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Vitamin D supplementation in pregnancy: A systematic review

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1. ABSTRACT

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Background—It is unclear whether the current evidence base allows definite conclusions to be made regarding the optimal maternal circulating concentration of 25(OH)-vitamin D during pregnancy, and how this might best be achieved. CRD42011001426.

Aim/ Research Questions—

1. What are the clinical criteria for vitamin D deficiency in pregnant women?
2. What adverse maternal and neonatal health outcomes are associated with low maternal circulating 25(OH)-vitamin D?
3. Does maternal supplementation with vitamin D in pregnancy lead to an improvement in these outcomes (including assessment of compliance and effectiveness)?
4. What is the optimal type (D_2 or D_3), dose, regimen and route for vitamin D supplementation in pregnancy?
5. Is supplementation with vitamin D in pregnancy likely to be cost-effective?

Methods—We performed systematic review and where possible combined study results using meta-analysis to estimate the combined effect size.

Major electronic databases were searched up to June 2012 covering both published and grey literature. Bibliographies of selected papers were hand-searched for additional references. Relevant authors were contacted for any unpublished findings and additional data if necessary.

Subjects: Pregnant women or pregnant women and their offspring.

Exposure: Either assessment of vitamin D status (dietary intake, sunlight exposure, circulating 25(OH)-vitamin D concentration) or supplementation of participants with vitamin D or vitamin D containing food e.g. oily fish.

Outcomes: Offspring: Birth weight, birth length, head circumference, bone mass, anthropometry and body composition, risk of asthma and atopy, small for gestational dates, preterm birth, type 1 diabetes, low birth weight, serum calcium concentration, blood pressure and rickets. Mother: Preeclampsia, gestational diabetes, risk of caesarean section and bacterial vaginosis.

Results—76 studies were included. There was considerable heterogeneity between the studies and for most outcomes there was conflicting evidence.

The evidence base was insufficient to reliably answer question 1 in relation to biochemical or disease outcomes.

For questions 2 and 3, modest positive relationships were identified between maternal 25(OH)-vitamin D and 1) offspring birth weight in meta-analysis of 3 observational studies using log-transformed 25(OH)-vitamin D concentrations after adjustment for potential confounding factors (pooled regression coefficient 5.63g/10% change maternal 25(OH)D, 95% CI 1.11,10.16), but not in those 4 studies using natural units, or across intervention studies; 2) offspring cord blood or postnatal calcium concentrations in a meta-analysis of 6 intervention studies (all found to be at high risk of bias; mean difference 0.05mmol/l, 95% CI 0.02, 0.05); and 3) offspring bone mass in observational studies judged to be of good quality, but which did not permit meta-analysis.

The evidence base was insufficient to reliably answer questions 4 and 5.

Limitations—Study methodology varied widely in terms of study design, population used, vitamin D status assessment, exposure measured and outcome definition.

Conclusions—The evidence base is currently insufficient to support definite clinical recommendations regarding vitamin D supplementation in pregnancy. Although there is modest evidence to support a relationship between maternal 25(OH)-vitamin D status and offspring birth weight, bone mass and serum calcium concentrations, these findings were limited by their observational nature (birth weight, bone mass) or risk of bias and low quality (calcium concentrations). High quality randomised trials are now required.

2. EXECUTIVE SUMMARY

Background

Low levels of serum 25(OH)-vitamin D have been observed in many populations, including pregnant women. Studies have demonstrated associations between low levels of serum 25(OH)-vitamin D during pregnancy and maternal/offspring health outcomes. However, many of these studies are observational in nature and it is unclear whether the current evidence base allows definite conclusions to be made regarding the optimal maternal circulating concentration of 25(OH)-vitamin D during pregnancy, and how this might best be achieved. The aim of this work was to provide a systematic review of the current evidence base linking maternal 25(OH)-vitamin D status to both maternal and offspring health outcomes, in order to answer the specific questions below:

Objectives

What are the clinical criteria for vitamin D deficiency in pregnant women?

What adverse maternal and neonatal health outcomes are associated with low maternal circulating 25(OH)-vitamin D?

Does maternal supplementation with vitamin D in pregnancy lead to an improvement in these outcomes (including assessment of compliance and effectiveness)?

What is the optimal type (D_2 or D_3), dose, regimen and route for vitamin D supplementation in pregnancy?

Is supplementation with vitamin D in pregnancy likely to be cost-effective?

Methods

Data sources

Completed studies (systematic reviews): DARE (Database of Abstracts of Reviews of Effects) (Centre for Reviews and Dissemination (CRD)), CDSR (Cochrane Database of Systematic Reviews), HTA (Health Technology Assessment database (CRD));

Completed studies (other study types): CENTRAL (Cochrane Register of Controlled Trials), Medline, Embase, Biosis, Google scholar, AMED (Allied and Complementary Database;

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Ongoing studies: National Research Register archive, UKCRN (United Kingdom Clinical Research Network) Portfolio, Current Controlled Trials, ClinicalTrials.gov;

Grey literature: Conference Proceedings Citation Index- Science (1990-present), Zetoc conference search, Scientific Advisory Committee on Nutrition website, Department of Health website, King's Fund Library database, Trip database, HTA website, HMIC (Health Management Information Consortium database) Bibliographies of selected papers were hand searched for additional studies. We contacted first authors and experts in several fields including metabolic bone disease, obstetrics, infant nutrition, child development and allergy for any unpublished findings.

Inclusion and exclusion criteria—Studies were selected if they fulfilled criteria based on the sample studied, the independent variable of interest (exposure), the outcomes and the study design.

Sample studied: Pregnant women or pregnant women and their offspring.

Exposure: Either assessment of vitamin D status (dietary intake, sunlight exposure, circulating 25(OH)-vitamin D concentration) or supplementation of participants with vitamin D or vitamin D containing food e.g. oily fish.

Outcomes

Primary: Maternal osteomalacia; Neonatal hypocalcaemia, rickets and reduced bone mass.

Secondary: Maternal quality of life; Neonatal body composition and bone mass, later offspring health outcomes (including asthma, diabetes, immune disease).

Study Design: Observational studies (case-control, cohort, cross-sectional), intervention studies

Studies were excluded if they were not written in English, were non-human studies, did not measure maternal vitamin D status in or immediately after pregnancy or supplement participants with Vitamin D in pregnancy, or where an outcome of interest was not measured. Systematic reviews were not included in the formal review but were used as a potential source of additional references via hand searching.

Data extraction—Data extraction was carried out by two reviewers. Disagreements were resolved in the same way as for screening of abstracts. Separate forms were used to mark or correct errors or disagreements and a database kept for potential future methodological work. Data were abstracted onto an electronic form. This contained the following items: general information (e.g. date of data extraction, reviewer ID); study characteristics (e.g. study design, inclusion/exclusion criteria,); study population characteristics; method of assessment of vitamin D status; baseline data (e.g. age, sex, ethnicity, measures of vitamin D status/ supplementation); quality criteria; outcomes (what they were and how they were ascertained); confounding factors; analysis (statistical techniques, sample size based on power calculation, adjustment for confounding, losses to follow up); results (direction of

relationship, size of effect and measure of precision of effect estimate such as 95% confidence interval or standard error).

Assessment of validity and quality—Quality assessment of studies occurred initially during data extraction and secondly in the analysis of review findings. The quality of included studies was assessed by the two reviewers, using a checklist of questions. The questions used, while based initially on CRD guidelines, were refined through piloting and agreement with the advisory group. Aspects of quality assessed included appropriateness of study design, ascertainment of exposure and outcome, and consideration of the effects of important confounding factors. Quality assessment also incorporated specific issues related to vitamin D. Quality data were used in narrative description of quality, and to produce composite validity scores with which to assign a quality level to each study such that studies could be stratified during synthesis of evidence.

Data synthesis—The aim of this part of the review was to investigate whether effects were consistent across studies and to explore reasons for apparent differences. We used both descriptive (qualitative) and quantitative synthesis; our capacity for the latter was determined by the evidence available. Where meta-analysis was possible, we used standard analytical procedures[1]. Only independent studies were meta-analysed. Thus, where a study contained two treatment arms, these were not included in the same analysis. We used the Q-statistic to define statistical heterogeneity, with a $p<0.1$ to define statistical significance. The I^2 statistic (percentage of variability in the results that is due to heterogeneity) was used to quantify the degree of heterogeneity across studies. Results were presented as forest plots, either as random effects models, if significant heterogeneity was detected, or as fixed effects models if minimal heterogeneity was detected. All analysis was performed using Stata v11.0 (Statacorp, Texas, USA).

Results

Included/ excluded studies—22,961 citations were identified from the initial database search up to 3rd January 2011. A subsequent additional search from 3rd January 2011 to 18th June 2012 identified another 2,448 citations, yielding a total of 25,409 citations. A further 66 citations were identified from other sources (e.g. grey literature, bibliographies). After duplicate citations were removed, 16,842 citations were screened. Of these, 16,669 were excluded on the basis of the content of the title and/or the abstract (if available). A further 8 papers could not be found despite thorough searching, thus 16,677 records were excluded. A total of 165 full-text articles were retrieved for detailed assessment and of these 76 papers were included in the review. A total of 89 papers retrieved for assessment were excluded. Around a third of these (n=34) were abstracts. 21 papers had no relevant maternal or offspring outcome; 11 papers had no estimate of maternal vitamin D status; 10 papers used data from other papers included in the review; 8 papers were either review articles, letters, editorials or commentaries with no new results; 1 paper was of a non-human study and 4 papers reported on an outcome not assessed in any other paper (maternal breast cancer, offspring schizophrenia, offspring multiple sclerosis and offspring influenza A). The results relating to the specific research questions are detailed below.

What are the clinical criteria for vitamin D deficiency in pregnant women?

The highly heterogeneous and variable quality of the identified studies resulted in an evidence base that did not allow this question to be reliably answered, either in terms of biochemical relationships, or disease outcomes.

What adverse maternal and neonatal health outcomes are associated with low maternal circulating 25(OH)-vitamin D?

Does maternal supplementation with vitamin D in pregnancy lead to an improvement in these outcomes (including assessment of compliance and effectiveness)?

These results relevant to these two study questions are itemised by individual health outcome below:

Birth weight—Nineteen observational studies were identified. Composite bias scores ranged from −2 to +8, with seven of the nineteen studies scored as having a low risk of bias. Six studies demonstrated a significant positive relationship between maternal vitamin D status and offspring birth weight; one study found a significant negative association. Of the remaining studies, seven suggested a non-significant positive association between the two variables and three found a non-significant negative association.

Nine intervention trials were identified. Seven of these studies were rated as having a high chance of bias on the composite score (−2 to −9); only the two most recent studies were assessed as having a low risk of bias (composite bias score 5 and 10 respectively). Sample sizes ranged from 40 to 350 and interventions were highly variable. Three studies demonstrated significantly greater birth weight in offspring of supplemented mothers. The remainder showed no significant difference in infant birth weight regardless of supplementation (birth weight was non-significantly higher in the supplemented group in 2 of these, non-significantly lower in the supplemented group in one; birth weight was not presented in the remaining two.

Meta-analysis of 3 observational studies found weak positive associations between log-transformed maternal 25(OH)-vitamin D concentrations and offspring birth weight after adjustment for potential confounders (pooled regression coefficient 5.63g/10% change maternal 25(OH)D, 95% CI 1.11,10.16).

Birth length—Twelve observational studies were identified. One study was assessed as having a high risk of bias (composite score −2, high risk) with the others demonstrating composite scores between +1 and +8. Two studies found a significantly positive relationship between maternal vitamin D status and offspring birth length; however, neither study directly measured maternal serum 25(OH)-vitamin D concentration in pregnancy. Of the remaining studies, four showed a non-significant positive association and four showed a non-significant inverse association. A further study observed a significant positive association between maternal vitamin D status and offspring length at one month.

Two intervention trials were identified. Both were assessed to have a high risk of bias (composite bias score of both −2, high risk). In one, offspring birth length of women supplemented with vitamin D was greater than for unsupplemented women; the other found no significant association but a trend towards higher birth length in the supplemented group. Both studies were assessed to have a high risk of bias.

Head circumference—Eleven observational studies were identified, none of which found a significant relationship between maternal vitamin D status and offspring head circumference. Composite bias scores ranged from −2 to +8, with six studies having a low risk of bias. There was a non-significant trend towards greater head circumference with greater maternal vitamin D status in five studies, and a non-significant inverse relationship in four studies.

Two intervention studies were identified, both of which were assessed as having a high risk of bias (composite bias score −2 in both). One study demonstrated significantly greater offspring head circumference in supplemented mothers; the other found no association, but a non-significant trend towards greater head circumference in supplemented mothers.

Offspring bone mass—Eight observational studies were identified, all of which were assessed as being of medium to low risk of bias, with composite bias scores ranging from 3 to 7. Five demonstrated a significant positive relationship between maternal vitamin D status and offspring bone outcomes (which included whole body, lumbar, femoral and tibial bone mineral content (BMC), and whole body and lumbar spine bone mineral density (BMD)). Of the remaining studies, no significant association was observed between maternal vitamin D status and offspring radial and whole body BMC.

One intervention study was identified, which found no difference in offspring forearm BMC (measured within five days of birth) between supplemented and unsupplemented mothers. There was a non-significant trend towards higher forearm BMC in the supplemented group. This study was assessed to have a high risk of bias.

Offspring anthropometry and body composition—Six observational studies were identified, four of which demonstrated a significant relationship between maternal vitamin D status and offspring body composition and anthropometric variables (including skinfold thickness, lean mass and fat mass). Two studies found no significant relationship between maternal vitamin D status and the offspring anthropometric variables measured. Composite bias scores ranged from 3 to 8 indicating a medium to low risk of bias. Two intervention studies were identified; both were assessed to have a high risk of bias (composite bias score −2 for both). One demonstrated no effect of maternal vitamin D supplementation on offspring triceps skinfold thickness, whereas the other did find evidence of a positive effect.

Offspring asthma and atopy—Ten observational studies were identified. Five studies found a significantly reduced risk of offspring asthma or atopy with higher maternal vitamin D status; conversely, three studies found a significant positive association between maternal vitamin D status and offspring risk of asthma or atopy. The remaining two studies found no significant association between late pregnancy 25(OH)-vitamin D and offspring lung

function at aged 6-7 years. All but one study was judged to be at moderate to high risk of bias, and no intervention studies were identified.

