and urban lifestyles may have in contributing to deficiency even in tropical countries.

Despite the lack of a statistical significance of the effect observed in our pooled analysis of SGA, we found fairly consistent evidence from trials suggesting that vitamin D has the potential to influence IUGR among deficient populations, supported by significant effects observed in the meta-analysis of data on gestational weight gain and low birthweight. The outcome with the greatest number of trials was mean birthweight, for which the findings suggested either a null or modest effect. It is well accepted that mean birthweight is limited in its ability to capture fetal growth restriction, partly because it also reflects gestational age.⁶³ We only found one observational study suggesting that risk of SGA might increase at higher levels of 25(OH)D, but many studies appeared to only examine 25(OH)D as a dichotomous categorical variable, reinforcing the importance for future observational studies to examine potential non-linear relationships across the entire distribution.⁶³ Studies also suggest that further exploration of heterogeneity in effects by race and/or vitamin D receptor genotype may be important.^{58, 63}

Some, but not all studies, suggested an effect of vitamin D on risk of pre-eclampsia. In addition to the studies we reviewed, a trial using cod liver oil containing vitamin D along with multi-micronutrient supplement found a significant 32% reduction in preeclampsia risk, and a trial of vitamin D and calcium from India indicated a non-significant benefit on preeclampsia.^{73, 74} It has been speculated that early pregnancy, when the placenta is still developing, might be the most etiologically relevant time period for vitamin D supplementation on pre-eclampsia but this hypothesis requires further testing and received limited support from the one observational study to explore the importance of timing of supplementation during pregnancy.⁷⁵

We found little evidence to evaluate the effect of vitamin D on preterm birth or any of its obstetric precursors. Approximately 25–40% of all preterm births are thought to be associated with intrauterine infection.⁷⁶ An influence of vitamin D status on bacterial infections during pregnancy is plausible and is supported by the consistency of findings of several cross-sectional observational studies in the U.S. suggesting inverse relationships between 25(OH)D and bacterial vaginosis during pregnancy.^{15, 77, 78} Larger observational

studies or trials with more detailed outcome evaluation are needed to assess the potential for vitamin D to influence risk of preterm birth.

Both the observational study from Massachusetts and the trial from South Carolina provide support for an effect of vitamin D on risk of primary Caesarian-section.^{1,5} In apparent contrast to these findings, two studies excluded from our analysis due to their non-prospective nature suggest no association between mode of delivery or dystocia and maternal vitamin D status.^{79, 80} Heterogeneity in these associations is not entirely unexpected since decision-making related to Caesarian delivery may vary across settings. Given the strength of the association observed in the study from Massachusetts, the role of vitamin D in regulation of calcium (which may help to initiate labor and influence muscle function), and the potential role on pre-eclampsia, further exploration would be worthwhile.⁸¹

Neonatal and early childhood morbidity, mortality, and growth

Maternal serum levels of 25(OH)D during pregnancy are correlated with cord blood and neonatal levels of 25(OH)D and could be an important influence on neonatal and early childhood health and growth, particularly since breastmilk is a poor source of vitamin D in absence of high dose maternal supplementation.⁵ A growing number of studies suggest the importance of adequate vitamin D status during childhood to the prevention of respiratory infections. A study from Ethiopia found that children with rickets had a 13 fold higher risk of pneumonia compared with controls⁵ while a trial in Afghanistan found that vitamin D supplementation of children diagnosed with pneumonia significantly reduced both the risk of repeat episodes during 90 days of followup by 22% as well as increasing the time to repeat episode.⁸² Limitations of the studies we identified include reliance on maternal reports of doctor's diagnosis, little specificity of outcomes, and in the case of the study from England showing increased risk associated with better vitamin D status, a lack of adjustment for potential confounders such as access to health care or education.⁵⁴ Infections remain an important cause of neonatal and early childhood mortality in many countries, and trials of maternal vitamin D supplementation in such settings should also include follow-up of children for respiratory infections (and HIV in high prevalence settings).^{48, 49, 83}

