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[Intervention Review]

Vitamin D supplementation for women during pregnancy

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ABSTRACT

Background

Vitamin D deficiency or insufficiency is thought to be common among pregnant women. Vitamin D supplementation during pregnancy has been suggested as an intervention to protect against adverse pregnancy outcomes.

Objectives

To examine whether oral supplements with vitamin D alone or in combination with calcium or other vitamins and minerals given to women during pregnancy can safely improve maternal and neonatal outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (23 February 2015), the International Clinical Trials Registry Platform (31 January 2015), the Networked Digital Library of Theses and Dissertations (28 January 2015) and also contacted relevant organisations (31 January 2015).

Selection criteria

Randomised and quasi-randomised trials with randomisation at either individual or cluster level, evaluating the effect of supplementation with vitamin D alone or in combination with other micronutrients for women during pregnancy.

Data collection and analysis

Two review authors independently i) assessed the eligibility of studies against the inclusion criteria ii) extracted data from included studies, and iii) assessed the risk of bias of the included studies. Data were checked for accuracy. The quality of the evidence was assessed using the GRADE approach.

Main results

In this updated review we included 15 trials assessing a total of 2833 women, excluded 27 trials, and 23 trials are still ongoing or unpublished. Nine trials compared the effects of vitamin D alone versus no supplementation or a placebo and six trials compared the effects of vitamin D and calcium with no supplementation. Risk of bias in the majority of trials was unclear and many studies were at high risk of bias for blinding and attrition rates.

Vitamin D alone versus no supplementation or a placebo

Data from seven trials involving 868 women consistently show that women who received vitamin D supplements alone, particularly on a daily basis, had higher 25-hydroxyvitamin D than those receiving no intervention or placebo, but this response was highly heterogeneous. Also, data from two trials involving 219 women suggest that women who received vitamin D supplements may have a lower risk of pre-eclampsia than those receiving no intervention or placebo (8.9% versus 15.5%; risk ratio (RR) 0.52; 95% CI 0.25 to 1.05, *low quality*). Data from two trials involving 219 women suggest a similar risk of gestational diabetes among those taking vitamin D supplements or no intervention/placebo (RR 0.43; 95% CI 0.05, 3.45, *very low quality*). There were no clear differences in adverse effects, with only one reported case of nephritic syndrome in the control group in one study (RR 0.17; 95% CI 0.01 to 4.06; one trial, 135 women, *low quality*). Given the scarcity of data for this outcome, no firm conclusions can be drawn. No other adverse effects were reported in any of the other studies.

With respect to infant outcomes, data from three trials involving 477 women suggest that vitamin D supplementation during pregnancy reduces the risk preterm birth compared to no intervention or placebo (8.9% versus 15.5%; RR 0.36; 95% CI 0.14 to 0.93, *moderate quality*). Data from three trials involving 493 women also suggest that women who receive vitamin D supplements during pregnancy less frequently had a baby with a birthweight below 2500 g than those receiving no intervention or placebo (RR 0.40; 95% CI 0.24 to 0.67, *moderate quality*).

In terms of other outcomes, there were no clear differences in caesarean section (RR 0.95; 95% CI 0.69 to 1.31; two trials; 312 women); stillbirths (RR 0.35 95% CI 0.06, 1.99; three trials, 540 women); or neonatal deaths (RR 0.27; 95% CI 0.04, 1.67; two trials, 282 women). There was some indication that vitamin D supplementation increases infant length (mean difference (MD) 0.70, 95% CI -0.02 to 1.43; four trials, 638 infants) and head circumference at birth (MD 0.43, 95% CI 0.03 to 0.83; four trials, 638 women).

Vitamin D and calcium versus no supplementation or a placebo

Women who received vitamin D with calcium had a lower risk of pre-eclampsia than those not receiving any intervention (RR 0.51; 95% CI 0.32 to 0.80; three trials; 1114 women, *moderate quality*), but also an increased risk of preterm birth (RR 1.57; 95% CI 1.02 to 2.43, three studies, 798 women, *moderate quality*). Maternal vitamin D concentration at term, gestational diabetes, adverse effects and low birthweight were not reported in any trial or reported only by one study.

Authors' conclusions

New studies have provided more evidence on the effects of supplementing pregnant women with vitamin D alone or with calcium on pregnancy outcomes. Supplementing pregnant women with vitamin D in a single or continued dose increases serum 25-hydroxyvitamin D at term and may reduce the risk of pre-eclampsia, low birthweight and preterm birth. However, when vitamin D and calcium are combined, the risk of preterm birth is increased. The clinical significance of the increased serum 25-hydroxyvitamin D concentrations is still unclear. In light of this, these results need to be interpreted with caution. Data on adverse effects were lacking in all studies.

The evidence on whether vitamin D supplementation should be given as a part of routine antenatal care to all women to improve maternal and infant outcomes remains unclear. While there is some indication that vitamin D supplementation could reduce the risk of pre-eclampsia and increase length and head circumference at birth, further rigorous randomised trials are required to confirm these effects.

PLAIN LANGUAGE SUMMARY

Vitamin D supplementation for women during pregnancy

Vitamin D is produced by the human body from exposure to sunlight and can also be consumed from foods such as fish-liver oils, fatty fish, mushrooms, egg yolks, and liver. Vitamin D has many functions in the body; it helps maintain bone integrity and calcium homeostasis.

During pregnancy, vitamin D deficiency or insufficiency may develop. Vitamin D supplementation during pregnancy has been suggested to safely improve pregnancy and infant outcomes. This review included 15 randomised controlled trials involving 2833 women. Nine trials compared the effects of vitamin D alone with no supplementation or a placebo and six trials compared the effects of vitamin D and calcium with no supplementation.

The results show that the provision of vitamin D supplements during pregnancy improves the women's vitamin D levels, as measured by 25-hydroxyvitamin D concentrations at term and may reduce the risk of delivering a baby prematurely (less than 37 weeks of

gestation), result in a lower risk of high blood pressure in women and reduce the risk of a low birthweight baby (less than 2500 g). However, it appears that when vitamin D and calcium are combined, the risk of preterm birth is increased. Data on adverse effects for the mother were not well reported.

The clinical significance of the increase in women's vitamin D levels is unclear and results should be interpreted with caution, as only a few small trials of low quality assessed these outcomes.

With the available evidence, it is unclear whether vitamin D supplementation should be given as part of routine antenatal care to improve maternal and infant outcomes. While there is some indication that vitamin D supplementation could reduce the risk of high blood pressure and increase length and head circumference at birth, further rigorous randomised trials are required to confirm these effects. Currently, the number of high-quality trials with large sample sizes and outcomes reported is too limited to draw definite conclusions on its usefulness and safety.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Population: women during pregnancy
Setting: India, Iran, New Zealand, UK
Intervention: vitamin D alone
Comparison: no treatment/placebo (no vitamins or minerals)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no treatment/ placebo (no vitamins or minerals)	Risk with vitamin D alone				
Pre-eclampsia (ALL)	Study population		RR 0.52 (0.25 to 1.05)	219 (2 RCTs)	⊕⊕◯◯ LOW [1,2]	
	155 per 1000	80 per 1000 (39 to 163)				
	Moderate					
	124 per 1000	64 per 1000 (31 to 130)				
Gestational diabetes (ALL)	Study population		RR 0.43 (0.05 to 3.45)	219 (2 RCTs)	⊕◯◯◯ VERY LOW [1,3]	
	24 per 1000	10 per 1000 (1 to 82)				
	Moderate					
	27 per 1000	12 per 1000 (1 to 94)				
Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (ALL)	The mean maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (ALL) in the intervention group was 47.24 higher (35.17 to 59.31 higher)			868 (7 RCTs)	⊕⊕◯◯ LOW [1,4]	

Adverse effects	Study population		RR 0.17 (0.01 to 4.06)	135 (1 RCT)	⊕⊕◯◯ LOW [3]
	22 per 1000	4 per 1000 (0 to 90)			
Preterm birth (less than 37 weeks' gestation) (ALL)	Study population		RR 0.36 (0.14 to 0.93)	477 (3 RCTs)	⊕⊕⊕◯ MODERATE [1]
	99 per 1000	36 per 1000 (14 to 92)			
	Moderate				
	46 per 1000	17 per 1000 (6 to 43)			
Low birthweight (less than 2500 g) (ALL)	Study population		RR 0.40 (0.24 to 0.67)	493 (3 RCTs)	⊕⊕⊕◯ MODERATE [1]
	199 per 1000	80 per 1000 (48 to 133)			
	Moderate				
	193 per 1000	77 per 1000 (46 to 129)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Most studies contributing data had design limitations (high risk for allocation concealment and attrition bias).
[2] Wide confidence interval crossing the line of no effect.

[3] Wide confidence interval crossing the line of no effect & few events.
[4] Statistical heterogeneity (I^2 > 60%). Considerable variation in size of effect.

BACKGROUND

Description of the condition

Vitamin D metabolism

Vitamin D is a fat-soluble vitamin which comes primarily from exposure to sunlight, and is found naturally only in a few foods, such as fish-liver oils, fatty fish, mushrooms, egg yolks, and liver (Holick 2007a; Holick 2008). There are two physiologically active forms of vitamin D collectively called *calciferol*: D_2 and D_3. Vitamin D_2 (also called *ergocalciferol*) is synthesised by plants while vitamin D_3 (also called *cholecalciferol*) is subcutaneously produced in humans from 7-dehydrocholecalciferol upon exposure to ultraviolet light B (UVB) radiation (DeLuca 2004). Vitamin D in supplements is found as either vitamin D_2 or D_3. The latter may be three times more effective than vitamin D_2 in raising serum concentrations of vitamin D and maintaining those levels for a longer time particularly during the winter months; also, its metabolites have superior affinity for vitamin D-binding proteins in plasma (Armas 2004; Logan 2013; McCullough 2007). As vitamin D has a short half-life, adequate vitamin D intake is necessary in order to ensure sustained circulating levels.

Both D_2 and D_3 forms share a similar metabolism. They are first hydroxylated in the liver to form 25 hydroxyvitamin D (25(OH)D or *calcidiol)*, and then in the kidney to 1,25 di hydroxyl vitamin D (1,25 $(OH)_2$ D or *calcitriol)* in response to parathyroid hormone (PTH) levels. Calcitriol is considered an important pre-hormone with active metabolites that are involved in metabolic processes including bone integrity and calcium homeostasis (Wagner 2008). The major sites of vitamin D action include the skin, intestine, bone, parathyroid gland, immune system, and pancreas as well as the small intestine and colon in the human fetus (Theodoropoulos 2003). Additionally, vitamin D helps maintain normal levels of glucose in the blood, by binding and activating the vitamin D receptor in the pancreatic beta cells, regulating the release of insulin in response to the level of circulating glucose (Clifton-Bligh 2008; Maghbooli 2008; Palomer 2008; Xuan 2013). Vitamin D also indirectly affects glucose metabolism via the regulation of calcium homeostasis (Xuan 2013).

There is a unique relationship between vitamin D and calcium. PTH is responsible for raising the calcium concentration in the blood through bone resorption, while calcitriol inhibits PTH and allows an increase of serum calcium concentration from sources other than the bone. In the presence of calcitriol, renal and intestinal calcium and phosphorus absorption is augmented leading to an improved calcium status.

Vitamin D status

Serum calcidiol or 25-hydroxyvitamin D can be used to assess vitamin D status, as it reflects the sum of the vitamin D produced cutaneously and that obtained from foods and supplements (Jones 2008). This metabolite is difficult to measure, with large variations between methods and among laboratories, even when the same methods are used which may be explained by differences in sample pretreatment or the solvent extraction system used (Hollis 2004; Lankes 2015).

Recently, the Institute of Medicine defined adequate vitamin D status as having serum 25-hydroxyvitamin D concentrations greater than 50 nmol/L (or 20 ng/mL) in both the general population and pregnant women (Institute of Medicine 2010). Some investigators propose that concentrations around 80 nmol/L (32 ng/mL) are optimal, since they suppress PTH levels and lead to the greatest calcium absorption and the highest bone mass, reducing the rates of bone loss, falls, and fractures (Dawson-Hughes 2005; Dawson-Hughes 2008). It is uncertain whether these higher levels proposed for non pregnant adults are also adequate for pregnant women.

Vitamin D status is affected by factors that regulate its production in the skin (i.e. skin pigmentation, latitude, dressing codes, season, aging, sunscreen use, and air pollution) and by factors affecting its absorption or metabolism (Holick 2007b; Maghbooli 2007). Melanin acts as a filter for ultraviolet (UV) rays hence reducing the production of vitamin D by the skin. Hispanic and black populations in the United States may have a higher melanin content, and thus have reduced vitamin D photosynthesis (endogenous synthesis from exposure to sunlight) (Clemens 1982), explaining the variations in vitamin D concentration among ethnic groups living in the same geographical areas (Brooke 1980; Egan 2008; Ganji 2012; Matsuoka 1991; Nesby-O'Dell 2002; Rockell 2005). An individual's skin phototype reflects the extent of sun-burning versus subsequent tanning after an initial moderate sun exposure after a long period of little or no exposure (Gilchrest 2008). Phototypes I and II have rapid vitamin D photosynthesis after a minimal erythematic dose (MED). In contrast, prototype VI has little vitamin photosynthesis following the same MED dose (Clemens 1982). Differences in latitude have also been shown to influence the concentration of vitamin D, and individuals from countries in high and low latitudes have lower vitamin D levels. The importance of UV rays is further shown by the seasonal variation in the concentration of vitamin D between summer and winter, with higher levels during the summer compared with the winter months (Holick 2007b; Levis 2005). Vitamin D metabolism is also affected in obese individuals, as vitamin D is deposited in body fat stores, making it less bioavailable (Arunabh 2003). More recently, this low vitamin D status in obese individuals has been explained by a simple volumetric dilution of vitamin D in the fat mass (Drincic 2012), resulting in a higher prevalence of low levels of 25-hydroxyvitamin D and these are more prevalent among overweight and obese individuals compared with normal weight individuals (Vilarrasa 2007; Vimaleswaran 2013; Wortsman 2000). In the same context, sedentary activity is also associated with low vitamin D levels as it may be linked with diminished sunlight ex-

posure (Ohta 2009).

Magnitude of vitamin D deficiency

Vitamin D deficiency (VDD) may be a common health problem worldwide (Bandeira 2006; Palacios 2014; van Schoor 2011). A recent review found a high prevalence of low vitamin D status in infants, children, adolescents, adults and elders worldwide, even in countries with sun exposure all year round (Palacios 2014). The highest reported prevalence was found in the Middle East, particularly in girls and women, although there is a lack of data in most countries of South America and Africa.

In pregnancy, vitamin D deficiency and vitamin D insufficiency are also common. A recent review included 17 studies in pregnant and lactating women (two in America, six in Europe, one in Africa, seven in Asia, one in Oceania) (Palacios 2014). Low vitamin D status (defined as concentrations < 50 nmol/L) was found in 33% of US and 24% Canadian pregnant women, respectively. In Europe, the prevalence of low vitamin D status was 45% in Belgium, 35% in UK, 44% in the Netherlands, 20% in Spain and 77% in Germany. In addition, prevalence of vitamin D deficiency (defined as < 30 nmol/L) was 12% in Belgium, 4% in England and 23% in the Netherlands. The only study reported in Africa reported a very low prevalence of low vitamin D status (1%) in a sample of 139 pregnant women from Tanzania. In Asia, the prevalence of low vitamin D status in pregnant women was very high: 90% in Turkey, 67% in Iran, 72% in Pakistan, 70% to 83% in Kuwait, 96% in India and 69% in China. Prevalence of vitamin D deficiency was also very high: 50% in Turkey, 45% in Pakistan, 38% to 41% in Kuwait and 60% in India. In Australia, low vitamin D status was found in 48% and vitamin D deficiency was found in 15% of pregnant women.

Seasonal variation increases the risk of VDD in pregnancy, with a greater prevalence of VDD during the winter months compared with the summer months (Nicolaidou 2006; O'Riordan 2008). Differences in latitude have also been shown to influence the concentration of vitamin D in a majority of pregnant women (Sloka 2009).

Maternal vitamin D status and health outcomes

Vitamin D status during pregnancy is the most important stage of the lifecycle, as the fetus completely relies on this source during this period for its development. During pregnancy, 1,25-dihydroxyvitamin D increases early during pregnancy and continues to increase until delivery (Moller 2013). This large increase in 1,25-dihydroxyvitamin D appears to be dependent on available 25-dihydroxyvitamin D levels but independent on calcium metabolism, which is a unique feature of pregnancy that allows such high levels of 1,25-dihydroxyvitamin D (Pludowski 2013). Therefore, maintaining high enough levels of 25-dihydroxyvitamin D are important to sustain the increased levels of 1,25-dihydroxyvitamin D important during pregnancy. Such levels are still yet to be determined but several studies have shown that maternal vitamin D status is significantly associated with fetal and neonatal vitamin D status (El Koumi 2013; Sachan 2005) and that maternal vitamin D status is associated with health outcomes during pregnancy and neonatal and infant development. These associations will be described below.

Vitamin D status and hypertensive disorders during pregnancy

Maternal vitamin D deficiency in pregnancy has been associated with an increased risk of pre-eclampsia (new-onset gestational hypertension and proteinuria after 20 weeks of gestation), a condition associated with an increase in maternal and perinatal morbidity and mortality (Bodnar 2007; Holick 2008; Li 2000b; MacKay 2001; Xiong 1999). A recent meta-analysis including eight studies found a significant association between vitamin D deficiency and risk of pre-eclampsia, which was more evident in those that defined vitamin D deficiency as 25(OH)D 50 nmol/L (20 ng/mL), and in those from the USA (Tabesh 2013). Similarly, another meta-analysis including 31 studies also found a 78% higher risk of pre-eclampsia in pregnant women with low vitamin D status (odds ratio (OR) 1.79; 95% confidence interval (CI) 1.25 to 2.58) (Aghajafari 2013).

Women with pre-eclampsia have lower concentrations of 25-hydroxyvitamin D compared with women with normal blood pressure (Diaz 2002; Frenkel 1991; Halhali 1995; Halhali 2000; Tolaymat 1994). The low levels of urinary calcium (hypocalciuria) in women with pre-eclampsia may be due to a reduction in the intestinal absorption of calcium impaired by low levels of vitamin D (August 1992; Halhali 1995). Additionally, pre-eclampsia and vitamin D deficiency are directly and indirectly associated through biologic mechanisms including immune dysfunction, placental implantation, abnormal angiogenesis, excessive inflammation, and hypertension (Bodnar 2007; Cardus 2006; Evans 2004; Hewison 1992; Li 2002). Vitamin D may influence early placental development and thus, the development of pre-eclampsia through its role in gene regulation and expression; yet more studies are needed to confirm this.

Vitamin D status and other maternal conditions

Maternal vitamin D deficiency in early pregnancy has been associated with elevated risk for gestational diabetes mellitus (Farrant 2009; Zhang 2008). A recent meta-analysis of 31 observational studies found that low vitamin D levels increased the risk of gestational diabetes in 49% (OR 1.49; 95% CI 1.18 to 1.89) (Aghajafari 2013). Similar results were found in another meta-analysis of 24 observational studies (Wei 2013). Poor control of maternal diabetes in early pregnancy is inversely correlated with low bone mineral content in infants, as is low maternal vitamin D status (Namgunga 2003). VDD may lead to a high bone turnover, bone loss, osteomalacia (softening of the bones) and myopathy (muscle

weakness) in the mother in addition to neonatal and infant VDD (El Koumi 2013; Glerup 2000; Lips 2001).

An adequate vitamin D status may also protect against other adverse pregnancy outcomes. For example, maternal vitamin D deficiency has been linked to caesarean section (Merewood 2009; Scholl 2012), but the mechanisms involved are unclear. It has been suggested that vitamin D deficiency during pregnancy may reduce pelvic muscle strength and control (Scholl 2012), but this needs to be confirmed.

Low prenatal and perinatal maternal vitamin D concentrations can affect the function of other tissues, leading to a greater risk of multiple sclerosis, cancer, insulin-dependent diabetes mellitus, and schizophrenia later in life (McGrath 2001).

Vitamin D status and preterm birth and low birthweight

A potential inverse association between maternal vitamin D status and preterm birth (less than 37 weeks' gestation) has been reported (Dawodu 2011; Morley 2006). Conversely, not all the studies show significant associations between maternal calcidiol levels and any measure of the child's size at birth or during the first months of life (Bodnar 2010; Farrant 2009; Gale 2008; Morley 2006).

A recent meta-analysis of 24 observational studies confirmed the association between low vitamin D levels (< 50 nmol/L) and increased risk of preterm birth (OR 1.58; 95% CI 1.08 to 2.31) (Wei 2013). Furthermore, two meta-analyses also found significant associations between low vitamin D status and small-for-gestational age (Theodoratou 2014; Wei 2013). With respect to birthweight, a recent meta-analysis including three observational studies found a weak positive association between maternal vitamin D status and birthweight after adjustment for potential confounders (Harvey 2014), but another meta-analysis including four observational studies did find a significant association between these variables (Theodoratou 2014).

There is not much information on maternal vitamin D status and low birthweight or preterm birth in children born from HIV-infected pregnant women (Mehta 2009). Studies have reported a high prevalence of vitamin D deficiency among HIV-infected pregnant women (Eckard 2013; Mave 2012).

Vitamin D status and postnatal growth

Some observational studies suggest that vitamin D levels during pregnancy influence fetal bone development and children's growth (Bodnar 2010; Brooke 1980; Ioannou 2012; Mahon 2010; Morley 2006). However, there is inconsistent information between maternal vitamin D status and head circumference, as a recent systematic review of observational studies found a non-significant positive association in five studies but also a non-significant inverse association in four studies between these outcomes (Harvey 2014). However, a study found that head circumference in children nine years of age was significantly associated with maternal calcidiol levels (Gale 2008). With respect to maternal vitamin D status and infants' bone mass, there are also inconsistent results (Akcakus 2006; Harvey 2014; Javaid 2006; Viljakainen 2010).

It is not clear if maternal vitamin D deficiency leads to neonatal rickets, since rickets is usually identified later in childhood. Early studies indicate a possible risk for neonatal rickets in the offspring of women with osteomalacia, abnormal softening of the bone by deficiency of phosphorus, calcium or vitamin D (Ford 1973). More recent studies have found that vitamin D deficiency (serum levels lower than 25 nmol/L) was identified in 92% of rachitic (having rickets) Arab children and 97% of their mothers compared with 22% of nonrachitic children and 52% of their mothers (Dawodu 2005). A positive correlation was found between maternal and child vitamin D levels.

In addition, analyses using data from pregnant women participating in the Southampton Women's Survey, a prospective longitudinal study, found in fetuses of mothers with low vitamin D status a greater femoral metaphyseal cross-sectional area and a higher femoral splaying index at 19 and 34 weeks' gestation (Mahon 2010) and a significant association between fetal femur volume and vitamin D status (Ioannou 2012), which has been suggested to be possibly related to early rickets development (Harvey 2014).

Vitamin D status and immune response

Vitamin D has direct effects on both adaptive and innate immune systems (Miller 2010; Walker 2009). In children, vitamin D insufficiency is linked to autoimmune diseases such as type 1 diabetes mellitus, multiple sclerosis, allergies and atopic diseases (Bener 2009; Miller 2010; Pierrot-Deseilligny 2010). Various studies have also shown that vitamin D deficiency is strongly associated with tuberculosis, pneumonia, and cystic fibrosis (Chocano-Bedoya 2009; Hall 2010; Nnoaham 2008; Williams 2008) and both prenatal and perinatal vitamin D deprivation might influence early-life respiratory morbidity as this vitamin is important for lung growth and development (Devereux 2007; Litonjua 2009).

Vitamin D may have positive effects on the immune system by up-regulating the production of the antimicrobial peptides by macrophages and endothelial cells (Wang 2004), which may inactivate viruses and suppress inflammation (Cantorna 2008), and subsequently reduce the severity of infections.

Vitamin D toxicity

Vitamin D excess leads to hypercalcaemia (calcium levels are 10.5 mg/dL or higher) and hypercalciuria (urinary excretion of calcium exceeds 250 mg/day in women), which is associated with renal and kidney stones (Heaney 2008). Toxicity in adults usually appear at doses of vitamin D higher than 10,000 international units (IU)/d (250 µg/d), although most of the evidence is based on short-term exposures (less than six months) (Hathcock 2007; Heaney 2008; Institute of Medicine 2010; Vieth 1999). Single-dose supplements providing 7.5 mg (300,000 IU) or more may also be harmful (Roth 2011a).

The potential for vitamin D-induced teratogeneses (birth defects) and adverse effects in the offspring (e.g. growth restriction, delayed ossification, craniofacial hypoplasia) has been suggested by a few studies in rats and rabbits (Ariyuki 1987; Chan 1979; Friedman 1969; Ornoy 1968; Ornoy 1969). However, there are considerable limitations in extrapolating such findings to humans, in whom adverse fetal effects have not reportedly occurred following maternal ingestion of maintenance doses as high as 5 mg (200,000 IU) of vitamin D per day. Overall, animal and human studies show that fetal excess of vitamin D metabolites are unlikely to occur when maternal concentrations are within a normal range (Roth 2011a).

Description of the intervention

Some health organisations recommend vitamin D supplementation during pregnancy and lactation. However, there are variations in the recommended dose for supplementation ranging from 200 to 400 IU/d (5 to 10 µg/d) (Canadian Paediatric Society 2007; UK Department of Health 2009). The American Academy of Pediatrics (Wagner 2008) suggests that healthcare professionals who provide obstetric care should consider monitoring maternal vitamin D status by measuring its concentrations in pregnant women. However, there is controversy regarding the 25-hydroxyvitamin D levels that are considered adequate or optimal for overall health. The US Institute of Medicine has determined that concentrations greater than 50 nmol/L or 20 ng/mL are adequate based on the current studies available (Institute of Medicine 2010), although many investigators consider that optimal levels should be higher (greater than 75 nmol/L or 30 ng/mL) (Dawson-Hughes 2005; Hollick 2009). It has been suggested that a supplemental dose of vitamin D of 1000 to 1600 IU (25 to 40 µg/d) might be necessary to achieve the optimal level of this vitamin in the body (Dawson-Hughes 2005). This dose is expected to raise serum 25-hydroxyvitamin D by 1.2 nmol/L for every μg (40 IU) of vitamin D_3 given orally to individuals with low 25-hydroxyvitamin D levels; those with higher baseline concentrations would have smaller increments with the same dose (Dawson-Hughes 2005). However, the dose of vitamin D needed to have an effect during pregnancy or to prevent or treat vitamin D deficiency is not clear. Some researchers have suggested that doses around 1000 IU/d may be needed in order for pregnant women to maintain a blood concentration of vitamin D of more than 50 nmol/L (20 ng/mL) (Heaney 2003; Hollis 2004; Hollis 2007; Vieth 2001). Others have suggested providing vitamin D as weekly doses of 5000 IU (125 μg/wk) (Utiger 1998) or a single dose of 200,000 IU (5 mg) or greater (Mallet 1986; Sahu 2009; Yu 2009).

Since vitamin D can also be synthesised by the skin upon exposure to sunlight, increasing casual sun exposure for reaching the optimal serum levels has been recommended (Holick 2002). However, as excessive UV radiation is a carcinogen, it might be worth obtaining additional vitamin D from foods or supplements.

How the intervention might work

Vitamin D supplementation improves maternal vitamin D status during pregnancy (Delvin 1986; Yu 2009), which in turn may have a direct influence on the fetal and neonatal supply of vitamin D (Brooke 1980). The potential effect of gestational vitamin D supplementation in preventing preterm birth (less than 37 weeks' gestation) and low birthweight (less than 2500 g) has been suggested (Maxwell 1981), although there is limited information on the additional benefit of vitamin D supplementation over other nutritional interventions during pregnancy such as iron and folic acid supplementation on the risk of low birthweight (Christian 2003). There is also a potential effect of maternal vitamin D supplementation on neonatal growth (Marya 1988). Vitamin D supplementation during pregnancy may be necessary to ensure adequate concentrations of vitamin D in breast milk during lactation (Butte 2002).

Why it is important to do this review

This review updates a previous Cochrane review (De-Regil 2012) and incorporates new evidence on the effects and safety of oral vitamin D supplementation in pregnancy for the well being of the mother and newborn.

OBJECTIVES

To examine whether oral supplements of vitamin D alone or in combination with calcium or other vitamins and minerals given to women during pregnancy can safely improve maternal and neonatal outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We intended to include randomised and quasi-randomised trials with randomisation at either individual or cluster level, but we only found randomised controlled trials with individual randomisation. We did not include cross-over trials or any other observational designs (e.g. cohort or case-control studies) in this meta-analysis but we considered such evidence in the discussion, where relevant.

Types of participants

Pregnant women of any gestational or chronological age, parity (number of births) and number of fetuses. Pregnant women with pre-existing conditions (i.e. gestational diabetes) were excluded.

Types of interventions

Vitamin D supplementation during pregnancy irrespective of dose, duration or time of commencement of supplementation. We included trials testing vitamin D alone or in combination with other micronutrients as long as the intervention and the control group were treated similarly. Specifically, we assessed the following comparisons:

1. oral vitamin D supplements alone versus no intervention/placebo (no vitamins or minerals);
2. oral vitamin D + calcium supplements versus no intervention/placebo (no vitamin or minerals);
3. oral vitamin D + calcium supplements versus oral calcium supplements (but no vitamin D);
4. oral vitamin D + calcium + other vitamins and minerals supplements versus oral calcium + other vitamins and minerals supplements (but no vitamin D);
5. oral vitamin D + calcium + other vitamins and minerals supplements versus other oral vitamins and minerals supplements (but no vitamin D+ calcium).

We planned to exclude studies where vitamin D was provided by injection.

Types of outcome measures

Maternal antenatal clinical and laboratory outcomes and infant clinical and laboratory outcomes as described below.

Primary outcomes

Maternal

1. Pre-eclampsia (as defined by trialists).
2. Gestational diabetes (as defined by trialists).
3. Vitamin D concentration at term (25-hydroxyvitamin D in nmol/L).
4. Adverse effects (e.g. hypercalcaemia, kidney stones).

Infant

1. Preterm birth (less than 37 weeks' gestation).
2. Low birthweight (less than 2500 g).

Secondary outcomes

Maternal

1. Impaired glucose tolerance (as defined by trialists).
2. Caesarean section.
3. Gestational hypertension (as defined by trialists).
4. Maternal death (death while pregnant or within 42 days of termination of pregnancy).

Infant

1. Birth length (cm).
2. Head circumference at birth (cm).
3. Birthweight (g).
4. Admission to special care (including intensive care) during the neonatal period (within 28 days after delivery).
5. Stillbirth (as defined by trialists).
6. Neonatal death (within 28 days after delivery).
7. Apgar score less than seven at five minutes.
8. Neonatal infection (e.g. respiratory infections within 28 days after delivery).
9. Very preterm birth (less than 32 weeks' gestation).

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (23 February 2015).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE, Embase and CINAHL, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

In addition, we searched the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) for any ongoing or planned trials on 31 January 2015 and the Networked Digital Library of Theses and Dissertations (NDLTD) for grey literature on 28 January 2015 (*see:* Appendix 1).

Searching other resources

For the identification of ongoing and unpublished studies, we contacted on different institutions including the WHO Departments of Reproductive Health and Research and the Department of Nutrition for Health and Development, the WHO regional offices, UNICEF, the Micronutrient Initiative (MI), the Global Alliance for Improved Nutrition (GAIN) and the US Centers for Disease Control and Prevention (CDC) (31 January 2015).
We did not apply any date or language restrictions but we only found English language papers.

Data collection and analysis

For methods used in the previous version of this review, please see De-Regil 2012.
For this update, we used the following methods.

Selection of studies

Two review authors (LL, JP) independently assessed for inclusion all the references identified through the search. All the papers were assessed in duplicate and we resolved any disagreements through discussion or, if required, we consulted a third author (LMD).
If studies were published only as abstracts, or study reports contained little information on methods, we attempted to contact the authors to obtain further details of study design and results. We were able to screen all the potentially eligible studies.

Data extraction and management

We designed a form to extract data. For included studies, all review authors extracted the data using the agreed form. CP entered data into Review Manager software (RevMan 2014), and JPR and LMD checked for accuracy.
We analysed dichotomous data in terms of average risk ratio and we analysed continuous data in terms of mean difference. There was no need to use the standard mean difference as trials did not report outcomes in different scales.

Assessment of risk of bias in included studies

Two review authors (LL, JP) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion and consulted a third author (LMD).

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal the allocation sequence and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes);
- unclear.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

We classified blinding as 'high risk of bias' if the blinding status of a trial was unclear or the trial was open.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.
We assessed methods used to blind outcome assessment as:

- low risk of bias;
- high risk of bias;
- unclear.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We assessed losses to follow-up and post-randomisation exclusions systematically for each trial.

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. We assessed methods as:

- low risk of bias;
- high risk of bias;
- unclear.

We considered follow-up to be 'low risk of bias' if more than 80% of participants initially randomised in a trial were included in the analysis and any loss was balanced across groups, unclear if the percentage of initially randomised participants included in the analysis was unclear, and 'high risk of bias' if less than 80% of those initially randomised were included in the analysis or if loss was imbalanced in different treatment groups.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other sources of bias

We assessed whether each study was free of other problems that could put it at risk of bias: We noted for each included study any important concerns we had about other possible sources of bias:

- low risk of further bias;
- high risk of further bias;
- unclear whether there is a risk of further bias.

(7) Overall risk of bias

We summarised the risk of bias at two levels: within studies (across domains) and across studies.

For the first, we made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and for primary outcomes, we explored the impact of the level of bias through undertaking a Sensitivity analysis.

Assessment of the quality of the evidence using the GRADE approach

For the assessment across studies, the main findings of the review are set out in the Summary of findings for the main comparison and Summary of findings 2 prepared using GRADEpro Guideline Development Tool. The primary outcomes for each comparison are listed with estimates of relative effects along with the number of participants and studies contributing data for those outcomes, where available. For each outcome, two review authors independently assessed the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Balshem 2010), which involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias; this results in one out of four levels of quality (high, moderate, low or very low). This assessment was limited only to the trials included in this review.

Measures of treatment effect

Dichotomous data

For dichotomous data, we present results as average risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference as the outcomes were measured in the same way between trials; there was no need to use the standardised mean difference to combine trials.

Unit of analysis issues

Cluster-randomised trials

We planned to include cluster-randomised trials in the analyses along with individually-randomised trials but we did not find eligible studies with this design. We planned to adjust the standard errors of the results from cluster-randomised studies using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), if sufficient information was available to allow for this. We planned to use an estimate of the intra cluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources were used, we planned to report this and to conduct sensitivity analyses to investigate the effect of variation in the ICC.

If we had identified both cluster-randomised trials and individually-randomised trials, we would have combined the results from both if there was little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit would be considered as unlikely.

Studies with more than two treatment groups

For studies with more than two intervention groups (multi-arm studies), we combined groups to create a single pair-wise comparison (Higgins 2011) and included the disaggregated data in the corresponding subgroup category. When the control group was shared by two or more study arms, we divided the control group (events and total population) over the number of relevant subgroup categories to avoid double counting the participants. The details are described in the Characteristics of included studies tables.

Cross-over trials

We did not consider cross-over trials eligible for inclusion.

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and analysed all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either the Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

Had we included 10 or more studies in the meta-analysis, we would have investigated reporting biases (such as publication bias) by using funnel plots. We planned to assess funnel plot asymmetry visually. If asymmetry were suggested by a visual assessment, we would have performed exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We intended to use fixed-effect meta-analysis for combining data where it would be reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.
Since we detected substantial statistical heterogeneity, we used random-effects meta-analysis to produce an overall summary of an average treatment effect across trials. We treated the random-effects summary as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials.
As we used random-effects analyses, we present the results as the average treatment effect with its 95% confidence interval, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

We planned to investigate any substantial heterogeneity on the primary outcomes by using subgroup analyses as follows:

1. by start of supplementation: less than 20 weeks versus 20 weeks of pregnancy, or more;
2. by pre-gestational body mass index (kg/m^2): underweight (lower than 18.5) versus normal weight (18.5 to 24.9) versus overweight (25 or higher) versus unknown/mixed;
3. by supplementation scheme/regimen: single versus daily versus weekly;
4. by skin pigmentation based on Fitzpatrick skin tone chart (Fitzpatrick 1988): three or less versus four or more versus mixed/unknown;
5. by latitude: between the Tropics of Cancer and Capricorn versus north of the Tropic of Cancer or south of the Tropic of Capricorn;
6. by season at the start of pregnancy: summer versus winter versus mixed/unknown/unreported.

Pragmatically, we decided not to conduct subgroup analyses in those outcomes with three or less trials.
We assessed subgroup differences by interaction tests available within RevMan (RevMan 2014). We reported the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We intended to conducted a sensitivity analysis based on the quality of the studies, however, as only one study was considered of high quality, we did not perform this analysis. We considered a study to be of high quality if it was assessed as having low risk of bias in both the randomisation and allocation concealment and additionally a low risk of bias in either blinding or losses to follow-up.