Offspring born small for gestational age (SGA)—Seven observational studies were identified. All achieved a composite bias score of between +1 and +7 indicating a low to medium risk of bias. One study found a significantly increased risk of infants being SGA if maternal 25(OH)-vitamin D <30 nmol/l. A second study found a U-shaped relationship between SGA and maternal 25(OH)-vitamin D concentration in white women only, with the lowest risk between 60-80 nmol/l. No relationship was seen in black women. A third study of pregnant women with early onset preeclampsia found significantly lower serum 25(OH)D in those women with SGA infants compared to the control groups. The four remaining studies found no significant relationship; two of these found a non-significant trend towards greater SGA risk in women with lower vitamin D status. Data were not given for the other two studies.

Two intervention trials were identified, one judged at low and the other high risk of bias, and neither of which found a significant difference in SGA risk in women supplemented with vitamin D compared to unsupplemented mothers. There was however a non-significant trend towards higher SGA risk in the unsupplemented group in both studies.

Offspring preterm birth—Seven observational studies were identified, ranging from low to high risk of bias. One study found that the risk of threatened premature delivery was significantly increased in mothers with lower 25(OH)-vitamin D. Six studies found no significant relationship. No intervention trials were identified.

Offspring Type 1 diabetes mellitus—Three observational studies were identified, judged to be at medium or low risk of bias. One study found a significantly increased risk of type 1 diabetes in the offspring with lower maternal concentration of 25(OH)-vitamin D in late pregnancy. The remaining studies found no significant relationship. No intervention studies were identified.

Offspring low birth weight (LBW)—Three observational studies were identified, with composite bias scores ranged from −2 to 3 indicating a medium to high risk of bias. One study found a significantly reduced risk of LBW offspring with adequate, compared with inadequate, maternal vitamin D and calcium intake. The remaining studies found no significant association. No intervention studies were identified.

Offspring serum calcium concentration—One observational study, at low risk of bias, was identified which found no significant association between maternal 25(OH)-vitamin D at delivery and offspring cord calcium.

Six intervention trials were identified, all judged to be at high risk of bias (composite scores −9 to −1). Offspring serum calcium was significantly higher in the supplemented group in five of these studies. The remaining study found a non-significant trend towards higher cord blood calcium in the supplemented group. Meta-analysis of the intervention studies demonstrated a weak positive association (mean difference in serum calcium concentration

in offspring of supplemented vs unsupplemented mothers: 0.05mmol/l, 95% CI 0.02, 0.05). Factors which might increase risk of symptomatic hypocalcaemia, such as ethnicity and breast (compared with formula) feeding were not adequately addressed.

Offspring blood pressure—Two observational studies were identified, judged to be at medium risk of bias, and neither of which found a significant relationship between maternal 25(OH)-vitamin D concentration and offspring blood pressure. No intervention trials were identified.

Preeclampsia—Eleven observational studies were identified, judged to be at low to medium risk of bias. Five studies found a significant inverse relationship between maternal vitamin D status and risk of preeclampsia, the remaining six studies found no significant relationship. Meta-analysis was possible for four studies, suggesting an inverse relationship between 25(OH)D and preeclampsia risk, but which did not achieve statistical significance. One intervention trial was identified; no difference in risk of preeclampsia was seen in mothers supplemented with vitamin D compared with unsupplemented women.

Gestational diabetes—Eight observational studies were identified, judged to be at low to medium risk of bias. Three studies found a significant inverse relationship between risk of gestational diabetes and maternal vitamin D status. No intervention studies were identified.

Caesarean section—Six observational studies were identified, judged to be at low to medium risk of bias. Two studies found an inverse relationship between risk of Caesarean section and maternal vitamin D status. The remaining four studies found no significant relationship, although a non-significant inverse trend was observed in two studies (the remaining two studies did not provide adequate data to assess trend). No intervention trials were identified.

Maternal bacterial vaginosis—Three observational studies were found, judged to be at low to medium risk of bias, and all of which found that lower maternal 25(OH)-vitamin D was significantly associated with an increased risk of bacterial vaginosis in pregnancy. No intervention trials were identified.

What is the optimal type (D_2 or D_3), dose, regimen and route for vitamin D supplementation in pregnancy?

The marked variation in dose, route, study population, methods of exposure and outcome evaluation, and lack of comparative investigations, meant that the evidence base was insufficient to reliably answer this question.

Is supplementation with vitamin D in pregnancy likely to be cost-effective?

No studies including health economic evaluations in relation to specific disease outcomes were identified.

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Conclusions

There was some evidence to support a positive relationship between maternal vitamin D status and offspring birth weight (meta-analysis of observational studies), neonatal calcium concentrations (meta-analysis of randomised controlled trials) and offspring bone mass (observational studies). Recurring themes in each disease area included marked heterogeneity between studies in terms of design, definition of exposure and outcome, dose, timing, route, statistical analysis, treatment of potential confounding factors. In no single disease area did the evidence base unequivocally support the use of vitamin D supplementation during pregnancy.

Implications for health care—The fundamental conclusion is that the current evidence base does not allow the study questions to be definitively answered. It is therefore not possible to make rigorously evidence-based recommendations regarding maternal vitamin D supplementation during pregnancy.

Recommendations for research—This systematic review has identified important gaps in the evidence, and clearly further high-quality research is needed. In many areas well-designed large prospective cohort studies are most appropriate as the next step. In others, the evidence base is sufficient to suggest randomised controlled trials. Without such a rigorous approach, there is a risk that public health policy will be made on the basis of optimistic evaluations of conflicting and heterogeneous studies. Although modest doses of vitamin D during pregnancy are likely to be relatively safe, at least in the short term, there is a dearth of long-term data to inform the potential long-term effects of maternal vitamin D supplementation on offspring health. As with most interventions, it is probably optimistic to expect that there will be no risk of adverse events.

3. BACKGROUND

3.1. Epidemiology of vitamin D serum concentrations

There are very few data on vitamin D levels in pregnant women across a population representative of the UK as a whole; the available studies, however, suggest that low serum 25(OH)-vitamin D concentrations are common in this group. In one cohort in Southampton, composed of white Caucasians, 31% had concentrations of circulating 25(OH)-vitamin D lower than 50 nmol/l and 18% less than 25 nmol/l.[2] A recent US study of a population representative of the national demographic distribution revealed that 80% of black pregnant women had levels less than 50 nmol/l; the figures for Hispanic and white pregnant women were 45% and 13% respectively[3]. In Asian cohorts in the northern hemisphere the burden is even higher.[4-8] possibly reaching 90% or greater: A study of non-pregnant South-Asian women in the North of England, many of whom were of child-bearing age, demonstrated that 94% had circulating levels of 25(OH)-vitamin D ≤37.5 nmol/l and 26% ≤12.5 nmol/l[9]; a survey of the UK (non-pregnant) population revealed low levels of 25(OH)-vitamin D in 50%[10]. As the main source of vitamin D is synthesis in the skin under the influence of UVB radiation from sun light exposure, ethnicity (dark skin), covering and northerly latitudes (as in UK) are all major risk factors for low concentrations.[11] The vitamin D axis is thought to be highly influential in the acquisition of bone mineral and significant changes in women's

vitamin D and calcium homeostasis occur during pregnancy in order to provide the fetus with adequate calcium to mineralise its rapidly growing skeleton. Evidence that maternal vitamin D status influences neonatal calcium homeostasis has come from studies of Asian immigrants, among whom reduced serum 25(OH)-vitamin D concentrations are accompanied by increased parathyroid hormone levels. Maternal vitamin D deficiency in pregnancy has been associated with neonatal hypocalcaemia[12] and other adverse birth outcomes, such as craniotabes and widened growth plates, suggestive of rachitic (rickets-like) change.[13] Indeed a recent study demonstrated rachitic-like widening of the fetal distal femoral metaphysis relative to its length, scanned by ultrasound at 19 and 34 weeks, in fetuses of mothers with low levels of circulating 25(OH)-vitamin D, implying a relatively early effect,[14] findings confirmed in a further cohort.[15] Infants of mothers with low vitamin D intake may have lower calcium levels at day four post-delivery.[16] Anecdotally infant rickets is becoming more common in dark-skinned communities in the UK, probably due to low infant intake of vitamin D from the mother, secondary to maternal deficiency, initially via the placenta in utero and then via breast milk post-natally.[17-20] However accurate population-wide epidemiological data are lacking, and the 25(OH)-vitamin D concentration, below which an individual is considered deficient, is the subject of much debate (see section 1.7).

3.2. Intervention studies

There have been several, mainly small, intervention studies examining this issue (Table 1). Thus in one study 506 women were supplemented at 12 weeks gestation to 400 IU/day vs. 633 placebo.[21] Levels of 25(OH)-vitamin D were higher in maternal, umbilical cord, and infant serum (day 3 and 6) in the supplemented group. This was not a randomised trial, but supplemented women from one clinic vs. placebo in another clinic. Another study compared 59 Asian women, supplemented with 1000 IU in the last trimester of pregnancy[4], with 67 controls. Calcium levels were higher in the supplemented mothers, and there was a lower incidence of symptomatic neonatal hypocalcaemia and growth retardation amongst babies of supplemented mothers. Again in an Asian population[5], 25 mothers were randomised to 1200 IU vitamin D per day, 20 mothers to 600,000 IU twice (7^{th} and 8^{th} month), and 75 mothers to placebo. In this study there was no difference in calcium and alkaline phosphatase levels between mothers taking 1200 IU/day and those taking placebo. However, those taking 600,000 IU twice had higher maternal and cord calcium and lower alkaline phosphatase than placebo. In a second study[6] the same group supplemented 100 Asian-Indian women with 600 000 IU twice (again at 7^{th} and 8^{th} months) vs. 100 controls and found again, higher maternal and cord calcium and lower alkaline phosphatase. There have been two studies in French populations: 15 women were randomised to receive 1000 IU per day from 3^{rd} trimester vs. 15 controls.[7] Day 4 neonatal calcium and 25(OH)-vitamin D levels were higher in the supplemented group. In the second study 21 French women received 1000 IU per day in the last trimester and 27 received 200 000 IU once during 7^{th} month and 29 acted as controls[8]. Here neonatal calcium at day 2 and 6 was similar in all groups, but maternal serum 25(OH)-vitamin D was greater in both intervention groups than in the controls. In the one study, measuring bone mineral at birth[22] there was no difference in radial BMC in offspring of 19 Asian mothers who had taken 1000 IU vitamin D per day compared with 45 controls. However this lack of observed effect is likely to reflect both the small numbers of

subjects and the poor sensitivity of single photon absorptiometry in measuring the tiny amount of bone mineral in the baby's distal radius.

3.3. Safety of vitamin D supplementation in pregnancy

None of these studies listed above has suggested that vitamin D supplementation during pregnancy carries a significant risk. Human beings have evolved to cope with as much as 25,000 IU vitamin D formation daily in the skin. Although rat studies using the equivalent of 15,000,000 IU per day have resulted in extra-skeletal calcifications, there is no evidence that doses below 800,000 IU per day have any adverse effect. Two studies[23;24] have examined the children of hypoparathyroid women given 100,000 IU vitamin D daily for the duration of pregnancy and found no morphological or physiological adverse consequences. These children were followed for up to 16 years. Recent work has demonstrated a moderate increase in atopy in children of mothers in the highest quarter of serum vitamin D in pregnancy, where levels were greater than 30 ng/ml.[25] However, in this study the numbers were small with only 6 cases of atopy (asthma, eczema) by 9 years in the top quartile of maternal vitamin D, 4 each in the middle quartiles and 2 in the bottom. These numbers, even in the highest quartile, were actually lower than the figure for the general population. Additionally, in the Southampton Women's Survey, there was no association between maternal 25(OH)-vitamin D status and atopic or non-atopic eczema at 9 months of age[26]. This finding needs to be further examined in larger studies, but suggests, for safety, that the optimal intervention would be to supplement those mothers found to be deficient in vitamin D, rather than all pregnant mothers.