The importance of vitamin D to linear growth during childhood was considered at least as early the 1930's.^{84, 85} The strongest support for a direct role of vitamin D supplementation on child growth comes from the trial in the UK which found beneficial effects on linear growth at 9 months but not prior to that time.⁷⁰ It is difficult to explain the inconsistencies between these findings and observations from the Netherlands showing that children born to vitamin D deficient mothers appeared to have greater growth velocity, although residual confounding and vitamin D supplementation practices during early childhood in the latter study have been offered as explanations.⁵⁷

Policy implications and future research directions

Despite growing interest in the relationships between vitamin D status during pregnancy and perinatal and infant health outcomes, the epidemiological evidence base remains weak for all of the outcomes we included in our review. Noting compelling evidence of a potential role of vitamin D on a number of perinatal and maternal health outcomes, more randomized trials of vitamin D supplementation during pregnancy in deficient populations are needed to evaluate the potential for vitamin D supplementation to prevent adverse outcomes. Such trials should be undertaken in settings in which vitamin D deficiency is likely to be a risk: latitude, cultural practices of head covering, urban lifestyle, poor dietary intake of vitamin D, and season are all factors that may be useful to consider when selecting populations for such trials.

Dosage for such trials should be guided by population 25(OH)D levels at baseline and desired target levels.⁸⁶ The threshold used to define optimal serum 25(OH)D levels is contentious, though many researchers have argued that levels of at least 75–80nmol or even higher are desirable based on observational studies and estimates of circulating levels from living under UV-rich conditions similar to which humans evolved.^{32, 37} Recent research from the multi-dose trial of pregnant women suggests that serum levels of 25(OH)D exceeding 100nmol/L may be needed to optimize production of 1,25(OH)D.⁵

The fat soluble properties of vitamin D mean that intermittent (e.g. weekly or monthly) dosage is possible, which may be particularly useful in countries with weak health infrastructure, but also raises the need to consider potential adverse effects due to toxicity. The upper limit of intake above which adverse health outcomes such as hypercalcaemia during pregnancy ensue is uncertain. The US tolerable upper limit for women of reproductive age including pregnant women was recently set at 4000 IU/day though it has been argued that there is little evidence of toxicity of higher levels up to 10,000 IU/day.³³ Dosages administered during recent trials without adverse effects include daily provision of up to 4,000 IU/day vitamin D₃ throughout pregnancy in the trial from South Carolina⁵ (though women with high baseline serum levels were excluded from the highest dose group and supplementation began at 16 weeks), provision of a weekly dose of 35,000 IU D₃ during the third trimester in Bangladesh⁸⁷, and one time doses of 200,000 IU vitamin D₃ in the third trimester of pregnancy.^{42, 51} Monitoring of adverse events in clinical trials using high intermittent dosing may also be an important consideration.⁸⁸

Lastly, we note that the vast majority of studies published to date on vitamin D and perinatal health outcomes have been undertaken in high income countries. While populations in these settings may be at greater risk for vitamin D deficiency due to lower UV light exposure, more research is needed in populations from low income countries, which may have lower dietary intake, higher disease burden, and for which vitamin D deficiency may be a growing problem associated with urbanization.