RESULTS

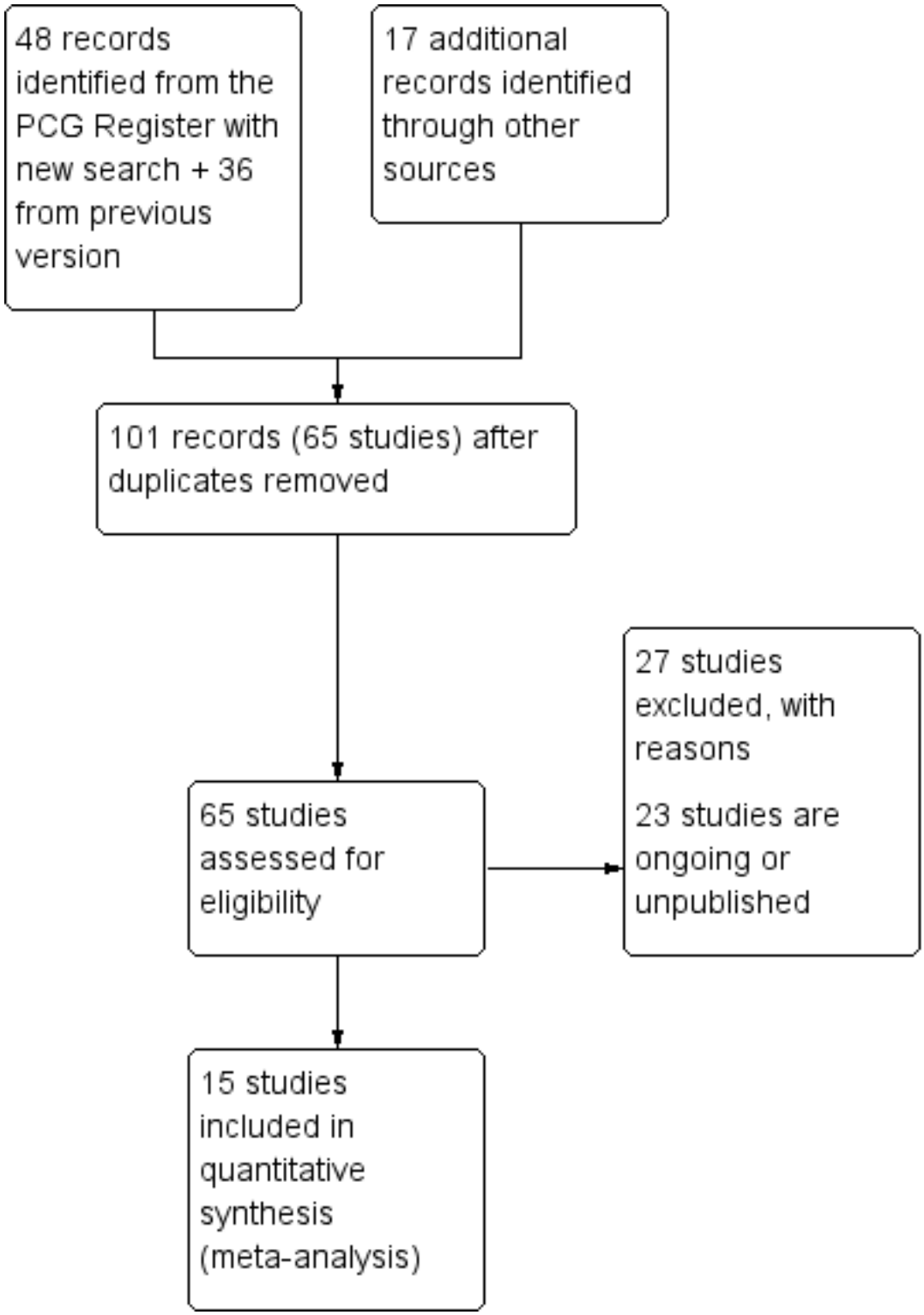
Description of studies

Results of the search

The updated search of the Cochrane Pregnancy and Childbirth Group's Trials Register found 48 reports for possible inclusion and the additional search strategy identified 17 references. After removal of duplicates, there were 101 reports (65 studies) overall in this updated to assess.

We now include 15 trials (Asemi 2012; Asemi 2013a; Brooke 1980; Delvin 1986; Diogenes 2013; Grant 2013; Li 2000a; Mallet 1986; Marya 1987; Marya 1988; Mazurkevich 2013; Roth 2010; Sablok 2015; Taherian 2002; Yu 2008) involving 2833 women. We excluded 27 trials and we have identified 23 ongoing or unpublished trials (Bhatia 2012b; Benson 2009; Bhutta 2011; Bisgaard 2009; Ghasemi 2014; Goldring 2010; Habib 2010; Hacker 2010; Harvey 2012; Jannati 2012; Jelsma 2013; Judkins 2011; Kachhawa 2014; Lalooha 2012; Lindqvist 2010; McLean 2012; Mirghafourvand 2013, Mozzafari 2010; Nausheen 2014; Rasmussen 2009 Roth 2013b; Simsek 2011; Wagner 2013). (See: Figure 1).

Figure 1. Study flow diagram for this update



Details of these studies are provided in: Characteristics of included studies; Characteristics of excluded studies; Studies awaiting classification tables.

Included studies

Settings

All the studies included in this review were carried out in the 1980s and during the 2000s. Trials were conducted in Bangladesh (Roth 2010), Brasil (Diogenes 2013), China (Li 2000a), France (Delvin 1986; Mallet 1986), India (Marya 1987; Marya 1988; Sablok 2015), Iran (Asemi 2012; Asemi 2013a; Taherian 2002), New Zealand (Grant 2013), Russia (Mazurkevich 2013) and the United Kingdom (Brooke 1980; Yu 2008).

Latitude

The latitude of the settings was north of the Tropic of Cancer, also referred to as the Northern tropic in 13 trials (Asemi 2012; Asemi 2013a; Brooke 1980; Delvin 1986; Li 2000a; Mallet 1986; Marya 1987; Marya 1988; Mazurkevich 2013; Roth 2010; Sablok 2015; Taherian 2002; Yu 2008). One trial was conducted between the Tropics of Cancer and Capricorn (Grant 2013), and one study was conducted just were the tropic of Capricorn lies (Diogenes 2013).

Seasonality

The seasons varied among studies with some trials occurring during the winter-spring period (Delvin 1986); winter (Mallet 1986); summer (Roth 2010; Yu 2008); spring-summer period (Asemi 2013a), or mixed/unknown/unreported in five trials (Asemi 2012; Li 2000a; Marya 1987; Marya 1988; Mazurkevich 2013; Taherian 2002). Four trials were carried out in different seasons to avoid distortion of the results due to seasonal variation in sunlight hours (Brooke 1980; Diogenes 2013; Grant 2013; Sablok 2015).

Participants

The sample size from all the studies was small and ranged between 40 (Delvin 1986) and 400 women (Marya 1987). In all the studies, women were recruited and received the supplements at 20 or more weeks' gestation (Asemi 2012; Asemi 2013a; Brooke 1980; Delvin 1986; Diogenes 2013; Grant 2013; Li 2000a; Mallet 1986; Marya 1987; Marya 1988; Mazurkevich 2013; Roth 2010; Sablok 2015; Taherian 2002; Yu 2008).

Pre-gestational body mass index (kg/m^2)

Pre-gestational body mass index of the participants was reported only in five trials (Asemi 2012; Asemi 2013a; Diogenes 2013; Sablok 2015; Taherian 2002). The rest of the trials did not report this (Brooke 1980; Delvin 1986; Grant 2013; Li 2000a; Mallet 1986; Marya 1987; Marya 1988; Mazurkevich 2013; Roth 2010; Yu 2008). One study stratified for pre intervention BMI (in kg/m^2; less than 30 and 30 or more) before randomisation (Asemi 2013a).

Skin pigmentation based on Fitzpatrick skin tone chart

In one trial (Brooke 1980), women were first-generation immigrants mostly from India, Pakistan, Bangladesh, Sri Lanka, Mauritius and east Africa. One trial described the participants as being Indian, Asian, Middle Eastern, Black or Caucasian (Yu 2008), and another trial described the participants as white women (Mallet 1986). The trial by Asemi 2012 reported that women were Iranian and the study by Diogenes 2013 reported that women most were mixed blacks and whites. One trial (Grant 2013) was carried out among Pacific, European and Maori women. The remaining trials did not report the characteristics of the participants in terms of ethnicity or skin pigmentation (Asemi 2013a; Delvin 1986; Li 2000a; Marya 1987; Marya 1988; Mazurkevich 2013; Roth 2010; Sablok 2015; Taherian 2002). None used the Fitzpatrick skin tone chart.

Interventions

Nine trials compared provision of oral vitamin D supplement in comparison with placebo or no intervention (Asemi 2013a; Brooke 1980; Delvin 1986; Grant 2013; Mallet 1986; Marya 1988; Roth 2010; Sablok 2015; Yu 2008), while six trials compared provision of oral vitamin D plus calcium supplements versus no intervention or placebo (Asemi 2012, Diogenes 2013; Li 2000a; Marya 1987; Mazurkevich 2013; Taherian 2002).

No studies evaluated the effects of either oral vitamin D plus calcium supplements versus calcium (comparison 3), nor oral vitamin D plus calcium and other micronutrients supplements in comparison with other micronutrients supplements (excluding vitamin D) (comparison 4), nor oral vitamin D + calcium + other vitamins and minerals supplements versus other oral vitamins and minerals supplements (but no vitamin D + calcium) (comparison 5).

Dose and vitamin D form

The dose of vitamin D provided varied in the included trials as well as the regimen.

The daily doses used were 200 IU vitamin D in five trials (Asemi 2012; Diogenes 2013; Li 2000a; Mazurkevich 2013; Taherian 2002); 400 IU vitamin D in two trials (Asemi 2013a; Li 2000a); 800 IU vitamin D in another trial (Yu 2008); 1000 IU vitamin D in four trials (Brooke 1980; Delvin 1986; Grant 2013; Mallet 1986); 1200 IU vitamin D in one trial (Marya 1987); and 2000 IU vitamin D in a one group in Grant 2013.

For single-dose supplementation of vitamin D, the dose varied from 200,000 IU vitamin D in a group in one study (Yu 2008); 600,000 IU vitamin D in one trial (Marya 1988); and 35,000 IU vitamin D per week (Roth 2010).

For the study by Sablok 2015, the dose depended upon the level of serum 25(OH)-D levels at baseline; it varied from one dose of 60, 000 IU (if serum 25(OH)-D levels were > 50 nmol/L), two doses of 120,000 IU (if serum 25(OH)-D levels were 25-50 nmol/L), or four doses of 120,000 IU (if serum 25(OH)-D levels < 25 nmol/L).

The vitamin D was provided in the form of cholecalciferol-D3 in 10 trials (Asemi 2012; Asemi 2013a; Delvin 1986; Diogenes 2013; Grant 2013; Li 2000a; Mazurkevich 2013; Roth 2010; Sablok 2015; Taherian 2002) and as ergocalciferol-D2 in three trials (Brooke 1980; Mallet 1986; Yu 2008). Two trials do not report the vitamin D form used (Marya 1987; Marya 1988).

Overall, the total provision of supplemental vitamin D provided throughout pregnancy varied. Eight trials provided 56,000 IU vitamin D or less (Asemi 2012; Asemi 2013a; Delvin 1986; Diogenes 2013; Grant 2013; Li 2000a; Mazurkevich 2013; Taherian 2002); five trials provided more than 56,000 to 200,000 IU vitamin D (Brooke 1980; Mallet 1986; Marya 1987; Sablok 2015; Yu 2008), and three trials provided more than 200,000 IU of vitamin D (Marya 1988; Roth 2010; Sablok 2015) throughout pregnancy.

Doses of calcium in the studies providing vitamin D and calcium supplementation

The doses of calcium provided along with the vitamin D ranged from 375 mg of calcium (Marya 1987); 500 mg of calcium as calcium carbonate (Asemi 2012; Taherian 2002); 600 mg calcium (Diogenes 2013; Li 2000a) (as calcium carbonate in Diogenes 2013), and 1250 mg of calcium as calcium carbonate (Mazurkevich 2013).

Health worker cadre

The trials were mostly carried out in the context of antenatal care and the administration of the supplements and the antenatal care was provided by the researchers themselves or through health allied personnel. The outcomes measurements were carried out by different groups according to the nature of the outcome, whether it was clinical, biochemical, anthropometric, or dietary assessments. A more detailed description of the health worker cadre is presented in Characteristics of included studies.

Start of supplementation

The start of the supplementation in the included trials were all in the period of 20 weeks of pregnancy, or more. The supplementation started during the third month of pregnancy (Delvin 1986); at 20 weeks of gestation (Sablok 2015; Taherian 2002); at 20 to 24 weeks of gestation (Li 2000a; Marya 1987); 23 to 29 weeks of gestation (Diogenes 2013); at 25 weeks of pregnancy (Asemi 2012; Asemi 2013a); 26 to 30 weeks of gestation (Grant 2013); 26 to 29 weeks' gestation (Roth 2010); 27 weeks of gestation (Yu 2008); 28 to 32 weeks of gestation (Brooke 1980); second pregnancy trimester until term (Mazurkevich 2013); last trimester of pregnancy (Mallet 1986) and 7th and 8th month of pregnancy (Marya 1988).

Supplementation scheme/regimen

In nine trials there was a group receiving the vitamin D supplements daily (Asemi 2012; Brooke 1980; Delvin 1986; Diogenes 2013; Grant 2013; Li 2000a; Mallet 1986; Marya 1987; Taherian 2002). In three trials the single dose provided was either once weekly or once a month (Marya 1987; Roth 2010; Yu 2008). In the study by Sablok 2015, the supplementation was either once at 20 weeks, twice at 20 and 24 weeks or four times at 20, 24, 28 and 32 weeks of gestation.

Laboratory methodology for the assessment of vitamin D status

Different laboratory methods were used to measure vitamin D status as serum 25-hydroxyvitamin D [25(OH)D] concentrations. Three trials (Asemi 2012; Asemi 2013a; Sablok 2015) used a commercial ELISA kit (Immuno Diagnostic Systems) for their determinations; one trial used a chemiluminescent enzyme-labelled immunometric assay (Diogenes 2013); another trial used isotope-dilution liquid chromatography-tandem mass spectrometry (Grant 2013); or high-performance liquid chromatography tandem mass spectroscopy (LCMS/MS) (Roth 2010). Two trials used a competitive protein binding assay (Brooke 1980; Mallet 1986), and one trial used a radioligand assay (Delvin 1986). In one trial, the laboratory method was not reported (Yu 2008). Other trials did not report on this outcome (Marya 1987; Marya 1988; Mazurkevich 2013).

See Characteristics of included studies for a detailed description of the studies, including vitamin D doses used and regimens compared.

Excluded studies

We excluded 27 studies. The main reason for exclusion was that the comparisons were among different doses of vitamin D (Bhatia 2012a; Dawodu 2013; Hashemipour 2013; Litonjua 2014; Marya 1981; Mutlu 2013; Roth 2013a; Shakiba 2013; Soheilykhah 2011; Stephensen 2011; Wagner 2010b; Wagner 2010c; Yap 2014), without placebo or no treatment control. In addition, four trials were not randomised trials (Ala-Houhala 1986; Cockburn 1980; Das 2009; Ito 1994). Three trials (Czech-Kowalska 2013; Taheri 2014; von Hurst 2009) were conducted on non pregnant women; three other trials were carried out in pregnant women with gestational diabetes (Asemi 2013b; Asemi 2014) or other chronic conditions (Etemadifar 2015). One reference referred to a trial registered in 1986 on the Oxford Database of Perinatal Trials and reports the recruitment and follow-up completed in 1979, but there were no reports available and we were unable to locate the author who registered the trial (MacDonald 1986). Two trials were excluded for other various reasons (Hossain 2012; Hosseinzadeh 2012). For more detailed descriptions of excluded studies along with the reasons for exclusion, *see* Characteristics of excluded studies.

Risk of bias in included studies

Allocation

Sequence generation

We assessed nine trials as having adequate methods for generating the randomisation sequence. Six of these used computer-generated random number sequences (Asemi 2013a; Diogenes 2013; Grant 2013; Roth 2010; Sablok 2015; Yu 2008), and the other three trials used a random numbers table (Asemi 2012; Mallet 1986; Taherian 2002) to randomise the intervention groups. The other trials reported the studies as randomised but the methods used to generate the sequence were not described (Brooke 1980; Delvin 1986; Li 2000a; Marya 1987; Marya 1988; Mazurkevich 2013).

Allocation concealment

We judged that five trials had adequate methods of allocation concealment (Asemi 2013a; Asemi 2012; Grant 2013; Roth 2010; Yu 2008). The remaining trials did not report the methods used to conceal the allocation (Brooke 1980; Delvin 1986; Diogenes 2013; Li 2000a; Mallet 1986; Marya 1987; Marya 1988; Mazurkevich 2013; Taherian 2002), if any. Sablok 2015 was as high risk, as participants were assigned to either no intervention or intervention and the intervention dosage depended on the vitamin D status, there was a selection bias based on status of vitamin D at baseline.

Blinding

Blinding of participants, staff and outcome assessors

Investigators in three trials attempted to blind participants and staff by using placebos of similar appearance to active treatment or coded or opaque bottles. Three trials were double blinded (Asemi 2013a; Grant 2013; Roth 2010) and two trials were single blinded (Asemi 2012; Diogenes 2013). In the trial by Asemi 2013a), all tablets were packed identically and coded by the producer to guarantee blinding. In the trial by Grant 2013, treatments were sequentially numbered with an identical numbering code, the bottles were identical in colour, shape, and volume and the tablets were identical in colour, consistency, and taste, such that study staff and participants were unaware of the treatment status. One trial was reported as blinded (Brooke 1980), although it was unclear whether the blinding was specifically for the participants, outcome assessor or care provider. Another trial (Delvin 1986), described that participants were allocated to the intervention by a "blind randomisation process"; however, given that the participants in the control group did not receive an intervention it is unlikely that the trial was blind. Eight trials were not reported as blinded (Delvin 1986; Li 2000a; Mallet 1986; Marya 1987; Mazurkevich 2013; Sablok 2015; Taherian 2002; Yu 2008). While lack of blinding may not represent a serious source of bias for some outcomes (e.g. serum indicators), other outcomes (i.e. reporting of side effects) may have been affected by knowledge of the treatment group.

Incomplete outcome data

With six exceptions Asemi 2012; Asemi 2013a; Grant 2013; Roth 2010; Taherian 2002; Yu 2008), lack of reporting on attrition, missing data and lack of intention-to-treat analyses were serious problems in almost all of the included studies. Two trials excluded participants if they had maternal illness (such as diabetes) or pregnancy complications so that they could receive treatment, but these exclusions are not well-documented (Brooke 1980; Marya 1988). One trial (Marya 1987) only reported biochemical data for those who developed pre-eclampsia and some of the other participants with no pre-eclampsia, but not for all the randomised participants. The attrition rate was unclear in one trial (Mallet 1986), and another study had unbalanced losses between the study arms (Delvin 1986). Loss was not balanced across groups in one trial (Sablok 2015).

Selective reporting

We did not have access to study protocols and therefore, formally assessing reporting bias was not possible. One study (Marya 1987) reported data only for some subgroups. Insufficient studies contributed data to allow us to carry out exploration of possible publication bias by using funnel plots.

Other potential sources of bias

Full details of 'Risk of bias' assessments are included in the Characteristics of included studies table. We have also included figures that summarise our 'Risk of bias' assessments (Figure 2; Figure 3).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

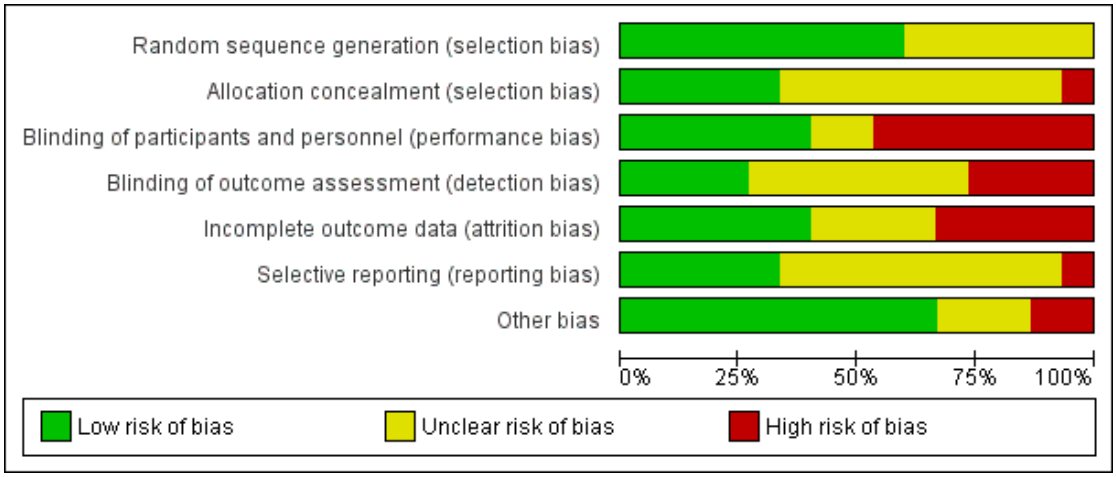
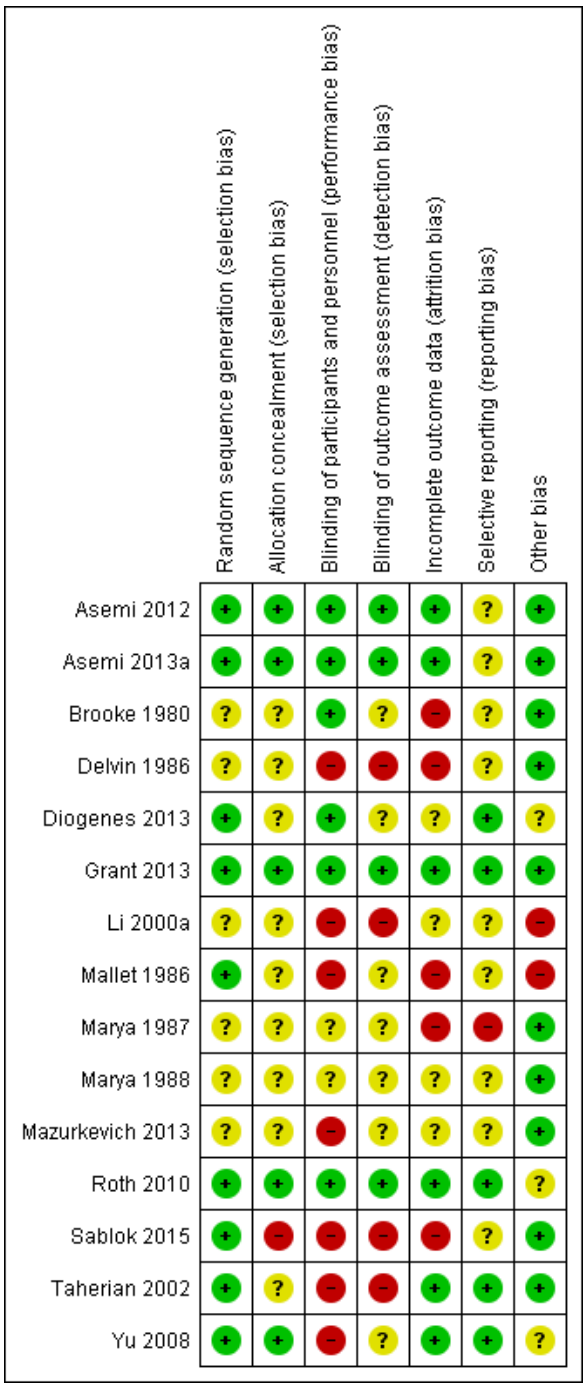


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison** Vitamin D alone versus no treatment/placebo (no vitamins or minerals); **Summary of findings 2** Vitamin D + calcium versus no treatment/placebo (no vitamin or minerals)

In this updated review we included 15 trials assessing a total of 2833 women. We organised the summary results by comparison and by primary and secondary outcomes.

In the Data and analyses tables, we set up all four prespecified comparisons but outcome data were only available for two of these. We have not added outcomes to those comparisons without data (comparisons three and four). For the comparisons with data, we set up tables for all primary outcomes (even where no data were available) not only to highlight gaps in the current research evidence, but also to be able to add any data that may become available in future updates.

See Data and analyses for detailed results on primary and secondary outcomes.

For each of the comparisons, we have indicated the number of studies contributing data and the total number of women recruited in these studies. However, for some outcomes only one or two studies provided data and due to loss to follow-up, denominators for particular outcomes may have been considerably less than the randomised sample. Therefore, we have indicated the number of studies contributing data and the number of women included in that analysis.

(1) Oral vitamin D alone supplements versus no intervention/placebo (no vitamins or minerals) (nine studies, 1251 participants)

Nine studies involving 1251 women were included in this comparison (Asemi 2013a; Brooke 1980; Delvin 1986; Grant 2013; Mallet 1986; Marya 1988; Roth 2010; Sablok 2015; Yu 2008). The following trials were assessed as having low risk of bias: Asemi 2013a; Grant 2013; Roth 2010.

Maternal primary outcomes

Pre-eclampsia (as defined by trialists)

Data from two trials (Asemi 2013a; Sablok 2015) involving 219 women suggest a trend that women who received vitamin D supplements had a lower risk of pre-eclampsia than those women receiving no intervention or placebo; but the statistical significance was borderline (8.9% versus 15.5%; average risk ratio (RR) 0.52; 95% confidence interval (CI) 0.25 to 1.05) (Analysis 1.1).

Gestational diabetes (as defined by trialists)

Data from two trials (Asemi 2013a; Sablok 2015) involving 219 women did not find a clear difference in the risk of gestational diabetes between women receiving vitamin D supplementation and women receiving no intervention, or in the placebo group (RR 0.43; 95% CI 0.05 to 3.45) (Analysis 1.2).

Maternal vitamin D concentration at term (25-hydroxyvitamin D in nmol/L)

The data from seven trials (Asemi 2013a; Brooke 1980; Delvin 1986; Grant 2013; Mallet 1986; Roth 2010; Sablok 2015) involving 868 women consistently show that women who received vitamin D supplements had higher 25-hydroxyvitamin D concentrations than those women who received no intervention or a placebo. The response to supplementation was highly heterogeneous (Tau^2 = 554.9, I^2 = 99% and Chi^2 test for heterogeneity P < 0.00001) and ranged from 16.3 nmol 25-hydroxyvitamin D per litre (95% CI 13.6 to 19.0) (Mallet 1986) to 152 nmol 25-hydroxyvitamin D per litre (95% CI 127 to 177) (Brooke 1980); the large effect reported in this study contributes importantly to the observed heterogeneity. The average mean difference (MD) between groups was 54.73 nmol 25-hydroxyvitamin D per litre (95% CI 36.60 to 72.86) (Analysis 1.3) but this result should be interpreted cautiously.

The subgroup analysis suggests that women who received vitamin supplementation on a daily basis reached a higher concentration of vitamin D at the end of the pregnancy compared with women who received a single dose, with an average mean difference between groups of 44.12 nmol 25-hydroxyvitamin D per litre (95% CI 30.24 to 58.00); however, this was highly heterogeneous (Tau^2 = 417, I^2 = 99% and Chi^2 test for heterogeneity P < 0.00001) (Analysis 1.6). With respect to the other subgroup analyses, no conclusions can be reached at this point as some of the subgroups only had one or two trials and the results may be misleading (Analysis 1.4; Analysis 1.5; Analysis 1.8; Analysis 1.9).

Adverse effects (nephritic syndrome)

A single study including 135 women reported on this outcome (Yu 2008). There was no clear evidence difference in the risk of nephritic syndrome between women receiving vitamin D supplementation and women not receiving the intervention or in the placebo group (RR 0.17; 95% CI 0.01 to 4.06) (Analysis 1.15). Given the scarcity of data for this outcome and the wide CIs, no firm conclusions can be drawn.

Infant primary outcomes

Preterm birth (less than 37 weeks' gestation)

Data from three trials (Asemi 2013a; Grant 2013; Sablok 2015) involving 477 women suggest that women who received vitamin D supplements during pregnancy had a lower risk of having a preterm birth than those women receiving no intervention or placebo (3.3% versus 9.9%; average RR 0.36; 95% CI 0.14 to 0.93) (Analysis 1.10).

Low birthweight (less than 2500 g)

The data from three trials (Brooke 1980; Marya 1988; Sablok 2015) involving 493 women suggest that women receiving vitamin D supplements during pregnancy less frequently had a baby with a birthweight below 2500 g than those women receiving no intervention or placebo (9.2% versus 19.6%; average RR 0.40; 95% CI 0.24 to 0.67) (Analysis 1.11).

Maternal secondary outcomes

Caesarean section

Two studies including 312 women reported on this outcome (Roth 2010; Sablok 2015). The data from this trial suggest that the women receiving vitamin D supplementation were as likely to experience a caesarean section than women who did not receive supplementation or placebo (RR 0.95; 95% CI 0.69 to 1.31) (Analysis 1.13) but given the scarcity of data for this outcome, no firm conclusions can be drawn.

No trials reported on our other pre-specified maternal secondary outcomes: impaired glucose tolerance (as defined by trialists); gestational hypertension (as defined by trialists) or maternal death.

Infant secondary outcomes

Length at birth (cm)

The data from four trials (Brooke 1980; Marya 1988; Roth 2010; Sablok 2015) involving 638 women suggest that there was a trend (P = 0.06) for a higher birth length among infants from women taking vitamin D supplementation during pregnancy compared to women in the no treatment or placebo group (MD 0.70; 95% CI -0.02 to 1.43) (Analysis 1.17). There was heterogeneity in the response to the supplementation (Tau^2 = 0.42; I^2 = 77% and Chi^2 test for heterogeneity P = 0.004).

Head circumference at birth (cm)

Four trials involving 638 women (Brooke 1980; Marya 1988; Roth 2010; Sablok 2015) reported on this anthropometric measurement. Results suggest that infants born to women who received vitamin D supplements during pregnancy had a significantly higher mean head circumference at birth than infants born to women who did not receive vitamin D supplements (MD 0.43; 95% CI 0.03 to 0.83) (Analysis 1.18). There was some heterogeneity in the response to the supplementation (Tau^2 = 0.12; I^2 = 72% and Chi^2 test for heterogeneity P = 0.01).

Birthweight (g)

Five trials involving 715 women (Brooke 1980; Mallet 1986; Marya 1988; Roth 2010; Sablok 2015) reported on this outcome. Results suggest that there was no difference of weight at birth in infants from women who received vitamin D supplements in comparison with women who did not receive vitamin D supplements (MD 66.60; 95% CI -137.22 to 270.41) (Analysis 1.19). There was some substantial heterogeneity among trials in terms of the size of the treatment (Tau^2 = 50335; I^2 = 95% and Chi^2 test for heterogeneity P < 0.00001). However, when the study by Mallet 1986 is excluded from the analysis, heterogeneity is reduced from 95% to 34% and a significant difference is observed in favour of the vitamin D supplemented group (MD 146.50, 95% CI 67.78 to 225.21, four studies, 638 women). The standard deviations for this study are very small and so we have concerns that these may not be reported correctly.

Stillbirth (as defined by trialists)

Three studies (Grant 2013; Roth 2010; Yu 2008) including 540 women reported this outcome. The data from this trials suggest that the women receiving vitamin D supplementation are as likely to have a stillbirth as women who receive no intervention or placebo (RR 0.35; 95% CI 0.06 to 1.99) (Analysis 1.21).

Neonatal death (within 28 days after delivery)

Two studies (Roth 2010; Yu 2008) including 282 women reported this outcome. There was no clear evidence difference in the risk of neonatal death between women receiving vitamin D supplementation and women not receiving the intervention or in the placebo group (RR 0.27; 95% CI 0.04 to 1.67) (Analysis 1.22), but given the scarcity of data for this outcome no firm conclusions can be drawn.

Apgar score less than seven at five minutes

One study including 165 women did not find clear differences in Apgar scores between groups (RR 0.53, 95% CI 0.11 to 2.53) (Analysis 1.23).

No trials reported on our other pre-specified infant secondary outcomes: admission to special care (including intensive care) during the neonatal period (within 28 days after delivery); neonatal infection (e.g. respiratory infections) or very preterm birth (less than 34 weeks' gestation).

(2) Oral vitamin D + calcium supplements versus no treatment/placebo (no vitamin or minerals) (six studies, 1688 participants)

Six included trials involving 1688 women made this comparison (Asemi 2012; Diogenes 2013; Li 2000a; Marya 1987; Mazurkevich 2013; Taherian 2002).

Maternal primary outcomes

Pre-eclampsia (as defined by trialists)

Three trials (Asemi 2012; Marya 1987; Taherian 2002) including 1114 women reported on this outcome. The data from this trial suggest that women receiving vitamin D and calcium supplementation combined are less likely to have pre-eclampsia as women who receive no intervention or placebo (5% versus 9%; average RR 0.51; 95% CI 0.32 to 0.80) (Analysis 2.1).

Gestational diabetes (as defined by trialists)

A single study including 54 women reported on this outcome (Asemi 2012). There was no clear evidence difference in the risk of gestational diabetes between women receiving vitamin D and calcium supplementation and women not receiving the intervention or in the placebo group (RR 0.33; 95% CI 0.01 to 7.84) (Analysis 2.2), but given the scarcity of data for this outcome and the wide CIs, no firm conclusions can be drawn.

Maternal vitamin D levels at term (25-hydroxyvitamin D in nmol/L)

No studies reported on this outcome.

Adverse effects

No studies reported on any adverse effects.

Infant primary outcomes

Preterm birth (less than 37 weeks' gestation)

Three studies with 798 participants reported on this outcome (Asemi 2012; Diogenes 2013; Taherian 2002). Women who received vitamin D and calcium supplementation are more likely to deliver prior to 37 weeks of gestation compared to women who received no treatment or placebo (RR 1.57; 95% CI 1.02 to 2.43; low quality) (Analysis 2.4).

Low birthweight (less than 2500 g)

No studies reported on this outcome.

Maternal secondary outcomes

Gestational hypertension

One trial reported on this outcome in 59 participants (Li 2000a). There was no clear difference in the risk of gestational hypertension between women receiving vitamin D and calcium supplement and women not receiving the intervention or on the placebo group (RR 0.26; 95% CI 0.06 to 1.12) (Analysis 2.8).

No trials reported on our pre-specified maternal secondary outcomes: impaired glucose tolerance (as defined by trialists); caesarean section; side effects (e.g. hypercalcaemia, kidney stones) or maternal death.

Infant secondary outcomes

Neonatal death (within 28 days after delivery)

One trial (Taherian 2002) reported on this outcomes with one death during the study period in the unsupplemented group (RR 0.20; 95% 0.01 to 4.15, one study, 660 participants) (Analysis 2.16).

No trials reported on our pre-specified infant secondary outcomes: length at birth (cm); head circumference at birth (cm); weight at birth (g); admission to special care (including intensive care) during the neonatal period (within 28 days after delivery); stillbirths (as defined by trialists); Apgar score less than seven at five minutes; neonatal infection (e.g. respiratory infections) or very preterm birth (less than 34 weeks' gestation).

(3) Oral vitamin D + calcium supplements versus calcium supplements (but no vitamin D) (no studies)

No studies were included in this comparison.

(4) Oral vitamin D + calcium + other vitamins and minerals supplements versus calcium + other vitamins and minerals supplements (but no vitamin D) (no studies)

No studies were included in this comparison.

(5) Oral vitamin D + calcium + other vitamins and minerals supplements versus other vitamins and minerals supplements (but no vitamin D + calcium) (no studies)

No studies were included in this comparison.

Subgroup analysis

We attempted to conduct a subgroup analysis but in all the outcomes very few studies contributed data. Indeed, for several subgroups all the trials were in the same subgroup category or only one trial was allocated to one of the subgroup categories impeding any judgements.

As more data become available, in updates of the review, we hope to explore possible subgroup differences by carrying out both visual exploration and formal statistical tests.

ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Population: women during pregnancy
Setting: Brazil, India, Iran
Intervention: Vitamin D + calcium + other vitamins and minerals
Comparison: other vitamins and minerals (but no vitamin D+ calcium)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no treatment/ placebo (no vitamin or minerals)	Risk with vitamin D + calcium				
Pre-eclampsia (ALL)	Study population		RR 0.51 (0.32 to 0.80)	1114 (3 RCTs)	⊕⊕⊕◯ MODERATE [1]	
	93 per 1000	48 per 1000 (30 to 75)				
	Moderate					
	90 per 1000	46 per 1000 (29 to 72)				
Gestational diabetes (ALL)	Study population		RR 0.33 (0.01 to 7.84)	54 (1 RCT)	⊕⊕◯◯ LOW [2]	
	37 per 1000	12 per 1000 (0 to 290)				
Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (ALL)				(0 studies)		No trial assessed this outcome.
Adverse effects				(0 studies)		No trial assessed this outcome.

Preterm birth (less than 37 weeks' gestation) (ALL)	Study population		RR 1.57 (1.02 to 2.43)	798 (3 RCTs)	⊕⊕⊕◯ MODERATE [1]	**Because there were zero events in some of the groups in two out of three of the included trials, GRADEpro GDT did not produce corresponding risks for a moderate risk population
	73 per 1000	114 per 1000 (74 to 177)				
	Moderate					
	**	**				
Low birthweight (less than 2500 g) (ALL)	Study population		Not estimable	(0 studies)		No trial assessed this outcome.
	Not pooled	Not pooled				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Most studies contributing data had design limitations (selection bias was unclear and high risk of attrition bias)
[2] Wide confidence interval crossing the line of no effect, few events & small sample size.

DISCUSSION

Summary of main results

This review evaluates the effects of vitamin D supplementation alone or in combination with calcium and other vitamins and minerals during pregnancy. It includes 15 small trials involving 2833 women, nine of which compared vitamin D alone versus no treatment or placebo and six trials provided vitamin D plus calcium in comparison with no intervention. No studies evaluated the effects of vitamin D plus calcium versus calcium or vitamin D plus calcium and other micronutrients in comparison with other micronutrients (but not vitamin D).