3.4. Maternal vitamin D status, offspring wheezing and diabetes

In contrast to the findings above, another epidemiological study suggested an inverse relationship between maternal dietary intake of vitamin D in pregnancy and later wheezing in the offspring.[27] However, a study of vitamin D supplementation in infants again suggested a positive relationship such that greater infant supplementation was associated with increased later wheezing.[28] Hypponen found, in an adult population cohort, that circulating IgE levels (a marker of atopic tendency) were positively related to concentrations of 25(OH)-vitamin D but that this was only apparent at very high concentrations (>125nmol/l).[29] Animal studies have implicated 1,25(OH)-vitamin D as a modulator of immune balance between a tendency to autoimmunity and atopy, but these studies have again suggested influences in both directions.[30] Thus the data are inconsistent, and clearly any studies using dietary intake of vitamin D, rather than blood levels, as the marker of vitamin D status have the potential for confounding by UVB exposure and other lifestyle, anthropometric and health factors. It is possible that the relationships between vitamin D and atopy differ depending on timing (e.g. in pregnancy or postnatal life), or with 25 or 1,25(OH)-vitamin D, or are U-shaped such that both low and very high levels are detrimental. Finally a birth-cohort study from Finland demonstrated a reduced risk of type 1 diabetes in children who had been supplemented with vitamin D as infants.[31]

3.5. Longer term importance of maternal vitamin D repletion for offspring bone size and density

Recent work has suggested that maternal vitamin D deficiency during pregnancy may not solely influence the offspring's skeleton through overt rachitic change. Evidence is accruing that less profound maternal 25(OH)-vitamin D insufficiency may lead to sub-optimal bone size and density in the offspring post-natally, a situation likely to lead to an increased risk of osteoporotic fracture in the offspring in later life. Evidence that the risk of osteoporosis might be modified by environmental influences in early life comes from two groups of studies: (a) those evaluating bone mineral and fracture risk in cohorts of adults for whom birth and/or childhood records are available; and (b) those studies relating the nutrition, body build and lifestyle of pregnant women to the bone mass of their offspring.[32] Cohort studies in adults from the UK, USA, Australia and Scandinavia have shown that those who were heavier at birth or in infancy have a greater bone mass[33-36] and a reduced risk of fracture[37] in later life. These associations remain after adjustment for potential confounding factors, such as physical activity, dietary calcium intake, smoking and alcohol consumption. In a cohort of twins, intra-pair differences in birth weight were associated with bone mineral content in middle age, even among monozygous pairs.[38] Mother-offspring cohort studies based in Southampton have shown that maternal smoking, poor fat stores and excessive exercise in late pregnancy all have a detrimental effect on bone mineral accrual by the fetus, leading to reduced bone mass at birth.[39]

However, the strongest risk factor for poor bone mineral accrual documented in these mother-offspring cohort studies has been maternal vitamin D insufficiency. There was already some indication of the potential role played by maternal vitamin D status in pregnancy from a retrospective cohort study[40] showing that premature babies who were supplemented with vitamin D had an increased whole body bone mass at age 12 years, but these recent findings provided the first direct evidence for the importance of maternal vitamin D status during pregnancy on the child's skeletal growth. In a Southampton mother-offspring cohort, data on anthropometry, lifestyle and diet were collected from women during pregnancy and venous 25(OH)-vitamin D was measured by radio-immunoassay in late pregnancy[2]. Whole body, hip and lumbar spine bone area, BMC and BMD were measured in the healthy, term offspring at age 9 years. 31% of the mothers had reduced (insufficient or deficient) circulating concentrations of 25(OH)-vitamin D in late pregnancy. There was a positive association between maternal 25(OH)-vitamin D concentration in late pregnancy and whole body bone mineral content ($r=0.21$, $p=0.0088$) and density ($r=0.21$, $p=0.0063$) in the offspring at 9 years old, with a suggestion of a threshold effect at 40 nmol/l. Both the estimated exposure to ultraviolet B (UVB) radiation during late pregnancy and use of vitamin D supplements predicted maternal 25(OH)-vitamin D concentration ($p<0.001$ and $p=0.01$) and childhood bone mass ($p=0.03$). Reduced concentration of umbilical-venous calcium also predicted lower childhood bone mass ($p=0.03$), suggesting a possible role for placental calcium transport in this process.

Similar findings, linking reduced maternal 25(OH)-vitamin D concentration with lower offspring bone mass, have come from the Southampton Women's Survey (SWS)[41]. In this ongoing prospective cohort study of women aged 20-34 years, characterised before and

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during pregnancy, maternal 25(OH)-vitamin D status was measured by radio-immunoassay in late pregnancy and 556 healthy term neonates underwent whole body dual energy X-ray absorptiometry (DXA) within 20 days of birth. Offspring of mothers who were insufficient or deficient (<40 nmol/l) in vitamin D in late pregnancy had lower bone mass than those of mothers who were replete. Thus the mean whole body bone area of the female offspring of deficient mothers was 112 cm^2 *vs.* 120 cm^2 in offspring of replete mothers (p=0.045). The mean whole body bone mineral content of offspring of deficient *vs.* replete mothers was 59g *vs.* 64g (p=0.046) respectively. There were weaker associations in the boys and there was no association with maternal alkaline phosphatase. Additionally, maternal UVB exposure during pregnancy was positively associated with whole body bone mineral content in the offspring aged 9 years in the Avon Longitudinal Study of Parents and Children (ALSPAC).[42]

3.6. Summary

Maternal vitamin D deficiency is important for maternal health, and also has implications for the offspring. In frank deficiency, most common in dark-skinned/ covered populations in the UK, neonatal hypocalcaemia, craniotabes and infant rickets are an increasing problem. However, evidence is accruing for the longer term implications of milder maternal vitamin D insufficiency in the broader population (including white Caucasian women). Thus children of mothers with low levels of circulating 25(OH)-vitamin D in pregnancy have reduced bone size and density, even in the absence of definite rachitic change. This is likely to lead to reduced peak bone mass and increased risk of osteoporotic fracture in later life. Furthermore maternal vitamin D status has been linked to allergy and asthma in the offspring. Thus the outcomes considered for this proposal will encompass both immediate maternal and neonatal health, but also longer term skeletal development and atopy in the child.

3.7. Considerations for appraisal of data

There are several factors which make any study of evidence surrounding vitamin D problematic. Firstly, the main source of vitamin D is from synthesis in the skin by the action of UVB radiation, with dietary intake usually forming a minor contribution to overall levels. Secondly, the physiology of vitamin D in pregnancy and its role in placental calcium transfer and offspring bone development (both linear growth and mineralisation) is unclear. Thirdly the definition of a normal range is difficult, even in non-pregnant populations, and techniques used to measure 25(OH)-vitamin D concentrations have widely different characteristics. Fourthly, dose-response and differences between use of vitamin D_2 and vitamin D_3 are unclear. Fifthly post-natal vitamin D intake by the offspring may confound any pregnancy relationships, and finally the definition of osteomalacia used is important (clinical syndrome or histological definition from bone biopsy). A detailed appraisal of these factors is given below.

Photosynthesis and metabolism of vitamin D—Vitamin D is a secosteroid which is synthesised in the skin by the action of sunlight. It plays a crucial role in bone metabolism and skeletal growth[43]. Around 95% is acquired via photosynthesis in the skin, with the minority from the diet[44]. There are two dietary forms: D_2, from plants, and D_3, from

animals; the latter mainly found in oily fish and fortified margarines and breakfast cereals[44]. Vitamin D is synthesised from the action of sunlight (wavelengths 290-315nm) on cutaneous 7-dehydrocholesterol, converting it to pre-vitamin D_3 [11;43]. Once formed, pre-vitamin D_3 undergoes membrane-enhanced temperature-dependent isomerisation to vitamin D_3 [43], which is translocated into the circulation where it binds to vitamin D-binding protein (DBP).[11] The main determinant of vitamin D synthesis in the skin is the level of sun exposure. The total amount of energy accrued from sunlight is dependent on duration and extent of skin exposure, but also on latitude and season. Thus pigmented skin andcovering, particularly relevant to the dark-skinned, and potentially covered ethnic minority groups in the UK, reduce synthesis; using sun-block with a factor higher than 8 almost completely prevents formation of vitamin D[44]. At latitudes of 48.5° (Paris, France), the skin is unable to form vitamin D between the months of October through to March.[43] In northern latitudes this results in a seasonal variation in levels of vitamin D, with a peak over the summer months and a trough in the winter[11]. Use of sunscreen during the summer may prevent adequate synthesis of vitamin D and subsequent storage in fat for the winter months, thus leading to deficiency; greater adiposity is also associated with reduced levels[11]. Circulating vitamin D is converted in the liver to 25(OH)-vitamin D (calcidiol), which is the main circulating store. This step, which involves the cytochrome P450 system, is not tightly regulated and thus an increase in photosynthesis of vitamin D in the skin will lead to an increase in 25(OH)-vitamin D in the circulation[11;45], bound to DBP. Excess 25(OH)-vitamin D is converted to 24,25(OH)-vitamin D which is thought be relatively metabolically inactive[11]. The 25(OH)-vitamin D-DBP complex enters renal tubule cells by membrane-bound megalin transport, where the enzyme 1-α-hydroxylase converts it to $1,25(OH)_2$-vitamin D (calcitriol), which is the active compound[45]. Although the kidney is the primary site for conversion of circulating 25(OH)-vitamin D, many tissues, such as macrophages, osteoblasts, keratinocytes, prostate, colon and breast express the 1-α-hydroxylase enzyme[43;46;47]. Since anephric patients have very low levels of $1,25(OH)_2$-vitamin D in the blood, it seems likely that these extra-renal sites function at the paracrine level, and do not play a major role in calcium homeostasis[44].

Food sources, recommended intakes and dose response—Few foods contain significant amounts of vitamin D. The most effective sources are oily fish (for example salmon, mackerel) and fortified foods such as margarine and breakfast cereal. The amount of vitamin D derived from fish is modest: wild salmon contains around 400 IU per 3.5 oz. (100g).[11] There is much controversy over the recommended daily intake of vitamin D. Older guidance has suggested 200 IU per day for children and adults up to 50 years old and 400–600 IU for older adults.[48] However, humans have evolved to synthesise much higher levels of vitamin D in the skin: 30 minutes exposure at midday in the summer sun at a southerly latitude in a bathing suit will release around 50,000 IU into the circulation within 24 hours in white persons[49]. Previous guidelines were not based on any rigorous assessment of the effects of levels and more recent dosing studies have shown that supplementation with 200-400 IU per day is unlikely to maintain levels of 25(OH)-vitamin D over winter months, let alone replenish stores in somebody who is frankly vitamin D deficient.[50] Thus a daily maintenance dose of around 1000 IU per day may be more appropriate in people without

adequate sunshine exposure, with higher initial dosing required to reverse frank deficiency.[51]

Physiology of vitamin D in pregnancy—During pregnancy there is an increase in $1,25(OH)_2$-vitamin D, which may be largely due to an increase in vitamin D binding protein.[52] This rise is associated with an increase in intestinal calcium absorption (to around 80% intake), and an absorptive hypercalciuria.[52] There does not seem to be a rise in maternal parathyroid hormone or 25(OH)-vitamin D during pregnancy, suggesting that the rise in $1,25(OH)_2$-vitamin D may be due to another factor, such as parathyroid hormone-related peptide, which may be secreted by the placenta.[53] Studies of maternal bone mass in pregnancy have been conflicting, but most suggest a probable decrease, with a possibly greater decrease in lactation.[54-58] The vitamin D receptor (VDR) appears to develop after birth in the infant intestine, and thus calcium absorption is a passive process immediately after birth.[59] The role of vitamin D in utero is uncertain, although 25(OH)-vitamin D does cross the placenta.[60] In a mouse model, lack of VDR did not significantly affect placental calcium transport or skeletal mineralisation[59]; conversely in the rat, $1,25(OH)_2$-vitamin D did seem to influence placental calcium flux.[61] Additionally chondrocytes are an extrarenal source of 1a-hydroxylase activity (and so conversion of 25(OH)-vitamin D to $1,25(OH)_2$-vitamin D.[62] This observation therefore suggests a possible mechanism by which maternal 25(OH)-vitamin D status might influence bone size in the fetus. Further evidence to support this notion comes from mouse models in which the gene for 1α-hydroxylase (Cyp27b1) was either knocked out or over-expressed in chondrocytes leading to altered growth plate morphology.[63] Few data exist in humans at the level of cell biology. Some suggestions have come from recent epidemiological work described above, in which maternal 25(OH)-vitamin D concentrations positively predicted offspring bone mass at birth[64], and at 9 years old[2], with umbilical cord calcium concentrations and placental calcium transporters[65] implicated in the mechanisms.

Normal range and measurement of vitamin D—Circulating 25(OH)-vitamin D is the major store of vitamin D and is the most appropriate for measurement. $1,25(OH)_2$-vitamin D is an adaptive hormone, and therefore its level will reflect prevailing conditions such as calcium intake, and thus defining a normal level may not be meaningful[44]. The concept of what is the normal range for 25(OH)-vitamin D is highly controversial at the moment. One view is that, given that humans seem to have evolved to require much higher levels of vitamin D than are observed in the UK currently, the process of measuring levels in a population and defining a lower cut-off of the distribution as deficient is likely not to be valid. Historically in the UK, serum levels have been classed as “replete” (>50 nmol/l), insufficient (25 to 50 nmol/l) or deficient (<25 nmol/l). (Older studies often use ng/ml as the unit of measurement: 1 ng/ml = 2.5 nmol/l). The Institute of Medicine in the US has recently reiterated the 50 nmol/l threshold as the desirable level of circulating 25(OH)-vitamin D[66]. The distinction between replete and insufficient/ deficient has been made on the basis of whether there is a secondary rise in parathyroid hormone. Other approaches to definition have been based on fractional calcium absorption and bone turnover markers. However, a recent review of the available studies relating 25(OH)-vitamin D concentration to PTH concentration found, across the 70 studies, that a continuous relationship was observed in

eight studies, no relationship in three and a thresholded relationship in the remaining 59[67]. Where a threshold was detected, this varied between 25 and 125 nmol/l. Studies of fractional calcium absorption are similarly heterogeneous[68]. Furthermore, in an autopsy-based study of 675 cadavers[69], although bone mineralisation defects (osteomalacia) were not observed in any individual with 25(OH)-vitamin D > 75 nmol/l, in those with levels below 25 nmol/l, a substantial proportion were found to have normal bone histology. Taken with the range of attempts to define cut-offs for deficiency, these results clearly make the point that extrapolation from 25(OH)-vitamin D concentration alone to disease is difficult at the level of the individual.

There are several different methods available to measure 25(OH)-vitamin D. The gold standard is seen to be gas chromatography-mass spectrometry (GC-MS), but this technique is slow, expensive and time-consuming. Most labs use commercial kit assays, which are usually radio-immunometric assays (RIA; for example, IDS, Diasorin, Nicholls), although a chemi-luminescence assay also exists (Diasorin Liaison). The assays tend to be less accurate than GC-MS and high-performance liquid chromatography (HPLC), and also discriminate less well between the D_2 and D_3 forms.[70] Comparison of the Diasorin RIA kits with HPLC showed good correlation for D_3, but D_2 tended to be slightly underestimated[71]. A national system now exists to standardise measurement of 25(OH)-vitamin across laboratories in the UK (Vitamin D External Quality Assessment Scheme http://www.deqas.org/), and the US National Institutes of Health are leading a global programme aimed at standardisation of 25(OH)-vitamin D assays across both platform and laboratory (http://ods.od.nih.gov/Research/VitaminD.aspx#vdsp).

Infant post-natal vitamin D intake—Infant feeding, supplementation and sunlight exposure are strong determinants of post-natal infant 25(OH)-vitamin D levels and bone health.[72] Concentrations of 25(OH)-vitamin D in breast milk depend on the mother's blood levels and so if the mother is deficient in vitamin D during pregnancy, she is likely to continue to be deficient through lactation, yielding a double-insult to the child in the absence of adequate sun exposure. Clearly post-natal vitamin D supplementation of either the mother (whilst breast feeding) or the infant directly, together with maternal or childhood sun exposure, could confound any early outcomes attributed to maternal vitamin D status in pregnancy.