Summary

In a systematic review of the literature we found only a low level of evidence relating vitamin D supplementation or intake during pregnancy on perinatal and infant health related outcomes. Emerging evidence suggesting plausible effects on intra-uterine growth restriction, pre-eclampsia, and both maternal and infant infections as important outcomes in need of further research in low income settings. Several trials have recently been completed or are underway including in Pakistan and Bangladesh that should help to clarify the importance of vitamin D supplementation as an intervention for perinatal, maternal, and infant health outcomes.^{5, 89} Vitamin D is an essential nutrient with well-established roles in calcium metabolism and the prevention of rickets that are important for policymakers to consider alongside the outcomes reviewed here.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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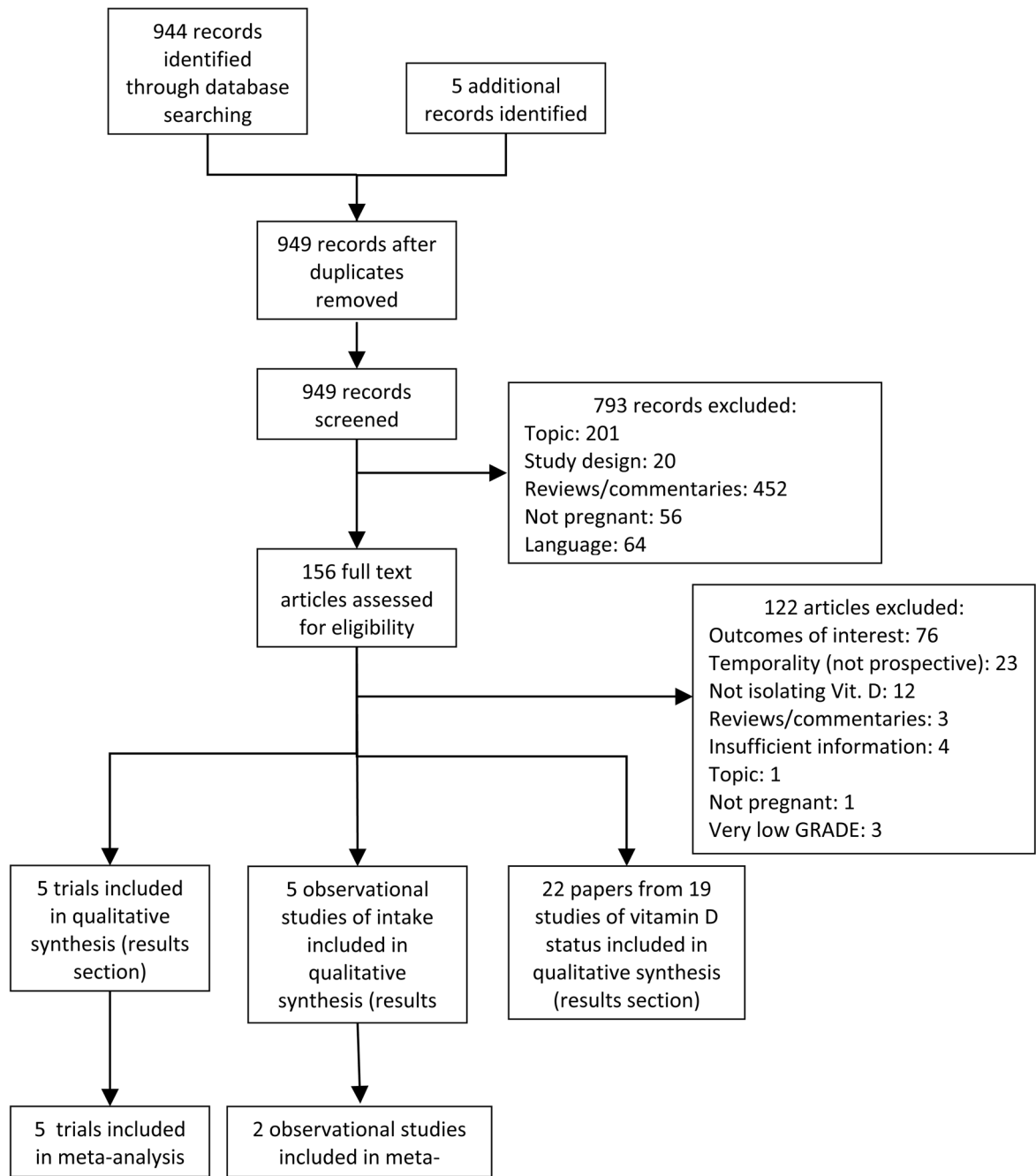
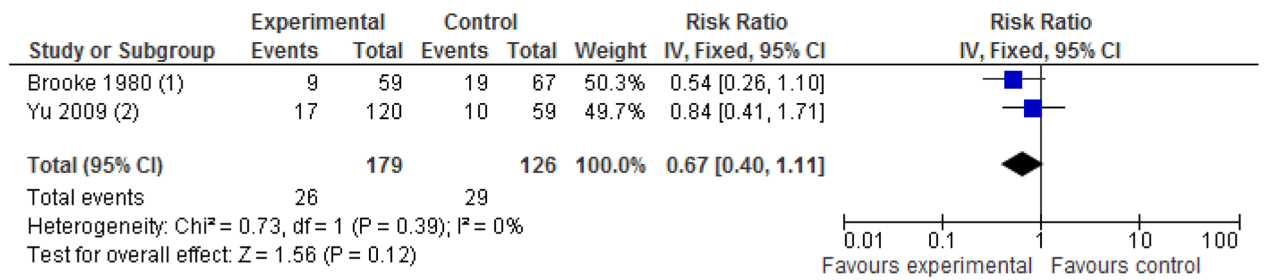