In comparison with the group that received no intervention or a placebo:

1. Women supplemented orally with vitamin D during pregnancy, particularly on a daily basis, had significantly higher concentrations of 25-hydroxyvitamin D at the end of pregnancy; however, the response to supplementation was highly heterogeneous. There was no statistically significant difference in the risk of pre-eclampsia but these results suggest a lower risk in those women receiving vitamin D supplementation alone (two trials). In women supplemented with vitamin D plus calcium (three trials) the reduction in the risk of pre-eclampsia reached statistical significance. No differences were seen in the other maternal outcomes.
2. Supplementation with vitamin D during pregnancy significantly reduced the risk of preterm birth (three trials) and of low birthweight (four trials). In addition, there was a higher birth length (four trials; borderline significance) and a higher head circumference in infants born to women who were supplemented with vitamin D during pregnancy. No differences were seen in birthweight between supplemented and no intervention or placebo groups. However, supplementation with vitamin D and calcium significantly increased the risk of preterm birth (three trials).
3. With respect to safety, few trials reported on adverse effects, with only one study reporting a single case of nephritic syndrome which occurred in a woman who did not receive any supplementation.

It is important to note that most trials included in this review were of low methodological quality. In addition, heterogeneity was detected for the outcomes of 25-hydroxyvitamin D, and in head circumference and length at birth. In particular, the inconsistencies in results with serum 25-hydroxyvitamin D levels could be related to the different doses used in the trials included and also in the difference in methods to assess serum 25-hydroxyvitamin D. This biomarker is difficult and complex, with high variability in results between methods used (Holick 2008). High performance liquid chromatography mass spectrometry is the best available method (Holick 2005), but only one trial used this method. Furthermore, there is a lack of data on the safety of the supplementation. Therefore, results should be interpreted with caution.

Overall completeness and applicability of evidence

Vitamin D supplementation during pregnancy aims to improve gestational and neonatal outcomes. However, although in this update we were able to more than double the studies included, there is still a limited number of trials reporting on all the outcomes of this review. Several maternal outcomes (impaired glucose tolerance, caesarean section, gestational hypertension, adverse effects or death) and infant outcomes (neonatal death, admission to special care (including intensive care) during the neonatal period within 28 days after delivery (neonatal period), Apgar score less than seven at five minutes, neonatal infection or very preterm birth) were either not reported or reported only by one trial.

Vitamin D supplementation appeared to raise serum 25-hydroxyvitamin D levels at the end of pregnancy. The clinical significance of this finding and the potential use of this intervention as a part of routine antenatal care are yet to be determined.

To the best of our knowledge, there are currently 23 ongoing studies that, once published, will further increase the body of evidence identified for this updated review. After their publication and overall assessment, conclusions on the effects and safety of this intervention may be updated once more. In addition, updates could include the dose-response of vitamin D supplementation on important pregnancy outcomes.

Quality of the evidence

Risk of bias in the majority of trials was unclear and many studies were at high risk of bias for blinding and the attrition rates (*see* Risk of bias in included studies). This is particularly the case of the older trials. In most of the newer trials included, the methods used to randomly assign participants and conceal allocation and the blinding of participants, care providers and outcome assessors were described. However, attrition was a problem in most of the studies.

We evaluated the quality of the body of evidence for the primary outcomes with the GRADE methodology for the first two comparisons (Summary of findings for the main comparison; Summary of findings 2). We considered that indirectness or publication bias were unlikely, but the risk of bias of the trials, the inconsistency (or the lack of studies), and the imprecision resulted in: evidence of low quality for pre-eclampsia, low birthweight, and adverse effects; very low quality for gestational diabetes, maternal vitamin D concentrations; and of moderate quality for preterm births in the comparison of supplementation with vitamin D alone versus no intervention or placebo. The quality of the evidence in the studies assessing supplementation of vitamin D plus calcium were low

quality for pre-eclampsia, gestational diabetes, and preterm births. No data were reported on the other primary outcomes (adverse effects; maternal vitamin D concentrations; and low birthweight) for this comparison.

Potential biases in the review process

We identified several potential biases in the review process. They were minimised in two ways: (1) eligibility for inclusion and data extraction were assessed independently by two review authors and (2) assessments of risk of bias and data entry were also assessed independently by two review authors. However, this type of review requires that we make a number of subjective judgements and others may have reached different decisions regarding assessments of eligibility and risk of bias. We would encourage readers to examine the Characteristics of included studies tables to assist in the interpretation of results.

Agreements and disagreements with other studies or reviews

This review updates the previous Cochrane review on vitamin D supplementation in pregnancy (De-Regil 2012). The previous review included six trials including a total of 1023 women and excluded eight studies, and 10 studies were still ongoing. It assessed the same maternal and infant outcomes; however, only a few of these outcomes were included in those trials, concluding that vitamin D supplementation in a single or continued dose during pregnancy increased serum 25-hydroxyvitamin D at term, but the clinical significance of this finding and the safety of this type of supplementation were still to be determined due to the low number of high-quality trials and outcomes reported. For this update, there were more studies reporting on the outcomes of interest and we concluded that there is some indication that vitamin D supplementation may lower the risk of pre-eclampsia, preterm birth and low birthweight. However, there are still insufficient data to confirm the effects on these maternal and infant health outcomes and to determine the effects on the other outcomes studied, as these were either not reported or assessed in only one trial.

A recent systematic review of vitamin D interventional studies during pregnancy found some similar results (Harvey 2014). From the seven trials assessing the effects of vitamin D supplementation on birthweight, three studies demonstrated significantly greater birthweight in infants from supplemented mothers while the other four did not find a significant effect. For birth length, two trials were identified; one found that supplementation with vitamin D led to greater birth length in infants of women who received supplementation, while the other trial found "no significant association but a trend towards higher birth length in the supplemented group" compared to the control group. In addition, in the two trials assessing offspring head circumference, one found a significantly greater head circumference while the other found a non-significant trend towards greater head circumference in supplemented mothers. Only one intervention was identified for pre-eclampsia (no difference in risk between groups) and no interventions were identified for preterm birth, low birthweight, gestational diabetes and caesarean section.

Another recent systematic review and meta-analysis of 13 trials (n = 2299) supplementing pregnant women with vitamin D assessed similar outcomes to the present review (Perez-Lopez 2015). This review included vitamin D alone versus no treatment or placebo; vitamin D plus calcium versus no treatment or placebo; and vitamin D plus calcium versus calcium (the placebo group included the low level of vitamin D, 400 IU/d). Serum 25-hydroxyvitamin D at term were significantly higher in the supplemented group compared with the control group (mean difference: 66.5 nmol/L, 95% confidence interval (CI) 66.2 to 66.7; 10 trials; 1468 women), similar to the present review. However, contrary to the present review, Perez-Lopez 2015 found that vitamin D supplementation did not influence the incidence of pre-eclampsia (three studies; 654 participants), low birthweight (four studies; 496 participants) and preterm birth (three studies; 384 participants), while it significantly increased birthweight (10 studies; 1489 participants) and birth length (six studies; 866 participants). Consistent with the present review, vitamin D supplementation did not influence the incidence of gestational diabetes mellitus (three studies; 384 participants), and caesarean section (four studies; 1028 participants). These differences in results between our meta-analysis may be due to inclusion of control groups with low levels of vitamin D (400 IU/d) in the latter.

Another review assessed the effect of vitamin D supplementation versus placebo, which included low vitamin D dose (400 IU/d) or no intervention during pregnancy for reducing the risk of pre-eclampsia (Hyppönen 2013). Of the four trials identified including 5871 women, vitamin D supplementation significantly reduced the risk of pre-eclampsia compared with the control group (odds ratio 0.66; 95% CI 0.52 to 0.83). In the present review, we found a trend in the reduction of pre-eclampsia risk in women supplemented with vitamin D during pregnancy compared to no supplementation.

Similar to our results, one review (Thorne-Lyman 2012) also found a 60% lower risk of low birthweight in women supplemented with vitamin D during pregnancy (three trials; 507 participants). However, no trend was observed in the reduction of preterm birth in the two trials included (529 participants) with vitamin D supplementation. This review included studies with low dose of vitamin D (400I IU/d) in the placebo or control group.

Overall, the available systematic reviews and meta-analyses have consistently shown that serum 25-hydroxyvitamin D levels are significantly improved with vitamin D supplementation. However, there are important differences in the results. While this review and another (Hyppönen 2013) showed a trend or a significant reduction in pre-eclampsia risk with vitamin D supplementation,

one review (Perez-Lopez 2015) did not find this. Also, differences were found in the reduction of preterm birth and low birthweight. As more studies are published, these mixed results may be elucidated.

We also reviewed the results of the excluded trials testing different vitamin D doses without a placebo group (the placebo included a lower dose of vitamin D supplementation) (see Table 1). It was evident from the majority of the trials that the higher vitamin D dose used led to significantly higher serum 25-hydroxyvitamin D at term or at the end of the supplementation period compared to the lower dose (usually 400 IU/d). The two studies assessing birthweight found that this was greater among infants of mothers supplemented with vitamin D at doses of 60,000 or 120,000 IU (total dose given once or twice) compared to women in the usual group (Bhatia 2012a) and mothers supplemented with 2000 IU/d (Stephensen 2011) compared to the control group (400 IU/d). Similarly, infant birth length and head circumference were greater in mothers supplemented with 60,000 or 120,000 IU compared to women in the usual group (Bhatia 2012a) or supplemented with 50,000 IU per week (+ calcium) compared to the control group (400 IU/d) (Hashemipour 2013). In addition, supplementation with 50,000 IU every two weeks significantly improved insulin resistance in one trial (Soheilykhah 2011), but supplementation with 5000 IU/d did not improve glucose levels in another study (Yap 2014).

With respect to safety, the trials reporting on maternal and infant safety-related outcomes suggest that vitamin D supplementation appears to be safe during pregnancy. However, most outcomes defined in this review (maternal death, neonatal admission to intensive care unit, Apgar score less than seven at five minutes, neonatal infection or very preterm birth) were not reported by any of the trials. The trial by Sablok 2015 reported the Apgar score less than three or seven, with no difference between supplemented or placebo groups. More trials are needed to report on these safety-related outcomes to have a definite conclusion.

The clinical significance of the increased serum 25-hydroxyvitamin D concentrations is unclear and results should be interpreted with caution, as only a few small trials of low quality assessed these outcomes. Also, we found heterogeneity in the results on serum 25-hydroxyvitamin D. This variability and inconsistency could be related to the differences in methods used to assess this outcome in the included trials.

The evidence on whether vitamin D supplementation should be given as a part of routine antenatal care to all women to improve maternal and infant outcomes therefore remains unclear. While there is some indication that vitamin D supplementation could reduce the risk of pre-eclampsia and increase length and head circumference at birth, further rigorous randomised trials are required to confirm these effects. Currently, the number of high-quality trials with large sample sizes and outcomes reported, including data on adverse effects, is too limited to draw definite conclusions on its usefulness and safety.

Implications for research

Additional rigorous high quality and larger randomised trials are required to evaluate the role of vitamin D supplementation in pregnancy. Future research should evaluate if an increase of serum 25-hydroxyvitamin D concentration is associated with improved maternal and infant outcomes in populations with different degrees of body mass index, skin pigmentation and settings. Also, the effects of vitamin D supplementation in women with a diagnosis of gestational diabetes or with increased risk of pre-eclampsia should be assessed.

Information on the most effective and safe dosage, the optimal dosing regimen (daily, intermittent or single doses), the timing of initiation of vitamin D supplementation, and the effect of vitamin D when combined with other vitamins and minerals are also needed to inform policy-making.

AUTHORS' CONCLUSIONS

Implications for practice

In this review update, new studies have added to the evidence base on the effects of supplementing pregnant women with vitamin D alone or with calcium on pregnancy outcomes. Supplementing pregnant women with vitamin D in a single or continued dose increases serum 25-hydroxyvitamin D at term but the results were highly variable. Supplementation with vitamin D and vitamin D plus calcium appears to reduce the risk of pre-eclampsia and vitamin D supplementation appears to reduce the risk of low birthweight and preterm delivery. However, it appears that when vitamin D and calcium are combined, the risk of preterm birth is increased.

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REFERENCES

References to studies included in this review

Asemi 2012 *{published data only}*

Asemi Z, Tabassi Z, Heidarzadeh Z, Khorammian H, Sabihi SS, Samimi M. Effect of calcium-vitamin D supplementation on metabolic profiles in pregnant women at risk for pre-eclampsia: a randomized placebo-controlled trial. *Pakistan Journal of Biological Sciences* 2012;**15**(7): 316–24.

Asemi 2013a *{published data only}*

Asemi Z, Samimi M, Tabassi Z, Shakeri H, Esmaillzadeh A. Vitamin D supplementation affects serum high-sensitivity C-reactive protein, insulin resistance, and biomarkers of oxidative stress in pregnant women. *Journal of Nutrition* 2013;**143**(9):1432–8.

Brooke 1980 *{published data only}*

* Brooke OG, Brown IRF, Bone CDM, Carter ND, Cleeve HJW, Maxwell JD, et al. Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. *British Medical Journal* 1980;**1**:751–4.

Brooke OG, Butters F, Wood C. Intrauterine vitamin D nutrition and postnatal growth in Asian infants. *British Medical Journal* 1981;**283**:1024.

Maxwell JD, Ang L, Brooke OG, Brown IRF. Vitamin D supplements enhance weight gain and nutritional status in pregnant Asians. *British Journal of Obstetrics and Gynaecology* 1981;**88**:987–91.

Delvin 1986 *{published data only}*

Delvin EE, Salle BL, Glorieux FH, Adeleine P, David LS. Vitamin D supplementation during pregnancy: effect on neonatal calcium homeostasis. *Journal of Pediatrics* 1986; **109**:328–34.

Diogenes 2013 *{published data only}*

Bezerra, F. Calcium plus vitamin d supplementation during pregnancy of adolescent mothers: effects on maternal and infant bone mass, calcium and bone metabolism and breast milk composition. ClinicalTrials.gov (http://clinicaltrials.gov/) [accessed 2012] 2012.

* Diogenes ME, Bezerra FF, Rezende EP, Taveira MF, Pinhal I, Donangelo CM. Effect of calcium plus vitamin D supplementation during pregnancy in Brazilian adolescent mothers: a randomized, placebo-controlled trial. *American Journal of Clinical Nutrition* 2013;**98**(1):82–91.

Grant 2013 *{published data only}*

Grant C. Randomised placebo controlled study of vitamin D during pregnancy and infancy. Australian New Zealand Clinical Trials Register [www.anzctr.org.au] (accessed 17 August 2010) 2010.

Grant C, Stewart A, Scragg R, Milne T, Rowden J, Ekeroma A, et al. What dose of vitamin D supplementation is required in pregnancy and infancy to increase infants' serum 25-hydroxyvitamin D concentration > 20ng/ml?. Pediatric Academic Societies Annual Meeting; 2013 May 4-7; Washington DC, USA. 2013.

* Grant CC, Stewart AW, Scragg R, Milne T, Rowden J, Ekeroma A, et al. Vitamin D during pregnancy and infancy and infant serum 25-hydroxyvitamin D concentration. *Pediatrics* 2014;**133**(1):e143–53.

Li 2000a *{published data only}*

Li X, Gou W. Study on prevention of pregnancy induced hypertension and effect of platelet intracellular free ca-(2+) by calcium supplementation

[补钙预防妊高征及对血小板细胞内游离钙浓度的影响]. *Journal of Xi'an Medical University* 2000;**21**(1):46–8.

Mallet 1986 *{published data only}*

Mallet E, Gugi B, Brunelle P, Henocq A, Basuyau JP, Lemeur H. Vitamin D supplementation in pregnancy: a controlled trial of two methods. *Obstetrics & Gynecology* 1986;**68**:300–4.

Marya 1987 *{published data only}*

Marya RK, Rathee S, Manrow M. Effect of calcium and vitamin D supplementation on toxaemia of pregnancy. *Gynecologic and Obstetric Investigation* 1987;**24**(1):38–42.

Marya 1988 *{published data only}*

Marya RK, Rathee S, Dua V, Sangwan K. Effect of vitamin D supplementation during pregnancy on foetal growth. *Indian Journal of Medical Research* 1988;**88**:488–92.

Mazurkevich 2013 *{published data only}*

Mazurkevich M, Doronin G, Firsova T. State of placental complex during physiological pregnancy during correction

of mineral insufficiency. *Journal of Perinatal Medicine* 2013; **41**(Suppl 1):Abstract no:1213.

Roth 2010 *{published data only}*

Harrington J, Perumal N, Al Mahmud A, Baqui A, Roth DE. Vitamin D and fetal-neonatal calcium homeostasis: findings from a randomized controlled trial of high-dose antenatal vitamin D supplementation. *Pediatric Research* 2014;**76**(3):302–9.

Perumal N, Al Mahmud A, Baqui A, Raqib R, Roth D. Effect of high-dose vitamin D supplementation on blood pressure during the third trimester of pregnancy: A randomized controlled trial in Bangladesh. *American Journal of Epidemiology* 2012;**176**(1):80, Abstract no: 2.

Raqib R, Ly A, Akhtar E, Mily A, Perumal N, Al-Mahmud A, et al. Prenatal vitamin D3 supplementation suppresses LL-37 peptide expression in ex vivo activated neonatal macrophages but not their killing capacity. *British Journal of Nutrition* 2014;**112**(6):908–15.

Roth D. Antenatal vitamin D3 supplementation in Bangladesh: randomized controlled trial (AViDD-2). ClinicalTrials.gov (http://clinicaltrials.gov) [accessed 6 April 2011] 2010.

Roth DE, Al Mahmud A, Perumal N, Pezzack B, Raqib R, Baqui AH. Effect of prenatal third-trimester vitamin D3 supplementation (35,000 IU/week) on fetal and infant linear growth in Bangladesh: the AViDD trial. Pediatric Academic Societies Annual Meeting; 2013 May 4-7; Washington DC, USA. 2013.

* Roth DE, Al Mahmud A, Raqib R, Akhtar E, Perumal N, Pezzack B, et al. Randomized placebo-controlled trial of high-dose prenatal third-trimester vitamin D3 supplementation in Bangladesh: the AViDD trial. *Nutrition Journal* 2013;**12**:47.

Roth DE, Al Mahmud A, Raqib R, Baqui AH. Effects of high-dose antenatal 3rd-trimester vitamin D supplementation (35,000 IU/week) on maternal and newborn vitamin D status: A randomized placebo-controlled trial in Dhaka, Bangladesh. *FASEB Journal* 2012; **26**:[Abstract no. 392.3].

Roth DE, Al-Mahmud A, El Arifeen S, Raqib R, Black RE, Baqui AH. Randomized pilot trial of two oral vitamin d3 supplementation regimens during the third trimester of pregnancy in Bangladeshi women: effects on neonatal vitamin d status and safety. Pediatric Academic Societies and Asian Society for Pediatric Research Joint Meeting; 2011 April 30-May 3; Denver, Colorado, USA. 2011:1411.154.

Roth DE, Perumal N, Al A, Baqui AH. Maternal vitamin D3 supplementation during the third trimester of pregnancy: Effects on infant growth in a longitudinal follow-up study in Bangladesh. *Journal of Pediatrics* 2013; **163**(6):1605–11.

Sablok 2015 *{published data only}*

Sablok A, Batra A, Thariani K, Batra A, Bharti R, Aggarwal AR, et al. Supplementation of vitamin D in pregnancy and its correlation with feto-maternal outcome. Clinical Endocrinology 2015 Feb 14 [Epub ahead of print].

Taherian 2002 *{published data only}*

Taherian AA, Taherian A, Shirmani A. Prevention of preeclampsia with low-dose aspirin or calcium supplementation. *Archives of Iranian Medicine* 2002;**5**(3): 151–6.

Yu 2008 *{published data only}*

* Yu C, Newton L, Robinson S, Teoh TG, Sethi M. Vitamin D deficiency and supplementation in pregnant women of four ethnic groups. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2008;**93**(Suppl 1):Fa68.

Yu CK, Sykes L, Sethi M, Teoh TG, Robinson S. Vitamin D deficiency and supplementation during pregnancy. *Clinical Endocrinology* 2009;**70**(5):685–90.

References to studies excluded from this review

Ala-Houhala 1986 *{published data only}*

Ala-Houhala M, Koskinen T, Terho A, Koivula T, Visakorpi J. Maternal compared with infant vitamin D supplementation. *Archives of Disease in Childhood* 1986;**61**: 1159–63.

Asemi 2013b *{published data only}*

* Asemi Z, Hashemi T, Karamali M, Samimi M, Esmaillzadeh A. Effects of vitamin D supplementation on glucose metabolism, lipid concentrations, inflammation, and oxidative stress in gestational diabetes: a double-blind randomized controlled clinical trial. *American Journal of Clinical Nutrition* 2013;**98**(6):1425–32.

Asemi Z, Karamali M, Esmaillzadeh A. Favorable effects of vitamin d supplementation on pregnancy outcomes in gestational diabetes: a double blind randomized controlled clinical trial. *Hormone and Metabolic Research* 2015;**47**(8): 565–70.

Asemi 2014 *{published data only}*

Asemi Z, Karamali M, Esmaillzadeh A. Effects of calcium-vitamin D co-supplementation on glycaemic control, inflammation and oxidative stress in gestational diabetes: a randomised placebo-controlled trial. *Diabetologia* 2014;**57** (9):1798–806.

Bhatia 2012a *{published data only}*

Bhatia V, Katam K, Agarwal A, Das V, Ramesh V. Vitamin D supplementation in pregnancy and its effect on cord blood 25 hydroxycholecalciferol and anthropometry of the newborn. *Hormone Research in Paediatrics* 2013;**80**(Suppl 1):220.

Das V. Vitamin D and calcium nutrition in pregnancy-evaluation of optimal supplementation dose of vitamin D during antenatal period. Clinical Trials Registry - India (http://www.ctri.nic.in/) [accessed 2010] 2010.

* Kalra P, Das V, Agarwal A, Kumar M, Ramesh V, Bhatia E, et al. Effect of vitamin D supplementation during pregnancy on neonatal mineral homeostasis and anthropometry of the newborn and infant. *British Journal of Nutrition* 2012;**108**(6):1052–8.

Cockburn 1980 *{published data only}*

Cockburn F, Belton NR, Purvis RJ, Giles MM, Brown JK, Turner TL, et al. Maternal vitamin D intake and mineral

metabolism in mothers and their newborn infants. *British Medical Journal* 1980;**281**(6232):11–4.

Czech-Kowalska 2013 ***{published data only}***

Czech-Kowalska J, Latka-Grot J, Bulsiewicz D, Jaworski M, Pludowski P, Chazan B, et al. Influence of vitamin D supplementation on vitamin D status and bone mass during lactation - double blinded randomized control trial. *Annals of Nutrition & Metabolism* 2013;**63**(Suppl 1):796, Abstract no: PO1128.

Das 2009 ***{published data only}***

Bhatia V. A study of the effect of vitamin D supplementation in pregnant women, on the growth and biochemical features of the newborn baby and infant. Clinical Trials Registry - India (http://ctri.nic.in) [accessed 2010] 2010.

* Das V, Agarwal A, Bhatia V, Pandey A, Agarwal S, Saxena P, et al. Evaluation of vitamin d status and need for supplementation in pregnant women of a rural area of North India. *International Journal of Gynecology & Obstetrics* 2009;**107**(Suppl 2):S151.

Sahu M, Das V, Aggarwal A, Rawat V, Saxena P, Bhatia V. Vitamin D replacement in pregnant women in rural north India: a pilot study. *European Journal of Clinical Nutrition* 2009;**63**(9):1157–9.

Dawodu 2013 ***{published data only}***

Dawodu A, Saadi HF, Bekdache G, Javed Y, Altaye M, Hollis BW. Randomized controlled trial (RCT) of vitamin D supplementation in pregnancy in a population with endemic vitamin D deficiency. *Journal of Clinical Endocrinology & Metabolism* 2013;**98**(6):2337–46.

Etemadifar 2015 ***{published data only}***

* Etemadifar M, Janghorbani M. Efficacy of high-dose vitamin D3 supplementation in vitamin D deficient pregnant women with multiple sclerosis: Preliminary findings of a randomized-controlled trial. *Iranian Journal of Neurology* 2015;**14**(2):67–73.

Hashemipour 2013 ***{published data only}***

Hashemipour S. Effect of treatment of vitamin D deficiency during pregnancy on hypocalcemia. ClinicalTrials.gov (http://clinicaltrials.gov/) [accessed 5 February 2014] 2013.

* Hashemipour S, Ziaee A, Javadi A, Movahed F, Elmizadeh K, Javadi EH, et al. Effect of treatment of vitamin D deficiency and insufficiency during pregnancy on fetal growth indices and maternal weight gain: a randomized clinical trial. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2014;**172**:15–9.

Hossain 2012 ***{published data only}***

* Hossain N, Kanani F, Khanani R, Ayaz S, Pal L. Effect of maternal supplementation with vitamin D during pregnancy on neonatal serum vitamin D levels and anthropometric measurements. *International Journal of Gynecology and Obstetrics* 2012;**119**(Suppl 3):S372.

Hossain N, Kanani FH, Ramzan S, Kausar R, Ayaz S, Khanani R, et al. Obstetric and neonatal outcomes of maternal vitamin D supplementation: results of an open-label, randomised controlled trial of antenatal vitamin D supplementation in Pakistani women. *Journal of Clinical Endocrinology and Metabolism* 2013;**99**(7):2448–55.

Hosseinzadeh 2012 ***{published data only}***

* Hosseinzadeh-Shamsi-Anar M, Mozaffari-Khosravi H, Salami MA, Hadinedoushan H, Mozayan MR. The efficacy and safety of a high dose of vitamin d in mothers with gestational diabetes mellitus: A randomized controlled clinical trial. *Iranian Journal of Medical Sciences* 2012;**37**(3): 159–65.

Mozaffari-Khosravi H, Hosseinzadeh-Shamsi-Anar M, Salami MA, Hadinedoushan H, Mozayan MR. Effects of a single post-partum injection of a high dose of vitaminD on glucose tolerance and insulin resistance in mothers with first-time gestational diabetes mellitus. *Diabetic Medicine* 2012;**29**(1):36–42.

Ito 1994 ***{published data only}***

Ito M, Koyama H, Ohshige A, Maeda T, Yoshimura T, Okamura H. Prevention of preeclampsia with calcium supplementation and vitamin D3 in an antenatal protocol. *International Journal of Gynecology & Obstetrics* 1994;**47**(2): 115–20.

Litonjua 2014 ***{published data only}***

Litonjua AA, Lange NE, Carey VJ, Brown S, Laranjo N, O'Connor GT, et al. The Vitamin D Antenatal Asthma Reduction Trial (VDAART): Rationale, design, and methods of a randomized, controlled trial of vitamin D supplementation in pregnancy for the primary prevention of asthma and allergies in children. *Contemporary Clinical Trials* 2014;**38**:37–50.

MacDonald 1986 ***{published data only}***

MacDonald HN. Fetal and maternal benefits from calcium and vitamin D supplementation of pregnant Asians. Personal communication 1986.

Marya 1981 ***{published data only}***

Marya RK, Rathee S, Lata V, Mudgil S. Effects of vitamin D supplementation in pregnancy. *Gynecologic and Obstetric Investigation* 1981;**12**:155–61.

Mutlu 2013 ***{published data only}***

Mutlu GY, Ozsu E, Kalaca S, Yuksel A, Cizmecioglu FM, Hatun S. The evaluation of vitamin D supplementation dose during pregnancy in a high-risk population. *Hormone Research in Paediatrics* 2013;**80**(Suppl 1):92.

Mutlu GY, Ozsu E, Kalaca S, Yuksel A, Pehlevan Y, Cizmecioglu F, et al. Evaluation of vitamin D supplementation doses during pregnancy in a population at high risk for deficiency. *Hormone Research in Paediatrics* 2014;**81**(6):402–8.

Roth 2013a ***{published data only}***

* Roth DE, Al A, Raqib R, Akhtar E, Black RE, Baqui AH. Pharmacokinetics of high-dose weekly oral vitamin D3 supplementation during the third trimester of pregnancy in Dhaka, Bangladesh. *Nutrients* 2013;**5**(3):788–810.

Roth DE, Al-Mahmud A, El S, Raqib R, Black RE, Baqui AH. Randomized open-label trial of two weekly oral vitamin D3 supplementation regimens during the third trimester of pregnancy in Bangladeshi women: Effects on

maternal vitamin D status and safety. *FASEB Journal* 2011; **25**(Suppl):236.6.

Shakiba 2013 *{published data only}*
Shakiba M, Iranmanesh MR. Vitamin D requirement in pregnancy to prevent deficiency in neonates: A randomised trial. Singapore Medical Journal 2013; Vol. 54, issue 5: 285–8.

Soheilykhah 2011 *{published data only}*
Soheilykhah S. Effect of different doses of vitamin D on insulin resistance in pregnant women attending in Shahid Sadoughi and Mojibian prenatal clinics. Iranian Registry of Clinical Trials (http://www.irct.ir/) [accessed 2 August 2011] 2011.
* Soheilykhah S, Mojibian M, Moghadam MJ, Shojaoddiny-Ardekani A. The effect of different doses of vitamin D supplementation on insulin resistance during pregnancy. *Gynecological Endocrinology* 2013;**29**(4):396–9.

Stephensen 2011 *{published data only}*
* Stephensen CB. Effects of vitamin D supplementation during pregnancy on clinical outcomes and immune function. ClinicalTrials.gov (http://clinicaltrials.gov/) [accessed 21 May 2013] 2011.
Zerofsky M, Jacoby B, Stephensen C. A randomized controlled trial of vitamin D supplementation in pregnancy: Effects on vitamin D status and clinical outcomes. *FASEB Journal* 2014;**28**(1 Suppl 1):[Abstract no. 1041.5].

Taheri 2014 *{published data only}*
Taheri M, Baheiraei A, Rahimi A, Modarres M. Resolving vitamin d deficiency in the preconception period among high-risk reproductive women: A randomized controlled trial. *Iranian Red Crescent Medical Journal* 2014;**16**(1): e11175.

von Hurst 2009 *{published data only}*
* von Hurst PR. *The role of vitamin D in metabolism and bone health. A thesis presented in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Nutritional Science*. Vol. **1**, Albany: Massey University, 2009.
von Hurst PR, Stonehouse W, Coad J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient - a randomised, placebo-controlled trial. *British Journal of Nutrition* 2010;**103**(4):549–55.
von Hurst PR, Stonehouse W, Matthys C, Conlon C, Kruger MC, Coad J. Study protocol--metabolic syndrome, vitamin D and bone status in South Asian women living in Auckland, New Zealand: a randomised, placebo-controlled, double-blind vitamin D intervention. *BMC Public Health* 2008;**8**:267.

Wagner 2010a *{published data only}*
* Wagner CL, McNeil R, Hamilton SA, Davis DJ, Prudgen C, Winkler J, et al. Vitamin D (vitD) supplementation during pregnancy: Thrasher Research Fund RCT in SC community center networks. Pediatric Academic Societies 2010 Annual Meeting; 2010 May 1-4; Vancouver, Canada. 2010.
Wagner CL, McNeil R, Hamilton SA, Winkler J, Rodriguez Cook C, Warner G, et al. A randomized trial of vitamin D supplementation in 2 community health center networks in South Carolina. *American Journal of Obstetrics and Gynecology* 2013;**208**(2):137.e1–137.e13.

Wagner 2010b *{published data only (unpublished sought but not used)}*
Appelgren KE, Nietert PJ, Hulsey TC, Hollis BW, Wagner CL. Analyzing adherence to prenatal supplement: does pill count measure up?. *International Journal of Endocrinology* 2010;**2010**:1–8.
Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL. Vitamin D supplementation during pregnancy: Double-blind, randomized clinical trial of safety and effectiveness. *Journal of Bone and Mineral Research* 2011;**26**(10):2341–57.
Wagner CL. Evaluation of vitamin D requirements during pregnancy (ongoing trial). ClinicalTrials.gov (http://clinicaltrials.gov/) [accessed 21 March 2006] 2006.
* Wagner CL, Johnson D, Hulsey TC, Ebeling M, Shary J, Smith PG, et al. Vitamin D supplementation during pregnancy Part I NICHD/CTSA randomized clinical trial (RCT): safety consideration. Pediatric Academic Societies Annual Meeting; 2010 May 1-4; Vancouver, Canada. 2010.

Wagner 2010c *{published data only}*
* Wagner CL, Johnson D, Hulsey TC, Ebeling M, Shary J, Smith PG, et al. Vitamin D supplementation during pregnancy part 2 NICHD/CTSA randomized clinical trial (RCT): outcomes. Pediatric Academic Societies' 2010 Annual Meeting; 2010 May 1-4; Vancouver, Canada. 2010.
Wagner CL, McNeil RB, Johnson DD, Hulsey TC, Ebeling M, Robinson C, et al. Health characteristics and outcomes of two randomized vitamin D supplementation trials during pregnancy: A combined analysis. *Journal of Steroid Biochemistry & Molecular Biology* 2013;**136**:313–20.

Yap 2014 *{published data only}*
Yap C, Cheung NW, Gunton JE, Athayde N, Munns CF, Duke A, et al. Vitamin D supplementation and the effects on glucose metabolism during pregnancy: a randomized controlled trial. *Diabetes Care* 2014;**37**(7):1837–44.

References to ongoing studies

Benson 2009 *{published data only}*
Benson J. A randomised controlled trial on the effects of antenatal vitamin D supplementation to improve vitamin D levels in the maternal and cord blood at birth in vitamin D deficient pregnant women. Australian New Zealand Clinical Trials Registry (www.anzctr.org.au) [accessed 19 Jul 2014] 2009.
Rodda CP, Benson JE, Vinvent AJ, Whitehead CL, Polyakov A, Vollenhoven B. Maternal vitamin D supplementation during pregnancy prevents vitamin D deficiency in the newborn: A randomised controlled trial. *Osteoporosis International* 2011;**Suppl 4**:S521–S559.

Bhatia 2012b *{published data only}*

Bhatia V. Vitamin D supplementation in pregnancy: regimens and long term effects on offspring. Clinical Trials Registry - India (http://ctri.nic.in) [accessed 29 Jun 2014] 2012.

Bhutta 2011 *{published data only}*

Bhutta ZA. Study of vitamin D supplementation on improvement of gums health. ClinicalTrials.gov (http://clinicaltrials.gov) [accessed 5 August 2014] 2011.

Bisgaard 2009 *{published data only}*

Bisgaard H. Vitamin D supplementation during pregnancy for prevention of asthma in childhood (ABCvitaminD). ClinicalTrials.gov (http://clinicaltrials.gov/) [accessed 31 July 2009].

Ghasemi 2014 *{published data only}*

Ghasemi H. Comparison of effectiveness of vitamin D supplementation in decreasing the development of the gestational diabetes mellitus in pregnant women. IRCT Iranian Registry of Clinical Trials (www.irct.ir) [accessed 19 Jul 2014] 2014.

Goldring 2010 *{published data only}*

Goldring S. Effects of prenatal vitamin D supplementation on respiratory and allergic phenotypes and bone density in the first three years of life. UKCRN (http://public.ukcrn.org.uk) [accessed 6 April 2011] 2010.

Habib 2010 *{published data only}*

Habib MA. Evaluation of the effectiveness of vitamin D supplementation to pregnant women and their infants in Pakistan. ClinicalTrials.gov (http://clinicaltrials.gov/) [accessed 15 February 2011] 2010.

Hacker 2010 *{published data only}*

Hacker AN. Bone Health in Pregnancy (B-Hip). ClinicalTrials.gov (http://clinicaltrials.gov) [accessed 2010] 2010.

Harvey 2012 *{published data only}*

Cooper C. A randomised double-blind placebo-controlled trial of vitamin D supplements for pregnant women with low levels of vitamin D in early pregnancy. ISRCTN Registry (www.isrctn.com) [accessed 15 September 2015] 2008.

Harvey NC, Javaid K, Bishop N, Kennedy S, Papageorghiou AT, Fraser R, et al. MAVIDOS Maternal Vitamin D Osteoporosis Study: Study protocol for a randomized controlled trial. The MAVIDOS Study Group. *Trials* 2012; **13**:13.

Jannati 2012 *{published data only}*

Jannati M. The effect of 50000 IU Vitamin D supplement administered two weekly on neonatal and pregnant women outcome - GDM. IRCT Iranian Registry of Clinical Trials (www.irct.ir) [accessed 20 Jul 2014] 2012.

Jelsma 2013 *{published data only}*

Jelsma JG, van Poppel MN, Galjaard S, Desoye G, Corcoy R, Devlieger R, et al. DALI: Vitamin D and lifestyle intervention for gestational diabetes mellitus (GDM) prevention: an European multicentre, randomised trial - study protocol. *BMC Pregnancy and Childbirth* 2013;**13**: 142.

Judkins 2011 *{published data only}*

Judkins A. A randomised double blinded interventional trial to determine the effect of 50,000 IU vitamin D supplementation monthly or twice monthly from 20 weeks gestation. Australian New Zealand Clinical Trials Register (www.anzctr.org.au) [accessed 11 February 2011] 2011.

Kachhawa 2014 *{published data only}*

Kachhawa G. A randomized controlled trial to investigate the effects of vitamin D supplementation on maternal and new-born baby's vitamin D status in Asian-Indian subjects - VIDIMAN. Clinical Trials Registry - India (http://www.ctri.nic.in/) [accessed 19 Jul 2014] 2014.

Lalooha 2012 *{published data only}*

Lalooha F. The effect of vitamin D supplementation during pregnancy on newborn's anthropometric index. IRCT Iranian Registry of Clinical Trials (www.irct.ir) [accessed 17 August 2015] 2012.

Lindqvist 2010 *{published data only}*

Lindqvist P. Vitamin D supplementation for prevention of placenta mediated pregnancy complications. - Prevention of pregnancy complications with vitamin D. EU Clinical Trials Register (https://www.clinicaltrialsregister.eu) [accessed 19 Jul 2014] 2010.

McLean 2012 *{published data only}*

McLean M. Effect of high-dose versus low-dose vitamin D supplementation in pregnancy on maternal glucose metabolism and the risk of gestational diabetes. Australian New Zealand Clinical Trials Registry (www.anzctr.org.au) [accessed 19 Jul 2014] 2012.