Osteomalacia: definition—Osteomalacia is a bone disease caused by inadequate mineralisation of the bone protein matrix, most often, in the UK, as a result of low levels of vitamin D.[73] Inadequate calcium and phosphate are other potential causes, seen more frequently in developing countries or as a result of genetic abnormalities leading to phosphate loss. Although osteomalacia is therefore a histological term, it is used to describe the finding of low vitamin D status in a patient with bone/ muscle pain, weakness, waddling gait, skeletal fragility and appropriate biochemical abnormalities e.g. hypocalcaemia.[73] There are very few studies which have examined osteomalacia in pregnancy, although anecdotally the incidence of the clinical syndrome is rising in dark-skinned ethnic minorities in the UK. Clearly the definition of osteomalacia used in studies considered for this review will be critical as the symptoms of osteomalacia overlap considerably with those of chronic

pain syndromes such as fibromyalgia. Bone biopsy is the only way to diagnose osteomalacia histologically, but the interventional nature of this procedure means that it is unsuitable for large scale population studies. One recent study of 675 human subjects at autopsy has demonstrated that there is no threshold in circulating 25(OH)-vitamin D level below which osteomalacic changes on bone biopsy are always seen.[74]

4. EXISTING EVIDENCE SYNTHESIS

Two previous systematic reviews have been performed in this area. The most recent (Mahomed and Gulmezoglu[75]) from the Cochrane group, asked the question "What are the effects of vitamin D supplementation on pregnancy outcome?", and although published in 2009, the actual searches and conclusions were established in 1999. The authors searched for intervention studies registered on the Cochrane Pregnancy and Childbirth Group trials register (October 2001) and the Cochrane Controlled Trials Register (Issue 3, 2001). Thus more recent work and observational data, plus unpublished evidence were not included. We believe that a further Cochrane review is underway. Two trials of vitamin D supplementation in pregnancy (Mallet et al, 1986[8] and Brooke et al, 1980[4]; see table 1) were assessed worthy of inclusion but the authors concluded that there was insufficient evidence on which to base any recommendations. NICE (National Institute for Health and Clinical Excellence) produced guidelines for antenatal care in 2008 (CG62 http://www.nice.org.uk/nicemedia/live/11947/40115/40115.pdf). Again, the conclusion was that there was insufficient evidence to allow a recommendation regarding vitamin D supplementation in pregnancy, although the authors acknowledged that supplementation may be beneficial in high risk groups. Despite the lack of good evidence for population wide supplementation and the dose chosen, the Department of Health currently recommend that all pregnant women take 400 IU vitamin D daily:(http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/@sta/@perf/documents/digitalasset/dh_107667.pdf). Most recently, Aghajafari et al[76] published a systematic review focused on obstetric outcomes, finding a possible beneficial effect of higher concentrations of maternal vitamin D in terms of gestational diabetes, pre-eclampsia and bacterial vaginosis, small for gestational age infants and lower birth weight infants, but not delivery by caesarean section.

5. RESEARCH QUESTIONS

1. What are the clinical criteria for vitamin D deficiency in pregnant women?
2. What adverse maternal and neonatal health outcomes are associated with low maternal circulating 25(OH)-vitamin D?
3. Does maternal supplementation with vitamin D in pregnancy lead to an improvement in these outcomes (including assessment of compliance and effectiveness)?
4. What is the optimal type (D_2 or D_3), dose, regimen and route for vitamin D supplementation in pregnancy?
5. Is supplementation with vitamin D in pregnancy likely to be cost-effective?

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6. REVIEW METHODS

6.1. Design

Systematic review of evidence to address these five research questions, following the methods recommended by the Centre for Reviews and Dissemination (CRD), University of York (http://www.york.ac.uk/inst/crd/), with meta-analysis to generate a pooled effect size where study designs allowed.

The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: crd42011001426; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42011001426.

6.2. Inclusion criteria

Studies were selected if they fulfilled criteria based on the sample studied, the independent variable of interest (exposure), the outcomes and the study design:

Sample studied—This must include pregnant women or pregnant women and their offspring.

Exposure—This must include either assessment of vitamin D status (dietary intake, sunlight exposure, circulating 25(OH)-vitamin D concentration) or supplementation of participants with vitamin D or vitamin D containing food e.g. oily fish.

Outcomes

Primary: Neonatal hypocalcaemia, rickets in the offspring and offspring bone mass; maternal osteomalacia;

Secondary: Offspring body composition (including offspring birth weight, birth length, head circumference, anthropometry, risk of being born small for gestational age, risk of low birth weight); offspring preterm birth and later offspring health outcomes (including asthma and atopy, blood pressure and Type 1 diabetes); maternal quality of life (including pre-eclampsia, gestational diabetes, risk of caesarean section and bacterial vaginosis).

Study type and setting—Studies which reported data on individuals were included. Ecological and animal studies were excluded. Examples of eligible study designs, together with associated level of resulting evidence quality (Centre for Evidence Based Medicine www.cebm.net/index.aspx?o=1025) are shown below:

Level 1a Systematic review (with homogeneity) of randomised controlled trials;

Level 1b Individual randomised controlled trial (with narrow confidence interval);

Level 2a Systematic review (with homogeneity) of cohort studies;

Level 2b Individual cohort study;

Level 3a Systematic reviews (with homogeneity) of case-control studies;

Level 3b Individual case-control study

All studies which contributed relevant information were included, regardless of the setting. However, the setting was noted as part of data abstraction and was used in narrative synthesis. Studies were not excluded on the basis of publication date.

6.3. Exclusion criteria

Studies were excluded if they were not written in English, non-human studies, did not measure maternal vitamin D status in or immediately after pregnancy, or supplement participants with Vitamin D in pregnancy, or where an outcome of interest was not assessed. Systematic reviews were not included in the narrative, but used as a source of references through hand-searching.

6.4. Search strategy for identification of studies

The search strategy was informed by initial scoping exercises performed by an information specialist with extensive expertise in systematic reviews of effectiveness and observational evidence. The search aimed to identify studies which describe maternal vitamin D levels/ supplementation in relation to maternal and offspring outcomes which may be suitable for answering the questions posed in the review (Search terms are shown in Appendix 1). The following resources were searched from their start dates to the present day: Completed studies (systematic reviews): DARE (Database of Abstracts of Reviews of Effects) (Centre for Reviews and Dissemination (CRD)), CDSR (Cochrane Database of Systematic Reviews), HTA (Health Technology Assessment database (CRD)); Completed studies (other study types): CENTRAL (Cochrane Register of Controlled Trials), Medline, Embase, Biosis, Google scholar, AMED (Allied and Complimentary Database; Ongoing studies: National Research Register archive, UKCRN (UK Clinical Research Network) Portfolio, Current Controlled Trials, ClinicalTrials.gov; Grey literature: Conference Proceedings Citation Index- Science (1990-present), Zetoc conference search, Scientific Advisory Committee on Nutrition website, Department of Health website, King's Fund Library database, Trip database, HTA website, HMIC (Health Management Information Consortium database). Bibliographies of selected papers were hand searched. First authors and other experts in several fields including metabolic bone disease, obstetrics, infant nutrition, child development, and allergy were contacted for unpublished findings. Identification of unpublished research was considered important in order to avoid publication bias. Unpublished observational evidence may be difficult to find since observational studies are not registered in the way that randomised control trials (RCT) are. All relevant studies (published or unpublished) that satisfied selection criteria for the review were considered. There was also a possibility that inclusion of those identified may itself introduce bias, due to over-representation of the findings of groups known to reviewers. This was assessed at the analysis stage of the review. The initial search strategy included articles up to 3rd January 2011. A subsequent additional search from 3rd January 2011 to 18th June 2012 was also performed to look for studies published more recently.

Screening of abstracts—When applying selection criteria, all abstracts and potentially relevant papers were independently assessed by two reviewers (CH, and PC or RM) and

decisions shown to be reproducible. Disagreements over inclusion were resolved through consensus and, where necessary, following discussion with a third member of the review team (NH).

Data extraction—Data extraction was carried out by two reviewers. Disagreements were resolved in the same way as for screening of abstracts. Separate forms were used to mark or correct errors or disagreements and a database kept for potential future methodological work.

Data were abstracted onto an electronic form. This contained the following items: general information (e.g. date of data extraction, reviewer ID); study characteristics (e.g. study design, inclusion/exclusion criteria,); study population characteristics; method of assessment of vitamin D status; baseline data (e.g. age, sex, ethnicity, measures of vitamin D status/ supplementation); quality criteria; outcomes (what they were and how they were ascertained); confounding factors; analysis (statistical techniques, sample size based on power calculation, adjustment for confounding, losses to follow up); results (direction of relationship, size of the effect and measure of precision of effect estimate such as 95% confidence interval or standard error). The data extraction forms for different study types are included in appendix 2.

Effect modifiers/ confounders—The effect modifiers and confounding factors considered included: ethnicity, skin covering, season, sunlight exposure, alcohol intake, smoking, dietary calcium, physical activity, comorbidity (e.g. diabetes), current medication, maternal body mass index, infant feeding, infant supplementation and maternal post-natal supplementation if breast feeding. Inclusion of these factors was recorded for each study and used as a marker of quality. Where meta-analysis was performed to generate a pooled effect size, inclusion and adjustment for these factors in individual studies was again recorded and used in quality assessment.

Study quality assessment—Quality assessment of studies occurred initially during data extraction and secondly in the analysis of review findings. The quality of included studies was assessed by the two reviewers, using a checklist of questions. The questions used, while based initially on CRD guidelines, were refined through piloting and agreement with the advisory group. Aspects of quality assessed included appropriateness of study design, ascertainment of exposure and outcome, consideration of the effects of important confounding factors, rigour of analysis, sample size and response rates. Quality assessment also incorporated specific issues related to vitamin D. Quality criteria are summarised in appendix 3. Quality data were used in narrative descriptions of study quality, and to produce composite validity scores with which to assign a quality level to each study such that studies could be stratified during synthesis of evidence. Quality assessment tools were agreed by the advisory group and refined during piloting. Each study was allocated a score for each quality criterion to estimate the overall risk of bias: +1 indicated a low risk of bias, 0 for a medium risk and −1 for a high risk of bias. These scores were then added to give a composite score, indicating bias in relation to the review question for each study. This score was between −16 and +16 for intervention and case-control studies; cohort and cross-sectional studies were allocated a score of between −13 and +13. A total composite score < 0 indicated a high risk

of bias, a score between 0 and 4 indicated a medium risk of bias and scores of ≥ 5 indicated a low risk of bias. Vitamin D-specific issues are summarised below:

How is “vitamin D” assessed? (Dietary intake, supplement use, blood levels of 25(OH)-vitamin D, blood levels of 1,25(OH)-vitamin D, PTH concentration)

Are season and sunlight exposures including sunscreen use and skin covering considered?

Are ethnicity and skin pigmentation considered?

How is 25(OH)-vitamin D blood level assessed?

What assay is used?

Are D_2 and D_3 forms adequately measured and are quality data (e.g. DEQAS) given?

What definition of “normal range” for 25(OH)-vitamin D is used?

Is the concentration treated as categorical (e.g. deficient, insufficient, replete) or continuous?

Has infant post-natal vitamin D intake (breast, bottle feeding, supplementation) and sunlight exposure been considered?

Has maternal compliance with supplementation been assessed?

Synthesis of extracted evidence—The aim of this part of the review was to investigate whether effects were consistent across studies and to explore reasons for apparent differences. We used both descriptive (qualitative) and quantitative synthesis; our capacity for the latter was determined by the evidence available. Where meta-analysis was possible, we used standard analytical procedures[1]. Only independent studies were meta-analysed. Thus, where a study contained two treatment arms, these were not included in the same analysis. It was therefore not possible to include all treatment arms from all randomised controlled trials in the same analysis. Two main approaches were employed: Firstly a meta-analysis of low dose studies (total dose < 120,000 IU vitamin D, including relevant single treatment arm studies, and the low dose and placebo arms of studies with more than one treatment arm; and secondly a similar approach but including those studies/ study arms with high dose (total > 120,000 IU). Inevitably, the observed estimates of the effects reported in the studies included in the meta-analysis varied. Some of this variation is due to chance alone, since no study can be large enough in order to completely remove the random error. However, the reported effects may also vary due not only to chance but due to methodological differences between studies. This variation between studies defines statistical heterogeneity. Statistical analysis was performed using STATA version 12.1. Between-study statistical heterogeneity was assessed by Q-statistic and quantified by I^2 test[77;78]; values of I^2 index of 25%, 50% and 75% indicated the presence of low, moderate and high between trials heterogeneity respectively, while a p-value of <0.10 was considered to denote statistical significance of heterogeneity. Differences in mean birth weight and serum calcium between supplemented and unsupplemented groups in randomised control trials were analysed using weighted mean difference (WMD) and 95% confidence intervals

(CIs). Results from observational studies were also synthesised. Pooled regression coefficients and odds ratios (ORs) and the 95% CIs were calculated for continuous and dichotomous outcomes respectively. For all analyses performed, if no significant heterogeneity was noted, fixed effect model (FEM) analysis using the Mantel-Haenszel method was presented; otherwise, results of the random-effects model (REM) analysis using the DerSimonian-Laird method were presented.[79]

7. STUDIES INCLUDED IN THE REVIEW

22,961 citations were identified from the initial database search up to 3rd January 2011. A subsequent additional database search from 3rd January 2011 to 18th June 2012 identified another 2,448 citations, yielding a total of 25,409 citations. A further 66 citations were identified from other sources (e.g. grey literature, bibliographies). After duplicate citations were removed, 16,842 citations were screened. Of these, 16,669 were excluded on the basis of the content of the title and/or the abstract (if available). A further 8 papers could not be found despite thorough searching, thus 16,677 records were excluded. A total of 165 full-text articles were retrieved for detailed assessment and of these 76 papers were included in the review. A flow diagram of this selection process is included in appendix 4.