Figure 1.
Study flow

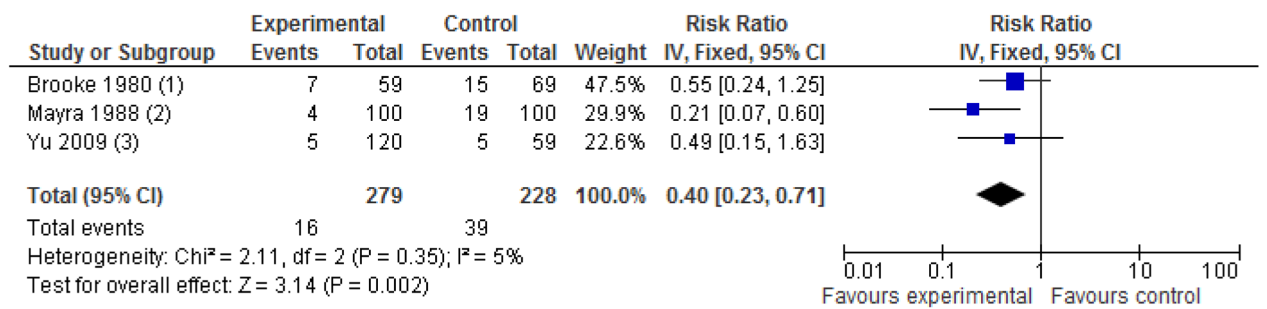
Combined daily or bolus supplementation and SGA



(1) Daily 1000 IU D2 vs placebo

(2) Intervention group pooled 800 IU/daily with bolus 200,000 IU group vs unsupplemented

Combined daily or bolus supplementation and low birthweight



(1) Daily 1000 IU D2 vs placebo

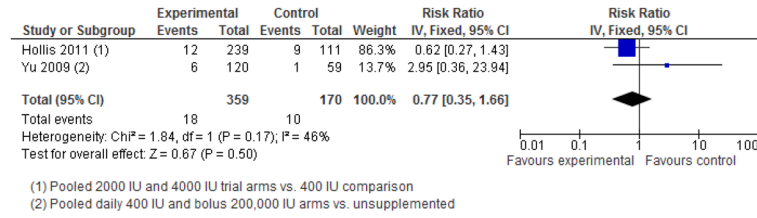
(2) Intervention group received 600,000 IU vitamin D3 at 7th and 8th month of gestation

(3) Intervention group pooled 800 IU/daily with bolus 200,000 IU group

Figure 2.