Mirghafourvand 2013 *{published data only}*

Mirghafourvand M. The effect of vitamin D and calcium plus vitamin D for leg cramps in pregnant women: a randomised controlled trial. IRCT Iranian Registry of Clinical Trials (www.irct.ir) (Accessed 20 Jul 2014).

Mozzafari 2010 *{published data only}*

Mozaffari H. Effect of vitamin D supplementation on glucose status, lipid profiles and inflammatory factors in mothers with a history of gestational diabetes. IRCT Iranian Registry of Clinical Trials (www.irct.ir) [accessed 20 Jul 2014] 2010.

Nausheen 2014 *{published data only}*

Nausheen S. Assessment of dose effectiveness of vitamin D supplementation during pregnancy. ClinicalTrials.gov (http://clinicaltrials.gov/) [accessed 2 September 2014] 2014.

Rasmussen 2009 *{published data only}*

Rasmussen G. Additional information on registered trial. Effects of vitamin D supplement before, during and after pregnancy on complications, birth weight and bone mineral density during lactation (gravita). Personal communication 2011.

Rasmussen GB. Effects of vitamin D supplement before and during pregnancy on birth weight (gravita).

ClinicalTrials.gov (http://clinicaltrials.gov/) [accessed 17 August 2010] 2009.

Roth 2013b *{published data only}*
Roth D. Maternal vitamin D for infant growth (MDIG) trial. ClinicalTrials.gov (http://clinicaltrials.gov/) [accessed 5 February 2014] 2013.

Simsek 2011 *{published data only}*
Simsek S. Vitamin D supplementation in gestational diabetes mellitus. Netherlands Clinical Trials Registry [accessed 31 May 2013] 2011.

Wagner 2013 *{published data only}*
Wagner CL. Preventing health disparities during pregnancy through vitamin D supplementation. ClinicalTrials.gov (http://clinicaltrials.gov/) [accessed 5 February 2014] 2013.

Additional references

Aghajafari 2013
Aghajafari F, Nagulesapillai T, Ronksley PE, Tough SC, O'Beirne M, Rabi DM. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies. *BMJ* 2013;**346**:f1169.

Akcakus 2006
Akcakus M, Koklu E, Budak N, Kula M, Kurtoglu S, Koklu S. The relationship between birthweight, 25-hydroxyvitamin D concentrations and bone mineral status in neonates. *Annals of Tropical Paediatrics* 2006;**26**(4): 267–75.

Ariyuki 1987
Ariyuki F. Growth retardation induced in rat fetuses by maternal fasting and massive doses of ergocalciferol. *Journal of Nutrition* 1987;**117**(2):342–8.

Armas 2004
Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. *Journal of Clinical Endocrinology and Metabolism* 2004;**89**(11):5387–91.

Arunabh 2003
Arunabh S, Pollack S, Yeh J, Aloia JF. Body fat content and 25-hydroxyvitamin D levels in healthy women. *Journal of Clinical Endocrinology and Metabolism* 2003;**88**(1):157–61.

August 1992
August P, Marcaccio B, Gertner JM, Druzin ML, Resnick LM, Laragh JH. Abnormal 1,25-dihydroxyvitamin D metabolism in preeclampsia. *American Journal of Obstetrics and Gynecology* 1992;**166**(4):1295–9.

Balshem 2010
Balshem H, Helfanda M, Schunemann HJ, Oxmand AD, Kunze R, Brozek J, et al. GRADE guidelines: rating the quality of evidence: introduction. *Journal of Clinical Epidemiology* 2010;**64**(4):401–6.

Bandeira 2006
Bandeira F, Griz L, Dreyer P, Eufrazino C, Bandeira C, Freese E. Vitamin D deficiency: a global perspective [Deficiência de vitamina D: uma perspectiva global]. *Arquivos Brasileiros de Endocrinologia e Metabologia* 2006;**50** (4):640–6.

Bener 2009
Bener A, Alsaied A, Al-Ali M, Al-Kubaisi A, Basha B, Abraham A, et al. High prevalence of vitamin D deficiency in type 1 diabetes mellitus and healthy children. *Acta Diabetologica* 2009;**4**(2):183–9.

Bodnar 2007
Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM. Maternal vitamin D deficiency increases the risk of preeclampsia. *Journal of Clinical Endocrinology and Metabolism* 2007;**92**(9):3517–22.

Bodnar 2010
Bodnar LM, Catov JM, Zmuda JM, Cooper ME, Parrott MS, Roberts JM, et al. Maternal serum 25-hydroxyvitamin D concentrations are associated with small-for-gestational age births in white women. *Journal of Nutrition* 2010;**140** (9):999–1006.

Butte 2002
Butte NF, Lopez-Alarcon MG, Garza C. *Nutrient adequacy of exclusive breastfeeding of the term infant during the first six months of life*. Geneva: World Health Organization, 2002.

Canadian Paediatric Society 2007
Canadian Paediatric Society, First Nations, Inuit and Métis Health Committee. Vitamin D supplementation: recommendations for Canadian mothers and infants. *Paediatrics & Child Health* 2007;**12**(7):583–98.

Cantorna 2008
Cantorna MT, Yu S, Bruce D. The paradoxical effects of vitamin D on type 1 mediated immunity. *Molecular Aspects of Medicine* 2008;**29**:369–75.

Cardus 2006
Cardus A, Parisi E, Gallego C, Aldea M, Fernandez E, Valdivielso JM. 1,25-Dihydroxyvitamin D3 stimulates vascular smooth muscle cell proliferation through a VEGF-mediated pathway. *Kidney International* 2006;**69**:1377–84.

Chan 1979
Chan GM, Buchino JJ, Mehlhorn D, Bove KE, Steichen JJ, Tsang RC. Effect of vitamin D on pregnant rabbits and their offspring. *Pediatric Research* 1979;**13**(2):121–6.

Chocano-Bedoya 2009
Chocano-Bedoya P, Ronnenberg AG. Vitamin D and tuberculosis. *Nutrition Reviews* 2009;**67**(5):289–93.

Christian 2003
Christian P, Khatry SK, Katz J, Pradhan EK, LeClerq SC, Shrestha SR, et al. Effects of alternative maternal micronutrient supplements on low birth weight in rural Nepal: double blind randomised community trial. *BMJ* 2003;**326**(7389):571.

Clemens 1982
Clemens TL, Adams JS, Henderson SL, Holick MF. Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. *Lancet* 1982;**319**:74–6.

Clifton-Bligh 2008
Clifton-Bligh RJ, McElduff P, McElduff A. Maternal vitamin D deficiency, ethnicity and gestational diabetes. *Diabetic Medicine* 2008;**25**(6):678–84.

Dawodu 2005
Dawodu A, Agarwal M, Sankarankutty M, Hardy D, Kochiyil J, Badrinath P. Higher prevalence of vitamin D deficiency in mothers of rachitic than nonrachitic children. *Journal of Pediatrics* 2005;**147**(1):109–11.

Dawodu 2011
Dawodu A, Nath R. High prevalence of moderately severe vitamin D deficiency in pre-term infants. Pediatrics International 2011; Vol. 53, issue 2:207–10.

Dawson-Hughes 2005
Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. *Osteoporosis International* 2005;**16**:713–6.

Dawson-Hughes 2008
Dawson-Hughes B. Serum 25-hydroxyvitamin D and functional outcomes in the elderly. *American Journal of Clinical Nutrition* 2008;**88**(2):527S–540S.

DeLuca 2004
DeLuca HF. Overview of general physiologic features and functions of vitamin D. *American Journal of Clinical Nutrition* 2004;**80**(6 Suppl):1689S–1696S.

Devereux 2007
Devereux G, Litonjua AA, Turner SW, Craig LC, McNeill G, Martindale S, et al. Maternal vitamin D intake during pregnancy and early childhood wheezing. *American Journal of Clinical Nutrition* 2007;**85**(3):853–9.

Diaz 2002
Diaz L, Arranz C, Avila E, Halhai A, Vilchis F, Larrae F. Expression and activity of 25-hydroxyvitamin D-1 alpha-hydroxylase are restricted in cultures of human syncytiotrophoblast cells from preeclamptic pregnancies. *Journal of Clinical Endocrinology and Metabolism* 2002;**87**(8):3876–82.

Drincic 2012
Drincic AT, Armas LA, Van Diest EE, Heaney RP. Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity. *Obesity (Silver Spring, Md.)* 2012;**20**(7):1444–8.

Eckard 2013
Eckard AR, Leong T, Avery A, Castillo MD, Bonilla H, Storer N, et al. Short communication: high prevalence of vitamin D deficiency in HIV-infected and HIV-uninfected pregnant women. *AIDS Research and Human Retroviruses* 2013;**29**(9):1224–8.

Egan 2008
Egan KM, Signorello LB, Munro HM, Hargreaves MK, Hollis BW, Blot WJ. Vitamin D insufficiency among African-Americans in the southeastern United States: implications for cancer disparities (United States). *Cancer Causes and Control* 2008;**19**(5):527–35.

El Koumi 2013
El Koumi MA, Ali YF, Abd El Rahman RN. Impact of maternal vitamin D status during pregnancy on neonatal vitamin D status. *Turkish Journal of Pediatrics* 2013;**55**(4):371–7.

Evans 2004
Evans KN, Bulmer JN, Kilby MD, Hewison M. Vitamin D and placental-decidual function. *Journal of the Society for Gynecologic Investigation* 2004;**11**(5):263–71.

Farrant 2009
Farrant HJ, Krishnaveni GV, Hill JC, Boucher BJ, Fisher DJ, Noonan K, et al. Vitamin D insufficiency is common in Indian mothers but is not associated with gestational diabetes or variation in newborn size. *European Journal of Clinical Nutrition* 2009;**63**(5):646–52.

Fitzpatrick 1988
Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. *Archives of Dermatology* 1988;**124**(6):869–73.

Ford 1973
Ford JA, Davidson DC, McIntosh WB, Fyfe WM, Dunnigan MG. Neonatal rickets in Asian immigrant population. *BMJ* 1973;**3**(5873):211–2.

Frenkel 1991
Frenkel Y, Barkai G, Mashiach S, Dolev E, Zimlichmann R, Weiss M. Hypocalciuria of preeclampsia is independent of parathyroid hormone level. *Obstetrics & Gynecology* 1991;**77**:822–5.

Friedman 1969
Friedman WF, Mills LF. The relationship between vitamin D and the craniofacial and dental anomalies of the supravalvular aortic stenosis syndrome. *Pediatrics* 1969;**43**(1):12–8.

Gale 2008
Gale CR, Robinson SM, Harvey NC, Javaid MK, Jiang B, Martyn CN, et al. Maternal vitamin D status during pregnancy and child outcomes. *European Journal of Clinical Nutrition* 2008;**62**(1):68–77.

Ganji 2012
Ganji V, Zhang X, Tangpricha V. Serum 25-hydroxyvitamin D concentrations and prevalence estimates of hypovitaminosis D in the U.S. population based on assay-adjusted data. *Journal of Nutrition* 2012;**142**(3):498–507.

Gilchrest 2008
Gilchrest BA. Sun exposure and vitamin D sufficiency. *American Journal of Clinical Nutrition* 2008;**88**:570S–577S.

Glerup 2000
Glerup H, Mikkelsen K, Poulsen L, Hass E, Overbeck S, Andersen H, et al. Hypovitaminosis D myopathy without biochemical signs of osteomalacic bone involvement. *Calcified Tissue International* 2000;**66**(6):419–24.

Halhali 1995
Halhali A, Bourgues H, Carrillo A, Garabedian M. Lower circulating insulin-like growth factor I and 1,25-

dihydroxyvitamin D levels in preeclampsia. *Revista de Investigacion Clinica* 1995;**47**(4):259–66.

Halhali 2000
Halhali A, Tovar AR, Torres N, Bourgues H, Garabedian M, Larrae F. Preeclampsia is associated with low circulating levels of insulin-like growth factor I and 1, 25-dihydroxyvitamin D in maternal and umbilical cord compartments. *Journal of Clinical Endocrinology and Metabolism* 2000;**85**(5):1828–33.

Hall 2010
Hall WB, Sparks AA, Aris RM. Vitamin D deficiency in cystic fibrosis. International Journal of Endocrinology 2010 [Epub ahead of print].

Harvey 2014
Harvey NC, Holroyd C, Ntani G, Javaid K, Cooper P, Moon R, et al. Vitamin D supplementation in pregnancy: a systematic review. *Health Technology Assessment* 2014;**18** (45):1–190.

Hathcock 2007
Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. *American Journal of Clinical Nutrition* 2007; **85**(1):6–18.

Heaney 2003
Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *American Journal of Clinical Nutrition* 2003;**77**(1):204–10.

Heaney 2008
Heaney RP. Vitamin D: criteria for safety and efficacy. *Nutrition Reviews* 2008;**66**(10 Suppl 2):S178–S181.

Hewison 1992
Hewison M. Vitamin D and the immune system. *Journal of Endocrinology* 1992;**132**(2):173–6.

Higgins 2011
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated March 2011]. The Cochrane Collaboration, 2009. Available from www.cochrane-handbook.org.

Holick 2002
Holick MF. Too little vitamin D in premenopausal women: why should we care?. *American Society for Clinical Nutrition* 2002;**76**:1, 3-4.

Holick 2005
Holick MF, Siris ES, Binkley N, Beard MK, Khan A, Katzer JT, et al. Prevalence of Vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *Journal of Clinical Endocrinology and Metabolism* 2005;**90**(6):3215–24.

Holick 2007a
Holick MF. Vitamin D deficiency. *New England Journal of Medicine* 2007;**357**(3):266–81.

Holick 2007b
Holick MF, Chen TC, Lu Z, Sauter E. Vitamin D and skin physiology: a D-lightful story. *Journal of Bone and Mineral Research* 2007;**22 Suppl 2**:V28–V33.

Holick 2008
Holick MF. Vitamin D deficiency: a worldwide problem with health consequences. *American Journal of Clinical Nutrition* 2008;**87**(4):1080S–1086S.

Hollick 2009
Holick MF. Vitamin D status: measurement, interpretation and clinical application. *Annals of Epidemiology* 2009;**19**: 73–8.

Hollis 2004
Hollis BW, Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. *American Journal of Clinical Nutrition* 2004; **80**(6 Suppl):1752S–178S.

Hollis 2007
Hollis B. Vitamin D requirement during pregnancy and lactation. *Journal of Bone and Mineral Research* 2007;**22 Suppl 2**:V39–V44.

Hyppönen 2013
Hyppönen E, Cavadino A, Williams D, Fraser A, Vereczkey A, Fraser WD, et al. Vitamin D and pre-eclampsia: original data, systematic review and meta-analysis. *Annals of Nutrition & Metabolism* 2013;**63**(4):331–40.

Institute of Medicine 2010
Food, Nutrition Board. Institute of Medicine. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington DC: National Academy Press, 2010.

Ioannou 2012
Ioannou C, Javaid MK, Mahon P, Yaqub MK, Harvey NC, Godfrey KM, et al. The effect of maternal vitamin D concentration on fetal bone. *Journal of Clinical Endocrinology and Metabolism* 2012;**97**(11):E2070–7.

Javaid 2006
Javaid MK, Crozier SR, Harvey NC, Gale CR, Dennison EM, Boucher BJ, et al. Princess Anne Hospital Study Group. Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. *Lancet* 2006;**367**:36–43.

Jones 2008
Jones G. Pharmacokinetics of vitamin D toxicity. *American Journal of Clinical Nutrition* 2008;**88**(2):582S–586S.

Lankes 2015
Lankes U, Elder PA, Lewis JG, George P. Differential extraction of endogenous and exogenous 25-OH-vitamin D from serum makes the accurate quantification in liquid chromatography-tandem mass spectrometry assays challenging. *Annals of Clinical Biochemistry* 2015;**52**(Pt 1): 151–60.

Levis 2005
Levis S, Gomez A, Jimenez C, Veras L, Ma F, Lai S, et al. Vitamin D deficiency and seasonal variation in an adult south Florida population. *Journal of Clinical Endocrinology and Metabolism* 2005;**90**(3):1557–62.

Li 2000b
Li DK, Wi S. Maternal pre-eclampsia/eclampsia and the risk of sudden infant death syndrome in offspring. *Paediatric and Perinatal Epidemiology* 2000;**14**(2):141–4.

Li 2002
Li Y, Kong J, Wei M, Chen ZF, Liu S, Cao LP. 1,25-dihydroxyvitamin D3 is a negative endocrine regulator of the renin-angiotensin system. *Journal of Clinical Investigation* 2002;**110**(2):229–39.

Lips 2001
Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocrine Reviews* 2001;**22**(4):477–501.

Litonjua 2009
Litonjua AA. Childhood asthma may be a consequence of vitamin D deficiency. *Current Opinion in Allergy and clinical immunology* 2009;**9**(3):202–7.

Logan 2013
Logan VF, Gray AR, Peddie MC, Harper MJ, Houghton LA. Long-term vitamin D3 supplementation is more effective than vitamin D2 in maintaining serum 25-hydroxyvitamin D status over the winter months. *British Journal of Nutrition* 2013;**109**(6):1082–8.

MacKay 2001
MacKay AP, Berg CJ, Atrash HK. Pregnancy-related mortality from preeclampsia and eclampsia. *Obstetrics & Gynecology* 2001;**97**(4):533–8.

Maghbooli 2007
Maghbooli Z, Hossein-Nezhad A, Shafaei AR, Karimi F, Madani FS, Larijani B. Vitamin D status in mothers and their newborns in Iran. *BMC Pregnancy and Childbith* 2007;**7**:1.

Maghbooli 2008
Maghbooli Z, Hossein-Nezhad A, Karimi F, Shafaei AR, Larijani B. Correlation between vitamin D3 deficiency and insulin resistance in pregnancy. *Diabetes/Metabolism Research and Reviews* 2008;**24**(1):27–32.

Mahon 2010
Mahon P, Harvey N, Crozier S, Inskip H, Robinson S, Arden N, et al. Low maternal vitamin D status and fetal bone development: cohort study. Journal of Bone and Mineral Research 2010; Vol. 25, issue 1:14–9.

Matsuoka 1991
Matsuoka LY, Wortsman J, Haddad JG, Kolm P, Hollis BW. Racial pigmentation and the cutaneous synthesis of vitamin D. *Archives of Dermatology* 1991;**127**(4):536–8.

Mave 2012
Mave V, Shere D, Gupte N, Suryavanshi N, Kulkarni V, Patil S, et al. SWEN India and Byramjee-Jeejeebhoy Medical College Clinical Trials Unit Study Team. Vitamin D deficiency is common among HIV-infected breastfeeding mothers in Pune, India, but is not associated with mother-to-child HIV transmission. *HIV Clinical Trials* 2012;**13**(5):278–83.

Maxwell 1981
Maxwell JD, Ang L, Brooke OG, Brown IR. Vitamin D supplements enhance weight gain and nutritional status in pregnant Asians. *British Journal of Obstetrics and Gynaecology* 1981;**88**(10):987–91.

McCullough 2007
McCullough M. Vitamin D deficiency in pregnancy: bringing the issues to light. *Journal of Nutrition* 2007;**137**:305–6.

McGrath 2001
McGrath J. Does 'imprinting' with low prenatal vitamin D contribute to the risk of various adult disorders?. *Medical Hypotheses* 2001;**56**(3):367–71.

Mehta 2009
Mehta S, Hunter DJ, Mugusi FM, Spiegelman D, Manji KP, Giovannucci EL, et al. Perinatal outcomes, including mother-to-child transmission of HIV, and child mortality and their association with maternal vitamin D status in Tanzania. Journal of Infectious Diseases 2009; Vol. 200, issue 7:1022–30.

Merewood 2009
Merewood A, Mehta SD, Chen TC, Bauchner H, Holick MF. Association between vitamin D deficiency and primary cesarean section. *Journal of Clinical Endocrinology and Metabolism* 2009;**94**(3):940–5.

Miller 2010
Miller J, Gallo RL. Vitamin D and innate immunity. *Dermatologic Therapy* 2010;**23**(1):13–22.

Moller 2013
Møller UK, Streym S, Mosekilde L, Heickendorff L, Flyvbjerg A. Frystyk J, et al. Changes in calcitropic hormones, bone markers and insulin-like growth factor I (IGF-I) during pregnancy and postpartum: a controlled cohort study. *Osteoporosis International* 2013;**24**(4):1307–20.

Morley 2006
Morley R, Carlin JB, Pasco JA, Wark JD. Maternal 25-hydroxyvitamin D and parathyroid hormone concentrations and offspring birth size. *Journal of Clinical Endocrinology and Metabolism* 2006;**91**(3):906–12.

Namgunga 2003
Namgunga R, Tsang RC. Bone in the pregnant mother and newborn at birth. *Clinica Chimica Acta* 2003;**333**(1):1–11.

Nesby-O'Dell 2002
Nesby-O'Dell S, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, Looker AC, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. *American Journal of Clinical Nutrition* 2002;**76**(1):187–92.

Nicolaidou 2006
Nicolaidou P, Hatzistamatiou Z, Papadopoulou A, Kaleyias J, Floropoulou E, Lagona E, et al. Low vitamin D status in mother-newborn pairs in Greece. *Calcified Tissue International* 2006;**78**(6):337–42.

Nnoaham 2008
Nnoaham KE, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. *International Journal of Epidemiology* 2008;**37**(1):113–9.

O'Riordan 2008
O'Riordan MN, Kiely M, Higgins JR, Cashman KD. Prevalence of suboptimal vitamin D status during pregnancy. *Irish Medical Journal* 2008;**101**(8):240, 242-3.

Ohta 2009
Ohta H, Kuroda T, Onoe Y, Orito S, Ohara M, Kume M, et al. The impact of lifestyle factors on serum 25-hydroxyvitamin D levels: across-sectional study in Japanese women aged 19-25 years. *Journal of Bone and Mineral Metabolism* 2009;**27**(6):682–8.

Ornoy 1968
Ornoy A, Menczel J, Nebel L. Alterations in the mineral composition and metabolism of rat fetuses and their placentas induced by maternal hypervitaminosis D2. *Israel Journal of Medical Sciences* 1968;**4**(4):827–32.

Ornoy 1969
Ornoy A, Nebel L, Menczel Y. Impaired osteogenesis of fetal long bones.Induced by maternal hypervitaminosis D2. *Archives of Pathology* 1969;**87**(6):563–71.

Palacios 2014
Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem?. *Journal of Steroid Biochemistry and Molecular Biology* 2014;**144**(Pt A):138–45.

Palomer 2008
Palomer X, González-Clemente JM, Blanco-Vaca F, Mauricio D. Role of vitamin D in the pathogenesis of type 2 diabetes mellitus. *Diabetes, Obesity and Metabolism* 2008; **10**(3):185–97.

Perez-Lopez 2015
Pérez-López FR, Pasupuleti V, Mezones-Holguin E, Benites-Zapata VA, Thota P, Deshpande A, et al. Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controlled trials. *Fertility and Sterility* 2015; **103**(5):1278–88.

Pierrot-Deseilligny 2010
Pierrot-Deseilligny C, Souberbielle JC. Is hypovitaminosis D one of the environmental risk factors for multiple sclerosis?. *Brain* 2010;**133**(Pt 7):1869–88.

Pludowski 2013
Pludowski P, Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB, et al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. *Autoimmunity Reviews* 2013;**12**(10): 976–89.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rockell 2005
Rockell JE, Green TJ, Skeaff CM, Whiting SJ, Taylor RW, Williams SM, et al. Season and ethnicity are determinants of serum 25-hydroxyvitamin D concentrations in New Zealand children Aged 5-14 y. *Journal of Nutrition* 2005; **135**:2602–8.

Roth 2011a
Roth DE. Vitamin D supplementation during pregnancy: safety considerations in the design and interpretation of clinical trials. *Journal of Perinatology* 2011;**31**(7):449–59.

Sachan 2005
Sachan A, Gupta R, Das V, Agarwal A, Awasthi PK, Bhatia V. High prevalence of vitamin D deficiency among pregnant women and their newborns in northern India. *American Journal of Clinical Nutrition* 2005;**81**(5):1060–4.

Sahu 2009
Sahu M, Das V, Aggarwal A, Rawat V, Saxena P, Bhatia V. Vitamin D replacement in pregnant women in rural north India: a pilot study. *European Journal of Clinical Nutrition* 2009;**63**(9):1157–9.

Scholl 2012
Scholl TO, Chen X, Stein P. Maternal vitamin D status and delivery by cesarean. *Nutrients* 2012;**4**(4):319–30.

Sloka 2009
Sloka S, Stokes J, Randell E, Newhook LA. Seasonal variation of maternal serum vitamin D in Newfoundland and Labrador. *Journal of Obstetrics and Gynaecology Canada: JOGC* 2009;**31**(4):313–21.

Tabesh 2013
Tabesh M, Salehi-Abargouei A, Tabesh M, Esmaillzadeh A. Maternal vitamin D status and risk of pre-eclampsia: a systematic review and meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2013;**98**(8):3165–73.

Theodoratou 2014
Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. *BMJ* 2014;**348**(g2035.): 1–19.

Theodoropoulos 2003
Theodoropoulos C, Demers C, Delvin E, Ménard D, Gascon-Barré M. Calcitriol regulates the expression of the genes encoding the three key vitamin D3 hydroxylases and the drug-metabolizing enzyme CYP3A4 in the human fetal intestine. *Clinical Endocrinology* 2003;**58**(4):489–99.

Thorne-Lyman 2012
Thorne-Lyman A, Fawzi WW. Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis. *Paediatric and Perinatal Epidemiology* 2012;**26**(Suppl 1):75–90.

Tolaymat 1994
Tolaymat A, Sanchez-Ramos L, Yergey AL, Vieira NE, Abrams SA, Edelstein P. Pathophysiology of hypocalciuria in preeclampsia: measurement of intestinal calcium

absorption. *International Journal of Gynecology & Obstetrics* 1994;**83**(2):283.

UK Department of Health 2009
UK Department of Health. Maternal nutrition: Vitamin D. UK Department of Health (http://www.dh.gov.uk/en/Healthcare/Children/Maternity/Maternalandinfantnutrition/Maternalnutrition/index.htm) (accessed 2009).

Utiger 1998
Utiger RD. The need for more vitamin D. *New England Journal of Medicine* 1998;**338**(12):828–9.

van Schoor 2011
van Schoor NM, Lips P. Worldwide vitamin D status. *Best Practice & Research. Clinical Endocrinology & Metabolism* 2011;**25**(4):671–80.

Vieth 1999
Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *American Journal of Clinical Nutrition* 1999;**69**(5):842–56.

Vieth 2001
Vieth R, Chan PCR, MacFarlane GD. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. *American Journal of Clinical Nutrition* 2001;**73**(2):288–94.

Vilarrasa 2007
Vilarrasa N, Maravall J, Estepa A, Sánchez R, Masdevall C, Navarro MA, et al. Low 25-hydroxyvitamin D concentrations in obese women: their clinical significance and relationship with anthropometric and body composition variables. *Journal of Endocrinological Investigation* 2007;**30**(8):653–8.

Viljakainen 2010
Viljakainen HT, Saarnio E, Hytinantti T, Miettinen M, Surcel H, Makitie O, et al. Maternal vitamin D status determines bone variables in the newborn. *Journal of Clinical Endocrinology and Metabolism* 2010;**Epub**:1391.

Vimaleswaran 2013
Vimaleswaran KS, Berry DJ, Lu C, Tikkanen E, Pilz S, Hiraki LT, et al. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomisation analysis of multiple cohorts.. *PLoS Medicine* 2013;**10**(2):e1001383.

Wagner 2008
Wagner CL, Greer FR, American Academy of Pediatrics Section on breastfeeding and American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics* 2008;**122**(5):1142–52.

Walker 2009
Walker VP, Modlin RL. The vitamin D connection to pediatric infections and immune function. *Pediatrics Research* 2009;**65(5 Pt 2)**:106R–113R.

Wang 2004
Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, et al. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. *Journal of Immunology* 2004;**173**:2909–12.

Wei 2013
Wei SQ, Qi HP, Luo ZC, Fraser WD. Maternal vitamin D status and adverse pregnancy outcomes: a systematic review and meta-analysis. *Journal of Maternal-fetal & Neonatal Medicine* 2013;**26**(9):889–99.

Williams 2008
Williams B, Williams AJ, Anderson ST. Vitamin D deficiency and insufficiency in children with tuberculosis. *Pediatric Infectious Disease Journal* 2008;**27**(10):941–2.

Wortsman 2000
Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *American Journal of Clinical Nutrition* 2000;**72**(3):690–3.

Xiong 1999
Xiong X, Mayes D, Demianczuk N, Olson DM, Davidge ST, Newburn-Cook C, et al. Impact of pregnancy-induced hypertension on fetal growth. *American Journal of Obstetrics and Gynecology* 1999;**180**(1 Pt 1):207–13.

Xuan 2013
Xuan Y, Zhao HY, Liu JM. Vitamin D and type 2 diabetes mellitus (D2). *Journal of Diabetes* 2013;**5**(3):261–7.

Yu 2009
Yu CK, Sykes L, Sethi M, Teoh TG, Robinson S. Vitamin D deficiency and supplementation during pregnancy. *Clinical Endocrinology* 2009;**70**(5):685–90.

Zhang 2008
Zhang C, Qiu C, Hu FB, David RM, Van Dam RM, Bralley A, et al. Maternal plasma 25-hydroxyvitamin D concentrations and the risk for gestational diabetes mellitus. *PLoS ONE* 2008;**3**(11):e3753.

References to other published versions of this review

De-Regil 2012
De-Regil LM, Palacios C, Ansary A, Kulier R, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews* 2012, Issue 2. [DOI: 10.1002/14651858.CD008873.pub2

Mahomed 1999
Mahomed K, Gülmezoglu AM. Vitamin D supplementation in pregnancy. *Cochrane Database of Systematic Reviews* 1999, Issue 1. [DOI: 10.1002/14651858.CD000228

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Asemi 2012

Methods	Randomised single-blinded controlled trial with 2 arms: vitamin D plus calcium and placebo
Participants	54 pregnant women at risk for pre-eclampsia, primigravida, aged 18-35 years old carrying singleton pregnancy at their third trimester attending maternity clinics affiliated to Kashan University of Medical Sciences, Kashan, Islamic Republic of Iran (latitude: 33.9889° N, 51.4772° E) Exclusion criteria: maternal severe pre-eclampsia, IUFD, placenta abortion, preterm delivery and GDM
Interventions	Participants were randomly allocated to 1 of 2 groups: group 1 (n = 27): women received 500 mg of carbonate calcium plus 200 IU of vitamin D (cholecalciferol-D3) daily for 9 weeks; group 2 (n = 27): women received placebo. The intervention lasted 9 weeks overall, starting at 25 weeks of pregnancy until week 34. Participants were asked not to alter their routine physical activity or usual diets and not to consume any supplement other than the one provided to them by the investigators Health worker cadre: the trial was carried out in maternity clinics affiliated to Kashan University of Medical Sciences, Kashan, Islamic Republic of Iran and the investigators provided the supplements to the participants
Outcomes	Maternal: body weight and height, BMI, fasting plasma glucose levels, serum total cholesterol, triglycerol concentrations, serum HDL-cholesterol, serum LDL-cholesterol levels, dietary intakes, total HDL: cholesterol ratio, gestational diabetes, severe pre-eclampsia, preterm delivery Laboratory method used for assessment of vitamin D concentrations: serum 25-hydroxyvitamin D [25(OH)D] concentrations were measured using a commercial ELISA kit (Immuno Diagnostic Systems). The inter- and intra-assay coefficient of variation for serum 25(OH)D assays ranged from 5% to 7.5%
Notes	• Total dose of supplementary vitamin D during pregnancy: 56,000 IU vitamin D or less; • start of supplementation: 20 weeks of pregnancy or more; • pre-gestational BMI (kg/m^2): overweight; • supplementation scheme/regimen: daily; • skin pigmentation based on Fitzpatrick skin tone chart (Fitzpatrick 1988): mixed/unknown; • latitude: north of the Tropic of Cancer; • season at the start of pregnancy: mixed/unknown. Source of funding: grant from the Vice-Chancellor for research, KUMS, and Iran

Risk of bias

Bias	Authors' judgement	Support for judgement

Asemi 2012 (*Continued*)

Random sequence generation (selection bias)	Low risk	Trial reported randomisation performed by the use of computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Trial reported that the appearance of the placebo capsules, such as colour, shape, size, and packaging, was identical to the vitamin D3 capsules
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were blind to the interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial is reported as blinded, although it is not specifically described if all were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up of 3 women in the vitamin D group due to preterm delivery (n = 1), IUFD (n = 1), and placental abruption (n = 1). 3 women in the placebo group were also excluded for the following reasons: GDM (n = 1), preterm delivery (n = 1), and severe pre-eclampsia (n = 1)
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	The study appears to be free of other sources of bias.

Asemi 2013a

Methods	Randomised, double-blind, placebo-controlled clinical trial with 2 arms: vitamin D and placebo, during March 2012 to September 2012
Participants	48 pregnant women, primigravida, aged 18-40 years old at 25 weeks of gestation and a singleton pregnancy attending maternity clinics affiliated with Kashan University of Medical Sciences, Kashan, Islamic Republic of Iran. Women with pre-eclampsia, hypertension, GDM, IUFD, or those with a history of rheumatoid arthritis, hepatic or renal failure, metabolic bone disease and malabsorption, or thyroid, parathyroid, or adrenal diseases were excluded from the analysis. Also, smokers and those taking medications including nonsteroidal antiinflammatory drugs and aspirin were excluded
Interventions	Participants were randomly assigned to receive 1 of 2 groups: group 1 (n = 24) received 400 IU vitamin D (cholecalciferol-D3) supplements daily; and group 2 (n = 24) received placebo for 9 weeks. Additionally, all participants also consumed 400 μg (0.4 mg) folic acid daily from the beginning of pregnancy and 60 mg elemental iron (as ferrous sulphate)

Asemi 2013a (*Continued*)

	daily from the second trimester Health worker cadre: the trial was carried out in maternity clinics affiliated to Kashan University of Medical Sciences, Kashan, Islamic Republic of Iran and the investigators provided the supplements to the participants. A trained midwife at the maternity clinic performed anthropometric measurements at study baseline and at 6 weeks after the intervention
Outcomes	Maternal: weight, height, BMI, systolic blood pressure and diastolic blood pressure, serum calcium concentrations, serum 25-hydroxyvitamin D [25(OH)D], serum hs-C-reactive protein, fasting plasma glucose, serum cholesterol, LDL-cholesterol, HDL-cholesterol concentrations, serum insulin, quantitative Insulin sensitivity check index (QUICKI) score, plasma total antioxidant capacity, plasma total glutathione, GDM, preterm delivery, IUFD, placental abruption, severe pre-eclampsia Laboratory method used for assessment of vitamin D concentrations: serum 25-hydroxyvitamin D [25(OH)D] concentrations were measured using a commercial ELISA kit (Immuno Diagnostic Systems)
Notes	• Total dose of supplementary vitamin D during pregnancy: 56,000 IU vitamin D or less; • start of supplementation: 20 weeks of pregnancy or more; • pre-gestational BMI (kg/m^2): overweight (25 or higher); • supplementation scheme/regimen: daily in a 9-week period; • skin pigmentation based on Fitzpatrick skin tone chart (Fitzpatrick 1988): mixed/unknown; • latitude: north of the Tropic of Cancer; • season at the start of pregnancy: spring-summer period. Source of funding: the Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random assignment was performed by the use of computer-generated random numbers
Allocation concealment (selection bias)	Low risk	A trained midwife at the maternity clinic performed the randomised allocation sequence and assigned participants to the groups. Placebo pills contained microcrystalline cellulose and were packed in identical tablets and coded by the producer to guarantee blinding
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were blind to the interventions

Asemi 2013a (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Measurements of laboratory were performed in a blinded fashion, in duplicate, in pairs (before/after intervention) at the same time, in the same analytical run, and in random order to reduce systematic error and inter assay variability
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 in each group were lost to follow-up but the outcomes are accounted for as they are clinical outcomes of interest for this review
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	The study appears to be free of other sources of bias.