8. STUDIES EXCLUDED FROM THE REVIEW

A total of 89 papers retrieved for assessment were excluded. Around a third of these (n=34) were abstracts. 21 papers had no relevant maternal or offspring outcome; 11 papers had no estimate of maternal vitamin D status; 10 papers used data from other papers included in the review; 8 papers were either review articles, letters, editorials or commentaries with no new results; 1 paper was of a non-human study and 4 papers reported on an outcome not assessed in any other paper (maternal breast cancer, offspring schizophrenia, offspring multiple sclerosis and offspring influenza A).

9. QUALITY ASSESSMENT OF INCLUDED STUDIES

Summary tables of the quality assessment scores for each included study can be found in Appendix 5. Studies are divided according to design (case- control, cohort, cross-sectional, intervention study) and listed in alphabetical order of first author.

10. RESULTS OF THE REVIEW

The majority of the results relate to study questions two and three (what adverse maternal and neonatal health outcomes are associated with low maternal circulating 25(OH)-vitamin D; Does maternal supplementation with vitamin D in pregnancy lead to an improvement in these outcomes (including assessment of compliance and effectiveness?). These are presented in detail below. Significant associations between maternal vitamin D and outcomes are described as either positive or negative. Effect sizes, if available from the original paper, are presented in the supplementary tables for each outcome (Appendix 6, Tables 8-31). Very few studies were identified which could directly inform the other questions. These are discussed in section 11.

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10.1. Offspring birth weight

Observational studies (Appendix 6, Table 8)—Nineteen observational studies linking maternal vitamin D status to offspring birth weight were identified. These were all of either cross-sectional (n=5) or cohort (n=14) design. Maternal vitamin D status was assessed by maternal serum 25(OH)-vitamin D concentration in fourteen studies, dietary intake in four studies and ambient UVB radiation during the last trimester of pregnancy in one. Sample sizes ranged from 84 to 13,904. Few studies considered all confounding factors of relevance to the review question. Composite bias scores ranged from −2 to +8, with seven of the nineteen studies scored as having a low risk of bias. Of the fourteen studies relating maternal serum 25(OH)-vitamin D concentration to offspring birth weight, only three studies demonstrated a significant positive association; one study found a significant negative association. In contrast, three of the four studies assessing the influence of maternal vitamin D intake during pregnancy on offspring birth weight found a significant positive association. One study found no significant association between ambient UVB exposure in pregnancy and offspring birth weight.

Armirlak[80] (composite bias score 2, medium risk) found a positive association between maternal 25(OH)-vitamin D at delivery and offspring birth weight in a cross-sectional study of 84 healthy Arab and South Asian women with uncomplicated deliveries. Maternal 25(OH)-vitamin D was generally low with a mean of 18.5 nmol/l. A large Australian study (Bowyer[81], composite bias score 4, medium risk) of 971 pregnant women found that offspring birth weight was significantly lower in those women with 25(OH)-vitamin D deficiency (<25 nmol/l) even after adjusting for gestational age, maternal age and overseas maternal birth place. Similarly, in the Amsterdam Born Children and their Development (ABCD) study incorporating 3,730 pregnant women, Leffelaar[82] (composite bias score 4, medium risk) found that early pregnancy maternal 25(OH)-vitamin D less than 30 nmol/l was significantly associated with a lower offspring birth weight, even after adjusting for multiple confounding factors. However, when serum 25(OH)-vitamin D was analysed as a continuous variable a significant association with birth weight was no longer seen. Mannion[83] (Canada, composite bias score 1, medium risk), Scholl[84] (USA, composite bias score 2, medium risk) and Watson[85] (New Zealand, composite bias score 3, medium risk) attempted to assess maternal vitamin D intake during pregnancy via food frequency questionnaires at various stages of gestation. Mannion and Scholl found that maternal vitamin D intake was positively associated with offspring birth weight. Similar findings were made by Watson assessing maternal vitamin D intake at 4 months; however a relationship was no longer observed when maternal vitamin D intake was measured again at 7 months.

Only one study found a negative association between offspring birth weight and maternal 25(OH)-vitamin D. Weiler[86] (composite bias score 3, medium risk) found that offspring birth weight was significantly lower in women with adequate vitamin D status (defined by the study group as 25(OH)-vitamin D ≥37.5 nmol/l). However, the number of participants in this study was low overall and only 18 women had 25(OH)-vitamin D <37.5 nmol/l. In addition, of those women with serum 25(OH)-vitamin D concentration <37.5 nmol/l, a

significantly higher percentage were of non-white race (67%) compared to those with an adequate concentration of 25(OH)-vitamin D (25%).

Twelve observational studies reported no significant association between maternal vitamin D status and offspring birth weight. Four of these studies were from Asia (Ardawi[87], Sabour[88], Magbooli[89], Farrant[90]), three from the UK (Gale[25], Harvey[64], Sayers[42]), two from Australia (Morley[91], Clifton-Bligh[92], one from the US (Dror[93]), one from Finland (Viljakainen[94]) and one from Africa (Prentice[95]). Ten had measured maternal 25(OH)-vitamin D during pregnancy or at delivery, one had assessed vitamin D intake during pregnancy and the largest study of 13,904 pregnant women had assessed maternal UV sun exposure in the last trimester as a proxy measure of vitamin D status.

Evidence synthesis—Results from studies that analysed log-transformed vitamin D were synthesised separately from results of studies that analysed vitamin D in its original units. The studies included in the first meta-analytic model were Harvey 2008, Gale 2008 and Farrant 2009, using log-transformed units. The combined estimate of the unadjusted regression coefficients for changes in birth weight (grams) per 10% increase in vitamin D was positive but did not reach statistical significance (pooled regression coefficient 0.47, 95% CI −3.12,4.05; Appendix 7, Figure 2)). In contrast, when adjusted estimates were synthesised (with adjustments being gestational age, maternal age, maternal BMI, ethnicity and parity where possible), there were significant differences in birth weight (grams) for 10% increase in vitamin D (pooled regression coefficient 5.63, 95% CI 1.11,10.16; Appendix 7, Figure 3). Amirlak, Prentice, Leffelaar and Dror analysed vitamin D in its original units. All four studies provided adjusted estimates, whereas all but Amirlak also provided unadjusted regression coefficients. No significant differences in birth weight (grams) per 25 nmol/l increase in vitamin D were found in either combined unadjusted associations (pooled regression coefficient 0.47, 95% CI −1.14,2.09; Appendix 7, Figure 4) or combined adjusted (as per paper) associations (pooled regression coefficient 0.12, 95% CI −1.84, 2.08; Appendix 7, Figure 5).

Intervention studies (Appendix 6, Table 9)—Nine intervention trials were identified, only two of which was within the last 20 years; the earliest from 1980. Sample sizes ranged from 40 to 350. Seven of these studies were rated as having a high chance of bias on the composite score (−2 to −9); only the most recent studies by Yu[96] and Hollis[97] were assessed as having a low risk of bias (composite bias score 5 and 10 respectively). Eight studies reported randomisation, although only one study (Brooke[4]) was of a double-blind design and this was also the only study that was placebo-controlled. In seven of the studies intervention took place in the last trimester of pregnancy; one study intervened in months 6 and 7 of pregnancy and one study supplemented from weeks 12-16 onwards. Interventions were highly variable, including 1000 IU daily of ergocalciferol, two doses of 60,000 IU cholecalciferol, two doses of 600,000 IU cholecalciferol, a single oral dose of 200,000 IU and 1200 IU cholecalciferol in combination with 375mg calcium daily. Change in maternal serum 25(OH)-vitamin D concentration before and after supplementation was given in three studies only. Three of the eight studies (all from India) demonstrated a statistically significantly greater birth weight in offspring of supplemented than unsupplemented

mothers. The remainder showed no difference in infant birth weight regardless of supplementation.

Two Indian studies, both by Marya et al[5;6] (composite bias scores −6 and −2 respectively, high risk) demonstrated significantly higher birth weights in infants born to women supplemented with high dose cholecalciferol (given as two doses of 600,000 IU in months 7 and 8 gestation). The earlier of these studies also had a third arm of women supplemented with 1200 IU vitamin D plus 375mg calcium throughout the third trimester of pregnancy. Birth weights of infants in this group were also significantly higher than in the unsupplemented group but not by as much as in the high dose supplement group. The third study reporting a positive association between maternal vitamin D supplementation and offspring birth weight was also from India (Kaur[98], composite bias score −7, high risk). Again significantly higher infant birth weight was found in the supplemented group (2 doses of 60,000 IU cholecalciferol in months 6 and 7) compared to the unsupplemented group, although the number of participants in this study was low (n=25 in each arm). Of note, none of the three studies measured maternal 25(OH)-vitamin D at any point during pregnancy, and were assessed to have a high risk of bias.

Three UK studies had investigated the effect of maternal vitamin D supplementation in the third trimester of pregnancy on offspring birth weight. Brooke[4] (composite bias score −2, high risk) and Congdon[22] (composite bias score −9, high risk) recruited only Asian women residing in the UK, whereas Yu[96] (composite bias score 5, low risk) included equal numbers of four ethnic groups (Caucasian, Black, Asian, Middle Eastern). None of the studies reported a significant difference in offspring birth weight between the supplemented and unsupplemented groups, even despite Brooke demonstrating significantly higher maternal 25(OH)-vitamin D concentrations in the supplemented group at term. Two studies, both from France (Delvin[7], composite bias score −2, high risk; Mallet[8], composite bias score −3, high risk) also failed to demonstrate a significant difference in offspring birth weight with maternal vitamin D supplementation. The most recent, and largest study (Hollis[97], composite bias score 10, low bias risk) randomised 350 pregnant women residing in the US to either 400 IU/day, 2000 IU/day or 4000 IU/day of oral vitamin D3from 12-16 weeks gestation until delivery. Although maternal serum 25(OH) D at delivery was higher in those women receiving the higher dose supplement regimes, there was no significant difference in offspring birthweight between the three groups.

Evidence synthesis—Two meta-analyses were performed to combine the published evidence of an effect of vitamin D supplementation on birth weight. The first included Brooke 1980, Marya 1981 (low dose of vitamin D), Congdon 1983, Mallet 1986 (low dose of vitamin D) and Kaur 1991 (Appendix 7, Figure 6). Due to statistically significant heterogeneity in the results (I^2 86.3%, $p<0.001$), a random-effects model was fitted. The combined estimate showed a non-significant difference in birth weight between the unsupplemented and supplemented group (mean weighted difference: 116.23g, 95% CI −57.0, 289.5). The second meta-analytical model included Brooke 1980, Marya 1981 (high dose of vitamin D), Congdon 1983, Mallet 1986 (high dose of vitamin D), Marya 1988 and Kaur 1991 (Appendix 7, Figure 7). Again, here, due to statistically significant heterogeneity (I^2 96%, $p<0.001$) a random effects model was fitted and the combined results did not show

a significant difference in birth weight between the supplemented and the non-supplemented groups (mean weighted difference: 147.3g, 95% CI −112.5, 407.15).

Discussion—The results of the included studies were conflicting, with some demonstrating positive associations between 25(OH)-vitamin D concentration and birth weight and some no relationship. The observation studies were, on the whole, of greater quality than the intervention studies, with almost all of the latter assessed as having a high risk of bias. Meta-analysis revealed weak positive associations across three observational studies, after adjustment for potential confounders, between log-transformed 25(OH)-vitamin D concentrations and offspring birth weight. However, confounding factors considered varied across the studies, and the potential for residual confounding is large. Despite these caveats, the relationships were generally positive, albeit not statistically significant, across the majority of identified studies, suggesting that further exploration in a well-designed, randomised, placebo-controlled, double-blind trial might be appropriate.

10.2. Offspring birth length

Observational studies (Appendix 6, Table 10)—Twelve observational studies including maternal vitamin D status and offspring birth length were identified; nine of the these were cohort in design with the remaining three being cross-sectional studies. The number of participants in each study ranged from 120 to 10,584. Maternal vitamin D status was assessed by serum 25(OH)-vitamin D concentration in ten studies and by dietary intake in two; in the remaining study maternal ambient UVB exposure during late pregnancy was used as a surrogate marker of vitamin D status. One study was assessed as having a high risk of bias (composite score −2, high risk) with the others demonstrating composite scores between +1 and +8. Consideration of potential confounding factors was variable. Two studies identified a positive relationship between maternal vitamin D status and offspring birth length, neither of which directly measured maternal 25(OH)-vitamin D. The remaining ten studies showed no relationship. We did not identify any studies that demonstrated an inverse relationship between maternal vitamin D status in pregnancy and offspring birth length.

Sabour[88] (composite bias score −2, high risk) in a cross-sectional study of 449 pregnant women in Iran, found that offspring birth length was significantly higher in mothers with adequate vitamin D intake (defined by the authors as >200 IU vitamin D/day). This study was assessed to have a high risk of bias and maternal serum 25(OH)-vitamin D was not measured, as vitamin D status was estimated from a food frequency questionnaire of dietary intake. The second study showing a positive relationship came from Sayers[42] (composite bias score 3, medium risk) using data from the large UK cohort, ALSPAC). In this study, again maternal serum 25(OH)-vitamin D was not directly measured but estimated using maternal UVB exposure in the last 98 days before birth as a surrogate. Maternal UVB exposure in late pregnancy was positively associated with offspring birth length. Additionally Leffelaar[82] measured offspring length at one month and found that infants born to mothers with 25(OH)-vitamin D <30 nmol/l (the threshold used by the authors for vitamin D deficiency) had a significantly lower length at one month even after adjusting for multiple

confounders including gestational age, season of blood sample, maternal height, maternal age, smoking pre-pregnancy, smoking in pregnancy, educational level, ethnicity and parity).

The remaining ten studies found no significant relationship between maternal vitamin D status and offspring birth length. Of these studies nine used maternal 25(OH)-vitamin D as the predictor and six were assessed to have a low risk of bias. Two studies were from the Middle East (Ardawi[87], composite bias score 5, low risk; Magbooli[89], composite bias score 1, medium risk) two from Australia (Morley[91], composite bias score 8, low risk; Clifton-Bligh[92], composite bias score 6, low risk), two from North America (Mannion[83], composite bias score 1, medium risk; Dror[93], composite bias score 7, low risk) and the remainder from the UK (Gale[25], composite bias score 4, medium risk), Finland (Viljakainen[94], composite bias score 3, medium risk), India (Farrant[90], composite bias score 5, low risk) and Africa (Prentice[95], composite bias score 5, low risk).