Trials of vitamin D supplementation and risk of low birthweight and small-for-gestational age

Daily or bolus supplementation and preterm delivery (<37 weeks)



Daily or bolus supplementation and mean gestational age at delivery (in weeks)

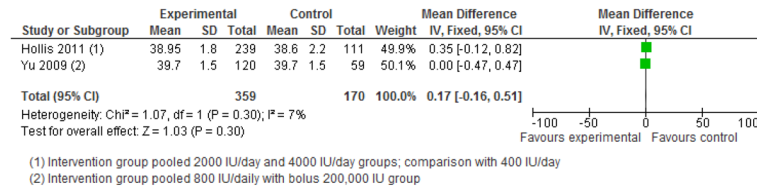


Figure 3. Trials of vitamin D supplementation and risk of preterm delivery and mean duration of gestation

Table 1

Primary outcomes covered by this review

1	Low birthweight due to intrauterine growth restriction
1a	Small for gestational age
1b	Low birthweight
1c	Mean birthweight
1d	Weight gain during pregnancy
1e	Mean heel-crown length at delivery
2	Preterm birth
2a	Preterm birth (<37 weeks)
2b	Early preterm birth (<34 weeks) ^a
2c	Mean gestational age at delivery
3	Neonatal growth, morbidity, and mortality
3a	Early infant mortality (first 6 weeks) ^a
4	Infant or child growth, morbidity, and mortality
4a	Mean weight ^a
4b	Mean height ^a
4c	Low weight-for-age ^a
4d	Low height-for-age ^a
4e	All-cause mortality ^a
4f	Mortality due to measles, diarrhea, ALRI, or malaria ^a
4g	Mother to child transmission of HIV ^a
4h	Morbidity (diarrhea, measles, malaria, ALRI) ^a
5	Maternal morbidity and mortality
5a	Mortality (all cause) ^a
5b	Mortality due to hemorrhage, sepsis, or obstructed labor ^a
5c	Delivery complications (C-section) ^a
5d	Pre-eclampsia

^aIndicates outcomes for which outcomes from more than one study could not be extracted for meta-analysis

Table 2

Description of intervention studies of vitamin D supplementation and observational studies of vitamin D intake (including supplements) eligible for inclusion in meta-analyses