Brooke 1980

Methods	Randomised double-blind controlled trial; 2-arm design with individual randomisation
Participants	126 Asian pregnant women 28-32 weeks of gestation attending the antenatal clinic at St George's Hospital, London, United Kingdom (latitude: 51°30'N, north of tropic of Cancer). All pregnant women were first-generation immigrants mostly from India, Pakistan, Bangladesh, Sri Lanka, Mauritius and east Africa Exclusion and elimination criteria: preterm deliveries, congenital malformations and maternal illnesses likely to affect fetal growth (such as diabetes) although these data are not presented
Interventions	Participants were randomly allocated to 1 of 2 groups: group 1 (n = 59 at the end of the trial): women received daily 1000 IU vitamin D (ergocalciferol-D2) daily (estimated total dose: 56000-84000 IU); group 2 (n = 67 at the end of the trial) received a placebo until term Start of supplementation: weeks 28-32 gestation. Length of the intervention/follow-up: 8-12 weeks from supplementation to term Health worker cadre: St George's Hospital Medical School, London, United Kingdom. Medical doctors that were part of the team conducted the measurements and provided the supplements
Outcomes	Maternal: maternal weight gain, dietary vitamin D intake, 25-hydroxyvitamin D (25-OHD) concentrations in cord blood and at term. Plasma calcium (adjusted for albumin concentration), inorganic phosphate, bilirubin, albumin concentrations and total alkaline phosphatase activity, alanine transaminase and γ -glutamyl transferase activities, vitamin D binding globulin concentration, compliance Infant: weight, crown-heel length, crown-rump length, rump-heel length, occipitofrontal head circumference, forearm length, lower leg length, triceps and subscapular skinfold thickness, fontanelle area, plasma cholecalciferol at day 3 and day 6. weight, length and head circumference at 3, 6, 9 and 12 months

Brooke 1980 (*Continued*)

	Laboratory method used for assessment of vitamin D concentrations: Serum 25-OHD concentration was measured by competitive protein binding assay after chromatographic purification of lipid extracts of serum
Notes	• Total dose of supplementary vitamin D during pregnancy: 5 more than 56,000 to 200,000 IU; • start of supplementation: 20 weeks of pregnancy or more; • pre-gestational BMI (kg/m^2): unknown/mixed; • supplementation scheme/regimen: daily; • skin pigmentation based on Fitzpatrick skin tone chart (Fitzpatrick 1988): mixed/unknown; • latitude: north of the Tropic of Cancer; • season at the start of pregnancy: authors report that to avoid distortion of the results due to seasonal variation in sunlight hours the trial was carried out during autumn and winter 1977, the whole of 1978 and spring and summer 1979. Source of funding: The pathological research fund, St George's Hospital Medical School, and the South-west Thames Regional Health Authority

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial reported random allocation to the groups, although the method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants received either vitamin D or placebo.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	High risk	Unclear number of randomised participants. Preterm deliveries, congenital malformations, and maternal illnesses likely to affect fetal growth (such as diabetes) were eliminated from the trial. There is not complete documentation of the exclusions
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	The study appears to be free of other sources of bias. There were no significant baseline differences between the groups

		in maternal age, parity, height, vegetarian: non-vegetarian ratio or the distribution of the various countries of origin

Delvin 1986

Methods	Randomised trial; 2-arm design with individual randomisation
Participants	40 pregnant women attending their compulsory visit during the third month of pregnancy at the Obstetrical Unit of the Hopital Edouard Herriot, Lyon, France (latitude: 45° 45' 0" N north of tropic of Cancer). Inclusion criterion: singleton pregnancy at term and uneventful vaginal deliveries. Pre-gestational BMI and skin pigmentation not reported
Interventions	Participants were randomly assigned to 1 of 2 groups at the time of the compulsory visit: group 1 (n = 20): women received daily 1000 IU vitamin D (cholecalciferol-D3) (estimated total dose: 55,000 IU); group 2 (n = 20): women received no supplement during the last trimester of pregnancy for 12 weeks from start of supplementation to term Health worker cadre: compliance was verified by a weekly visit by a midwife
Outcomes	Maternal: serum (during last trimester of pregnancy) and cord blood immunoreactive parathyroid hormone (iPTH), 25-hydroxyvitamin D (25-OHD), 1-alfa,25-dihydroxyvitamin D ($1,25(OH)_2D$), total calcium, ionised calcium, magnesium, inorganic phosphate Infant: immunoreactive parathyroid hormone (iPTH), 25-hydroxyvitamin D (25-OHD), 1-alfa,25-dihydroxyvitamin D ($1,25(OH)_2D$), total calcium, ionised calcium, magnesium, inorganic phosphate at 4 days of age Laboratory method used for assessment of vitamin D concentrations: Serum 25-OHD and 1,25(OH) D levels were measured by radioligand assays with slight modifications. With sample volumes of 0.75 to 1.5 mL, the inter assay variation coefficient for the 2 assays were 8% and 10%, respectively
Notes	• Total dose of supplementary vitamin D during pregnancy: 56,000 IU vitamin D or less; • start of supplementation: 20 weeks of pregnancy, or more; • pre-gestational BMI (kg/m^2): unknown/mixed; • supplementation scheme/regimen: daily; • skin pigmentation based on Fitzpatrick skin tone chart (Fitzpatrick 1988): mixed/unknown; • latitude: north of the Tropic of Cancer; • season at the start of pregnancy: winter-spring. All selections were performed in December, and all deliveries occurred in June. Source of funding: Shriners of North America, the France-Quebec Exchange Program, and INSERM Grant 121023

Risk of bias

Delvin 1986 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial reported as randomised but the method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	1 group received supplements while the other received no treatment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Compliance was verified by the midwife. As 1 group received supplements and the other received no intervention it is clear that the midwife knew which women were in each group
Incomplete outcome data (attrition bias) All outcomes	High risk	1 participant from the control group (5%) and 5 (25%) from the vitamin D supplemented group. Laboratory methods reported for 25 to 30 participants (depending on the outcome) out of 40 originally randomised
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	The study appears to be free of other sources of bias.

Diogenes 2013

Methods	Randomised, placebo-controlled trial; 2-arm design with individual randomisation
Participants	84 pregnant adolescents (13-19 years of age) primigravidae (pregnant for the first time) with singleton pregnancies and 23-29 weeks of gestation attending prenatal care at the Maternidade Escola, Universidade Federal do Rio de Janeiro, Brazil (latitude: 22.9083° S, 43.1964° W) from September 2009 to June 2011 and intending to exclusively or predominantly breast feed Women with chronic health problems, pregnancy complications, smokers, users of nutritional supplements besides iron plus folate supplements provided during standard prenatal care, and mothers who decided not to breast feed were excluded from the study
Interventions	Participants were randomly assigned to: 1 of 2 groups: group 1 (n = 43) received a commercially available supplement (Rexall Sundown®) containing 600 mg calcium (as calcium carbonate) plus 200 IU vitamin D (cholecalciferol-D3) daily; group 2 (n = 41) received placebo (capsules of microcrystalline cellulose and corn starch; Quintessencia)

Diogenes 2013 (*Continued*)

	daily Health worker cadre: capsules of calcium plus vitamin D or placebo were provided monthly to participants by a member of the research team during prenatal visits. Compliance was controlled by counting the remaining capsules at each visit and by telephone reminders. Calcium and vitamin D dietary intake was assessed by at least 3 24-hour dietary recall questionnaires applied by a trained nutritionist. Standing height and body weight were measured by using a stadiometer (Seca) and a calibrated electronic scale (Filizola), respectively. The same operator performed all scanning and calibration
Outcomes	Maternal: 1 measurement at 5 and 20 weeks postpartum, serum 25(OH)D, parathyroid hormone, insulin-like growth factor (IGF-I), lumbar spine PA, bone mineral content, serum prolactin and estradiol Laboratory method used for assessment of vitamin D concentrations: Serum 25(OH) D, intact parathyroid hormone (PTH), and IGF-I were analysed by using a chemiluminescent enzyme-labelled immunometric assay
Notes	• Total dose of supplementary vitamin D during pregnancy: 56,000 IU vitamin D or less; • start of supplementation: 20 weeks of pregnancy or more. The supplementation started from 26 weeks of pregnancy (baseline) until parturition; • pre-gestational BMI (kg/m^2): normal weight; • supplementation scheme/regimen: daily; • skin pigmentation based on Fitzpatrick skin tone chart (Fitzpatrick 1988): mixed/unknown; • latitude: the city lies on the Tropic of Capricorn; • season at the start of pregnancy: all year round. Source of funding: Conselho Nacional de Desenvolvimento Cient fico e Tecnologico [grant 471872/2008-3 (to CMD) and a doctoral fellowship (to MELD)] and the Fundacao Carlos Chagas Filho de Amparo a' Pesquisa do Estado do Rio de Janeiro (grant E-26/102.759/2008; to CMD), Brazil

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random assignment was done by a member of the research team in a 1:1 ratio within permuted blocks of size 10
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were randomly and single-blinded assigned to 1 of the 2 groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment.

Diogenes 2013 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Out of 43 patients in the intervention group: decided not to breast feed (n = 1), lost to follow-up (n = 2), pregnancy complications (n = 1), time constrains (n = 3), no reason given (n = 4), moved out of area (n = 2). Analysed at 5 weeks postpartum (n = 30) Out of 41 patients in the placebo group: decided not to breast feed (n = 1), other health issues (n = 1), lost to follow-up (n = 2), pregnancy complications (n = 2), time constrains (n = 3), no reason given (n = 5) , moved out of area (n = 1). Analysed at 5 week postpartum (n = 26) 9 mothers were lost for the 20-week measurement, which reduced the effective sample size for the bone change over the postpartum time assessment. Nevertheless, the magnitude of significant differences between groups in bone measures at the lumbar spine at 20 weeks postpartum, after adjustment for confounding factors, probably reduced the potential bias because of uncontrolled factors, such as the unknown bone status before pregnancy
Selective reporting (reporting bias)	Low risk	The trial was approved by the Ethical Committee of Maternidade Escola, Universidade Federal do Rio de Janeiro (www.clinicaltrials.gov; NCT01732328)
Other bias	Unclear risk	The study appears to be free of other sources of bias.

Grant 2013

Methods	Randomised, double-blind, placebo-controlled multi-arm parallel study
Participants	260 pregnant women 26-30 weeks' gestation, with a singleton pregnancy attending community based primary care maternity clinic in Auckland, New Zealand (latitude 36°S) from April 2010 to July 2011 and then their infants, from birth to age 6 months Women already taking vitamin D supplementation 200 IU per day, a history of renal stones or hypercalcaemia, or any serious pregnancy complication at enrolment were excluded from the study
Interventions	Participants were randomly assigned to 1 of 3 mother/infant groups: group 1 (n = 87) women received placebo from 26-30 weeks of pregnancy until parturition and their infants also received placebo from 0-6 months of age; group 2 (n = 87) women received

Grant 2013 (*Continued*)

	1000 IU vitamin D (cholecalciferol-D3) from 26-30 weeks of pregnancy until parturition and their infants received 400 IU vitamin D from 0-6 moths of age; group 3 (n = 86) women received 2000 IU vitamin D (cholecalciferol-D3) from 26-30 weeks of pregnancy until parturition and their infants received 800 IU from birth to 6 months of age Health worker cadre: the study was conducted by the research team but it is not reported who provided the supplements or measured the outcomes
Outcomes	Maternal: serum 25(OH)D concentration. Infant: serum 25(OH)D concentration. Laboratory method used for assessment of vitamin D concentrations: serum 25(OH)D concentration was measured using isotope-dilution liquid chromatography-tandem mass spectrometry in a Vitamin D External Quality Assurance Scheme-certified laboratory
Notes	• Total dose of supplementary vitamin D during pregnancy: 56,000 IU vitamin D or less; • start of supplementation: 20 weeks of pregnancy or more; • pre-gestational BMI (kg/m^2): unknown/mixed; • supplementation scheme/regimen: daily; • skin pigmentation based on Fitzpatrick skin tone chart (Fitzpatrick 1988): mixed/unknown; • latitude:between Tropics of Cancer and Capricorn; • season at the start of pregnancy: all year round. Source of funding: Health Research Council of New Zealand, grant number 09/215R. Dr Mitchell is supported by Cure Kids. Study medicine was prepared by the Ddrops Company (Woodbridge, Ontario, Canada)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Trial reported computer-generated randomisation list.
Allocation concealment (selection bias)	Low risk	The allocation sequence was concealed from research staff involved in recruitment. Trial reported randomly allocated treatment to each participant and labelled identical study medicine bottles such that study staff and participants were unaware of the treatment status
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study statistician randomly allocated a treatment to each participant and labelled identical study medicine bottles such that study staff and participants were unaware of the treatment status

Grant 2013 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study staff and participants were unaware of the treatment status
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported compliance did not differ between groups. Placebo group: discontinued intervention during pregnancy (n = 3), withdrew at 30 & 32 weeks of gestation (n = 2), late fetal death at 37 weeks of gestation (n = 1). Lower dose vitamin D group: discontinued intervention during pregnancy (n = 3), withdrew @ 32 weeks of gestation (n = 2), moved from region @ 36 weeks of gestation (n = 1). Higher dose vitamin D group: discontinued intervention during pregnancy (n = 3), withdrew @ 29 & 38 weeks of gestation (n = 2), moved from region @ 36 weeks of gestation (n = 1)
Selective reporting (reporting bias)	Low risk	Registration was with the Australian NZ Clinical Trials Registry (ACTRN12610000483055)
Other bias	Low risk	The study appears to be free of other sources of bias.

Li 2000a

Methods	Clinical controlled trial with 3 arms.
Participants	88 pregnant women with a predisposition to pregnancy-induced hypertension, at 20-24 weeks' gestation, a BMI index of lower than 24, and an arterial pressure of < 11.3 kPa attending an outpatient clinic and labour ward of the First Afiffliated Hospital of Xi'an Medical University, Xi'an, China
Interventions	Participants were divided into 3 groups: group 1 (n = 29) received a daily dose of a tablet containing 600 mg of calcium and 200 IU of vitamin D (Caltrate-D) daily from 20-24 weeks until deliver; group 2 (n = 29) received 1200 mg of calcium and 400 IU vitamin D (Caltrate-D) daily from 20-24 weeks until deliver; group 3 (n = 30) received no intervention from 20-24 weeks until delivery Health worker cadre: not reported.
Outcomes	Blood pressure, ionised calcium and platelet intracellular calcium, incidence rates of pregnancy-induced hypertension
Notes	• Total dose of supplementary vitamin D during pregnancy: 56,000 IU vitamin D or less; • start of supplementation: 20 weeks of pregnancy or more;

Li 2000a (*Continued*)

	• pre-gestational BMI (kg/m^2): unknown/mixed; • supplementation scheme/regimen: daily; • skin pigmentation based on Fitzpatrick skin tone chart (Fitzpatrick 1988): mixed/unknown; • latitude:north of Tropic of Cancer; • season at the start of pregnancy: all year round. Source of funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The assignment of the groups method is not reported.
Allocation concealment (selection bias)	Unclear risk	It is unclear if there was allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	2 groups received an intervention while women from group 3 received no intervention. There is no report on blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	2 groups received an intervention while women from group 3 received no intervention. There is no report on blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up not reported.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to make a judgement.
Other bias	High risk	The details of the methods are not available. The report is rather short

Mallet 1986

Methods	Randomised controlled trial; 3-arm design with individual randomisation
Participants	77 white pregnant women 18-36 years of age in the last trimester of pregnancy living in Northwest of France (latitude: 49° 26' 0" N north of tropic of Cancer). Pre-gestational BMI not reported
Interventions	Participants were randomly assigned to 1 of 3 groups: group 1 (n = 21) women received daily 1000 IU of vitamin D (ergocalciferol-D2) for the last 3 months of pregnancy (estimated total dose throughout pregnancy: 90,000 IU); group 2 (n = 27) women received a single dose of 200,000 IU (5 mg) vitamin D at the 7th month of pregnancy; group 3 (n = 29) women received no supplement and served as controls Length of the intervention/follow-up: 12 weeks from start of supplementation to term

	Health worker cadre: the study was conducted by the research team at the maternity of Balvedere, Rouen, Frances but the roles are not described. It is unclear who provided the supplements and measured the outcomes
Outcomes	Maternal: 24-hour urinary calcium excretion after 6 weeks supplementation, calcium, 25-hydroxyvitamin D (25-OHD) and1-alfa,25-dihydroxyvitamin D (1,25$(OH)_2$D) metabolites of vitamin D from serum and cord during labour and delivery Infant: serum calcium levels at days 2 and 6 of life, birthweight. Laboratory method used for assessment of vitamin D concentrations: for 25 OHD and 1,25 $(OH)_2$ D determinations the following techniques were used: extraction with chloroform-methanol-water according to Preece, double step purification, first on a Sephadex LH 20 column with chloroform hexan 45-55 vol/vol as solvent, then on a high-pressure liquid pression system according to Shepard. Plasma metabolites were measured by competitive assay using rat protein for 25 OHD and chicken intestine cytosol for 1, 25 $(OH)_2$ D according to Jongen. Assay sensitivity for 1,25 $(OH)_2$ D was 5 pmol/tube and for 25 OHD was 25 pmol/tube.
Notes	• Total dose of supplementary vitamin D during pregnancy: more than 56,000 to 200,000 IU; • start of supplementation: 20 weeks of pregnancy or more; • pre-gestational BMI (kg/m^2): unknown/mixed; • supplementation scheme/regimen: single/daily; • skin pigmentation based on Fitzpatrick skin tone chart (Fitzpatrick 1988): mixed/unknown; • latitude: north of the Tropic of Cancer; • season at the start of pregnancy: winter pregnancy. Infants born during February and March. Source of funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by random numbers table.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different interventions were used: daily dose or single dose or no supplement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	High risk	It is unclear if there was attrition, but given the uneven number of participants reported it is likely that there were losses to

Mallet 1986 (*Continued*)

		follow-up
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	High risk	Groups are reported with notorious different sample size. It is unclear whether the numbers reflect the participants who finished the trial (unclear and uneven losses to follow-up); a non randomised process; or a selection bias in which randomised participants did not receive the intervention

Marya 1987

Methods	Randomised controlled trial; 2-arm design with randomisation at individual level
Participants	400 pregnant women 20-35 years of age, attending the antenatal clinic of Medical College Hospital in Rohtak, India (latitude: 76° 34' 0' north of Tropic of Cancer). Pre-gestational BMI and skin pigmentation not reported
Interventions	Participants were allocated to 1 of 2 groups: group 1 (n = 200) received a daily supplement containing 1200 IU vitamin D and 375 mg calcium (estimated total dose from week 20-24 of gestation to term:134,400-168,000 IU); group 2 (n = 200) received no supplement from 20-24 weeks of pregnancy until delivery Length of the intervention/follow-up: 20-24 weeks from start of supplementation to term Health worker cadre: not specified.
Outcomes	Maternal: pre-eclampsia (defined as blood pressure of 140 mmHg or higher systolic and/or 90 mmHg diastolic along with proteinuria higher than 300 mg/24 hours); systolic and diastolic blood pressure at 24, 28, 32 and 36 weeks of gestation. Serum calcium and creatinine Laboratory method used for assessment of vitamin D concentrations: not assessed
Notes	Biochemical analyses were made for those who developed pre-eclampsia (n = 12) and also in a group of women with no pre-eclampsia (n = 25) and a control group of non pregnant women. The results of the stratified analysis are not reported in this review • Total dose of supplementary vitamin D during pregnancy: more than 56,000 to 200,000 IU; • start of supplementation: 20 weeks of pregnancy, or more; • pre-gestational BMI (kg/m^2): unknown/mixed; • supplementation scheme/regimen: daily; • skin pigmentation based on Fitzpatrick skin tone chart (Fitzpatrick 1988): mixed/unknown; • latitude: north of the Tropic of Cancer; • season at the start of pregnancy: mixed/unknown. Source of funding: not reported.

Marya 1987 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	400 pregnant women, of these 200 were randomly selected and put on a daily supplement of calcium and vitamin D Method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	There is insufficient information to permit judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only data on biochemical were reported for those who developed pre-eclampsia and some of those with no pre-eclampsia and a group of non pregnant controls
Selective reporting (reporting bias)	High risk	Outcomes reported for some subgroups only.
Other bias	Low risk	The study appears to be free of other sources of bias.

Marya 1988

Methods	Randomised clinical trial; 2-arm design with individual randomisation
Participants	200 pregnant women, aged 22-35 years old, attending the antenatal clinic of the Medical College Hospital, Rohtak, India (latitude: 76° 34' 0' north of Tropic of Cancer). Inclusion criterion: uncomplicated single pregnancy. Exclusion criteria: pre-eclampsia, antepartum haemorrhage, premature delivery. Pre-gestational BMI and skin pigmentation not reported
Interventions	Participants were allocated to 1 of the following groups: group 1 (n = 100) women received 2 doses of 600,000 IU (each dose at 7th and 8th month of pregnancy (estimated total dose: 1,200,000 IU); group 2 (n = 100): women received no intervention Length of the intervention/follow-up: 12 weeks from start of supplementation to term Health worker cadre: not specified.

Outcomes	Maternal: venous and cord serum calcium, serum proteins, inorganic phosphate, alkaline phosphatase, weight. Radiological examination on women with abnormal biochemistry or osteomalacia symptomatology. Side effects: back age, leg-pains, general weakness, cramps Infant: birthweight, low birthweight, crown-heel length, head circumference, mid-arm circumference within 24 hours after birth. Skinfold thickness (triceps and infrascapular) Laboratory method used for assessment of vitamin D concentrations: not assessed
Notes	• Total dose of supplementary vitamin D during pregnancy: more than 200,000 IU of vitamin D; • start of supplementation: 20 weeks of pregnancy or more; • pre-gestational BMI (kg/m^2): unknown/mixed; • supplementation scheme/regimen: 2 single doses were provided at 7th and 8th month of pregnancy; • skin pigmentation based on Fitzpatrick skin tone chart (Fitzpatrick 1988): mixed/unknown; • latitude: north of the Tropic of Cancer; • season at the start of pregnancy: mixed/unknown. Source of funding: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'200 pregnant women, of these 100 were randomly selected (supplemented group) had been administered two doses of vitamin D.' Method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	There is insufficient information to permit judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up are not documented although exclusions included pregnancy complications. Result tables mention that each arm was comprised of 100 women, a number that corresponds to that described for the treatment allocation

Marya 1988 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	The study appears to be free of other sources of bias.

Mazurkevich 2013

Methods	Randomised control trial.
Participants	72 pregnant women with physiological pregnancy aged 18-35 with low alimentary consumption of calcium (< 600 mg/day) who attended to Moscow State University of medicine and dentistry, department of obstetrics and gynaecology. (Latitude: 55.7500° N, 37.6167° E)
Interventions	Participants were randomly assigned to 1 of 2 groups: group 1 (n = 43): 1250 mg of calcium carbonate and 200 IU of vitamin D (cholecalciferol-D3) from the second pregnancy trimester until term, in 2 takes a day; group 2 (n = 29): did not undergo the intended preventive measures Health worker cadre: not reported.
Outcomes	Maternal: resistance of uterine arteries, resistance of umbilical arteries, uterine-placental circulation Infant: fetal-placental circulation, intrauterine growth retardation, assessed by dopplerometry Laboratory method used for assessment of vitamin D concentrations: not assessed
Notes	• Total dose of supplementary vitamin D during pregnancy: 56,000 IU or less IU; • start of supplementation: 20 weeks of pregnancy, or more; • pre-gestational BMI (kg/m^2): unknown/mixed; • supplementation scheme/regimen: daily; • skin pigmentation based on Fitzpatrick skin tone chart (Fitzpatrick 1988): mixed/unknown; • latitude: north of the Tropic of Cancer; • season at the start of pregnancy: mixed/unknown. Source of funding: not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"72 pregnant women with physiological pregnancy aged 18-35 with low alimentary consumption of calcium (<600 mg/day) were randomised into two groups." Method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.

Mazurkevich 2013 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	It is not reported whether the trial was blinded to participants, outcome assessor or care providers
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There is insufficient information to permit judgement.
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	The study appears to be free of other sources of bias.

Roth 2010

Methods	Randomised placebo-controlled trial.
Participants	160 pregnant women aged 18 < 35 years old, attending to the International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh (latitude: 23.7000° N, 90.3750° E, north of the Tropic of Cancer). Inclusion criteria: patients with residence in Dhaka, with plans to have the delivery performed at the Shimantik maternity centre, and to stay in Dhaka throughout the pregnancy and 1 month past the delivery, with gestational age of 26th to 29th (inclusive), estimated based on the first day of the last menstrual period. Exclusion criteria: Use of any dietary supplement containing more than 400 IU/day (10 mcg/day) of vitamin D within the month prior to enrolment, or refusal to stop taking supplemental vitamin D at any dose after enrolment, current use of anti-convulsant or anti-mycobacterial (tuberculosis) medications, severe anaemia (haemoglobin concentration < 70 g/L), complicated medical or obstetric history: cardiovascular disease, uterine haemorrhage, placenta praevia, threatened abortion, hypertension, pre-eclampsia, preterm labour, or multiple gestation), prior history of delivery of an infant with a major congenital anomaly, birth asphyxia, or perinatal death (stillbirth or death within first week of life)
Interventions	Participants were randomly assigned to 1 of 2 groups: group 1 (n = 80): women received vitamin D (cholecalciferol-D3) 35,000 IU per week, started at 26-29 weeks' gestation, until delivery; group 2 (n = 80): women received placebo control administered weekly from 26-29 weeks' gestation until delivery Health worker cadre: supplement doses were measured in disposable plastic syringes and orally administered by study personnel
Outcomes	Maternal: serum 25-hydroxyvitamin D concentration, serum calcium concentration, urine Ca:Cr ratio Infant: immune function, infant growth, postnatal vitamin D status, serum calcium Laboratory method used for assessment of vitamin D concentrations: Serum 25(OH)D was quantified by high-performance liquid chromatography tandem mass spectroscopy (LCMS/MS) in the Department of Pathology and Laboratory Medicine at the Hospital

Roth 2010 (*Continued*)

	for Sick Children
Notes	• Total dose of supplementary vitamin D during pregnancy: more than 200,000 IU; • start of supplementation: 20 weeks of pregnancy or more; • pre-gestational BMI (kg/m^2): unknown/mixed; • supplementation scheme/regimen: daily; • skin pigmentation based on Fitzpatrick skin tone chart (Fitzpatrick 1988): mixed/unknown; • latitude: north of the Tropic of Cancer; • season at the start of pregnancy: summer. Source of funding: The Thrasher Research Fund, Salt Lake City, USA

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Trial reported computer-generated randomisation list.
Allocation concealment (selection bias)	Low risk	The allocation sequence was prepared by International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh personnel not otherwise involved in the study, and was concealed from investigators
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial reported that participants and research staff (including lab personnel) were blinded to allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial reported that participants and research staff (including lab personnel) were blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 160 participants recruited and randomly assigned to either vitamin D (35,000 IU/week) or placebo, 13 were lost to follow-up prior to delivery (6 in the placebo group and 7 in the vitamin D group), all because of having left the Dhaka area
Selective reporting (reporting bias)	Low risk	This trial was registered at ClinicalTrials.gov (NCT01126528) and all outcomes were reported as per registration
Other bias	Unclear risk	The study appears to be free of other sources of bias.

Sablok 2015

Methods	Randomised controlled trial with 2 arms, with randomisation at the individual level from years 2010 to 2012
Participants	180 primigravidae women with singleton pregnancy at 14-20 weeks in the Department of Obstetrics and Gynaecology in Safdarjung Hospital, New Delhi, India (28°38′08 N, 77°13′28 E north of Tropic of Cancer). Pregnant women with pre-existing osteomalacia, known hyperparathyroidism, renal, liver dysfunction, tuberculosis, sarcoidosis and women not willing to comply to the study protocol were excluded
Interventions	Participants were randomly assigned to 1 of 2 groups: group 1 (n = 60) women did not receive any supplementation of vitamin D; group 2 (n = 120) women received vitamin D (cholecalciferol-D3) supplementation in dosages depending upon the level of serum 25 (OH)-D levels estimated at entry into the study. Participants from this second group with sufficient levels of vitamin D (serum 25(OH)-D levels > 50 nmol/L), received only 1 dose of 60,000 IU vitamin D (cholecalciferol-D3) at 20 weeks; participants with insufficient levels of vitamin D (serum 25(OH)-D levels 25-50 nmol/L) received 2 doses of 120, 000 IU vitamin D (cholecalciferol-D3) at 20 weeks and 24 weeks; and participants with deficient levels of vitamin D status (serum 25(OH)-D levels < 25 nmol/L) received 4 doses of 120,000 IU vitamin D cholecalciferol-D3) at 20, 24, 28 and 32 weeks Health worker cadre: unclear what the roles of the researchers and other workers in the health worker cadre
Outcomes	Maternal: preterm labour, pre-eclampsia, GDM, serum 25(OH)-D concentration, serum calcium, phosphorus and serum ALP levels. Infants: Apgar score, birthweight, low birthweight, 25(OH)-D concentration in cord blood, small-for-gestational age; appropriate for gestational age Laboratory method used for assessment of vitamin D concentrations: Serum 25(OH)D was quantified by sandwich ELISA
Notes	• By total dose of supplementary vitamin D during pregnancy: more than 56,000 to 200,000 IU to more than 200,000 IU of vitamin D; • by start of supplementation: 20 weeks of pregnancy, or more; • by pre-gestational BMI (kg/m^2): healthy weight; • by supplementation scheme/regimen: single given at different weeks of gestation in the supplemented group; • by skin pigmentation based on Fitzpatrick skin tone chart (Fitzpatrick 1988): mixed/unknown; • by latitude: north of the Tropic of Cancer; • by season at the start of pregnancy: all year round. Authors report that sufficient levels of vitamin D were seen in 93.3% patients who had more than 4 hours of sun exposure every day as compared to 18.5% in those with less than 1 hour of daily sun exposure. Source of funding: self-funded.

Risk of bias

Bias	Authors' judgement	Support for judgement

Sablok 2015 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomisation was performed using computer-generated random number tables
Allocation concealment (selection bias)	High risk	As participants were assigned to either no intervention or intervention and the intervention dosage depended on the vitamin D status, there was a selection bias based on status of vitamin D at baseline
Blinding of participants and personnel (performance bias) All outcomes	High risk	1 group received no intervention at all and the other different doses of vitamin D at different times
Blinding of outcome assessment (detection bias) All outcomes	High risk	1 group received no intervention at all and the other different doses of vitamin D at different times
Incomplete outcome data (attrition bias) All outcomes	High risk	The level of attrition was different in groups 1 and 2: 3/60 (5%) participants in group 1 and 12/120 (10%) participants in group 2 were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement.
Other bias	Low risk	The study appears to be free of other evident sources of bias

Taherian 2002

Methods	Randomised controlled study with 3 arms.
Participants	990 nulliparous women attending antenatal outpatient clinics of Isfahan Health Centers (32.6333° N, 51.6500° E north of Tropic of Cancer) between April 1998 and March 2001, with singleton pregnancies, first prenatal visit before 20 weeks of gestation, systolic/diastolic blood pressure lower than 130/80 mmHg, and no proteinuria detectable by a dipstick Women with history of cardiovascular, renal or endocrinologic problems, medical or obstetric complications and those with known hazardous condition (multifetal gestation, hydatidi-form mole) were excluded
Interventions	Participants were randomly assigned to 1 of 3 groups: group 1 (n = 330) received 75 mg aspirin each day from 20th week of gestation until delivery; group 2 (n = 330) received a tablet containing 500 mg calcium carbonate + 200 IU vitamin D (cholecalciferol-D3) daily from 20th week of gestation until delivery; and group 3 (n = 330) received no intervention. All cases received standard prenatal care Health worker cadre: the women were examined by trained staff every 4 weeks through the 28 weeks of gestation, and every 2 weeks through the 36th week and weekly thereafter.

Taherian 2002 (*Continued*)

	Blood pressure was measured by a certified examiner
Outcomes	Maternal: blood pressure, bodyweight, BMI, maternal height, urine protein measurements, maternal weight gain, duration of gestation Infant: neonatal weight at birth, the presence of respiratory distress syndrome, sepsis, jaundice and intrauterine growth retardation, fetal or neonatal death
Notes	• Total dose of supplementary vitamin D during pregnancy: less than 56,000 IU; • start of supplementation: 20 weeks of pregnancy or more; • pre-gestational BMI (kg/m^2): normal weight (18.5 to 24.9); • supplementation scheme/regimen: daily; • skin pigmentation based on Fitzpatrick skin tone chart (Fitzpatrick 1988): mixed/unknown; • latitude: north of the Tropic of Cancer; • season at the start of pregnancy: April 1998 to March 2001. Source of funding: Research Deputy of Isfahan University of Medical Sciences grant (No: 76085)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By table of random numbers.
Allocation concealment (selection bias)	Unclear risk	There is no mention of any allocation. It is unclear whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment
Blinding of participants and personnel (performance bias) All outcomes	High risk	There is no mention of the study being blinded to participants of health care providers
Blinding of outcome assessment (detection bias) All outcomes	High risk	There is no mention of the study being blinded to participants of health care providers
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition reported.
Selective reporting (reporting bias)	Low risk	It appears unlikely. This study was conducted to evaluate the effect of low-dose aspirin or calcium supplements, taken during pregnancy, on the incidence of pre-eclampsia in nulliparous healthy women

Taherian 2002 (*Continued*)

Other bias	Low risk	The study appears to be free of other evident sources of bias

Yu 2008

Methods	Randomised controlled trial; 4 x 3 block design with randomisation at individual level
Participants	180 pregnant women (45 Indian Asians, 45 Middle Eastern, 45 Black and 45 Caucasian) women at 27 weeks' gestation attending the routine antenatal clinic at St Mary's Hospital, London, United Kingdom (latitude: 51°30'N north of tropic of Cancer). Exclusion criteria: pre-existing sarcoidosis, osteomalacia, renal dysfunction and tuberculosis. Pre-gestational BMI and skin pigmentation (in addition to ethnicity) not reported. The study took place between April 2007 and November 2007
Interventions	Participants were randomised in blocks of 15 within each of the 4 ethnic groups to 3 groups; group 1 (n = 60) women received a daily dose of vitamin D (ergocalciferol D2) at 800 IU (estimated total dose 72,800 IU); group 2 (n = 60): women received a stat dose of 200,000 IU of calciferol; group 3 (n = 60): women received no treatment Length of the intervention/follow-up: 13 weeks from start of supplementation to term Health worker cadre: each woman collected her tablets directly from the hospital pharmacy department or her local pharmacy
Outcomes	Maternal: maternal and cord 25-hydroxyvitamin D levels at delivery, maternal PTH and corrected calcium levels at delivery, adverse events Infant: small-for-gestational age was defined as birthweight less than the 10th percentile after adjustments for gestation at delivery, infant sex, maternal ethnicity, parity, height and weight Laboratory method used for assessment of vitamin D concentrations: not specified
Notes	Women who did not speak English were only included if a health advocate was able to interpret and a leaflet was provided in their language • Total dose of supplementary vitamin D during pregnancy: more than 56,000 to 200,000 IU; • start of supplementation: 20 weeks of pregnancy or more; • pre-gestational BMI (kg/m^2): unknown/mixed; • supplementation scheme/regimen: single and daily; • skin pigmentation based on Fitzpatrick skin tone chart (Fitzpatrick 1988): mixed/unknown; • latitude: north of the Tropic of Cancer; • season at the start of pregnancy: summer. April to November 2007; summer. Source of funding: Institute of Obstetrics and Gynaecology Trust, Wolfson and Weston Research Centre for Family Health, Imperial College, Du Cane Road, Hammersmith Hospital, London W12 0NN, UK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Yu 2008 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-generated random number lists were drawn up by an independent researcher, with randomisation in blocks of 15
Allocation concealment (selection bias)	Low risk	The person seeing the pregnant women allocated the next available number on entry to the trial, and each woman collected her tablets directly from the hospital pharmacy department or her local pharmacy
Blinding of participants and personnel (performance bias) All outcomes	High risk	All study personnel and participants were not blinded to treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 loss to follow-up on group 3.
Selective reporting (reporting bias)	Low risk	The study was approved by St Mary's Hospital Ethics Committee (Ref: 06/Q0702/172) and the Medicines and Healthcare products Regulatory Agency
Other bias	Unclear risk	Women were randomised within each ethnic group. It is not clear if the ethnicity can be clearly established as it was self reported. Women who did not speak English were included only if a health advocate was able to interpret and a leaflet was provided in their language (English, Arabic, Bengali and Farsi) although the ability to read was not clearly established

BMI: body mass index
GDM: gestational diabetes mellitus
HDL: high-density lipoprotein
IGF-I: insulin-like growth factor
IU: international units
IUFD: intrauterine fetal death
LDL: low-density lipoprotein
PA: physical activity
PTH: parathyroid hormone

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ala-Houhala 1986	49 healthy, well-nourished mothers delivering in January 1984 in the maternity wards and outpatient clinic of the Department of Paediatrics of the University Central Hospital of Tampere, Finland (latitude 61°N) and exclusively breastfeeding their infants, were divided in succession into 3 groups: group 1 (n = 17): mothers were given 2000 IU vitamin D_3 a day, infants not supplemented; group 2 (n = 16): mothers were given 1000 IU vitamin D_3 a day, infants not supplemented; group 3 (n = 16): mothers were not supplemented, and their breast fed infants were given 400 IU of vitamin D_2 a day. During pregnancy, 33 mothers had no vitamin D supplementation, 8 mothers received 500 IU a day of vitamin D during the second trimester of pregnancy, and 8 mothers received 500 IU a day throughout the pregnancy. The mothers from these 3 groups supplemented in pregnancy were distributed in the postpartum maternal vitamin D supplementation and infant vitamin D supplementation interventions This is not a randomised trial and the intervention includes mothers at postpartum and their infants
Asemi 2013b	54 pregnant women aged 18-40 years diagnosed with GDM by a 100-g oral glucose-tolerance test at 24-28 weeks' gestation attending maternity clinics affiliated with Kashan University of Medical Sciences, Kashan, Islamic Republic of Iran (latitude: 33.9889° N, 51.4772° E), during March 2012 to September 2012 and further analysis during January 2013 to April 2013. Participants were randomly assigned to 1 of 2 groups: group 1 (n = 27), women received capsules containing 50,000 IU vitamin D (cholecalciferol-D3) (D-Vitin 50000; Zahravi Pharm Co) 2 times during the study (at baseline and at day 21 of the intervention): group 2 (n = 27), women received 2 placebos (Barij Essence Co) at the same times. The duration of the study was 6 weeks; however, vitamin D was given only 2 times during the 6 weeks. Additionally, all participants also consumed 400 μg (0.4 mg) folic acid daily from the beginning of pregnancy and 60 mg elemental iron (as ferrous sulphate) daily from the second trimester. The trial was carried out in maternity clinics affiliated to Kashan University of Medical Sciences, Kashan, Islamic Republic of Iran and the investigators provided the supplements to the participants. A trained midwife at the maternity clinic performed anthropometric measurements at study baseline and at 6 weeks after the intervention. All pregnant women in the study had a diagnosis of gestational diabetes. The type of participant is outside the scope of this review
Asemi 2014	56 pregnant women 18-40 years of age with gestational diabetes and 24-28 weeks' gestation attending prenatal care at maternity clinics affiliated to Kashan University of Medical Sciences, Kashan, Iran were randomly assigned to 1 of 2 groups: group 1 (n = 28) received 1000 mg calcium per day and a 50,000 U vitamin D (cholecalciferol-D3) pearl twice during the study (at study baseline and on day 21 of the intervention); group 2 (n = 28) received 2 placebos at the same times. Participants with premature preterm rupture of the membrane, placenta abruption, pre-eclampsia, eclampsia, chronic hypertension, hypothyroidism, urinary tract infection, kidney or liver diseases, stressful life conditions, smokers or using oestrogen therapy or women requiring insulin therapy during the intervention (FPG > 5.8 mmol/L and 2 hours postprandial blood sugar > 6.7mmol/L).were excluded. All participants were also consuming 400 μg (0.4 mg) folic acid daily from the beginning of pregnancy and 60 mg elemental iron (as ferrous sulphate) from the second trimester. The calcium supplement and its placebo were manufactured by Tehran Shimi Pharmaceutical Company (Tehran, Iran). Vitamin D and its placebo were manufactured by Dana Pharmaceutical Company (Tabriz, Iran) and Barij Essence Pharmaceutical Company (Kashan, Iran). The trial was carried out in maternity clinics affiliated to Kashan University of Medical Sciences, Kashan, Islamic Republic of Iran and the investigators provided the supplements to the participants. A trained midwife at the maternity clinic performed anthropometric measurements at study baseline and at 6 weeks after the intervention. Outcomes measured included serum 25-hydroxyvitamin D [25(OH)D] concentrations, FPG, serum calcium, cholesterol, triacylglycerol, LDL-cholesterol and HDL-cholesterol, serum insulin, serum high-sensitivity C-reactive protein, plasma total antioxidant capacity, plasma total glutathione, plasma malondialdehyde. Participants were pregnant