Intervention studies (Appendix 6, Table 11)—Two randomised controlled trials of vitamin D supplementation in pregnancy included birth length as an outcome; both were assessed to have a high risk of bias (composite bias score of both −2, high risk). A double-blind placebo controlled trial (Brooke[4]) found no significant difference in offspring birth length in UK Asian women supplemented with 1000 IU ergocalciferol per day in the last trimester compared to the control group. In contrast, a larger Indian study by Marya[6] found that birth length was significantly higher in women supplemented with a much higher dose of vitamin D (two doses of 600,000 IU cholecalciferol in the 7th and 8th month of gestation), compared to unsupplemented women.

Discussion—Again, the majority of the observational studies suggested no relationship between maternal 25(OH)-vitamin D status and offspring birth length. One of the studies which showed a significant association was large and prospective, but used ambient UVB radiation rather than a direct measure of vitamin D status. Of the 2 randomised trials to investigate birth length, one found a statistically significant relationship and the other did not. Thus the results are mixed but do not support the use of maternal vitamin D supplementation to reduce the risk of low birth length.

10.3. Offspring head circumference

Observational studies (Appendix 6, Table 12)—Eleven observational studies assessed the relationship between maternal vitamin D status in pregnancy and offspring head circumference. Eight of the studies were of cohort design, with the remaining three being cross-sectional studies. Participant numbers ranged from 120 to 559. Maternal vitamin D status was assessed by serum 25(OH)-vitamin D concentration in nine studies; the remainder used dietary intake (Sabour[88] and Mannion[83]). Composite bias scores ranged from −2 to +8, with six studies having a low risk of bias. Of those relating maternal serum 25(OH)-vitamin D to offspring head circumference at birth, no study found a statistically significant relationship, regardless of when during pregnancy 25(OH)-vitamin D was measured.

Three studies were from the Middle East: Ardawi[87] and Magbooli[89] found no association with offspring head circumference at birth and maternal 25(OH)-vitamin D measured at delivery. Likewise, Sabour[88] observed no difference in offspring head circumference in

women taking <200 IU vitamin D per day compared to those taking >200 IU vitamin D today. Two Australian studies (Morley[91] and Clifton-Bligh[92]) measured maternal vitamin 25(OH)-vitamin D in the third trimester of pregnancy and also found no significant association between maternal 25(OH)-vitamin D concentration and offspring head circumference. Morley also measured 25(OH)-vitamin D in early pregnancy and again a relationship was not demonstrated. Similar findings were made by Mannion[83] (a Canadian study using estimated dietary intake of vitamin D in pregnancy as the predictor), Gale[25] (UK, 25(OH)-vitamin D measured in the 3rd trimester), Farrant[90] (India, 25(OH)-vitamin D measured in the 3rd trimester), Prentice[95] (The Gambia, Africa,25(OH)-vitamin D measured in the 2nd and 3rd trimester), Viljakainen[94] (Finland, mean of early pregnancy and postpartum 25(OH)-vitamin D concentration used) and Dror[93] (USA, measured perinatally).

Intervention studies (Appendix 6, Table 13)—Offspring head circumference at birth was an outcome in two randomised controlled trials of vitamin D supplementation in pregnancy, both of which were assessed as having a high risk of bias (composite bias score −2 in both). Brooke[4] included 126 Asian patients and randomised in a double-blind fashion to either placebo or 1000 IU daily ergocalciferol in the last trimester. Head circumference did not differ between the treatment and placebo groups. In contrast, Marya[6] randomised 200 Indian women to either no supplement or to two doses of 600,000 IU cholecalciferol in the last trimester and found that head circumference at birth was significantly higher in the supplemented group compared to the unsupplemented group.

Discussion—Thus the majority of the observational studies demonstrated no association between maternal 25(OH)-vitamin D status in pregnancy and offspring head circumference at birth. One of the intervention studies found a positive relationship between supplement use and head circumference. It should be noted that this study generally found statistically significant relationships for most of the measured outcomes and was considered to be of high risk of bias. The evidence base is insufficient to recommend vitamin D supplementation for the optimization of, or prevention of low, head circumference.

10.4. Offspring bone mass

Observational studies (Appendix 6, Table 14)—Eight observational studies that included offspring bone mass outcomes were identified. Five of these were cohort studies with the remaining three being cross-sectional in design. All studies were assessed as being of medium to low risk of bias, with composite bias scores ranging from 3 to 7. The age at which offspring were assessed ranged from within 24 hours of birth to 9.9 years. Bone outcome measures also varied across the studies and included whole body, lumbar spine, radial mid-shaft, tibial and femoral bone mineral content (BMC), whole body and lumbar spine bone area, whole body and tibial bone mineral density, tibial cross-sectional area (CSA) and whole body BMC adjusted for bone area (aBMC). Most studies (six of eight) used DXA to assess bone mass; two studies used peripheral quantitative computed tomography (pQCT) and one study used single photon absorptiometry (SPA) in addition to DXA. Seven studies measured maternal 25(OH)-vitamin D during pregnancy or at delivery, one study used UVB exposure in the third trimester of pregnancy as a measure of maternal

vitamin D status. Five studies demonstrated a positive relationship between maternal vitamin D status and offspring bone health; three studies showed no relationship.

Weiler[86] (composite bias score 3, medium risk, n=50) found that neonates born to mothers with adequate maternal 25(OH)-vitamin D at delivery (defined by the authors as >37.5 nmol/l) had significantly higher whole body and femoral BMC per unit body weight compared to those with insufficient maternal vitamin D concentration (<37.5 nmol/l) even after adjustment for multiple confounders. There was no significant difference in infant lumbar spine, femoral or whole body BMC between the two groups however. Viljakainen[94] (composite bias score 3, medium risk) also measured neonatal bone mass, in a Finnish cohort of 125 primiparous Caucasian women. Tibial bone mass was assessed by pQCT and those with maternal 25(OH)-vitamin D above the median (42.6 nmol/l) had significantly higher tibial BMC and cross-sectional area (CSA) than those below the median, even after adjusting for confounders including maternal height and birth weight. However, when the age of the offspring at pQCT was included in the regression model, a significant relationship between maternal 25(OH)-vitamin D and offspring tibial BMC was no longer seen. No relationship was seen between maternal 25(OH)-vitamin D and tibial bone mineral density (BMD). A subsample of 55 children were also assessed again at 14 months (Viljakainen, 2011[99]. Tibial BMC was no longer significantly different by maternal 25(OH)-vitamin D status. Tibial CSA however, remained significantly lower in those with maternal 25(OH)-vitamin D below the median. Two cohort studies from the UK also demonstrated significant associations between maternal vitamin D status and offspring bone mass measured later in childhood. Javaid[2] 2006 measured maternal 25(OH)-vitamin D in late pregnancy and offspring bone mass by DXA at mean 8.9 years in a cohort of 198 pregnant women. Positive associations were observed between maternal 25(OH)-vitamin D and offspring whole body and lumbar spine BMC, lumbar spine bone area (BA) and whole body and lumbar spine BMD after adjustments were made for offspring gestational age at delivery and offspring age at DXA. Sayers[42] found that maternal UVB exposure in late pregnancy was positively associated with offspring BMC, BA and BMD in 6955 children at mean age 9.9 years. No relationship was seen with aBMC and maternal UVB exposure.

Three studies found no associations between maternal 25(OH)-vitamin D and offspring bone mass. Two studies (Akcakus[100] and Dror[93]), both cross-sectional in design and with a similar number of participants, measured maternal 25(OH)-vitamin D at delivery and used DXA to assess offspring bone mass up to the first month of life. A third study (Prentice[95]) measured mid and late pregnancy 25(OH)-vitamin D in a cohort of 125 pregnant Gambian women taking part in a larger clinical trial of vitamin supplementation. Offspring underwent assessment of bone mineral content and bone area using single photon absorptiometry of the midshaft radius; a subset also underwent whole body DXA at ages 2, 13 and 52 weeks. Again, no statistically significant relationship between maternal 24(OH)-vitamin D and offspring BMC at any time-point was observed. It should be noted that mean maternal 25(OH)-vitamin D levels in this cohort were much higher than any other study with an average at 103 nmol/l for mid-pregnancy and 111 nmol/l for late pregnancy and none of the women in the study were considered vitamin D deficient.

Intervention studies (Appendix 6, Table 15)—One clinical trial of maternal vitamin D supplementation and its effect on offspring bone mass was identified. Congdon[22] randomised 64 Asian women in the UK to either no supplement or 1000 IU vitamin D plus calcium daily in the third trimester. Offspring had their forearm BMC measured within 5 days of birth, although the type of equipment used to measure this was not recorded. No difference in offspring radial BMC was observed between the two groups. This study was assessed to have a high risk of bias (composite bias score −9) and maternal serum vitamin D concentration in pregnancy was not recorded at any time-point.

Discussion—Five of the eight observational studies relating maternal 25(OH)-vitamin D status to offspring bone outcomes demonstrated positive associations. The one small intervention study identified did not, but the methodology is unclear and a statistically significant result is unlikely based on the sample size. Thus observational studies suggest that maternal 25(OH)-vitamin D status may influence offspring bone development, but do not allow public health recommendations to be made. Further high-quality intervention studies are required here, such as the ongoing MAVIDOS Maternal Vitamin D Osteoporosis Study.[101]

10.5. Offspring anthropometric and body composition measures

Observational studies (Appendix 6, Table 16)—Six observational studies (five cohort and one cross-sectional) have examined the relationships between maternal vitamin D status and a variety of anthropometric measures in the offspring. Composite bias scores ranged from 3 to 8 indicating a medium to low risk of bias. Five studies had measured maternal serum 25(OH)-vitamin D in pregnancy (four in the third trimester and one at delivery); one study used maternal UVB exposure during the last trimester of pregnancy as a surrogate estimate of maternal vitamin D status. Anthropometric measurements of the offspring ranged across the studies and included skinfold thickness, limb circumference, and muscle area. Five studies used DXA to measure offspring fat and/or lean mass. Four studies demonstrated a significant relationship between offspring anthropometry and maternal 25(OH)-vitamin D; the remaining two showed no relationship.

Morley[91] measured offspring subscapular, triceps and suprailiac skinfold thickness using Harpenden callipers, along with mid-upper arm and calf circumferences using measuring tape in 374 Australian neonates. Although there no was significant association between maternal 25(OH)-vitamin D at 11 weeks gestation and any of the neonatal outcome measures, a weak inverse association was observed between maternal 25(OH)-vitamin D measured at 28-32 weeks and neonatal subscapular and triceps skinfold thickness. This association was weakened further but still remained statistically significant after adjustments were made for offspring sex, maternal height, whether the offspring was a first child, maternal smoking and season of blood sample. No significant association with maternal 25(OH)-vitamin D was found with the other offspring anthropometric outcomes assessed. Krishnaveni[102] also assessed offspring subscapular and triceps skinfolds, using callipers, in addition to arm muscle area, waist circumference, fat mass, percent body fat, fat-free mass and percent fat-free mass, using a combination of measuring tape and bioimpedence, in an older cohort of Indian children aged 5 years (n=506) and again at age 9.5 years (n=469).

Children born to mothers with late pregnancy vitamin D deficiency (25(OH)-vitamin D concentration <50 nmol/l) had significantly reduced arm-muscle area in comparison with children born to mothers with adequate levels. No significant relationship was observed with the other anthropometric measurements at either time-point.

Of the four studies using DXA to measure offspring fat and/or lean mass, two reported no relationship with maternal vitamin D status. Weiler[86] used DXA to measure whole body fat in a group of 50 neonates in Canada. No significant difference was observed between those born to mothers with 25(OH)-vitamin D concentration <37.5 nmol/l at delivery and those born to mothers with 25(OH)-vitamin D >37.5 nmol/l. Gale[25] found no significant association between maternal 25(OH)-vitamin D in late pregnancy and offspring fat mass or lean mass in 178 UK children aged 9 years. Fat and lean mass tended to be lower in children born to mothers in the lowest quarter of 25(OH)-vitamin D distribution but this did not achieve significance. In contrast, Sayers[42] using maternal UVB exposure in late pregnancy as a surrogate measure for vitamin D status found that offspring lean mass at mean age 9.9 years was positively associated with maternal UVB exposure. No significant association was seen with fat mass however. In contrast, Crozier[103] (composite bias score 8, low risk) found that maternal serum 25(OH)-vitamin D in late pregnancy was positively associated with offspring fat mass at birth, measured by DXA, after adjusting for confounders. Interestingly no significant relationship was seen between maternal 25(OH)-vitamin D and offspring fat mass at 4 years, and a negative relationship was seen at 6 years of age. No significant relationship was observed between maternal 25(OH)-vitamin D and offspring's fat-free mass at any time-point.

Intervention studies (Appendix 6, Table 17)—Two intervention studies were identified and have been described earlier. Both studies were assessed to have a high risk of bias (composite bias score −2 for both). Brooke[4] found no difference in neonatal triceps skinfold thickness or forearm length between those born to supplemented mothers and placebo group mothers. Marya[6] found significantly greater mid-upper arm circumference, and triceps and subscapular skinfold thicknesses in neonates of supplemented than unsupplemented mothers (all $p<0.01$).

Discussion—The identified observational studies demonstrated a variety of modest relationships between maternal 25(OH)-vitamin D status and offspring anthropometric measures, with some finding positive relationships between maternal 25(OH)-vitamin D status and measures of offspring muscle and fat mass. Consistent with other anthropometric outcomes in their study, Marya et al found greater skinfold thicknesses in the supplemented than unsupplemented group. The evidence base is therefore insufficient to warrant recommendation of maternal vitamin D supplementation to optimise childhood anthropometric measures.

10.6. Offspring asthma and atopy

Observational studies (Appendix 6, Table 18)—Ten studies were identified that examined the relationships between maternal vitamin D intake during pregnancy, maternal serum 25(OH)-vitamin D level in pregnancy or cord blood 25(OH)-vitamin D concentration

and markers of atopy in the offspring. These were all observational cohort studies, ranging in size from 178 to 1724 mother-child pairs. Eight studies reported the outcome wheeze or asthma as determined by parental questionnaires at between 16 months and 9 years of age.