Study ID	Country and latitude ^a	Population	Intervention or exposure	Comments and GRADE assessment of risk of bias
Intervention studies				
Brooke (1980) ^{65, 70, 91}	UK (London) 51°N	Affluent Asian immigrants in 3 rd trimester. Excluded preterm deliveries, congenital malformations, and certain maternal illnesses. Mean 25(OH)D: 20.1 nmol/L at 28 weeks.	Randomized to a daily dose of 1) 1000 IU Vitamin D ₂ (n=59) or 2) Placebo (n=67) provided from 28–32 weeks gestation to delivery.	Double blind RCT. Small sample size GRADE: Moderate
Hollis (2011) ^{5, b}	US (South Carolina) 34°N	Multiethnic population, mean age 27 years, women with pregnancy <16 weeks gestation at enrollment. All participants received prenatal multivitamin/mineral supplement. Mean baseline 25(OH)D by group: 58.2–61.6 nmol/L.	Randomized to daily dose of 1) 400 IU vitamin D ₃ (n=111) 2) 2000 IU vitamin D ₃ (n=122) 3) 4000 IU vitamin D ₃ (n=117) provided from 12–16 wks until delivery. Women with baseline 25(OH)D levels >100nmol/L randomized to group 1 or 2.	Double blind RCT. Loss to follow-up, potential selection bias due to randomization process. Grade: Moderate
Mallet (1986) ⁸⁸	France (Northwest) 49°N	Caucasian population, mean age 25 y, analysis included at-term infants born at term during Feb. and Mar. Mean maternal 25(OH)D in the unsupplemented group was 9.4 nmol/L.	Random assignment to (1) 1000 IU vitamin D ₂ daily for last 3 months of pregnancy (n=21) (2) One-time dose of 200,000 IU in 7 th month of gest. (n=27) (3) No supplement (n=29).	Randomized non-placebo controlled trial; unclear whether women were randomized into the control group. GRADE: Moderate
Mayra (1988) ⁴⁷	India (Rohtak) 28°N	Singleton pregnancies aged 22–35 years attending antenatal clinic of a medical college. Complications including pre-eclampsia, haemorrhage or premature delivery excluded. 25(OH)D levels not assessed.	Random selection to (1) 2 doses of 600,000 IU vitamin D ₃ , one each in month 7 and 8 of pregnancy (n=100) (2) No supplement (n=100).	Randomized non-placebo controlled trial; method of randomization unclear, no placebo, unclear dropout/number of exclusions. Grade: Low
Yu (2009) ^{43, b}	UK (London) 51°N	Multi ethnic hospital population recruited at 27 weeks gestation Excluded women with pre-existing sarcoidosis, osteomalacia, renal dysfunction, TB. Median 25(OH)D≈25nmol/L at 27 weeks.	Random selection to (1) Single oral dose of 200,000 IU Vit. D (n=60). (2): Daily supp. with 800 IU Vitamin D from 27 weeks to delivery (n=60) (3) No treatment (n=60)	Randomized non-placebo controlled trial. Small sample size, no placebo. GRADE: Moderate
Observational studies				
Haugen (2009) ⁷⁶	Norway (nationwide) 58°–71°N	23,423 nulliparous pregnant women from the Norwegian Mother and Child Cohort study with singleton births recruited at first ultrasound exam.	FFQ uses to assess intake of vitamin D for first 4–5 months of pregnancy and supp. use assessed at week 30.	Prospective cohort study. Supplement use validated with good correlation against reported use and biomarkers. Large sample size. GRADE: Moderate
Scholl (2009) ⁶⁴	U.S. (Camden, NJ) 39°N	Multiethnic cohort, data from 2,215 pregnancies enrolled at entry to prenatal care. Excluded those with serious non-obstetric problems.	Dietary intake of vitamin D and supplement use assessed using 3 24-hour recalls.	Large sample size, controlled for ethnicity, BMI, energy intake, intake of key nutrients, and gestational duration for birthweight. GRADE: Moderate
Camargo (2007) ⁶⁰	US (Massachusetts) 42°N	1194 mother-child pairs from Project Viva cohort. Excluded multiple gestations, non-English speakers, plans to move, and gestational age >22 weeks at initial appointment.	Dietary intake was collected using a validated semi-quantitative FFQ and intake from supplements was collected for 1 st and 2 nd trimesters	Large sample size, examination by unadjusted intake. Only presented unadjusted analysis for perinatal outcomes. GRADE: Low

Study ID	Country and latitude ^a	Population	Intervention or exposure	Comments and GRADE assessment of risk of bias
Oken (2007) ⁹²	US (Massachusetts) 42° N	1178 women from the Project Viva cohort recruited after median 10.4 weeks gestation. Excluded women with pre-existing hypertension.	Same as Camargo (2007) above	Large sample size, examination by quintiles of intake. GRADE: Low

^a Approximate latitude estimated by authors

^b Additional unpublished or in-press data was also provided by author

Table 3
 Summary of findings and overall assessment of quality of evidence for randomized trials and observational studies^a