(*Continued*)

	women with diagnosis of gestational diabetes. The type of participant is outside the scope of this review
Bhatia 2012a	299 pregnant women with 12 and 24 weeks of gestation of lower-middle and middle socio-economic groups attending the antenatal clinic in Queen Mary Hospital, Chhatrapati Sahuji Maharaj, India, were randomly assigned to 1 of 2 groups, group 1: received 1500 mcg cholecalciferol at induction into the study, or group 2 3000 mcg cholecalciferol at induction as well as at 28 weeks of gestation. All were prescribed 1 g of elemental calcium daily as calcium carbonate without vitamin D. Patients excluded from the study if they were already on calcium or vitamin D supplementation, anticonvulsants, antitubercular treatment or had any medical condition that affected calcium and vitamin D metabolism (including renal and hepatic disease). Only 97 women were followed up Both groups received vitamin D and calcium. This type of intervention is outside the scope of our review
Cockburn 1980	1139 pregnant women were assigned to 1 of 2 wards: group 1 (n = 506) Caucasian pregnant women assigned to 1 ward of the Simpson Memorial Maternity Pavilion, Edinburgh, United Kingdom during the 9 months from September to May, were given a daily dietary supplement of 400 IU of vitamin D2 from about the 12th week of pregnancy until delivery; group 2 women (n = 633) were assigned to another ward over the same period and were given a placebo containing no vitamin D. Outcomes included plasma concentrations of calcium, phosphorus, magnesium, total proteins, and 25-hydroxycholecalciferol at 24th and 34th weeks of pregnancy and at delivery. Infant plasma concentrations of calcium, phosphorus, magnesium, total proteins, and 25-hydroxycholecalciferol were measured from umbilical venous blood taken from the infants at birth and on capillary blood on the 6th day This is not a randomised trial.
Czech-Kowalska 2013	174 healthy postpartum women who had delivered babies at term in Poland, were randomised to 1 of 2 groups: group 1 (n = 70) received 1200 IU/d vitamin D (cholecalciferol-D3 as 800 IU/d alone + 400 IU/d from a multiple micronutrient supplements; group 2 (n = 67) received 400 IU/d vitamin D (cholecalciferol-D3 as placebo + 400 IU/d from multiple micronutrient supplements) during 6 months of lactation. Outcomes measured included serum 25-hydroxyvitamin D (S-25-OHD), PTH and densitometry after delivery, at 3 and 6 months postpartum. Serum and urinary calcium were assessed at 3 and 6 months postpartum. Participants from both groups received vitamin D supplements. The participants were postpartum women. The type of participant and the type of interventions are outside the scope of this review
Das 2009	150 consecutive pregnant women pregnant women during their second trimester from 6 villages of a poor socio-economic region in district Barabanki (latitude 26.8 ºN), Uttar Pradesh, north India. The participants were initially randomised to receive either no dose or 1 dose of 60,000 IU cholecalciferol under observation in the 5th gestational month. However, the first few results showed rampant vitamin D deficiency and no improvement at delivery despite good exposure to sun and calcium supplementation. Therefore, this randomisation was abandoned subsequently and 2 comparison groups were followed up, alternate women receiving either 60,000 IU in the 5th month or 120,000 IU, each in the 5th and 7th months of pregnancy This is not a randomised trial and the comparisons are outside the scope of this review
Dawodu 2013	192 Arab women between 12-16 weeks of gestation after their last menstrual period or by ultrasound assessment who had a singleton pregnancy; and planned to receive prenatal and delivery care in primary health care clinics affiliated with Tawam Hospital, Al Ain, United Arab Emirates. Exclusion criteria were pre-existing calcium and parathyroid conditions, active thyroid disease, liver or kidney disease, or type 1 diabetes, which are likely to affect vitamin D and calcium status. All participants received vitamin D supplementation in different regimens The type of intervention is outside the scope of this review

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Etemadifar 2015	45 pregnant women with confirmed multiple sclerosis who attended an outpatient clinic in Isfahan University of Medical Sciences, Iran aged 20-40 years with low serum 25-hydroxyvitamin D (25(OH)D) levels were randomly allocated to 2 groups in an open-label randomised, controlled clinical Phase I/II pilot study. 1 group received 50,000 IU/week vitamin D3 (n = 21) or routine care (n = 22) from 12 to 16 weeks of gestation till delivery. Inclusion criteria were women with a magnetic resonance imaging, clinical or laboratory-supported diagnosis of definite multiple sclerosis, stable neurological functioning for at least 1-month prior to study entry, and an expanded disability status scale (EDSS) score $\leq$ 6, serum 25(OH)D level < 20 ng/mL and a willingness to continue current medications for the duration of the study. The main outcome measures were mean change in serum 25(OH)D levels, EDSS score, and number of relapse events during pregnancy and within 6 months after delivery. Participants had a confirmed diagnosis of multiple sclerosis This type of participant is outside the scope of this review
Hashemipour 2013	160 pregnant women (24-26 weeks of gestation) who attended an obstetric clinic in Qazvin, Iran, from December 2011 to March 2012 were randomised, and included in 2 arms. Inclusion criteria were: gestational age of 24-26 weeks, singleton pregnancy and BMI of 19-26 kg/m2. Exclusion criteria at study enrolment were: diabetes before pregnancy, chronic hypertension, history of repeated abortion, rheumatoid arthritis, parathyroid disorders, hepatic or renal diseases, and use of aspirin, anticonvulsive and immunosuppressive drugs. Women in the control group received a multivitamin containing 400 IU vitamin D3 plus 200 mg elemental calcium each day until delivery. Women in the intervention group received a weekly dose of 50,000 IU oral vitamin D3 for 8 weeks (from 26 to 28 weeks of pregnancy) as well as the drug regimen (multivitamin and elemental calcium) given to the control group Both groups received vitamin D and calcium. This type of intervention is outside the scope of our review
Hossain 2012	200 pregnant women who attended the Department of Obstetrics & Gynaecology unit 3, Dow University and Civil Hospital Karachi, Pakistan aged between 18 and 40 years were randomised, and included in 2 arms. Participants were allocated to 1 of 2 groups: group 1 (n = 100) received along with ferrous sulphate, 4000 IU of vitamin D3; group 2 (n = 100) received routine antenatal care (ferrous sulphate and calcium). Both groups received above medications from 20 weeks of pregnancy until delivery. Maternal serum levels of 25(OH)D levels were done at the time of recruitment, and at the time of delivery. Neonatal levels were done within 48 hours of delivery This type of intervention is outside the scope of our review
Hosseinzadeh 2012	48 pregnant women with GDM (diagnosed by performing oral glucose tolerance test at 24-28th week of gestation) in Yazd, Iran were randomly assigned to 1 of 2 groups group 1 (n = 24) were assigned to received an intramuscular dose 300,000 IU of vitamin D and group 2 (n = 24) were assigned to receive no intervention. The participants were asked to refer to Yazd Diabetes Research Center 3-10 days after delivery for outcome assessments that included plasma glycosylated haemoglobin A1C (HbA1C), serum 25(OH) vitamin D3, PTH, serum calcium and phosphorus. Vitamin D was provided by intramuscular injection and not orally The type of intervention is outside the scope of this review
Ito 1994	876 singleton pregnant women with blood pressure lower than 140/90 mmHg at 20 weeks' gestation, and no evidence of proteinuria, who were attending the obstetric clinic of Kumamoto University Hospital, Japan were divided into 2 groups: group 1 (n = 666) women received conventional antenatal care; group 2 (n = 210 women) were managed under a protocol for the prediction of pre-eclampsia with an angiotensin sensitivity test and prevention of the condition by calcium supplementation. Participants from group 2 were further assigned to 1 of 4 groups according to their risk of developing pre-eclampsia, based on the angiotensin sensitivity test and the effective pressor dose: group A received 156 mg/day of oral elemental calcium (as calcium L-aspartate, Aspara-Ca from 22 weeks' gestation, followed by 312 mg/day oral elemental calcium

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	and vitamin D_3 (0.5 μg for 3 days) from 30 weeks' gestation to term. Participants in group B received 156 mg/day oral elemental calcium from 22 weeks' gestation and 312 mg/day oral elemental calcium from 30 weeks' gestation to term; group C received 312 mg/day oral elemental calcium from 30 weeks' gestation to term and group D received no supplementation This is not a randomised trial and the type of intervention is outside the scope of this review
Litonjua 2014	881 pregnant women with either a personal history of asthma or allergies or a similar history in the spouse or partner, between 18 and 40 years of age and at an estimated gestational age between 10 and 18 weeks, were recruited at a scheduled obstetrical prenatal visit at 3 clinical centres: Boston Medical Center (Boston, MA), Washington University at Saint Louis (St. Louis, MO), and Kaiser Permanente Southern California Region (San Diego, CA). Participants were randomised to either vitamin D (cholecalciferol, 4000 IU/day; equivalent to 100 μg/day) or placebo. All pregnant mother participants received prenatal vitamins containing 400 IU (10 μg/day) of cholecalciferol; thus, the vitamin D arm received a total of 4400 IU/day (110 μg/day) and the placebo arm received 400 IU/day (10 μg/day) Both groups received vitamin D supplements. This type of intervention is outside the scope of our review
MacDonald 1986	This trial was registered in 1986 on the Oxford Database of Perinatal Trials and reports the recruitment and follow-up completed in 1979. The registration form reports a randomised controlled trial to assess the efficacy of calcium and vitamin D supplementation versus placebo in the prevention of maternal and fetal hypocalcaemia. The reports indicates that the sample size was 55 Asian women with morbidity and laboratory results as primary outcomes but no further information is available
Marya 1981	45 Hindu pregnant women were randomly assigned to 1 of 2 groups: group 1 (n = 25) received tablets containing 1200 IU vitamin D and 375 mg calcium daily throughout the 3rd trimester; group 2 (n = 20) received oral single dose of 600,000 IU vitamin D_2 once during 7th month and 8th month (total 2 doses). This group was compared with group 3 (n = 75) who had not received vitamin D supplements during pregnancy. The results were also compared with data from 25 non pregnant, non-lactating healthy women. Patients with complications such as pre-eclampsia, antepartum haemorrhage or twin pregnancies were excluded The randomised study compares 2 doses of vitamin D supplementation The type of study, type of participants and types of interventions are outside the scope of this review
Mutlu 2013	91 pregnant women aged 16-42 years were admitted to Kocaeli Maternity and Children Hospital between April 2011 and April 2012. The participants were randomly divided into 3 groups: 600 IU/d (control group; n = 31); 1,200 IU/d (n = 31), and 2,000 IU/d (n = 32) of vitamin D. All groups received vitamin D supplements. This type of comparison is outside the scope of our review
Roth 2013a	28 pregnant women were enrolled at a maternal health clinic in inner-city Dhaka, Bangladesh Aged 18 to 34 years; at 27 to 30 weeks of pregnancy with no pre-existing medical conditions; current vitamin D supplement use; anti-convulsant or anti-mycobacterial medications; severe anaemia (haemoglobin concentration less than 70 g/L); hypertension at enrolment (systolic blood pressure 140 mmHg or higher or diastolic blood pressure 90 mmHg or higher on at least 2 measurements); major risk factors for preterm delivery or pregnancy complications; or previous delivery of an infant with a congenital anomaly or perinatal death. Participants were randomly assigned to 1 of 2 groups: group 1 (N = 14) were assigned to receive a single dose of vitamin D3 70,000 IU (1.75 mg, where 1 mg = 40,000 IU) on day 0 followed by vitamin D3 35,000 IU (0.875 mg) per week starting on day 7 and continuing until delivery); Group 2 (N = 14), were assigned to receive vitamin D3 14,000 IU (0.350 mg) per week starting on day 0 and continuing until delivery. A cohort of a non pregnant participants (N = 16) received the a single dose of vitamin D3 70,000 IU on day 0 followed by vitamin D3 35,000 IU per week starting on day 7 and continuing until the last dose on day 63 (total of

(*Continued*)

	10 doses). This group was used as a comparison group. All participants received vitamin D supplementation in different regimens. The type of intervention is outside the scope of this review
Shakiba 2013	51 healthy pregnant women from the beginning of their second trimester of pregnancy during the autumn and winter of 2009 in recruited from 2 primary care clinics in Yazd (31°53'50"N/54°22'04"E), Iran. Participants were distributed in 3 groups according to their serum 25(OH)D at the beginning of the second trimester of pregnancy. Participants with low concentrations (25(OH)D levels < 20 ng/mL) (n = 17) were treated with 200,000 IU (50,000 IU/week for 4 weeks) of vitamin D (as (cholecalciferol-D3), followed by supplementation with 50,000 IU/month vitamin D (cholecalciferol-D3). The other 34 participants were randomly assigned to 1 of 2 groups: group 1 received 50,000 IU/month vitamin D (cholecalciferol-D3); group 2 received 100,000 IU/month vitamin D (50,000 IU every 2 weeks) of vitamin D (cholecalciferol-D3) supplementation. All participants received vitamin D supplements. Only the participants with higher vitamin D status were randomised to different doses and regimens. The type of study design and the type of intervention are outside the scope of this review
Soheilykhah 2011	120 pregnant women were recruited from 2 prenatal clinics (Mojibian Hospital and Shahid Sadoughi Hospital) in Yazd, Iran, from 2009 to 2011. Exclusion criteria consisted of women with diabetes or gestational diabetes treated with insulin, women with thyroid or parathyroid disorders, polycystic ovary disease before pregnancy, BMI before pregnancy of more than 30 kg/m2 and women who received vitamin D supplementation during the prior 6 months. Participants were randomly assigned to 1 of 3 groups: group 1 received the DRI of 200 IU vitamin D (calciferol) daily, group 2 received 50,000 IU monthly (2000 IU daily) and group 3 received 50,000 IU every 2 weeks (4000 IU daily). Supplementation started in the 12th week of pregnancy and continued until delivery All groups received vitamin D supplements. This type of comparison is outside the scope of our review
Stephensen 2011	Pregnant women less than 20 weeks' gestation and over 18 years of age with no use of medications known to affect vitamin D metabolism, diagnosis of type 1 diabetes, history of thyroid, renal, or liver disease, problems with digestion or absorption participated in the study at USDA Western Human Nutrition Research Center and clinicians at UC Davis Medical Center. They were distributed into 2 groups, receiving: either 400 IU or 2000 IU of vitamin D per day for the duration of their pregnancy Both groups received vitamin D supplements. This type of intervention is outside the scope of our review
Taheri 2014	229 women 18-35 years old, who were confirmed to be vitamin D deficient (vitamin D < 75 nmol/L), were randomised into the intervention, and control groups and after 15 weeks consumption of the supplement (2000 IU/day oral vitamin D) and placebo. The study was conducted among reproductive women in a high-risk population for vitamin D deficiency The participants of the study were not pregnant women. The type of participant is outside the scope of this review
von Hurst 2009	235 South Asian women, aged 23-68 years, living in Auckland, New Zealand were recruited for the study and those who were insulin resistant - homeostasis model assessment 1 (HOMA1) > 1.93 and had serum 25-hydroxyvitamin D concentration < 50 nmol/L were randomly assigned to 1 of 2 groups: group 1 (n = 42) received 100 μg (4000 IU) vitamin D(3); group 2 (n = 39) received a placebo daily for 6 months The study participants were non-pregnant women. The type of participant is outside the scope of this review
Wagner 2010a	257 pregnant women 12-16 weeks' gestation were enrolled at Eau Claire Cooperative Health Center (ECCHC) in Columbia, SC, and Northwoods Community Health Center (NCHC) in North Charleston, SC, USA and were randomly assigned to receive either 2000 IU/d vitamin D versus 4000 IU/d vitamin D (cholecalciferol-D3), followed 1-month run-in at 2000 IU vitamin D daily. Participants were monitored for

(*Continued*)

	hypercalciuria, hypercalcaemia, and 25(OH)D status Both groups received vitamin D at different doses. The type of intervention is outside the scope of this review
Wagner 2010b	494 apparently healthy pregnant women (16-45 years of age) with 12-16 weeks' gestation of singletons attending prenatal care in Medical University of South Carolina, Charleston, South Carolina in South Carolina, United States were randomised into 1 of 3 groups stratified by race: group 1 received 400 IU vitamin D (cholecalciferol-D3)/day; group 2 received 2000 IU vitamin D (cholecalciferol-D3)/day; and group 3 received 4000 IU vitamin D (cholecalciferol-D3)/day until delivery. All women received daily multiple micronutrients supplements. 350 women continued until delivery. Outcomes included monthly 25-hydroxyvitamin D; $1,25(OH)_2D$; intact PTH, serum calcium, creatinine, phosphorus, and urinary calcium/creatinine levels, gestational age at delivery, birthweight, mode of delivery, co-morbidities of pregnancy, pre-eclampsia, gestational diabetes, any infection, preterm labour and premature birth All women received vitamin D supplementation at different doses. The type of intervention is outside the scope of this review
Wagner 2010c	This is an analysis of data from 2 randomised controlled trials by the same research group (Wagner 2010b; Wagner 2010a). In Wagner 2010b, women were randomised to 400, 2000, or 4000 IU vitamin D (cholecalciferol-D3)/day, stratified by race. In Wagner 2010a, participants were randomised to 2000 or 4000 IU vitamin D (cholecalciferol-D3)/day
Yap 2014	179 pregnant women 18 years of age or older, with singleton pregnancy, with plasma 25-hydroxivitamin D (25OHD) concentrations lower than 32 ng/mL, less than 20 weeks of gestation were randomly assigned to 1 of 2 groups: group 1 (n = 89) received 5000 IU/d of vitamin D (cholecalciferol-D3) until delivery; group 2 (n = 90) received 400 IU/d of vitamin D (cholecalciferol-D3) until delivery. Outcomes included glycaemia and glucose tolerance, gestational diabetes at 26-28 weeks of gestation; neonatal 25OHD, maternal hypertension, mode of delivery, prematurity, birthweight, crown-heel length, occipitofrontal head circumference. All participants received vitamin D supplements at different doses. The type of intervention is outside the scope of this review

BMI: body mass index
DRI: dietary references intakes
FPG: fasting plasma glucose
GDM: gestational diabetes mellitus
IU: international units
mcg: microgram
PTH: parathyroid hormone
25OHD: 25-hydroxycholecalciferol

Characteristics of ongoing studies *[ordered by study ID]*

Benson 2009

Trial name or title	A randomised controlled trial on the effects of antenatal vitamin D supplementation to improve vitamin D levels in the maternal and cord blood at birth in vitamin D deficient pregnant women
Methods	Randomised controlled trial.
Participants	Pregnant women between 14-18 weeks' gestation at risk, defined as: dark skinned, veiled; with vitamin D deficiency that has not commenced treatment prior to recruitment. Exclusion criteria: women taking barbiturates or anticonvulsants (decreased vitamin D absorption) and severe renal failure
Interventions	Participants will be individually randomised to 1 of 2 groups: group 1: 2000 international units (IU) of cholecalciferol orally daily commencing between 14 and 18 weeks' gestation. If still deficient at 28 weeks the dose will be doubled to 4000 IU orally daily until birth; group 2: No treatment during pregnancy. The mother will receive 300,000 IU cholecalciferol orally immediately and the baby 150,000 IU cholecalciferol orally immediately after birth
Outcomes	Maternal: vitamin D level. Infant: vitamin D level.
Starting date	1/04/2008.
Contact information	Name: Jodie Benson Address: co/ Monash Medical Centre Clayton Rd, Clayton Victoria 3168, Australia Tel: +61 3 95946666 Email: benson_jodie@hotmail.com
Notes	Sponsor: Royal Australian and New Zealand College of Obstetrics and Gynaecology, Australia ACTRN12609000142235.

Bhatia 2012b

Trial name or title	Vitamin D supplementation in pregnancy: regimens and long term effects on offspring
Methods	Randomised, parallel group, placebo-controlled trial.
Participants	Pregnant women attending antenatal clinic in Chhatrapati Shahuji Medical University (CSMMU), Uttar Pradesh, India, and in 14 to 20 weeks of pregnancy Exclusion criteria: chronic liver disease, renal disease or treatment with antitubercular or antiepileptic drugs or vitamin D in the previous 3 months
Interventions	Participants will be individually randomised to 1 of 3 groups: group 1: cholecalciferol: 400 units per day orally from recruitment till the end of pregnancy; group 2: cholecalciferol: 60,000 units orally every 4 weeks; group 3: cholecalciferol: 60,000 units orally every 8 weeks from recruitment till the end of pregnancy
Outcomes	Maternal: serum 25OHD. Infant: birthweight, length, head circumference and anterior fontanelle diameter, cord serum 25OHD, neonatal serum calcium

Bhatia 2012b (*Continued*)

Starting date	04-11-2011.
Contact information	Vijayalakshmi Bhatia Address: Department of endocrinology, SGPGIMS, Raebareli Road, Lucknow 226014 Lucknow, UTTAR PRADESH India Tel: +91-522-2494380 Email: vbhatia@sgpgi.ac.in Affiliation: Sanjay Gandhi Postgraduate Institute of Medical Sciences
Notes	Sponsor: Department of Biotechnology, Goverment of India. CTRI/2012/02/002395.

Bhutta 2011

Trial name or title	Study of vitamin D supplementation on improvement of gums health (vitamin D)
Methods	Randomised, parallel assignment, double blind.
Participants	Pregnant females from 12-20 weeks of gestation who agree to participate in the study with presence of at least 20 natural teeth in mouth excluding third molars. For controls: non pregnant, healthy females matched with pregnant women with respect to age and education. Exclusion criteria: pregnant females with high vitamin D levels, women with metabolic diseases such as diabetes (type 1 or 2), presence of acute dental or periodontal disease, presence of systemic disease and/or medication affecting the periodontium; receipt of systemic antibiotic treatment or dental prophylaxis in the previous 3 months and those who do not provide informed consent
Interventions	Participants will be individually randomised to 1 of 2 groups: group 1: vitamin D3 4000 mg per day, 1 tablespoon syrup per day; group 2: placebo, 1 table spoon syrup per day
Outcomes	Maternal: Periodontal Probing Depth, Interleukin 6 (IL-6), IL-2, IL-4, IL-10, TNF, IFN-γ and IL-17 levels
Starting date	June 2010.
Contact information	Farhan Raza Khan, Consultant, Dentistry, Aga Khan University
Notes	Sponsor: Aga Khan University, Pakistan. (www.clinicaltrials.gov; NCT01422122

Bisgaard 2009

Trial name or title	Vitamin D supplementation during pregnancy for prevention of asthma in childhood: an interventional trial in the ABC (Asthma Begins in Childhood) cohort
Methods	Randomised double-blind, placebo-controlled trial with 2 arms

Bisgaard 2009 (*Continued*)

Participants	Danish-fluent pregnant women 18 years of age or older, with 22-26 week of gestation living in Sealand, Denmark participating in the ABC-cohort. The mothers in ABC also participate in an interventional trial with fish oil supplementation, and the vitamin D randomisation is stratified by fish oil treatment group Women with intake of more than 400 IU of vitamin D during the previous 6 months, endocrinological disease such as calcium metabolic disorder, parathyroid disorder, thyroid disorder or diabetes type 1, tuberculosis, sarcoidosis or in need of diuretics or heart medication including calcium channel blockers are excluded
Interventions	Participants will be individually randomised to 1 of 2 groups: group 1: receives a daily supplement with 2400 IU of vitamin D_3 from week 24 of gestation to 1 week after delivery; group 2: receives placebo from week 24 of gestation to 1 week after delivery
Outcomes	Maternal: 25-OH-vitamin D, PTH, calcium, alkaline phosphatase concentrations 1 week postpartum Infant: upper and lower respiratory infections, allergy, eczema from 0-3 years of age
Starting date	Date of start: 03/2009. Status: recruiting participants.
Contact information	Hans Bisgaard, MD, DMSc Copenhagen Studies on Asthma in Childhood Copenhagen University Hospital of Copenhagen Gentofte, Denmark, 2820 Tel: +45 39777360 E-mail: bisgaard@copsac.com
Notes	Sponsor: Copenhagen Studies on Asthma in Childhood.

Ghasemi 2014

Trial name or title	Comparison of effectiveness of vitamin D supplementation in decreasing the development of the gestational diabetes mellitus in pregnant women
Methods	Single-arm study, not blinded.
Participants	75 pregnant women referring to obstetric clinic of Shahid Beheshti and Alzahra hospital in Esfahan city in 2012 (overall 225 persons). Inclusion criteria: patient satisfaction; normal BMI; gestational age below 16 weeks; no history of diabetes mellitus type 2 or GDM; no family history of diabetes mellitus type 1 in first degree relatives. Exclusion criteria: patient dissatisfaction; incorrect consumption of vitamin D supplementation; Follow-up discontinuation
Interventions	Participants will be individually randomised to 1 of 2 groups: group 1: vitamin D supplementation with dose of 50,000 unit every 2 weeks for 10 weeks; group 2: are not treated with vitamin D supplementation Persons with level of above 25 nmol/L, were selected as normal healthy control group
Outcomes	Maternal: gestational blood sugar level, serum vitamin D level.
Starting date	2012-03-20.

Ghasemi 2014 (*Continued*)

Contact information	Name: Dr. Hatav Ghasemi Tehrani Address: Isfahan- Alzahra Hospital-Gynecology Department Isfahan Tel: 00983116249032 Email: tehrani@med.mui.ac.ir Affiliation: Isfahan University Of Medical Iran, Islamic Republic Of Sciences
Notes	Sponsor: Isfahan University Of Medical Sciences.

Goldring 2010

Trial name or title	Effects of prenatal vitamin D supplementation on respiratory and allergic phenotypes and bone density in the first 3 years of life
Methods	Randomised interventional prevention trial.
Participants	180 mothers attending antenatal clinic at St Marys Hospital, London, United Kingdom. This is a follow-up trial of the infants of these trial participants. All of the offspring of the 180 mothers recruited in this trial are eligible and are invited to participate in this follow-up study when their children are 3 years of age
Interventions	Participants will be individually randomised to 1 of 2 groups: group 1 (n = 60): received no vitamin D; group 2 (n = 60): received 800 IU of vitamin D daily for the remainder of pregnancy; group 3 (n = 60) received a single oral dose of 200,000 IU vitamin D at 27 weeks' gestation
Outcomes	Infant: wheezing episode in the first 3 years of life, measured at 36-48 months, use of inhaled bronchodilators in the last 12 months, doctor-diagnosed rhinitis, any wheezing episode in the preceding 12 months, doctor-diagnosed asthma, doctor-diagnosed eczema, doctor-diagnosed food allergy, positive skin prick test responses, 25-hydroxyvitamin D levels, bronchodilator responsiveness, exhaled nitric oxide level (in parts per billion) , nasal secretions for inflammatory mediators, pulmonary airflow resistance and reactance at a range of frequencies using impulse oscillometry, total number of all wheezing episodes since birth and total number of upper and lower respiratory tract infections since birth, at 36-48 months
Starting date	Date of start: 01/03/2010. Status: ongoing. Anticipated end date: 31/05/2011.
Contact information	Dr Stephen Goldring Department of Paediatrics Wright-Fleming Institute, Norfolk Place, London W2 1PG , United Kingdom E-mail: sgoldring@nhs.net
Notes	Sponsor: Imperial College London (UK).

Habib 2010

Trial name or title	Evaluation of the effectiveness of vitamin D supplementation to pregnant women and their infants in Pakistan
Methods	Randomised controlled trial.
Participants	550 apparently healthy pregnant women 15-49 years of age from 20-22 weeks of gestation and their infants in Pakistan Pregnant women with pre-existing type 1 or type II diabetes, multiple fetuses, babies (twins, triplets), with high levels of vitamin D will be excluded. Infants with multiple congenital anomalies, serious birth injury, birth asphyxia, serious infections, very low birthweight, will be excluded
Interventions	Participants will be individually randomised to 1 of 2 groups: group 1 will receive a daily dose of 4000 IU of vitamin D from 20-22 weeks of pregnancy till the time of delivery; group 2 will receive placebo The infants will be stratified in 2 groups: group 1 will receive 400 IU of vitamin D for 6 months as intervention (if mothers are from group 1); group 2 will receive placebo (if mothers are from group 2)
Outcomes	Maternal: pre-eclampsia, gestational hypertension, poor weight gain during pregnancy, stillbirth rates, prevalence and risk factors for maternal vitamin D deficiency Infant: low birthweight, prematurity, neonatal seizures, infants with growth failure, signs and symptoms of vitamin D deficiency, infections: pneumonia, diarrhoea and receptor polymorphism, prevalence and risk factors for neonatal vitamin D deficiency
Starting date	Date of start: February 2010. Status: recruiting participants. Estimated study completion date: June 2011
Contact information	Muhammad Atif Habib, MBBS, MPH Project Office Aga Khan University Tel: +92 21 3 4864798 Email: atif.habib@aku.edu Principal investigator: Zulfiqar A Bhutta, FRCPCH, PhD Aga Khan University, Pakistan.
Notes	Sponsors: Aga Khan University and John Snow, Inc.

Hacker 2010

Trial name or title	Testing the calcium DRI during pregnancy: a study of bone health in black and white women
Methods	Randomised controlled trial.
Participants	120 African American or Caucasian primigravidae women 19-40 years of age in their first trimester of pregnancy in Children's Hospital & Research Center Oakland, California, USA Women who are smokers, have a pre-pregnancy BMI higher than 30, have a medical condition that affects bone or taking a medication that affects bone will be excluded
Interventions	Participants will be randomly assigned to 1 of 3 groups: group 1: will receive 1000 mg of calcium; group 2: will receive 2000 IU vitamin D; group 3: will receive a placebo The intervention will be provided from week 16 of pregnancy until delivery

Hacker 2010 (*Continued*)

Outcomes	Primary: Maternal: change in peripheral cortical and trabecular bone loss and gain during a reproductive cycle in black and white women Infant: none. Secondary: change in bone markers of bone formation and resorption during pregnancy and postpartum, differences in calcium absorption in late pregnancy among black and white women, differences in adaptive immune function tests and markers of inflammation during pregnancy Infant: none.
Starting date	Date of start: 05/2010. Status: currently recruiting participants. Expected study completion date: May 2013.
Contact information	Andrea N Hacker, MS, RD Children's Hospital & ResearchCenter Oakland, CA, USA Tel: +1 510 428-3885 Email: efung@mail.cho.org Principal Investigators: Ellen Fung, PhD, RD and Janet King, PhD, RD
Notes	Sponsors: Children's Hospital & Research Center Oakland and USDA, Western Human Nutrition Research Center, USA

Harvey 2012

Trial name or title	MAVIDOS Maternal vitamin D osteoporosis study: study protocol for a randomised controlled trial. The MAVIDOS Study Group
Methods	Randomised, double-blind, placebo-controlled trial.
Participants	Pregnant women over 18 years old, with a singleton pregnancy with less than 17 weeks' gestation at first assessment (based on last menstrual period (LMP) and dating scan), aiming to give birth at local maternity hospital, and with serum 25(OH)-vitamin D concentration is 25-100 nmol/L at nuchal fold/dating scan (10 to 17 weeks' gestation)
Interventions	Participants will be randomly assigned to 1 of 2 groups: group 1: will receive 1000 IU cholecalciferol orally daily; group 2: will receive placebo Starting from 14 weeks' gestation until delivery.
Outcomes	Infant: whole body bone mineral content of the neonate adjusted for gestational age and age at neonatal DXA scan, whole body bone area, bone mineral density, and size corrected bone mineral density (BMC adjusted for BA, length and weight), body composition adjusted for gestational age and age at DXA scan
Starting date	2008 Apr 11.
Contact information	Nicholas C Harvey MRC Lifecourse Epidemiology Unit, (University of Southampton), Southampton General Hospital, Southampton, United Kingdom

Harvey 2012 (*Continued*)

	Email: nch@mrc.soton.ac.uk
Notes	Sponsor: Southampton University Hospitals NHS Trust (UK). ISRCTN82927713

Jannati 2012

Trial name or title	The effect of 50,000 IU vitamin D supplement administered 2 weekly on neonatal and pregnant women outcome - GDM
Methods	Randomised controlled trial.
Participants	Pregnant women, aged between 15 and 48, who came to prenatal clinic of Shahid Sadoughi and Mojibian Hospitals during first trimester with no history of corticosteroids or anticonvulsants use during the last 3 months were included. Exclusion criteria: history of thyroid or parathyroid diseases; receiving vitamin D more than maintenance dose during the last 6 months; treatment with corticosteroids or anticonvulsants and history of diabetes mellitus before pregnancy
Interventions	Participants will be randomly assigned to 1 of 2 groups:group 1: vitamin D supplement, 50,000 IU tablet, every 2 weeks; group 2: vitamin D supplement, calcium-D tablet, 200 IU daily
Outcomes	Maternal: vitamin D values and GDM.
Starting date	July 2011.
Contact information	Dr Maryam Jannati Moghadam Tel: +983516240061 Email: m_janaty_m@yahoo.com Address: Ayatollah Kashani ST 8915635843 Yazd, Islamic Republic of Iran
Notes	Sponsor: Shahid Sadughi Yazd University of Medical Sciences.

Jelsma 2013

Trial name or title	DALI: vitamin D And lifestyle intervention for gestational diabetes mellitus (GDM) prevention
Methods	Randomised controlled trial with a factorial design.
Participants	Pregnant women with gestational age at recruitment < 12 weeks, and more than 18 years of age Inclusion criteria: pre-pregnancy BMI (self-reported weight, measured height) is >= 29 kg/m2), sufficiently fluent in major language of the country of recruitment, being able to be moderately physically active, giving written informed consent, agree to give birth in 1 of the participating hospitals. Exclusion criteria: pre-existing diabetes, diagnosed with (gestational) diabetes mellitus before randomisation, defined as fasting glucose ≥ 5. 1 mmol/L and/or 1 hour glucose ≥ 10 mmol/L and/or 2 hour glucose ≥ 8.5 mmol/L at baseline, not able to walk at least 100 metres safely, requirement for complex diets, advanced chronic conditions (e.g. valvular heart disease), significant psychiatric disease, unable to speak major language of the country of recruitment fluently, known abnormal calcium metabolism (hypo/hyperparathyroidism, nephrolithiasis, hypercalciuria) or hypercalciuria detected at screening (0.6 mmol/mmol creatinine in spot morning urine) and twin pregnancy

Jelsma 2013 (*Continued*)

Interventions	The design is that of 2 trials with a factorial design: PA, diet, PA & diet, control, vitamin D, PA & diet and placebo, vitamin D & PA & diet, placebo; to compare the impact of increased PA, enhanced nutrition and vitamin D supplementation either alone or in combination on maternal glucose tolerance, maternal weight gain and insulin sensitivity The doses of vitamin D that will be tested in the dosing study are 500, 1000 and 1500 IU/day. 1 of these doses will be used in the trial
Outcomes	Maternal: weight gain during pregnancy, fasting plasma glucose, HbA1c, fasting C peptide, leptin, triglycerides, free fatty acids, high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C), adiponectin 2. 3 beta-hydroxybutyrate, blood pressure, C-reactive protein Infant: neonatal growth, adiposity, adipo-insular axis, glucose-insulin axis, electrolyte concentrations, clinical outcomes and hypoxia exposure at birth, biparietal diameter, head circumference, abdominal circumference, femur length] and determinants of foetal body composition variables (lean body mass and fat body mass, C-peptide, glucose, leptin, triglycerides, 3- beta-hydroxybutyric acid, pH and erythropoietin, jaundice, hypocalcaemia, hypomagnesaemia
Starting date	21/11/2011.
Contact information	Dr David Simmons Addenbrooke's Treatment Centre Hills Road, Cambridge CB2 0QQ United Kingdom
Notes	Sponsor: European Union (EU) (Belgium) - Seventh Framework Programme (FP7)

Judkins 2011

Trial name or title	A randomised double-blinded interventional trial to determine the effect of 50,000 IU vitamin D supplementation monthly or twice monthly from 20 weeks' gestation
Methods	Randomised double-masked clinical trial with randomisation at the individual level. Method of sequence generation: serial tossing of a coin. Allocation will be not concealed
Participants	Pregnant women seeking maternity care with midwifery services involved in the study. Exclusion criteria: antenatal vitamin D level is > 75 nmol/L when enrolling in study
Interventions	Participants will be assigned to 1 of 2 groups: group 1: will receive 50,000 IU tablets twice monthly, 2 weeks apart; group 2: will receive 50,000 IU monthly and a placebo monthly, 2 weeks apart from 20 weeks' gestation until delivery of baby The placebo tablet contains lactose monohydrate, acacia, calcium carbonate, castor oil, maize starch, povidone, sucrose, purified talc, hydrated silica, powdered cellulose, magnesium stearate, shellac, gelatin, beeswax white, titanium dioxide and prepared theobroma
Outcomes	Infant: vitamin D levels taken from the cord blood samples at delivery. If emergencies at delivery prevent a cord blood sample being taken then a maternal venous blood sample will be taken for analysis

Judkins 2011 (*Continued*)

Starting date	Status: not yet recruiting participants.
Contact information	Dr Annie Judkins Newtown Union Health Service 14 Hall Ave, Newtown,. Wellington 6021, New Zealand Email: annie.judkins@nuhs.org.nz
Notes	Sponsors: Royal New Zealand College of GP's, New Zealand and Wellington Medical Research Foundation, New Zealand ACTR Number: ACTRN12610001044011.