Four of these seven studies used maternal vitamin D intake during pregnancy as the exposure and had composite bias scores of between −1 and 2 (Erkkola[104]; Devereux[27]; Miyake[105]; Camargo[106] 2007). These four studies all reported a lower risk of wheeze in offspring of mothers with higher vitamin D intakes during pregnancy although the definitions used for wheeze varied between studies; Miyake[105] included 763 mother-offspring pairs in a prospective cohort study in Osaka, Japan (bias score −1, high risk). Vitamin D intake was measured by FFQ between 5 and 39 weeks of pregnancy and the children followed up between 16 and 24 months of age using the International Study of Asthma and Allergy in Childhood (ISAAC) questionnaire. In this study, consumption of ≥172 IU/day vitamin D was associated with a reduced risk of both wheeze and eczema. Camargo[106] 2007 reported in a prospective cohort study in Massachusetts, USA which included 1194 mother-offspring pairs, that children born to mothers in vitamin D intake quartiles two (446-562 IU/day), three (563-658 IU/day) and four (659-1145 IU/day) had a reduced risk of recurrent wheeze (≥2 episodes of wheeze in children with a personal diagnosis of eczema or parental history of asthma) at 3 years compared to those born to mothers in the lowest quartile of vitamin D intake, but in contrast to Miyake 2010, there was no difference in the incidence of eczema. Erkkola[104] found a lower risk of persistent asthma (physician diagnosis and a requirement for asthma medication in the preceding 12 months) at 5 years in children born to mothers with higher vitamin D intake, but similarly to Camargo 2007, there was no reduced risk of atopic eczema. However, this Finnish study only included children who had HLA-DQB1 conferred susceptibility to type 1-diabetes. The composite bias score was −1 indicating a high risk of bias. Finally, Devereux[27] also reported a lowered risk of reported wheeze in the preceding year in 5 year old children born to mothers with the highest quintile of vitamin D intake at 32 weeks gestation (189-751 IU/day) compared to the lowest quintile (46-92 IU/day). There was no statistically significant reduction in the odds ratio for wheeze when quintiles two, three and four were compared to quintile one, but a significant overall trend (p=0.009).

Two studies assessed the associations between cord blood 25(OH)-vitamin D and parental report of wheeze and/or asthma. These studies had composite bias scores of 2 and 3 (medium risk of bias). Camargo[107] 2011 found in 823 children in New Zealand that the odds ratio for wheeze at 5 years of age decreased across categories of cord 25(OH)-vitamin D, but there was no association with incident asthma. Similarly, Rothers[108], found no association between cord 25(OH)-vitamin D and asthma (physician diagnosed and medication requirement in preceding year) at 5 years. Two studies, Gale[25] and Morales[109] assessed the association between maternal 25(OH)-vitamin D measured in pregnancy and parental reported wheeze or diagnosis of asthma. Gale[25] (composite bias score 4, medium bias risk) assessed the association between maternal 25(OH)-vitamin D in late pregnancy and parental report of asthma in 178 children. Exposure to the highest quarter of maternal concentrations of 25(OH)-vitamin D was associated with an increased risk of reported asthma at age 9 years compared with children whose maternal 25(OH)-vitamin D concentration had been in the lowest quarter of the distribution. In addition, the risk of offspring eczema at nine months

(assessed by either physical examination or parental report) was also higher in children in the highest quarter of maternal 25(OH)-vitamin D distribution compared to those in the bottom quarter. By 9 years of age however, although offspring in the highest quarter of maternal 25(OH)-vitamin D still tended to have a higher risk of reported eczema than those in the lowest quarter, the difference was no longer significant. In this study the number of cases of asthma or eczema per maternal 25(OH)-vitamin D quartile were low however, ranging from 2-15. Conversely, Morales[109] (composite bias score 3, medium bias risk) found no significant association between maternal 25(OH)-vitamin D measured at mean (SD) 12.6 (2.5) weeks and parent reported offspring wheeze at 1 year or 4 years, or asthma (defined as parental report of doctor diagnosis of asthma or receiving treatment for asthma) at age 4-6 years.

Four studies utilised other outcome markers of asthma and/or atopic disease; these studies were subject to less potential bias (composite bias scores −1 to 3). Two studies measured offspring spirometry; Cremers[110] 2011(bias score 3, medium risk) found no associations between maternal plasma 25(OH)-vitamin D at 36 weeks gestation and offspring Forced Expiratory Volume in 1 second (FEV_1) (p=0.99) or Forced Vital Capacity (FVC) (p=0.59) at 6-7 years in 415 mother-offspring pairs. Similarly Devereux[27] (bias score −1, high risk) did not identify any differences in lung function at 5 years of age across quintiles of maternal vitamin D intake at 32 weeks gestation. Two studies also undertook skin prick testing as a measure of atopic sensitization. Devereux[27] found maternal vitamin D intake at 32 weeks gestation was not associated with differences in atopic sensitisation to cat, timothy grass, egg or house dust mite at 5 years of age. Conversely, Rothers[108] (bias score 2, medium risk) found that those with cord blood 25(OH)-vitamin D ≥100 nmol/l, when compared to children with cord 25(OH)-vitamin D 50-74.9 nmol/l, had a greater risk of a positive response to a skin prick testing battery that included 17 aeroallergens common to the geographical area. Finally, 2 studies included offspring IgE concentration as a measure of atopy. Rothers[108] reported a non-linear relationship between cord 25(OH)-vitamin D and total and allergen-specific IgE for 6 inhalant allergens. The highest levels of IgE were identified in children with cord 25(OH)-vitamin D concentration <50 nmol/l and ≥100 nmol/l. Conversely, Nwaru[111] 2010 found increasing maternal vitamin D intake determined by FFQ was inversely associated with sensitisation (IgE>0.35ku/l) to food allergens (IgE>0.35ku/l) but not inhaled allergens at 5 years of age.

Intervention studies—No intervention studies examining the influence of vitamin D supplementation in pregnancy on offspring risk of asthma or atopy were identified.

Discussion—The studies on asthma were all observational; no intervention studies were identified. The investigations were marked by substantial heterogeneity in terms of study design, outcome definition and exposure definition and gave a variety of conflicting results. It is difficult to conclude any definitive relationship between maternal 25(OH)-vitamin D status and offspring asthma and no recommendation can be made. Further high-quality intervention studies are required here, such as the ongoing VDAART (Vitamin D Antenatal Asthma Reduction Trial, **ISRCTN NCT00920621**) and ABCVitamin D (Vitamin D

Supplementation During Pregnancy for Prevention of Asthma in Childhood **ISRCTN NCT00856947**) trials.

10.7. Offspring born small for gestational age (SGA)

Observational studies (see Appendix 6, Table 19)—Seven observational studies assessing the relationship between maternal 25(OH)-vitamin D and the risk of offspring being born small for gestational age (SGA) were identified. Of these, two were case-control studies, one was cross-sectional and four were cohort studies. All achieved a composite bias score of between +1 and +7 indicating a medium-low risk of bias. Five studies defined SGA as infants born below the 10th percentile of birth weight according to nomograms based on gender and gestational age. Three studies reported how gestational age was assessed (known dates of last menstrual period and/or fetal ultrasound in early pregnancy), with the remainder giving no explanation. All studies measured serum maternal 25(OH)-vitamin D concentration. The number of week's gestation when the sample was taken ranged from 11 weeks to delivery. One study defined SGA as infants born below the 3rd percentile of birth weight. Three studies (one nested case-control and one cohort study) reported a significant association between maternal 25(OH)-vitamin D and risk of SGA; the remaining four studies did not demonstrate a significant relationship.

Leffelaar[82] measured maternal 25(OH)-vitamin D concentration in women at 11-13 weeks gestation taking part in the large Amsterdam Born Children and their Development (ABCD) study. Of the 3,730 women in the cohort, 9.2% delivered SGA infants. Women with a serum 25(OH)-vitamin D concentration less than 30 nmol/l had a significantly higher risk of SGA infants compared to women with 25(OH)-vitamin D concentrations greater than 50 nmol/l; this relationship remained even after adjusting for gestational age, season of blood collection, sex of infant and maternal parity, age, smoking, pre-pregnancy BMI, educational level and ethnicity. No significant risk was observed however in women with 25(OH)-vitamin D concentration between 30-49.9 nmol/l. Bodnar[112] (composite bias score 7, low risk) found that the relationship between maternal 25(OH)-vitamin D and SGA varied according to race. In this nested case-control study from an overall cohort of 1198 nulliparous women, 111 cases were identified and compared to 301 randomly selected controls; all had 25(OH)-vitamin D measured before 22 weeks gestation. Amongst black mothers, no relationship between SGA risk and maternal 25(OH)-vitamin D concentration was observed. However, in white women, a U-shaped relationship was observed between the odds of delivering an SGA infant and maternal 25(OH)-vitamin D concentration. Significantly higher odds for SGA were observed in those with 25(OH)-vitamin D concentrations <37.5 and >75 nmol/l, with the lowest odds of SGA in women with 25(OH)-vitamin D concentrations 60-80 nmol/l. These relationships remained significant even after adjusting for pre-pregnancy BMI, smoking, socioeconomic score, season, maternal age, gestational age at blood sample, marital status, insurance status, conceptual multi-vitamin use and preconception physical activity. Finally, Robinson[113] (composite bias score 0; medium risk), in a case-control study of pregnant women, all of whom had early onset severe preeclampsia (as defined by the American College of Obstetrics and Gynecology), found that maternal serum vitamin D was significantly lower in cases with SGA infants

compared to controls. This study did not present an odds ratio, nor define SGA, and it was not clear at what stage of gestation maternal vitamin D was measured

A cross-sectional Turkish study of 100 pregnant women (Akcakus[100], composite bias score 4, medium risk), 30 of whom had SGA infants, found no difference in maternal mean 25(OH)-vitamin D at delivery in cases of SGA (maternal 25(OH)-vitamin D concentration 21.8 nmol/l) compared to infants appropriate for gestational age (maternal 25(OH)-vitamin D concentration 21.5 nmol/l). Average maternal concentrations of 25(OH)-vitamin D in this study were low, a reflection of the fact that most women in the study were veiled. A similar finding was observed by Mehta (composite bias score 3, medium risk) in the African cohort study of 1,078 women all infected with HIV. 74 cases of SGA were identified. Again no difference in mean maternal 25(OH)-vitamin D concentration measured in mid-pregnancy was observed between cases and normal deliveries. Shand[114] observed similar findings in a cohort study of Canadian women all with biochemical or clinical risk factors for preeclampsia. No significantly increased odds of SGA were observed in women with 25(OH)-vitamin D concentrations less than 75 nmol/l compared to over 75 nmol/l. In this study, cases of SGA were low (n=13). Finally a Spanish cohort study from Fernadez-Alonso[115] (composite bias score 3, medium risk) identified 46 cases of SGA out of a cohort of 466. No significant relationship between maternal 25(OH)-vitamin D and SGA infants was observed. Neither mean 25(OH)-vitamin D concentrations nor an odds ratio were reported.

Intervention studies (See Appendix 6, Table 20)—Two clinical trials of maternal vitamin D supplementation evaluated the relationship between maternal 25(OH)-vitamin D and risk of SGA infants. Both defined SGA as infants born below the 10th percentile for birth weight, although neither reported how gestational age was assessed. Neither observed a significant relationship. Brooke[4], in a double-blind placebo controlled randomised trial, allocated 67 pregnant women to either placebo (n=67) or vitamin D2 1000 IU per day in the last trimester of pregnancy (n=59). Both groups were similar in terms of maternal age, height, parity, offspring sex and length of gestation. In this British study all participants were Asian, with the majority of Indian ethnicity. Although the mean maternal 25(OH)vitamin D concentration was significantly higher in the supplemented group at delivery compared to the unsupplemented group, the percentage of SGA infants did not differ significantly between groups (19 in the placebo group versus 9 in the supplemented group). The composite bias score of this study was −2 indicating a high risk of bias. Yu[96] (composite bias score 5, low risk) reported similar findings in a more recent British clinical trial. Pregnant women was randomised to one of three arms; either no supplement (n=59), or oral vitamin D2 800 IU/day from 27 weeks onwards (n=60), or a single bolus dose of 200,000 IU vitamin D2 at 27 weeks gestation (n=60). Each group contained equal numbers of four ethnic groups (Caucasian, Black, Asian, Middle Eastern). No significant difference in the incidence of SGA was observed across the three groups.

Discussion—There was substantial variation in the methodology, exposure and outcome definitions for studies investigating the relationship between maternal 25(OH)-vitamin D status and risk of offspring being small for gestation age. Outcomes were conflicting. The 2

intervention studies which included this outcome, the more recent of which was deemed of reasonable quality, found that supplementation with vitamin D during pregnancy was not associated with reduced risk. There appears to be no evidence base with which to recommend maternal vitamin be supplemented for the prevention of offspring being small for gestational age neonatal.

10.8. Offspring preterm birth

Observational studies (Appendix 6, Table 21)—Seven observational studies relating maternal 25(OH)-vitamin D to the risk of premature birth were identified. (Three cohort, one cross-sectional, two case-control) One further cross-sectional study assessing the risk of threatened premature birth was also included. Two studies were case-control, three cohort and two cross-sectional. There was some disparity in the definition of preterm birth between studies. Most studies defined preterm birth as spontaneous delivery before 37 weeks gestation; one study used a threshold of less than 35 weeks. Only three studies reported how gestational age was measured: two studies used a combination of last menstrual period and/or fetal ultrasound; one study used the scoring system of Dubowitz**,** (based on examination of the neonate and scored on neurological and physical examination features). All studies measured maternal serum 25(OH)-vitamin D at some point during pregnancy or at delivery. Only one study found a significant relationship between maternal 25(OH)-vitamin D and risk of premature delivery.