Quality Assessment				Summary of Findings				
No. studies and study design	Heterogeneity of results?	Consistent size of effect?	Generalizable to population of interest?	Generalizable to intervention of interest?	Other sources of bias (e.g., major limitations in study design)	N	Statistical method	Effect estimate (95% CI)
Trials: Small-for-gestational age, Overall quality of evidence grade=Low								
2 RCT ^s ^{43, 63} (1 with 2 arms)	Low ($I^2=0\%$), $p=0.39$	Both protective	Both in the UK among deficient largely non-white populations	Similar dose; both in 3 rd trimester	Both small studies	305	RR, IV Fixed effects	0.67 (0.40, 1.11)
Trials: Weight gain during the third trimester (g), Overall quality of evidence grade=Low								
2 RCT ^s ^{47, 91}	High ($I^2=65\%$, $p=0.09$)	Yes—both showed weight gain in vit D group	India, Asian immigrants in the UK	Both in 3 rd trimester; 1 w/ daily 1000 IU vs. 1 with 600,000 IU at month 7 and 8.	Both small studies	326	MD, IV Random effects	11.8 g/day (3.4, 20.2)
Trials and Observational studies: Mean birthweight, Overall quality of evidence grade=Low								
1 Trials: 5 RCT ^s (3 w/2 int. arms) ^{3, 42, 46, 51, 52}	1 High ($I^2=70\%$, $p=0.0009$);	Most trials null; 1 increased weight, 1 arm decreased weight.	All in deficient populations; 1 from India remaining from high income settings.	Wide variety of doses tested ranging from 800 IU daily to 4000 IU daily and large bolus doses up to 2X 600,000 IU	Only 2 had blinded control groups; all small sample size; high or unclear dropout in two studies	932	MD, IV Random	58.1 [-63.9, 180.0]
2 Obs. studies: 2 studies ^{60, 64}	2 None ($I^2=0\%$, $p=0.49$)					1497	MD, IV Fixed	52.7 [3.5, 101.8]
Trials: Low birthweight (<2.5 kg), Overall quality of evidence grade=Low								
3 RCT ^s (1 with 2 int. arms) ^{42, 46, 52}	Low ($I^2=5\%$, $p=0.35$)	RR ranged from .21 to .55 (only 1 significant)	1 in India, others in London among Asian migrants and mixed pop.	Mix of daily sup. (800–1000 IU) and bolus dosing at high doses all in 3 rd trimester	Only 1 study placebo controlled	507	RR (IV, Fixed, 95% CI)	0.40 [0.23, 0.71]
Trials: Crown-heel length at birth (cm), Overall quality of evidence grade=Low								
2 RCT ^s ^{47, 70}	High ($I^2=82\%$, $p=0.02$).	One null, one with sig greater weight gain	One in India, one among Asian immigrants to the UK	1000 IU D ₂ ; Bolus 600,000 IU at month 7 and 8.	One unblinded	317	MD, IV. Random effects	1.02 (-0.26, 2.30) cm
Trials: Preterm delivery (<37 weeks), Overall quality of evidence grade=Low								

Quality Assessment						Summary of Findings		
No. studies and study design	Heterogeneity of results?	Consistent size of effect?	Generalizable to population of interest?	Generalizable to intervention of interest?	Other sources of bias (e.g., major limitations in study design)	N	Statistical method	Effect estimate (95% CI)
2 RCT's ^{5, 43} (both had 2 int. arms pooled here)	Moderate ($I^2=46%$, $p=0.17$)	Both null in opposite directions	Both in multi-ethnic populations in high income countries	(1) 4000 or 2000 IU vs. 400 IU (2) daily 800 or bolus 200,000 IU vs. nothing	One unblinded	529	RR, IV Fixed effects	0.77 [0.35, 1.66]
Trials and observational studies: Mean gestational age at delivery (in weeks), Overall quality of evidence grade=Low								
2 RCT's ^{5, 43} with 2 int. arms	Low($I^2=7%$, $p=0.30$);	All null	All in high income countries	Comparison of 4000/2000 IU vs. 400 IU and daily 800 IU vs. nothing;	One unblinded; 1 Obs. study did not adjust for confounding	529 1497	MD, IV, Fixed effects	0.17 [-0.16, 0.51] 0.08 [-0.12, 0.28]
2 Obs. Studies ^{60, 64}	None ($I^2=0%$, $p=0.75$);							
Observational studies: Pre-eclampsia, Overall quality of evidence grade=Very Low								
2 Obs. studies ^{76, 92}	None ($I^2=0%$, $p=0.33$)	Both null	Both in high income countries	1 comparison of <200 vs. >800 IU; 1 based on continuous exposure		12,626	OR, IV, Fixed effects	0.95 [0.86, 1.06]

^a Abbreviations used in table: RR=Risk ratio, MD=mean difference, IV=Inverse variance, pop.=populations, pos.=positive, neg.=negative, Obs.=observational, IU=international units, pop.=population, int.=intervention