Kachhawa 2014

Trial name or title	A randomised controlled trial to investigate the effects of vitamin D supplementation on maternal and newborn babies vitamin D status in Asian-Indian Subjects - VIDIMAN
Methods	Randomised, parallel group, placebo-controlled trial.
Participants	Pregnant women between 12-16 weeks of gestation, aged between 18 to 35 years. Participants agree for delivery conducted at the AIIMS. Exclusion criteria: participants will be excluded from the study if they have more than 1 gestation in current pregnancy, cardiovascular disease, more than 3 abortions, hypertension, pre-eclampsia or Rh isoimmunisation, prior history of delivery of an infant with chromosomal abnormalities or IUGR in previous pregnancy presence of any diagnosed systemic disease known to affect vitamin D status such as malabsorption states, liver and renal disorders, primary and tertiary hyperparathyroidism, have features suggestive of osteomalacia or severe VDD, pre-existing hypertension, diabetes (type 1 or 2), are taking or had taken vitamin D supplementation in last 2 months in doses exceeding 600 IU/day, are using medications known to interact with vitamin D metabolism (steroids,thiazide diuretics, phenytoin, phenobarbitone and antitubercular drugs), have known hypersensitivity to vitamin D preparations, have participated in any other investigational drug study in previous 3 months, have past history of bariatric surgery, are using Ultra-Violet (UV) radiations as a part of medical therapy, are diagnosed with albinism or have other condition associated with decreased skin pigmentation, have any medical condition that in the judgment of the investigator would jeopardise the participants' safety or evaluation of study drug for efficacy or safety. Additional exclusion criteria will be applied after biochemical screening: Having gestational diabetes between 12-16 weeks of pregnancy, have serum calcium more than 1 mg/dL above the upper limit of normal for age, have serum S.25(OH)D level more than 100 ng/mL
Interventions	Participants will be randomly assigned to 1 of 4 groups:group 1: participants will receive 1000 IU of vitamin D per day. Although dose of supplementation has been calculated from daily dose basis, but it will be given, orally as once a month dose (30,000 IU once a month orally,supervised in the hospital), supervised in the hospital till delivery; group 2: participants will receive 2000 IU of vitamin D per day. Although dose of supplementation has been calculated from daily dose basis, but it will be given, orally as once a month dose (60,000 IU once a month orally, supervised in the hospital) till delivery; group 3: participants will receive 4000 IU of vitamin D per day. Although dose of supplementation has been calculated from daily dose basis, but it will be given, orally as once a month dose (120,000 IU once a month orally, supervised in the hospital) till delivery; group 4: control group - participants will receive 600 IU of vitamin D per day. Although dose of supplementation has been calculated from daily dose basis, but it will be given, orally as once a month dose (18,000 IU once a month orally,supervised in the hospital) until delivery

Kachhawa 2014 (*Continued*)

Outcomes	Maternal: serum 25 hydroxyvitamin D, weight gain, pre-eclampsia, preterm labour, insulin resistance in mother Infant: fetal growth, newborn anthropometry and insulin resistance in newborn
Starting date	01-02-2014.
Contact information	Garima Kachhawa Address: Department of Obstetrics and Gynecology AIIMS , New Delhi-29 Department of Obstetrics and Gynecology AIIMS , New Delhi-29 110029 New Delhi, DELHI India Tel: 09868398231 Email: garimakachhawa2012@gmail.com All India Institute of Medical Sciences
Notes	Sponsor: Indian Council of Medical Research ICMR.

Lalooha 2012

Trial name or title	The effect of vitamin D supplementation during pregnancy on newborn's anthropometric index
Methods	An interventional, randomised, not blinded, parallel trial.
Participants	Pregnant women with a singleton pregnancy and gestational age between 24-28 week; BMI 19-26; vitamin D < 30 ng/mL. Exclusion criteria: the known history of liver, renal, parathyroid, bone, metabolic diseases or epilepsy or malabsorption, medications that influence the metabolism of vitamin D and calcium, recurrent abortion, diabetes or gestational diabetes, HTN or pre-eclampsia; fetus with anomalies, polyhydramnios, oligohydramnios or IUGR
Interventions	Participants will be randomly assigned to 1 of 2 groups: group 1: vitamin D capsule 50,000 U weekly for 8 weeks from 28 gestational age and multivitamin tablet include 400 IU vitamin D daily till termination; group 2: multivitamin tab include 400 IU vitamin D daily till termination
Outcomes	Infant: height, weight, and head circumference.
Starting date	1991-11-22.
Contact information	Dr Fatemeh Lalooha Valiasr street Qazvin Iran, Tel: +982812236374 Email: rramezaninezhad@qums.ac.ir Department of Gynecology, Kosar Hospital, Islamic Republic of Iran
Notes	Sponsor: Qhazvin University of Medical Sciences, Iran. Irct registration number : IRCT201205119491N2.

Lindqvist 2010

Trial name or title	Vitamin D supplementation for prevention of placenta mediated pregnancy complications
Methods	Randomised, controlled trial.
Participants	Pregnant women > 18 years of age, from 3 maternal health care units who agree to participate in the study Exclusion criteria: < 18 years of age, hyperparathyroidism and sarcoidosis
Interventions	Participants will be randomly assigned to 1 of 2 groups: group 1: will receive vitamin D, oral drops; group 2: will receive placebo
Outcomes	Maternal: pre-eclampsia, blood loss at delivery. Infant: blood flow in umbilical artery, growth restriction, and prematurity
Starting date	06/04/2011.
Contact information	N/A
Notes	Sponsor: Karolinska University Hospital. EudraCT Number: 2010-019483-37.

McLean 2012

Trial name or title	Effect of high-dose versus low-dose vitamin D supplementation in pregnancy on maternal glucose metabolism and the risk of gestational diabetes
Methods	Randomised controlled parallel trial.
Participants	Pregnant women, aged 18 or more, with less than 20 weeks' gestation at recruitment. Exclusion criteria: known diabetes, calcium metabolic disorder, multiple pregnancy
Interventions	Participants will be randomly assigned to 1 of 2 groups: group 1: will receive high-dose vitamin D supplementation (5000 IU/day); group 2: standard dose pregnancy vitamin supplementation (400 IU vitamin D daily) , administered as an oral capsule, from the time of the first antenatal clinic visit (around 12 weeks' gestation) until delivery
Outcomes	Maternal: diagnosis of gestational diabetes, determined by an oral glucose tolerance test (blood analysis after ingestion of 75 g oral glucose) performed at 26-28 weeks' gestation, or other evidence of hyperglycaemia recorded throughout pregnancy. Maternal glucose metabolism in late second trimester (26-28 weeks' gestation) assessed by glucose tolerance test (blood analysis after ingestion of 75 g oral glucose) Infant: weight at birth, infant length (assessed with a newborn stadiometer) and head circumference
Starting date	10/02/2010
Contact information	Mark McLean Address: Professor Mark McLean University of Western Sydney- Blacktown Clinical School Blacktown Hospital PO Box 6105 BLACKTOWN NSW 2148, Australia Tel: +61 2 9851 6073

McLean 2012 (*Continued*)

	Email: m.mclean@uws.edu.au
Notes	Sponsor: Hospital Westmead, Australia and University of Western Sydney, Australia ACTRN 12612001145897.

Mirghafourvand 2013

Trial name or title	The effect of vitamin D and calcium plus vitamin D for leg cramps in pregnant women: a randomised controlled trial
Methods	Randomised controlled trial.
Participants	Pregnant women with gestational age of 25-30 weeks aged 18 to 35 years old; having leg cramps at least twice a week; being literate. Exclusion criteria: having known thyroid, cardio-vascular, diabetes or renal diseases; intake of calcium and vitamin D supplementation during pregnancy; having allergy history to studied drugs
Interventions	Eligible women will be selected with convenience sampling and will be randomly assigned into 3 groups of 42 participants with block sizes of 3 and 6: group 1: will receive Vitamin D tablets (1000 units); group 2: will receive calcium-vitamin D tablets (300 mg calcium carbonate plus 1000 units vitamin D); group 3: the control group will receive placebo
Outcomes	Maternal: the number, severity and duration of leg cramps.
Starting date	2013-04-30.
Contact information	Dr. Mozhgan Mirghafourvand Address: Nursing & Midwifery Faculty,South Shariati Street 347-51745 Tabriz Iran, Islamic Republic Of Iran. Tel: +984114796770 Email: Mirghafourvandm@tbzmed.ac.ir; mirg1385@yahoo.com Affiliation: Tabriz University of Medical of Sciences
Notes	Sponsor: Tabriz University of Medical Sciences (Project number: 388) IRCT 2013040810324N12.

Mozzafari 2010

Trial name or title	Effect of vitamin D supplementation on glucose status, lipid profiles and inflammatory factors in mothers with a history of gestational diabetes
Methods	Randomised parallel trial.
Participants	Women between 20-45 years of age with gestational diabetes at their recent pregnancy from the list of GDM Diabetes Research Center of Yazd University, and without thyroid disease, kidney disease, bone disease, PCO, liver disease and not using anti-epilepsy drugs, glucocorticoids, and statins. Exclusion criteria: risk of any illness that requires medication and lack of any willingness to cooperate

Mozzafari 2010 (*Continued*)

Interventions	Participants will be randomly assigned to 1 of 2 groups:group 1: intramuscular injection of vitamin D with 300,000 IU dose; group 2: control: not receive any intervention
Outcomes	Maternal: glucose status, lipid profiles and inflammatory factors.
Starting date	2010-01-25.
Contact information	Dr Hassan Mozaffari Address: 3rd floor, Centeral Building of Shahid Sadughi University of Medical Sciences and Health Services, Shahid Bahonar sq.YAZD Iran, Islamic Republic of Iran. Tel: +983517249333 Email: mozaffari.kh@gmail.com Affiliation: Shahid Sadughi University of Medical Sciences and Health Services
Notes	Sponsor: Shahid Sadughi University of Medical Sciences and Health Services IRCT138902113840N1.

Nausheen 2014

Trial name or title	Assessment of dose effectiveness of vitamin D supplementation during pregnancy: a dose-comparison trial
Methods	Blind, randomised controlled trial with 3 arms.
Participants	315 pregnant women aged 15-45 years with less than 16 weeks of gestation in a hospital in Pakistan Pregnant women with pre-existing type 1 or type II diabetes, pre-existing hypertension, multiple fetuses, babies (twins, triplets) or with a diagnosis of pregnancy with a fetal anomaly in scan will be excluded
Interventions	Participants will be randomly assigned to 1 of 3 groups: groups 1 will receive a dose of 400 IU/day till the time of delivery; group 2 will receive 2000 IU/ day till the time of delivery; group 3 will receive 4000 IU/ day till the time of delivery
Outcomes	Vitamin D deficiency, pre-eclampsia, preterm labour, preterm birth, low birthweight, stillbirths
Starting date	June 2013.
Contact information	Dr Sidrah Nausheen, Division of Women & Child Health, Aga Khan University, Karachi, Pakistan
Notes	Sponsor: Aga Khan University, Pakistan.

Rasmussen 2009

Trial name or title	Effects of vitamin D supplement before and during and after pregnancy on complications, birthweight and bone mineral density during lactation
Methods	Double-blind, randomised, placebo-controlled trial.
Participants	400 apparently healthy women 30-35 years of age, all with concentrations of P-25-hydroxyvitamin D (25OHD)- lower than 50 nmol/L. All women included attempts to get pregnant. Visits take place at Clinic of Osteoporosis, Department of Endocrinology, at Aarhus University Hospital, Aarhus, Denmark Women with infertility, an intake of 400 IU or more vitamin D/day, cancer, history of alcohol or drug abuse, calcium metabolic disturbances or spontaneous abortion within last 6 months will be excluded
Interventions	Participants will be randomly assigned to 1 of 3 groups: group 1: will receive 35 µg per day cholecalciferol; group 2: will receive 70 µg per day cholecalciferol; group 3: will receive placebo. All women will receive 2 tablets daily from baseline until 16 weeks after delivery Intervention with cholecalciferol or placebo starts before pregnancy is achieved and continues until 4 months after the women has given birth.
Outcomes	Primary: Infant: birthweight. Maternal: none. Secondary: Infant: weight, crown-heel length and head circumference, and infections within 16 weeks after birth. Concentration of 25OHD in umbilical cord and venous sample 16 weeks after birth Maternal: postpartum effects of vitamin D supplement on maternal bone mineral density, concentration of 25OHD in mothers milk, incidence of pre-eclampsia and abortions
Starting date	Date of start: 12/2009. Status: recruiting participants. Estimated study completion date: December 2011.
Contact information	Gitte Bloch Rasmussen, MD Department of Endocrinology, Aarhus University Hospital University of Aarhus Tel: +45 89 4976 81 Email: gittebr@ki.au.dk
Notes	Sponsor: University of Aarhus, Denmark.

Roth 2013b

Trial name or title	Randomised placebo-controlled trial of maternal vitamin D supplementation during pregnancy and lactation to improve infant linear growth in Dhaka, Bangladesh (MDIG)
Methods	Randomised placebo-controlled trial.
Participants	Women aged 18 years and above with a gestational age of 17 to 24 completed weeks estimated based on recalled last menstrual period and/or ultrasound, who Intend to permanently reside in the trial catchment area for at least 18 months. Exclusion criteria: history of medical conditions that may predispose the participant

Roth 2013b (*Continued*)

	to vitamin D sensitivity, altered vitamin D metabolism and/or hypercalcaemia, or history of renal calculi, high-risk pregnancy based on 1 or more of the following findings by point-of-care testing: Severe anaemia: haemoglobin < 70 g/L assessed by Hemocue, Moderate-severe proteinuria: ≥ 300 mg/dL (3+ or 4+) based on urine dipstick, Hypertension: systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg, multiple gestation, major congenital anomaly, or severe oligohydramnios based on maternal history and/or ultrasound, unwillingness to stop taking non-study vitamin D or calcium supplements or a multivitamin with calcium and/or vitamin D, currently prescribed vitamin D supplements as part of a physician's treatment plan for vitamin D deficiency and previous participation in the same study
Interventions	Participants will be randomly assigned to one of 5 groups: group 1: prenatal period 0 IU; postpartum period 0 IU (placebo); group 2: prenatal period 4200 IU/week of vitamin D3 (= 600 IU/d); postpartum period 0 IU/week (placebo); group 3: prenatal period 16,800 IU/week of vitamin D3 (= 2400 IU/d); postpartum period 0 IU/week (placebo) Group 4: prenatal period 28,000 IU/week of vitamin D3 (= 4000 IU/d); postpartum period 0 IU/week (placebo); group 5: prenatal period 28,000 IU/week of vitamin D3 (= 4000 IU/d); postpartum period 28,000 IU/week (= 4000 IU/d) Overall: the prenatal period will start at enrolment (17-24 weeks' gestation) and last until delivery. The postpartum period will last from delivery until 6 months postpartum
Outcomes	Infant: infant length-for-age Z-Scores with prenatal supplementation, infant length-for-age Z-Scores with postpartum supplementation, serum calcium, stunting (LAZ < -2 SD below the median) at 1 and 2 years of age, attained length and LAZ at 2 years of age, birthweight, low birthweight %, small-for-gestational age %, preterm birth %, stillbirth %, acute respiratory infections and diarrhoea, biomarker concentrations, perinatal, neonatal and infant severe morbidity and mortality, epigenetic patterns of genes involved in vitamin D metabolism Maternal: severe morbidity and mortality.
Starting date	March 2014.
Contact information	Daniel Roth, MD Tel: +1 416 8135795 Email: daniel.roth@sickkids.ca
Notes	Sponsors: The Hospital for Sick Children, Canada; International Centre for Diarrhoeal Disease Research, Bangladesh; Shimantik; Bill & Melinda Gates Foundation, USA ClinicalTrials.gov Identifier: NCT01924013.

Simsek 2011

Trial name or title	Vitamin D supplementation in gestational diabetes mellitus.
Methods	Randomised clinical trial.
Participants	Women with gestational diabetes, defined by the WHO criteria: fasting glucose ≥ 7.0 mmol/L or; oral glucose tolerance test: 75 g glucose, 2-hour glucose ≥ 7.8 mmol/L recognised during pregnancy with a written informed consent, aged between 18-42. Exclusion criteria: impaired renal function: creatinine * 150 *mol/L or a creatinine clearance < 50 ml/min, to the discretion of the investigator, cardiac problems: decompensated heart failure (NYHA III and IV); diagnosis of unstable angina pectoris; myocardial infarction within the last

Simsek 2011 (*Continued*)

	12 months. Mental retardation, or psychiatric treatment for schizophrenia, organic mental disorder or bipolar disorder currently or in the past; Iinsufficient knowledge of the Dutch language; vitamin D plasma level ≥ 100 nmol/L or < 15 nmol/L; hypercalcaemia of any reason; granulomatous diseases influencing vitamin D levels; urolithiasis; pre-existent diabetes mellitus of any type; substance abuse, other than nicotine; participation in any other trials, involving investigational products within 30 days prior to trial entry; any condition that the Investigator and/or co-ordinating Investigator feels would interfere with trial participation or evaluation of results
Interventions	Participants will be randomly assigned to 1 of 2 groups: group 1: cholecalciferol 15,000 IU once a week during pregnancy; group 2: placebo 15,000 IU once a week during pregnancy
Outcomes	Primary: Maternal: insulin sensitivity (HOMA-index and β-cell function) measured through fasting insulin and blood glucose levels Secondary: Maternal: serum 25OHD, HbA1c values, blood pressure, thyroid function, lipid profile and BMI, pregnancy characteristics, maternal outcomes, and adverse effects Infant: neonatal outcome.
Starting date	1 Jul 2012.
Contact information	Drs. Y.H.M. Poel Medisch Centrum Alkmaar Wilhelminalaan 12 Tel: +31 (0)72 5484444 Email: y.h.m.poel1@mca.nl
Notes	Sponsor: Medisch Centrum Alkmaar. NTR Number: NTR3158.

Wagner 2013

Trial name or title	Preventing health disparities during pregnancy through vitamin D supplementation
Methods	Randomised control trial with 2 arms.
Participants	450 pregnant women (18-45 years of age) who presents to her obstetrician or midwife at the Medical University of SC (MUSC), Charleston, United States of America obstetrical facilities within the first 14 weeks after her last menstrual period with confirmation of a singleton pregnancy will be eligible for enrolment in the study. Women with diverse ethnic backgrounds (African-American, Asian, Caucasian and Hispanic) will be actively recruited Women with pre-existing calcium, uncontrolled thyroid disease, parathyroid conditions, or who require chronic diuretic or cardiac medication therapy including calcium channel blockers will not be eligible for enrolment into the study. Mothers with pre-existing sickle cell disease (not trait only), sarcoidosis, Crohn's disease, or ulcerative colitis may not participate in the study. In addition, because of the potentially confounding effect of multiple fetuses, mothers with multiple gestations will not be eligible for participation in the study A subgroup of approximately 100 participants with known diabetes, hypertension, HIV, or morbid obesity

Wagner 2013 (*Continued*)

	(BMI > 49) will participate in the study
Interventions	Participants will be randomly assigned to 1 of 2 groups: group 1 will receive vitamin D3 4000 IU in gummy form (participants will be asked to consume 4 gummies/day beginning at 10-14 weeks of your pregnancy) plus the daily multiple micronutrient supplement; group 2 will receive placebo gummy plus the standard multiple micronutrient supplement (containing also 400 IU vitamin D3
Outcomes	Maternal and neonatal health status as a function of maternal and infant vitamin D status
Starting date	January 2013.
Contact information	Dr Carol Wagner Medical University of South Carolina Charleston, South Carolina, United States, 29425 Tel: +1 843-792-2401 Email: wagnercl@musc.edu
Notes	Sponsor: Medical University of South Carolina, USA and W.K. Kellogg Foundation, USA

BMI: body mass index
DRI: dietary references intakes
GDM: gestational diabetes mellitus
HTN: hypertension
IU: international units
IUGR intrauterine growth restriction
LMP: last menstrual period
PA: physical activity
PCO: polycystic ovary
PTH: parathyroid hormone
Rh: Rhesus
SD: standard deviation
VDD: Vitamin D deficiency
25OHD: 25-hydroxycholecalciferol

DATA AND ANALYSES

Comparison 1. Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pre-eclampsia (ALL)	2	219	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.25, 1.05]
2 Gestational diabetes (ALL)	2	219	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.05, 3.45]
3 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (ALL)	7	868	Mean Difference (IV, Random, 95% CI)	54.73 [36.60, 72.86]
4 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by start of supplementation)	7	868	Mean Difference (IV, Random, 95% CI)	47.24 [35.17, 59.31]
4.1 Less than 20 weeks of pregnancy	1	32	Mean Difference (IV, Random, 95% CI)	32.45 [19.48, 45.42]
4.2 20 weeks of pregnancy or more	6	836	Mean Difference (IV, Random, 95% CI)	49.70 [36.62, 62.78]
4.3 Unknown/unreported/ mixed	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by pre-gestational body mass index (kg/m^2))	7	868	Mean Difference (IV, Random, 95% CI)	47.24 [35.17, 59.31]
5.1 Underweight (lower than 18.5)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Normal weight (18.5 to 24.9)	1	165	Mean Difference (IV, Random, 95% CI)	34.09 [12.51, 55.67]
5.3 Overweight (25 or higher)	2	308	Mean Difference (IV, Random, 95% CI)	19.54 [18.34, 20.74]
5.4 Unknown/unreported/ mixed	4	395	Mean Difference (IV, Random, 95% CI)	73.18 [21.00, 125. 36]
6 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by supplementation scheme/regimen)	8	1043	Mean Difference (IV, Random, 95% CI)	44.12 [30.24, 58.00]
6.1 Single dose	3	340	Mean Difference (IV, Random, 95% CI)	15.16 [5.68, 24.63]
6.2 Daily	6	703	Mean Difference (IV, Random, 95% CI)	57.80 [38.37, 77.23]
6.3 Weekly	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by skin pigmentation based on Fitzpatrick skin tone chart)	7	868	Mean Difference (IV, Random, 95% CI)	47.24 [35.17, 59.31]

7.1 Three or less	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Four or more	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 Unknown/unreported/ mixed	7	868	Mean Difference (IV, Random, 95% CI)	47.24 [35.17, 59.31]
8 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by latitude)	7	868	Mean Difference (IV, Random, 95% CI)	47.24 [35.17, 59.31]
8.1 Between Tropics of Cancer and Capricorn	1	260	Mean Difference (IV, Random, 95% CI)	19.13 [17.79, 20.47]
8.2 North of the Tropic of Cancer or South of the Tropic of Capricorn	6	608	Mean Difference (IV, Random, 95% CI)	55.73 [35.67, 75.80]
8.3 Unknown/unreported	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by season at the start of pregnancy)	7	868	Mean Difference (IV, Random, 95% CI)	47.24 [35.17, 59.31]
9.1 Summer	1	160	Mean Difference (IV, Random, 95% CI)	96.0 [88.19, 103.81]
9.2 Winter	1	77	Mean Difference (IV, Random, 95% CI)	16.30 [13.61, 18.99]
9.3 Mixed seasons	5	631	Mean Difference (IV, Random, 95% CI)	37.24 [27.46, 47.02]
10 Preterm birth (less than 37 weeks' gestation) (ALL)	3	477	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.14, 0.93]
11 Low birthweight (less than 2500 g) (ALL)	3	493	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.24, 0.67]
12 Impaired glucose tolerance	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13 Caesarean section	2	312	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.69, 1.31]
14 Gestational hypertension	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15 Adverse effects (nephritic syndrome) (ALL)	1	135	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.01, 4.06]
16 Maternal death (death while pregnant or within 42 days of termination of pregnancy) (ALL)	1	180	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17 Birth length (cm) (ALL)	4	638	Mean Difference (IV, Random, 95% CI)	0.70 [-0.02, 1.43]
18 Head circumference at birth (cm) (ALL)	4	638	Mean Difference (IV, Random, 95% CI)	0.43 [0.03, 0.83]
19 Birthweight (g) (ALL)	5	715	Mean Difference (IV, Random, 95% CI)	66.60 [-137.22, 270. 41]
20 Admission to special care (including intensive care) during the neonatal period (within 28 days after delivery) (ALL)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
21 Stillbirth (ALL)	3	540	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.06, 1.99]
22 Neonatal death (ALL)	2	282	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.04, 1.67]
23 Apgar score less than seven at five minutes	1	165	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.11, 2.53]
24 Neonatal infection	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
25 Very preterm birth	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Vitamin D + calcium versus no treatment/placebo (no vitamin or minerals)

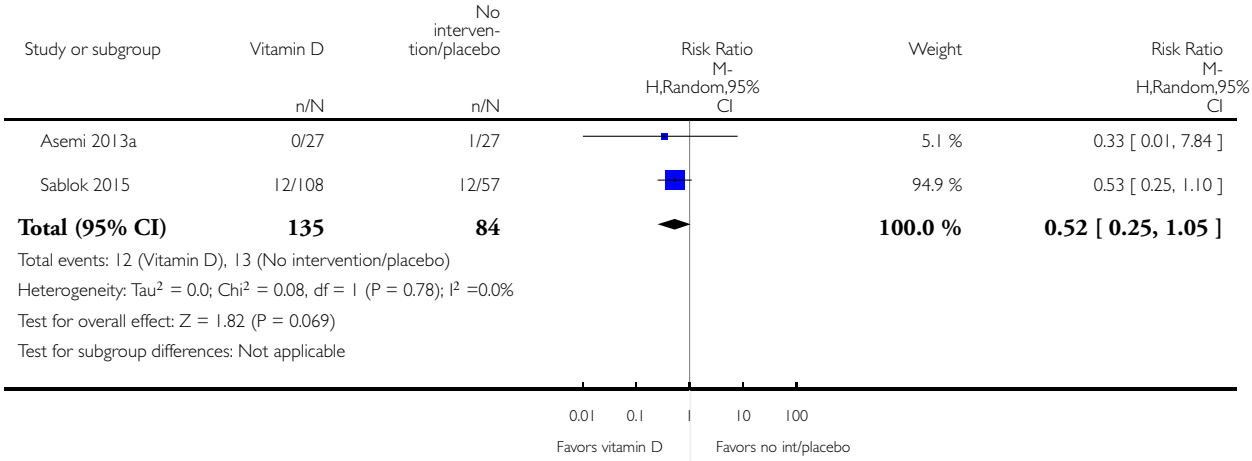
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pre-eclampsia (ALL)	3	1114	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.32, 0.80]
2 Gestational diabetes (ALL)	1	54	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.84]
3 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (ALL)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Preterm birth (less than 37 weeks' gestation) (ALL)	3	798	Risk Ratio (M-H, Random, 95% CI)	1.57 [1.02, 2.43]
5 Low birthweight (less than 2500 g) (ALL)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Impaired glucose tolerance	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Caesarean section	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Gestational hypertension	1	59	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.06, 1.12]
9 Adverse effects (ALL)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Maternal death (death while pregnant or within 42 days of termination of pregnancy)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Birth length (cm) (ALL)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12 Head circumference at birth (cm) (ALL)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13 Birthweight (g) (ALL)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
14 Admission to special care (including intensive care) during the neonatal period (within 28 days after delivery) (ALL)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15 Stillbirth (ALL)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16 Neonatal death (ALL)	1	660	Risk Ratio (M-H, Random, 95% CI)	0.2 [0.01, 4.15]
17 Apgar score less than seven at five minutes	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
18 Neonatal infection	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
19 Very preterm birth	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 1 Pre-eclampsia (ALL).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome: 1 Pre-eclampsia (ALL)

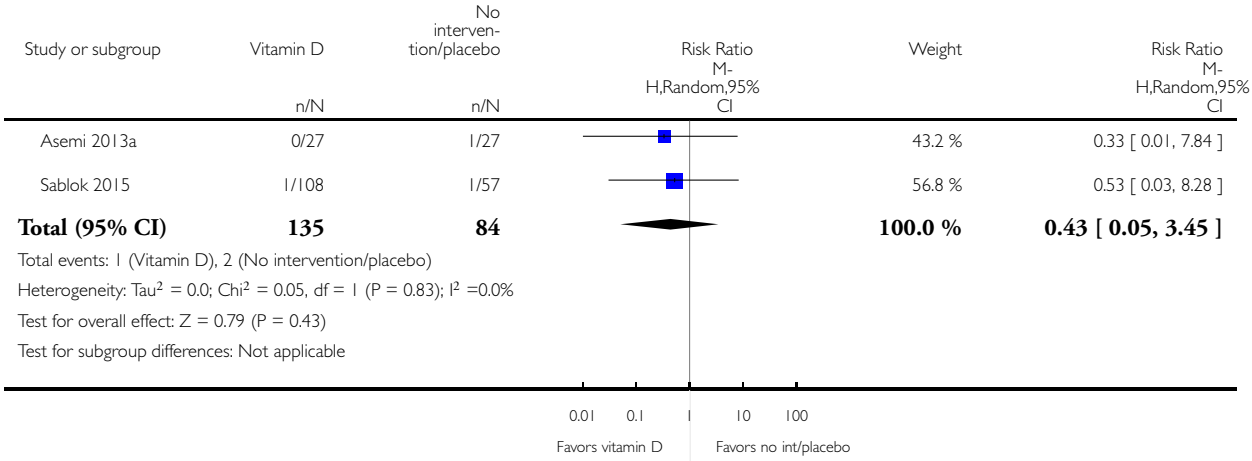


Analysis 1.2. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 2 Gestational diabetes (ALL).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome: 2 Gestational diabetes (ALL)



Analysis 1.3. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 3 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (ALL).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

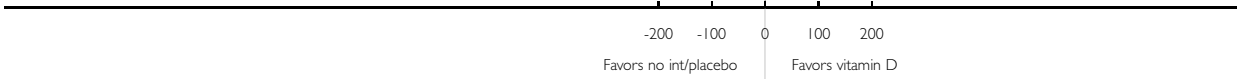
Outcome: 3 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (ALL)

Study or subgroup	Vitamin D		No intervention/placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Asemi 2013a	24	53.66 (4.49)	24	33.2 (2.75)		15.4 %	20.46 [18.35, 22.57]
Brooke 1980	59	168 (96.01)	67	16.2 (22.1)		11.9 %	151.80 [126.74, 176.86]
Delvin 1986	15	64.9 (17.47)	17	32.45 (19.97)		14.3 %	32.45 [19.48, 45.42]
Grant 2013	173	100 (11.9)	87	49.9 (13)		15.4 %	50.10 [46.84, 53.36]
Mallet 1986	48	25.3 (7.1)	29	9.4 (4.9)		15.4 %	15.90 [13.21, 18.59]
Roth 2010	80	134.4 (30.7)	80	38.4 (18.1)		15.0 %	96.00 [88.19, 103.81]
Sablok 2015	108	80.2 (51.53)	57	46.11 (74.21)		12.7 %	34.09 [12.51, 55.67]
Total (95% CI)	**507**		**361**			**100.0 %**	**54.73 [36.60, 72.86]**

Heterogeneity: $Tau^2 = 554.85$; $Chi^2 = 689.77$, df = 6 ($P<0.00001$); $I^2 = 99\%$

Test for overall effect: $Z = 5.92$ ($P < 0.00001$)

Test for subgroup differences: Not applicable



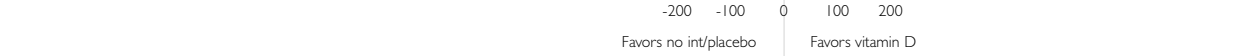
Analysis 1.4. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 4 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by start of supplementation).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome: 4 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by start of supplementation)

Study or subgroup	Vitamin D N	Mean(SD)	No interven-tion/placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Less than 20 weeks of pregnancy							
Delvin 1986	15	64.896 (17.472)	17	32.45 (19.968)		14.0 %	32.45 [19.48, 45.42]
Subtotal (95% CI)	**15**		**17**			**14.0 %**	**32.45 [19.48, 45.42]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.90 (P < 0.00001)							
2 20 weeks of pregnancy or more							
Asemi 2013a	24	53.66 (4.49)	24	33.2 (2.75)		16.6 %	20.46 [18.35, 22.57]
Brooke 1980	59	168 (96.01)	67	16.2 (22.1)		9.7 %	151.80 [126.74, 176.86]
Grant 2013	173	39.63 (5.15)	87	20.5 (5.2)		16.7 %	19.13 [17.79, 20.47]
Mallet 1986	48	25.7 (7.1)	29	9.4 (4.9)		16.6 %	16.30 [13.61, 18.99]
Roth 2010	80	134.4 (30.7)	80	38.4 (18.1)		15.6 %	96.00 [88.19, 103.81]
Sablok 2015	108	80.2 (51.53)	57	46.11 (74.21)		10.9 %	34.09 [12.51, 55.67]
Subtotal (95% CI)	**492**		**344**			**86.0 %**	**49.70 [36.62, 62.78]**
Heterogeneity: Tau^2 = 229.65; Chi^2 = 479.37, df = 5 (P<0.00001); I^2 =99%							
Test for overall effect: Z = 7.45 (P < 0.00001)							
3 Unknown/unreported/mixed							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**507**		**361**			**100.0 %**	**47.24 [35.17, 59.31]**
Heterogeneity: Tau^2 = 227.13; Chi^2 = 482.55, df = 6 (P<0.00001); I^2 =99%							
Test for overall effect: Z = 7.67 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 3.37, df = 1 (P = 0.07), I^2 =70%							



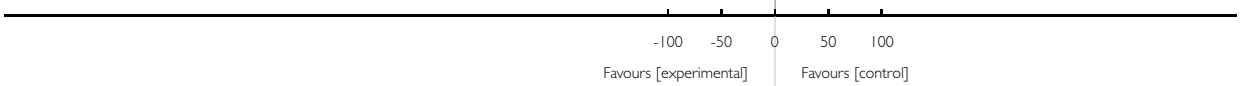
Analysis 1.5. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 5 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by pre-gestational body mass index (kg/m2)).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome: 5 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by pre-gestational body mass index (kg/m^2))

Study or subgroup	Vitamin D N	Mean(SD)	No intervention/placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Underweight (lower than 18.5)							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Normal weight (18.5 to 24.9)							
Sablok 2015	108	80.2 (51.53)	57	46.11 (74.21)		10.9 %	34.09 [12.51, 55.67]
Subtotal (95% CI)	**108**		**57**			**10.9 %**	**34.09 [12.51, 55.67]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.10 (P = 0.0020)							
3 Overweight (25 or higher)							
Asemi 2013a	24	53.66 (4.49)	24	33.2 (2.75)		16.6 %	20.46 [18.35, 22.57]
Grant 2013	173	39.63 (5.15)	87	20.5 (5.2)		16.7 %	19.13 [17.79, 20.47]
Subtotal (95% CI)	**197**		**111**			**33.3 %**	**19.54 [18.34, 20.74]**
Heterogeneity: Tau^2 = 0.07; Chi^2 = 1.09, df = 1 (P = 0.30); I^2 =8%							
Test for overall effect: Z = 31.91 (P < 0.00001)							
4 Unknown/unreported/mixed							
Brooke 1980	59	168 (96.01)	67	16.2 (22.1)		9.7 %	151.80 [126.74, 176.86]
Delvin 1986	15	64.896 (17.472)	17	32.45 (19.968)		14.0 %	32.45 [19.48, 45.42]
Mallet 1986	48	25.7 (7.1)	29	9.4 (4.9)		16.6 %	16.30 [13.61, 18.99]
Roth 2010	80	134.4 (30.7)	80	38.4 (18.1)		15.6 %	96.00 [88.19, 103.81]
Subtotal (95% CI)	**202**		**193**			**55.9 %**	**73.18 [21.00, 125.36]**
Heterogeneity: Tau^2 = 2780.41; Chi^2 = 456.42, df = 3 (P<0.00001); I^2 =99%							
Test for overall effect: Z = 2.75 (P = 0.0060)							
Total (95% CI)	**507**		**361**			**100.0 %**	**47.24 [35.17, 59.31]**
Heterogeneity: Tau^2 = 227.13; Chi^2 = 482.55, df = 6 (P<0.00001); I^2 =99%							
Test for overall effect: Z = 7.67 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 5.79, df = 2 (P = 0.06), I^2 =65%							



Analysis 1.6. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 6 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by supplementation scheme/regimen).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome: 6 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by supplementation scheme/regimen)

Study or subgroup	Vitamin D N	Mean(SD)	No intervention/placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Single dose							
Mallet 1986	27	26 (6.4)	29	9.4 (4.9)		12.0 %	16.60 [13.60, 19.60]
Sablok 2015	108	80.2 (51.53)	57	46.11 (74.21)		9.3 %	34.09 [12.51, 55.67]
Yu 2008	60	34 (15)	59	27 (19)		11.7 %	7.00 [0.84, 13.16]
Subtotal (95% CI)	**195**		**145**			**33.0 %**	**15.16 [5.68, 24.63]**
Heterogeneity: Tau^2 = 48.36; Chi^2 = 10.58, df = 2 (P = 0.01); I^2 =81%							
Test for overall effect: Z = 3.14 (P = 0.0017)							
2 Daily							
Asemi 2013a	24	53.66 (4.49)	24	33.2 (2.75)		12.0 %	20.46 [18.35, 22.57]
Brooke 1980	59	168 (96.01)	67	16.2 (22.1)		8.6 %	151.80 [126.74, 176.86]
Delvin 1986	15	64.896 (17.472)	17	32.45 (19.968)		10.9 %	32.45 [19.48, 45.42]
Grant 2013	173	100 (11.9)	87	49.9 (13)		11.9 %	50.10 [46.84, 53.36]
Mallet 1986	48	25.7 (7.1)	29	9.4 (4.9)		12.0 %	16.30 [13.61, 18.99]
Roth 2010	80	134.4 (30.7)	80	38.4 (18.1)		11.6 %	96.00 [88.19, 103.81]
Subtotal (95% CI)	**399**		**304**			**67.0 %**	**57.80 [38.37, 77.23]**
Heterogeneity: Tau^2 = 556.23; Chi^2 = 684.34, df = 5 (P<0.00001); I^2 =99%							
Test for overall effect: Z = 5.83 (P < 0.00001)							
3 Weekly							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**594**		**449**			**100.0 %**	**44.12 [30.24, 58.00]**
Heterogeneity: Tau^2 = 417.31; Chi^2 = 766.87, df = 8 (P<0.00001); I^2 =99%							
Test for overall effect: Z = 6.23 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 14.95, df = 1 (P = 0.00), I^2 =93%							

Analysis 1.7. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 7 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by skin pigmentation based on Fitzpatrick skin tone chart).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome: 7 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by skin pigmentation based on Fitzpatrick skin tone chart)

Study or subgroup	Vitamin D N	Mean(SD)	No intervention/placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Three or less							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Four or more							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
3 Unknown/unreported/mixed							
Asemi 2013a	24	53.66 (4.49)	24	33.2 (2.75)		16.6 %	20.46 [18.35, 22.57]
Brooke 1980	59	168 (96.01)	67	16.2 (22.1)		9.7 %	151.80 [126.74, 176.86]
Delvin 1986	15	64.9 (17.47)	17	32.45 (19.97)		14.0 %	32.45 [19.48, 45.42]
Grant 2013	173	39.63 (5.15)	87	20.5 (5.2)		16.7 %	19.13 [17.79, 20.47]
Mallet 1986	48	25.7 (7.1)	29	9.4 (4.9)		16.6 %	16.30 [13.61, 18.99]
Roth 2010	80	134.4 (30.7)	80	38.4 (18.1)		15.6 %	96.00 [88.19, 103.81]
Sablok 2015	108	80.2 (51.53)	57	46.11 (74.21)		10.9 %	34.09 [12.51, 55.67]
Subtotal (95% CI)	**507**		**361**			**100.0 %**	**47.24 [35.17, 59.31]**
Heterogeneity: Tau^2 = 227.13; Chi^2 = 482.55, df = 6 (P<0.00001); I^2 =99%							
Test for overall effect: Z = 7.67 (P < 0.00001)							
Total (95% CI)	**507**		**361**			**100.0 %**	**47.24 [35.17, 59.31]**
Heterogeneity: Tau^2 = 227.13; Chi^2 = 482.55, df = 6 (P<0.00001); I^2 =99%							
Test for overall effect: Z = 7.67 (P < 0.00001)							
Test for subgroup differences: Not applicable							

Analysis 1.8. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 8 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by latitude).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome: 8 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by latitude)

Study or subgroup	Vitamin D N	Mean(SD)	No intervention/placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Between Tropics of Cancer and Capricorn							
Grant 2013	173	39.63 (5.15)	87	20.5 (5.2)		16.7 %	19.13 [17.79, 20.47]
Subtotal (95% CI)	**173**		**87**			**16.7 %**	**19.13 [17.79, 20.47]**
Heterogeneity: not applicable							
Test for overall effect: Z = 28.08 (P < 0.00001)							
2 North of the Tropic of Cancer or South of the Tropic of Capricorn							
Asemi 2013a	24	53.66 (4.49)	24	33.2 (2.75)		16.6 %	20.46 [18.35, 22.57]
Brooke 1980	59	168 (96.01)	67	16.2 (22.1)		9.7 %	151.80 [126.74, 176.86]
Delvin 1986	15	64.896 (17.472)	17	32.45 (19.968)		14.0 %	32.45 [19.48, 45.42]
Mallet 1986	48	25.7 (7.1)	29	9.4 (4.9)		16.6 %	16.30 [13.61, 18.99]
Roth 2010	80	134.4 (30.7)	80	38.4 (18.1)		15.6 %	96.00 [88.19, 103.81]
Sablok 2015	108	80.2 (51.53)	57	46.11 (74.21)		10.9 %	34.09 [12.51, 55.67]
Subtotal (95% CI)	**334**		**274**			**83.3 %**	**55.73 [35.67, 75.80]**
Heterogeneity: Tau^2 = 576.57; Chi^2 = 469.64, df = 5 (P<0.00001); I^2 =99%							
Test for overall effect: Z = 5.44 (P < 0.00001)							
3 Unknown/unreported							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**507**		**361**			**100.0 %**	**47.24 [35.17, 59.31]**
Heterogeneity: Tau^2 = 227.13; Chi^2 = 482.55, df = 6 (P<0.00001); I^2 =99%							
Test for overall effect: Z = 7.67 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 12.73, df = 1 (P = 0.00), I^2 =92%							

Analysis 1.9. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 9 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by season at the start of pregnancy).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome: 9 Maternal vitamin D concentration at term (25-hydroxyvitamin D) (nmol/L) (by season at the start of pregnancy)

Study or subgroup	Vitamin D N	Mean(SD)	No intervention/placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Summer							
Roth 2010	80	134.4 (30.7)	80	38.4 (18.1)		15.6 %	96.00 [88.19, 103.81]
Subtotal (95% CI)	**80**		**80**			**15.6 %**	**96.00 [88.19, 103.81]**
Heterogeneity: not applicable							
Test for overall effect: Z = 24.09 (P < 0.00001)							
2 Winter							
Mallet 1986	48	25.7 (7.1)	29	9.4 (4.9)		16.6 %	16.30 [13.61, 18.99]
Subtotal (95% CI)	**48**		**29**			**16.6 %**	**16.30 [13.61, 18.99]**
Heterogeneity: not applicable							
Test for overall effect: Z = 11.89 (P < 0.00001)							
3 Mixed seasons							
Asemi 2013a	24	53.66 (4.49)	24	33.2 (2.75)		16.6 %	20.46 [18.35, 22.57]
Brooke 1980	59	168 (96.01)	67	16.2 (22.1)		9.7 %	151.80 [126.74, 176.86]
Delvin 1986	15	64.9 (17.47)	17	32.45 (19.97)		14.0 %	32.45 [19.48, 45.42]
Grant 2013	173	39.63 (5.15)	87	20.5 (5.2)		16.7 %	19.13 [17.79, 20.47]
Sablok 2015	108	80.2 (51.53)	57	46.11 (74.21)		10.9 %	34.09 [12.51, 55.67]
Subtotal (95% CI)	**379**		**252**			**67.8 %**	**37.24 [27.46, 47.02]**
Heterogeneity: Tau^2 = 84.40; Chi^2 = 113.20, df = 4 (P<0.00001); I^2 =96%							
Test for overall effect: Z = 7.46 (P < 0.00001)							
Total (95% CI)	**507**		**361**			**100.0 %**	**47.24 [35.17, 59.31]**
Heterogeneity: Tau^2 = 227.13; Chi^2 = 482.55, df = 6 (P<0.00001); I^2 =99%							
Test for overall effect: Z = 7.67 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 363.66, df = 2 (P = 0.00), I^2 =99%							

Analysis 1.10. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 10 Preterm birth (less than 37 weeks' gestation) (ALL).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome: 10 Preterm birth (less than 37 weeks' gestation) (ALL)

Study or subgroup	Vitamin D n/N	No intervention/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Asemi 2013a	1/27	1/27		11.3 %	1.00 [0.07, 15.18]
Grant 2013	0/171	4/87		10.0 %	0.06 [0.00, 1.04]
Sablok 2015	9/108	12/57		78.7 %	0.40 [0.18, 0.88]
Total (95% CI)	**306**	**171**		**100.0 %**	**0.36 [0.14, 0.93]**

Total events: 10 (Vitamin D), 17 (No intervention/placebo)

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 2.22$, df = 2 (P = 0.33); $I^2 = 10\%$

Test for overall effect: Z = 2.11 (P = 0.035)

Test for subgroup differences: Not applicable

Analysis 1.11. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 11 Low birthweight (less than 2500 g) (ALL).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome: 11 Low birthweight (less than 2500 g) (ALL)

Study or subgroup	Vitamin D n/N	No intervention/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Brooke 1980	7/59	15/69		37.7 %	0.55 [0.24, 1.25]
Marya 1988	4/100	19/100		24.1 %	0.21 [0.07, 0.60]
Sablok 2015	9/108	11/57		38.2 %	0.43 [0.19, 0.98]
Total (95% CI)	**267**	**226**		**100.0 %**	**0.40 [0.24, 0.67]**

Total events: 20 (Vitamin D), 45 (No intervention/placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.08$, df = 2 (P = 0.35); $I^2 = 4\%$

Test for overall effect: Z = 3.49 (P = 0.00048)

Test for subgroup differences: Not applicable

Analysis 1.13. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 13 Caesarean section.

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome: 13 Caesarean section

Study or subgroup	Vitamin D n/N	No intervention/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Roth 2010	44/73	44/74		85.5 %	1.01 [0.78, 1.32]
Sablok 2015	11/108	9/57		14.5 %	0.65 [0.28, 1.47]
Total (95% CI)	**181**	**131**		**100.0 %**	**0.95 [0.69, 1.31]**

Total events: 55 (Vitamin D), 53 (No intervention/placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.14$, df = 1 (P = 0.29); $I^2 = 12\%$

Test for overall effect: Z = 0.31 (P = 0.75)

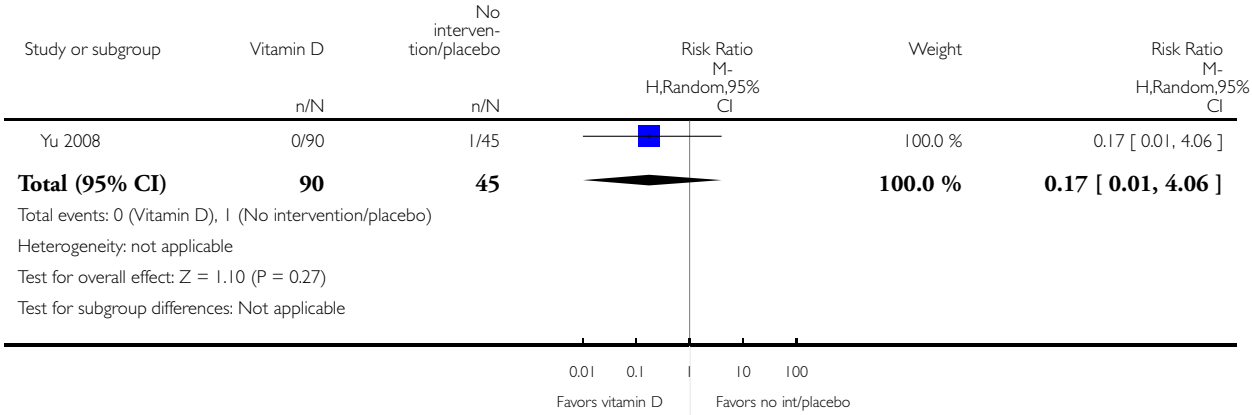
Test for subgroup differences: Not applicable

Analysis 1.15. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 15 Adverse effects (nephritic syndrome) (ALL).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome: 15 Adverse effects (nephritic syndrome) (ALL)



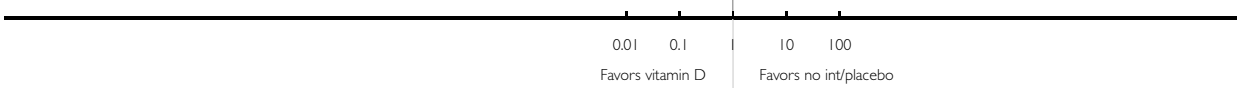
Analysis 1.16. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 16 Maternal death (death while pregnant or within 42 days of termination of pregnancy) (ALL).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome: 16 Maternal death (death while pregnant or within 42 days of termination of pregnancy) (ALL)

Study or subgroup	Vitamin D n/N	No intervention/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Sablok 2015	0/120	0/60			Not estimable
Total (95% CI)	**120**	**60**			**Not estimable**
Total events: 0 (Vitamin D), 0 (No intervention/placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					



Analysis 1.17. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 17 Birth length (cm) (ALL).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

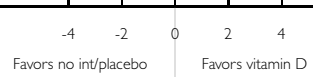
Outcome: 17 Birth length (cm) (ALL)

Study or subgroup	Vitamin D N	Mean(SD)	No interven-tion/placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Brooke 1980	59	49.7 (2.3)	67	49.5 (3.27)		20.7 %	0.20 [-0.78, 1.18]
Marya 1988	100	50.06 (1.79)	100	48.45 (2.04)		28.1 %	1.61 [1.08, 2.14]
Roth 2010	74	48.2 (2.5)	73	48 (2)		24.8 %	0.20 [-0.53, 0.93]
Sablok 2015	108	46.61 (1.8)	57	46 (2.1)		26.3 %	0.61 [-0.03, 1.25]
Total (95% CI)	**341**		**297**			**100.0 %**	**0.70 [-0.02, 1.43]**

Heterogeneity: $Tau^2 = 0.42$; $Chi^2 = 13.09$, df = 3 (P = 0.004); $I^2 = 77\%$

Test for overall effect: Z = 1.89 (P = 0.058)

Test for subgroup differences: Not applicable



Analysis 1.18. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 18 Head circumference at birth (cm) (ALL).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome: 18 Head circumference at birth (cm) (ALL)

Study or subgroup	Vitamin D N	Mean(SD)	No interven-tion/placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Brooke 1980	59	34.5 (0.76)	67	34.3 (1.63)		24.8 %	0.20 [-0.24, 0.64]
Marya 1988	100	33.99 (1.02)	100	33.41 (1.11)		29.6 %	0.58 [0.28, 0.88]
Roth 2010	73	32.9 (1.8)	74	33 (1.5)		21.5 %	-0.10 [-0.64, 0.44]
Sablok 2015	108	33.85 (0.96)	57	32.9 (1.6)		24.2 %	0.95 [0.50, 1.40]
Total (95% CI)	**340**		**298**			**100.0 %**	**0.43 [0.03, 0.83]**

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 10.66$, df = 3 (P = 0.01); $I^2 = 72\%$

Test for overall effect: Z = 2.13 (P = 0.033)

Test for subgroup differences: Not applicable

Analysis 1.19. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 19 Birthweight (g) (ALL).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

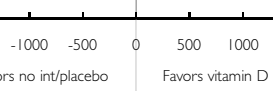
Outcome: 19 Birthweight (g) (ALL)

Study or subgroup	Vitamin D		No interven-tion/placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Brooke 1980	59	3157 (468.5)	67	3034 (469.3)		18.9 %	123.00 [-41.07, 287.07]
Mallet 1986	48	3280 (86)	29	3460 (70)		21.3 %	-180.00 [-215.23, -144.77]
Marya 1988	100	2990 (360)	100	2800 (370)		20.4 %	190.00 [88.82, 291.18]
Roth 2010	73	2802 (543)	74	2788 (378)		19.2 %	14.00 [-137.44, 165.44]
Sablok 2015	108	2600 (410)	57	2400 (310)		20.2 %	200.00 [88.39, 311.61]
Total (95% CI)	**388**		**327**			**100.0 %**	**66.60 [-137.22, 270.41]**

Heterogeneity: Tau^2 = 50334.96; Chi^2 = 88.39, df = 4 (P<0.00001); I^2 =95%

Test for overall effect: Z = 0.64 (P = 0.52)

Test for subgroup differences: Not applicable

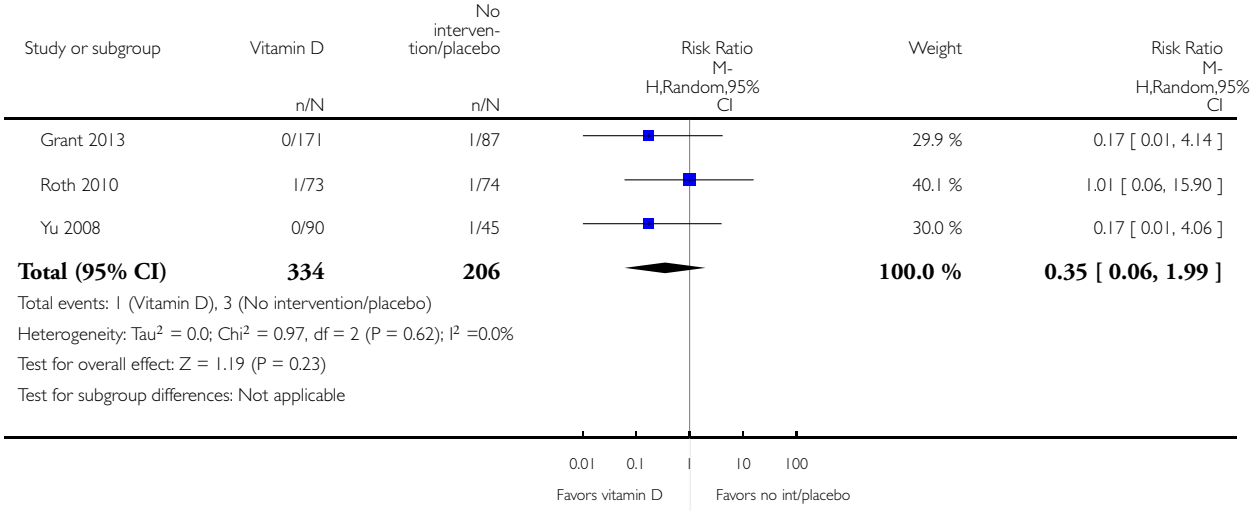


Analysis 1.21. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 21 Stillbirth (ALL).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome: 21 Stillbirth (ALL)

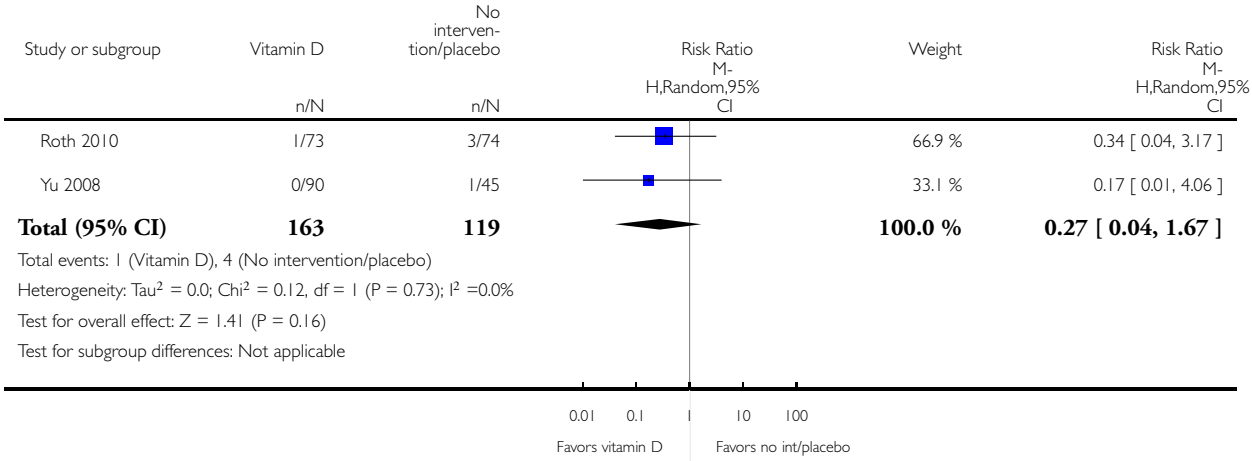


Analysis 1.22. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 22 Neonatal death (ALL).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome: 22 Neonatal death (ALL)



Analysis 1.23. Comparison 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals), Outcome 23 Apgar score less than seven at five minutes.

Review: Vitamin D supplementation for women during pregnancy

Comparison: 1 Vitamin D alone versus no treatment/placebo (no vitamins or minerals)

Outcome: 23 Apgar score less than seven at five minutes

Study or subgroup	Vitamin D n/N	No intervention/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Sablok 2015	3/108	3/57		100.0 %	0.53 [0.11, 2.53]
Total (95% CI)	**108**	**57**		**100.0 %**	**0.53 [0.11, 2.53]**
Total events: 3 (Vitamin D), 3 (No intervention/placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
Test for subgroup differences: Not applicable					

Analysis 2.1. Comparison 2 Vitamin D + calcium versus no treatment/placebo (no vitamin or minerals), Outcome 1 Pre-eclampsia (ALL).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 2 Vitamin D + calcium versus no treatment/placebo (no vitamin or minerals)

Outcome: 1 Pre-eclampsia (ALL)

Study or subgroup	Vitamin D+Calcium n/N	No intervention/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Asemi 2012	1/27	1/27		2.9 %	1.00 [0.07, 15.18]
Marya 1987	12/200	18/200		42.7 %	0.67 [0.33, 1.35]
Taherian 2002	13/330	33/330		54.4 %	0.39 [0.21, 0.73]
Total (95% CI)	**557**	**557**		**100.0 %**	**0.51 [0.32, 0.80]**

Total events: 26 (Vitamin D+Calcium), 52 (No intervention/placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.45$, df = 2 (P = 0.48); $I^2 = 0.0\%$

Test for overall effect: Z = 2.90 (P = 0.0037)

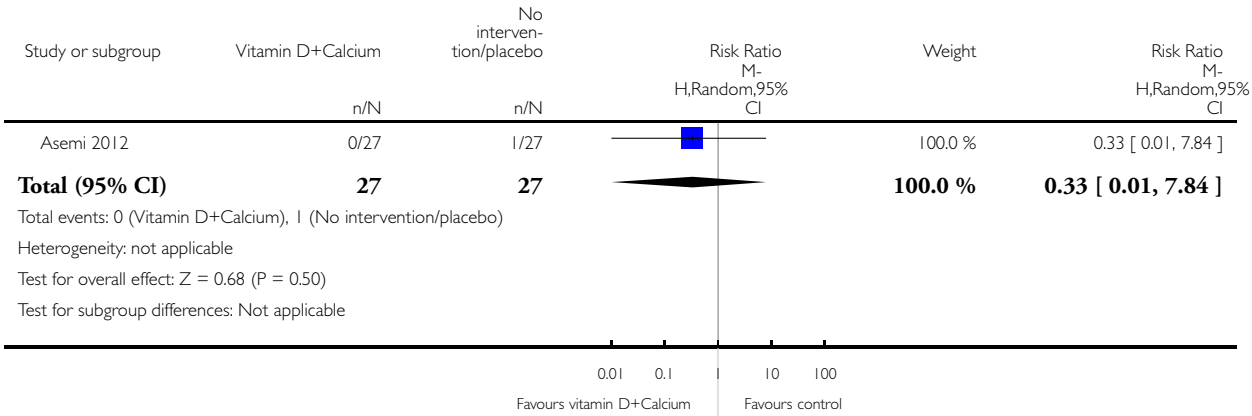
Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Vitamin D + calcium versus no treatment/placebo (no vitamin or minerals), Outcome 2 Gestational diabetes (ALL).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 2 Vitamin D + calcium versus no treatment/placebo (no vitamin or minerals)

Outcome: 2 Gestational diabetes (ALL)



Analysis 2.4. Comparison 2 Vitamin D + calcium versus no treatment/placebo (no vitamin or minerals), Outcome 4 Preterm birth (less than 37 weeks' gestation) (ALL).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 2 Vitamin D + calcium versus no treatment/placebo (no vitamin or minerals)

Outcome: 4 Preterm birth (less than 37 weeks' gestation) (ALL)

Study or subgroup	Vitamin D+Calcium n/N	No intervention/placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Asemi 2012	1/27	0/27		1.9 %	3.00 [0.13, 70.53]
Diogenes 2013	0/43	0/41			Not estimable
Taherian 2002	45/330	29/330		98.1 %	1.55 [1.00, 2.41]
Total (95% CI)	**400**	**398**		**100.0 %**	**1.57 [1.02, 2.43]**

Total events: 46 (Vitamin D+Calcium), 29 (No intervention/placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.16$, df = 1 (P = 0.69); $I^2 = 0.0\%$

Test for overall effect: Z = 2.03 (P = 0.043)

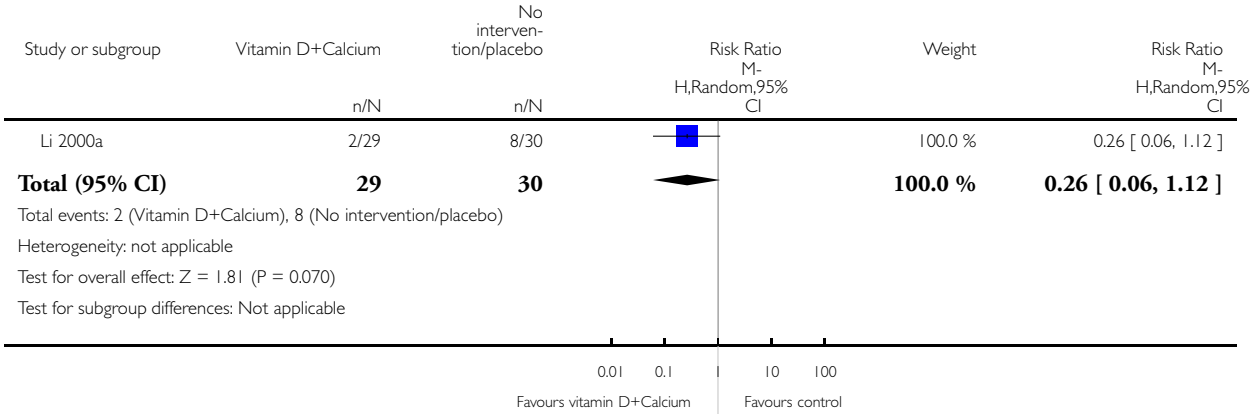
Test for subgroup differences: Not applicable

Analysis 2.8. Comparison 2 Vitamin D + calcium versus no treatment/placebo (no vitamin or minerals), Outcome 8 Gestational hypertension.

Review: Vitamin D supplementation for women during pregnancy

Comparison: 2 Vitamin D + calcium versus no treatment/placebo (no vitamin or minerals)

Outcome: 8 Gestational hypertension

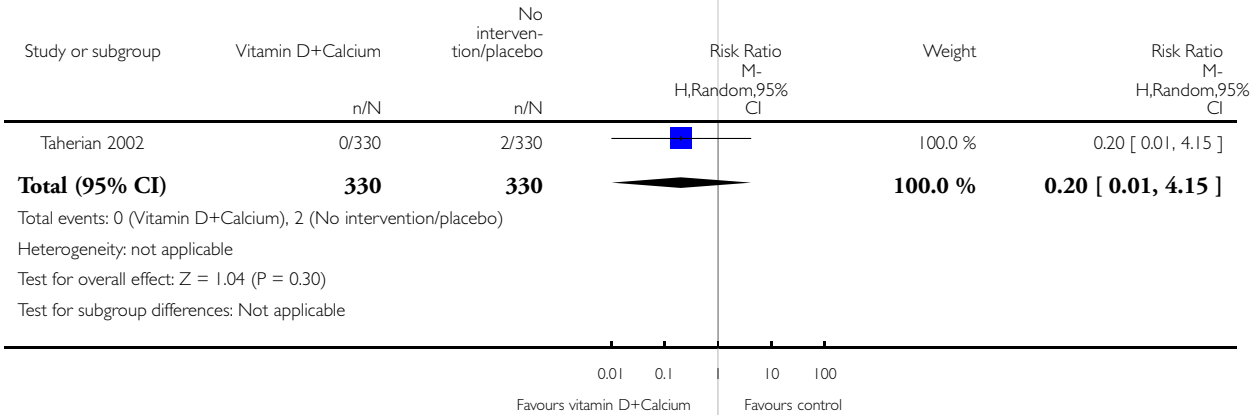


Analysis 2.16. Comparison 2 Vitamin D + calcium versus no treatment/placebo (no vitamin or minerals), Outcome 16 Neonatal death (ALL).

Review: Vitamin D supplementation for women during pregnancy

Comparison: 2 Vitamin D + calcium versus no treatment/placebo (no vitamin or minerals)

Outcome: 16 Neonatal death (ALL)



ADDITIONAL TABLES

Table 1. Review of excluded trials testing different vitamin D doses without a placebo group

Author	Location and setting	Participants (age, number, gestational week)	Randomisation process	Vitamin D supplement dose(s)	Type of vitamin D supplement	Results
Bhatia 2012a	India (antenatal clinics)	299 pregnant women; 12-24 weeks of gestation (lower middle and middle socio-economic)	Random number tables	60,000 IU; 120,000 IU; Usual care	Cholecalciferol	25OHD at term was higher in those on the higher dose compared to the lower dose. Birthweight, length and HC were greater in the supplemented groups versus usual care
Dawodu 2013	United Arab Emirates (primary and tertiary perinatal care centres)	192 pregnant women; 12-16 weeks of gestation	Stratified block design (seasonally balanced) using computer-generated lists	400 IU/d; 2,000 IU/d; 4000 IU/d	Cholecalciferol	25OHD at term was higher with 4000 IU/d versus 2000 IUd versus 400 IU/d ($P < 0.001$)
Hashemipour 2013	Iran (obstetric clinic)	160 pregnant women; 24-26 weeks of gestation; singleton pregnancy and BMI: 19-26 kg/m2	Computer-generated random numbers (open-label randomised)	400 IU/d (+200 mg calcium; 50,000 IU/week (+ calcium)	Cholecalciferol	Length, HC and weight were significantly higher in the intervention group compared with the control group
Litonjua 2014	US (prenatal clinical centres in Boston, Saint Louis, San Diego)	881 pregnant women, history of asthma/allergies; aged 18-40 years; 10-18 weeks' gestation	Stratified permuted blocks with randomly varied block sizes of 4 and 6, and 1 block allocation list per stratum	400 IU/d; 4400 IU/d	Cholecalciferol	Not published yet.

Table 1. Review of excluded trials testing different vitamin D doses without a placebo group (*Continued*)

Marya 1981	India	45 Hindu pregnant women	Not reported	No vitamin D; 1200 IU/d (+375 mg calcium); 600,000 IU (at 7th and 8th month)	Ergocalciferol	Supplementation with 1200 U/d led to significantly higher birth-weight and this was even higher in those taking the 2 doses of 600,000
Mutlu 2013	Turkey (Hospital)	91 pregnant women; aged 16-42 years; singleton	Reported: simple randomisation method	600 IU/d; 1,200 IU/d; 2,000 IU/d	Cholecalciferol	25OHD was significantly higher in the 2,000 IU/d group versus the other groups
Roth 2013a	Bangladesh (maternal health clinic)	28 pregnant women; aged 18-34 years; 27 to 30 weeks	Not specified	70,000 IU (single dose on day 0) + 35,000 IU/week (from day 7); 14,000 IU/week (from day 0; control group)	Cholecalciferol	A dose-response effect was observed in 25OHD with the higher dose versus control
Shakiba 2013	Iran (2 primary care clinics)	51 healthy pregnant women; second trimester of pregnancy; autumn and winter	Not specified	50,000 IU/month; 100,000 IU/month	Cholecalciferol	76% of neonates in group with 50,000 IU/d month and 100% of neonates in group with 100,000 IU/month had 25OHD > 20 ng/mL
Soheilykhah 2011	Iran (2 prenatal clinics)	120 healthy non-obese pregnant women; < 12th week of pregnancy	Not specified	200 IU/d; 50,000 IU/month; 50,000 IU every 2 weeks	Cholecalciferol	25OHD was higher in those on the higher dose versus middle versus lower doses. Supplementation with 50,000 IU every 2 weeks significantly improved insulin resistance

Table 1. Review of excluded trials testing different vitamin D doses without a placebo group (*Continued*)

Stephensen 2011	USA (Research Center and university care centres)	57 healthy pregnant women; <20 weeks' gestation;>18 years	Not specified	400 IU/d; 2,000 IU/d	Cholecalciferol	Greater increase in 25OHD and higher infant birthweight among those on the 2000 IU/d group
Wagner 2010b	USA (University prenatal care)	494 healthy pregnant women; aged 16-45 years; 12-16 weeks of gestation; singleton	Stratified blocked randomisation to balance by ethnicity.	400 IU/d; 2000 IU/d; 4000 IU/d. All women received daily multiple micronutrients supplements	Cholecalciferol	Greater increase in 25OHD among those on the 2000 IU/d and 4000 IU/d groups
Wagner 2010c	USA (University prenatal care)	257 healthy pregnant women; aged 16-45 years; 12-16 weeks of gestation; singleton	Randomisation stratified based on initial 25OHD, using lists generated by computer prior to the start of the study	2000 IU/d; 4000 IU/d. All women received daily multiple micronutrients supplements	Cholecalciferol	25OHD significantly increase in both groups from baseline. Preterm birth was inversely associated with 25OHD at delivery
Yap 2014	Australia	179 pregnant women; 18 years of age or older; singleton pregnancy; with low baseline 25OHD; < 20 weeks of gestation	Randomisation was in a 1:1 ratio, with a permuted block size of 6 and sequential assignment	400 IU/d; 5000 IU/d	Cholecalciferol	No difference in maternal OGTT between groups.

Abbreviations used
25OHD: 25-hydroxycholecalciferol
HC: head circumference
IU: international units
OGTT: oral glucose tolerance test

APPENDICES

Appendix 1. Search terms used for additional author searching

Authors searched the WHO International Clinical Trials Registry Platform (ICTRP) for any ongoing or planned trials (31 January 2015) and the Networked Digital Library of Theses and Dissertations (NDLTD) for grey literature on (28 January 2015) using the terms "vitamin D supplementation and pregnancy".

WHAT'S NEW

Date	Event	Description
30 June 2015	New citation required and conclusions have changed	Nine trials included for this update. The few trials that reported on the effects of vitamin D supplementation during pregnancy on low birthweight and preterm delivery suggest a lower risk on these outcomes with vitamin D in a single or continued dose. However, this result should be interpreted with caution due to the small number of trials and included pregnant women. Also, the quality of the evidence was low in most studies, with high heterogeneity
30 June 2015	New search has been performed	Search and methods updated. We included a new comparison to assess the effects of vitamin D + calcium + other vitamins and minerals versus other vitamins and minerals (but no vitamin D + calcium). We also moved adverse effects to primary outcomes

HISTORY

Date	Event	Description
10 May 2012	Amended	Error in 'Plain language summary' corrected: "Data from three trials involving 463 women show a trend for women who receive vitamin D supplementation during pregnancy to **less frequently** have a baby with a birthweight below 2500 grams than those women receiving no treatment or placebo"

CONTRIBUTIONS OF AUTHORS

For this update, Lia Lombardo and Juan Pablo Peña-Rosas assessed eligibility of the new trials and extracted the data in duplicate. Any differences were discussed and resolved with Luz Maria De-Regil. Cristina Palacios updated the background section. All contributed to the preparation of the updated review.

DECLARATIONS OF INTEREST

Luz Maria De-Regil is full-time staff member of the Micronutrient Initiative, an international organization that delivers vitamin interventions to children, women of reproductive age and pregnant women.

Cristina Palacios received payment from WHO for presenting preliminary results in the Vitamin D Workshop and for contributing to this updated version of the review. The other authors have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of the review (e.g. employment, consultancy, stock ownership, honoraria, expert testimony).

SOURCES OF SUPPORT

Internal sources

- Evidence and Programme Guidance, Department of Nutrition for Health and Development, World Health Organization, Switzerland.

Dr Juan Pablo Peña-Rosas is full time staff of the World Health Organization.

- Micronutrient Initiative, Canada.

Dr Luz Maria De-Regil is full time staff of the Micronutrient Initiative.

External sources

- Micronutrient Initiative (MI), Canada.

WHO acknowledges Micronutrient Initiative (MI) for their financial support to the Department of Nutrition for Health and Development for conducting systematic reviews on nutrition-specific and nutrition-sensitive interventions.

- The Bill & Melinda Gates Foundation, USA.

WHO thanks the Bill & Melinda Gates Foundation for their financial support to the Department of Nutrition for Health and Development for conducting systematic reviews on nutrition-specific and nutrition-sensitive interventions.

- Evidence and Programme Guidance, Department of Nutrition for Health and Development, World Health Organization, Switzerland.

Dr Lia Lombardo received partial funding for this work during the Summer Institute.

- UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In comparison with the previous version, this updated review has the following differences.

1. Types of outcome measures: we moved adverse effects from secondary to primary.

2. We extracted and reported data on the laboratory method used for assessment of vitamin D concentrations in blood samples.

3. We included a new comparison to assess the effects of vitamin D + calcium + other vitamins and minerals versus other vitamins and minerals (but no vitamin D + calcium).

4. We have removed the subgroup analysis on total dose of supplemental dose of vitamin D as the interpretation of this was confusing given the different regimens with different doses. We have however, kept the doses description by type of regimen in the description of the interventions.

INDEX TERMS

Medical Subject Headings (MeSH)

Calcium, Dietary [*administration & dosage]; Pregnancy Complications [*prevention & control]; Pregnancy Outcome; Premature Birth [prevention & control]; Randomized Controlled Trials as Topic; Vitamin D [administration & dosage; *analogs & derivatives; blood]; Vitamin D Deficiency [prevention & control]; Vitamins [*administration & dosage]

MeSH check words

Female; Humans; Pregnancy