Shibata[116] (composite bias score 4, medium risk) in a cross-sectional study of 93 Japanese pregnant women attending hospital for a routine medical check-up in Toyoake, Japan found that maternal 25(OH)-vitamin D measured after 30 weeks gestation was significantly lower in the 14 cases of threatened premature delivery (mean 25(OH)-vitamin D concentration 30.0 nmol/l) compared to normal pregnancies (mean 25(OH)-vitamin D concentration 37.9 nmol/l). Threatened premature delivery was defined as progressive shortening of cervical length (<20mm) as detected by transvaginal ultrasound before the 34th week of gestation, and/or elevation of granulocyte elastase level in the cervical mucus before 32 weeks gestation; plus the number of uterine contractions equal to or more than twice per 30 minutes (before the 32nd week of gestation).

In contrast, six studies did not demonstrate a significant relationship between maternal 25(OH)-vitamin D and premature delivery. A small case-control study by Delmas[117] found no difference in mean maternal 25(OH)-vitamin D concentration measured at delivery in the 10 cases of preterm birth (mean maternal 25(OH)-vitamin D concentration 44.9 nmol/l) compared to the 9 controls (mean maternal 25(OH)-vitamin D concentration 47.4 nmol/l). This study achieved a low composite bias score of −4 suggesting a high risk of bias. No adjustment or considerations for potential confounders were made. Similarly, a prospective cohort study from Tanzania of 1,078 pregnant African women infected with HIV and taking part in a clinical trial of vitamin use (Mehta[118], composite bias score 2, medium risk) found no increased relative risk of preterm or severe preterm birth (defined as spontaneous delivery before 34 weeks gestation) in women with a serum 25(OH)-vitamin D concentration measured at 12-27 weeks gestation less than 80 nmol/l compared to those with levels greater than 80 nmol/l. A nested case-control study in North Carolina, USA

(Baker[119], composite bias score 5, low risk) identified 40 cases and 120 controls matched by race/ethnicity in a 1:3 ratio and compared maternal 25(OH)-vitamin D measured at 11-14 weeks gestation. Again no significant difference in the odds ratio for preterm birth was found in women with 25(OH)-vitamin D less than 75 nmol/l compared to those with 25(OH)-vitamin D concentration greater than 75 nmol/l. Shand[114] in a cohort study of 221 pregnant women in Vancouver, Canada with either clinical or biochemical risk factors for preeclampsia found no significant relationship between maternal 25(OH)-vitamin D, measured between 10 weeks and 20 weeks 6 days gestation, and risk of preterm birth using three different thresholds of maternal 25(OH)-vitamin D (<37.5 nmol/l, <50 nmol/l, <75 nmol/l) after adjustment for maternal age, BMI, season, multivitamin use and smoking. The risk factors for preeclampsia included a past obstetric history of early-onset or severe preeclampsia, unexplained elevated α-fetoprotein ≥ 2.5 multiples of the median (MoM), unexplained elevated human chorionic gonadatrophin, or low pregnancy-associated plasma protein A ≤ 0.6 MoM. Hossain[120] 2011, in a cross-sectional study of 75 pregnant women in Pakistan (composite bias score 4, medium risk), found that mean maternal 25(OH)-vitamin D_3 at delivery tended to be higher in those who delivered preterm (mean 25(OH)-vitamin D_3 concentration 42.2 nmol/l) than those with full term deliveries (mean 25(OH)-vitamin D_3 concentration 32.9 nmol/l) but this did not achieve statistical significance and no adjustments for confounders were made. Finally, in a Spanish cohort study (Fernandez-Alfonso[115] (composite bias score 3, medium risk)) there was no significant difference in mean maternal 25(OH)-vitamin D concentration measured at 11-14 weeks in those who delivered preterm (n=33) and those who delivered at term (n=433); again, no consideration for confounding factors was made.

Intervention studies—No intervention studies were identified.

Discussion—The data relating maternal 25(OH)-vitamin D status to risk of offspring preterm birth are all observational. The results of the studies are varied but do not support the use of maternal supplementation to prevent this obstetric outcome.

10.9. Offspring Type I diabetes

Observational studies (Appendix 6, Table 22)—Three observational studies (two case-control and one cohort), all from Scandinavia, were identified, relating maternal 25(OH)-vitamin D status to the risk of type I diabetes mellitus in the offspring. Only one of these studies used 25(OH)-vitamin D concentration; the other two attempted to estimate vitamin D intake. Sorensen[121] (composite bias score 8, low risk) performed a case-control study of 109 children with type I diabetes (mean age 9 years) and 219 controls within a cohort of 29,072 individuals. 25(OH)-vitamin D concentration had been measured at a median of 37 weeks gestation. The mean 25(OH)-vitamin D concentration in the mothers of cases was 65.8 nmol per litre and in the mothers of controls was 73.1 nmol per litre. Compared with children of mothers whose levels were greater than 89 nmol per litre, children of mothers whose 25(OH)-vitamin D concentrations in late pregnancy were less than or equal to 54 nmol per litre were at increased risk of developing type I diabetes mellitus. Stene[122] (composite bias score 2, medium risk) performed a case-control study comparing 545 children with type I diabetes (mean age 10.9 years) with 1,668 matched

controls. Maternal use of vitamin D supplementation during pregnancy was assessed retrospectively by questionnaire and no association was found between maternal vitamin D supplementation in pregnancy and risk of offspring type I diabetes mellitus. Marjamaki[123] (composite bias score 6, low risk) studied a prospective cohort of 3,723 children who were at an increased genetic risk of developing diabetes. Amongst this cohort 74 children developed type I diabetes over the mean observation period of 4.3 years. Maternal vitamin D intake was assessed retrospectively from a food frequency questionnaire completed 1 to 3 months after delivery and which was focused on food and supplements taken in the eighth month of pregnancy. There was no statistically significant relationship observed between maternal vitamin D intake either from food or supplements, and risk of offspring type I diabetes mellitus.

A further study by Krishnaveni[102], (composite bias score 4, medium risk) using a cohort of 506 Indian children age 5 years (469 of whom were also followed-up to 9.5yrs.) did not measure rates of Type 1 diabetes mellitus per se, but measured fasting glucose, fasting insulin, insulin resistance and insulin increment 30 minutes after a glucose tolerance test in the children. No significant association was found between any of these offspring measurements at age 5 years and maternal 25(OH)-vitamin D concentration, measured at 28-32 weeks gestation. At age 9 years however a significant inverse relationship was observed between maternal 25(OH)-vitamin D concentration and offspring fasting insulin and insulin resistance after adjustment for child sex and age, maternal BMI, gestational diabetes, socioeconomic score, parity and religion.

Intervention studies—No intervention studies were identified.

Discussion—The 3 observational studies relating maternal serum 25(OH)-vitamin D status to risk of offspring type I diabetes were assessed to be of moderate to low risk of bias and were generally consistent in suggesting an inverse relationship. However one used vitamin D dietary intake and there are no intervention studies. Thus maternal vitamin D supplementation to prevent offspring type I diabetes cannot be recommended, however high-quality intervention studies are warranted.

10.10. Offspring low birth weight

Observational studies (Appendix 6, Table 23)—Three observational studies (two cross-sectional, one cohort) examining the relationship between infants born with low birth weight and maternal 25(OH)-vitamin D concentration were identified. All studies were from the developing world (Iran and Tanzania) and composite bias scores ranged from −2 to 3 indicating a high-medium risk of bias. The definition of low birth weight (offspring birth weight less than 2500g) was consistent across all three studies. Two studies directly measured maternal serum 25(OH)-vitamin D and reported no association with low birth weight infants. One study estimated vitamin D intake from a food frequency questionnaire and observed a significant relationship between vitamin D intake and offspring risk of low birth weight. This study from Sabour[88] used a food frequency questionnaire in 449 Iranian pregnant women completed at delivery to estimate maternal vitamin D intake during pregnancy. The incidence of low birth weight infants (n not given) was lower in women

with adequate intake of calcium and vitamin D (100mg calcium, 200 IU vitamin D/day compared to those with inadequate intake. This study achieved the lowest composite bias score (composite bias score −2) of these studies, indicating the highest risk of bias; no consideration for potential confounders was made.

Two studies reported no significant relationship between maternal 25(OH)-vitamin D and offspring low birth weight risk. Maghbooli[89] (composite bias score 1, medium risk) in a second cross-sectional study from Iran, measured maternal 25(OH)-vitamin D at delivery in 552 Iranian women. 5.4% (approx. n= 30) of the cohort had low birth weight offspring. No significant difference in mean maternal 25(OH)-vitamin D was observed between cases of low birth weight offspring and normal weight offspring (mean 25(OH)-vitamin D concentration in each group not given). Similarly Mehta[118] (composite bias score 3, medium risk) in a cohort study of 1,078 HIV infected women taking part in a vitamin supplement trial, found no significantly increased odds of low birth weight infants (n=80) in mothers with a 25(OH)-vitamin D concentration <80 nmol/l compared to those with a concentration >80 nmol/l. In this study a threshold of 80 nmol/l was used to divide maternal 25(OH)-vitamin D concentration into adequate or low. Adjusting the analysis for maternal multivitamin supplementation, age at baseline, CD4 count at baseline and HIV disease stage did not alter the findings.

Intervention studies—No intervention studies were identified.

Discussion—Of the 3 observational studies relating maternal 25(OH)-vitamin D status to risk of low birth weight in the offspring, only one demonstrated a positive result, suggesting that low birth weight was less likely where women took at least 100mg of calcium and 200 IU vitamin D daily. However this was judged to be at high risk of bias; the remaining 2 studies demonstrated no relationship and therefore maternal vitamin D supplementation cannot be recommended to prevent low birth weight. Larger prospective observational studies in several different populations would be sensible before moving to an intervention study.

10.11. Offspring serum calcium concentration

Observational studies (Appendix 6, Table 24)—One observational study examining the relationship between maternal vitamin D status and offspring serum calcium concentration was identified. In a cross-sectional study of 264 women in Saudi Arabia, Ardawi[87] found no significant correlation between maternal 25(OH)-vitamin D measured at delivery and offspring venous umbilical cord blood calcium concentration. A relationship was still not observed even if the group was divided using a maternal 25(OH)-vitamin D concentration of 20 nmol/l as a threshold. This study was assessed to have a low risk of bias (composite bias score 5), however no adjustments were made for potential confounding factors.

Intervention studies (Appendix 6, Table 25)—Seven clinical trials of maternal vitamin D supplementation were identified; all measured venous umbilical cord calcium concentration at delivery and three went on to measure offspring venous calcium again

within the first week of life. None of the trials were within the last 20 years and all were found to have a high risk of bias (composite bias score −9 to −1). Sample sizes ranged from 40 to 1,139. Five studies reported adequate randomisation, however only two trials were placebo-controlled and only one was of double-blind design. Supplementation strategies were highly variable: six trials supplemented pregnant women with vitamin D in the last trimester; one study supplemented from 12 weeks onwards. There was also much diversity with regards to the type of supplementation used, ranging from 1000 IU ergocalciferol daily (with or without calcium) in the last trimester to bolus oral dosing of 600,000 IU cholecalciferol twice in the last trimester. Six studies reported higher offspring calcium concentrations in the supplemented group compared to the unsupplemented group; one trial showed no difference in offspring venous calcium regardless of maternal vitamin D supplementation strategy.

Brooke[4] (composite bias score −2, high risk), in a trial of ergocalciferol supplementation of Asian women living in the UK in their last trimester of pregnancy, found no difference in umbilical cord calcium concentration between groups, but neonatal serum calcium was greater in offspring of supplemented mothers than mothers who had received placebo at three and six days postnatally. There were five cases of symptomatic hypocalcaemia in the control group but none in the treatment group. Higher rates of breastfeeding were observed in the treatment group which in itself was positively associated with offspring venous calcium concentration and was not controlled for in analysis. Similar findings were noted in a larger (n=1139) British study by Cockburn[21] (composite bias score −1, high risk) and in a French study by Delvin[7] (Composite bias score −2, high risk). Neither study found a difference in venous cord calcium concentrations between the supplemented and unsupplemented groups, but both found higher infant venous calcium concentrations at days 6 and 4 respectively in the supplemented group. The third, and most recent, British study (Congdon[22]) found that offspring cord calcium was significantly higher in Asian women supplemented with daily 1000 IU vitamin D plus calcium in the last trimester compared to Asian women who received no supplement. This study was assessed to have the highest risk of bias with a composite bias score of −9. The number of subjects in this trial was low with only 19 receiving supplement, and details of whether randomisation or blinding occurred were not reported. These findings are in agreement with two Indian studies, both by Marya et al[5;6](1981, composite bias score −6, high risk; 1989 composite bias score −2, high risk). Both studies found that cord calcium concentrations were significantly higher in those mothers supplemented with two doses of 600,000 IU cholecalciferol in months 7 and 8 of gestation compared to the unsupplemented group.

In contrast, a French study (Mallet[8], composite bias score −3, high risk) found no effect of maternal vitamin D supplementation in the third trimester on cord calcium concentration, regardless of whether supplement was 1000 IU per day for 3 months or as a single high dose of 200,000 IU in the 7th month of gestation.

Evidence synthesis—The available published results were combined in two separate models. The first meta-analysis included Cockburn, Brooke, Marya 1981 (low dose of vitamin D), Mallet (low dose of vitamin D) and Delvin (Appendix 7, Figure 8). Owing to statistically significant heterogeneity in the results (I^2=67.6%, p=0.015), a random – effects

model was fitted. Serum calcium concentration in supplemented group did not differ from that in the unsupplemented group (mean difference: 0.01mmol/l, 95% CI −0.02,0.04). The second meta-analytic model included the studies Cockburn, Brooke, Marya 1981 (high dose of vitamin D), Mallet (high dose of vitamin D), Delvin 1986 and Marya 1988 (Appendix 7, Figure 9). As in the previous model, a random-effects model was fitted due to significant heterogeneity (I^2=90%, p<0.001). The combined results showed that the mean difference of serum calcium concentration between the supplemented and the unsupplemented groups was significantly different from 0 (Mean difference: 0.05mmol/l, 95% CI 0.02, 0.05).

Discussion—The majority of the intervention studies and the one observational study consistently demonstrated positive relationships between maternal 25(OH)-vitamin D status and offspring serum calcium concentrations measured either in venous umbilical cord serum or from postnatal venesection. Some also found a reduced risk of hypocalcaemia in the neonate. Meta-analysis of higher dose intervention studies also suggested a positive effect. However, these intervention studies were all felt to be at high risk of bias and none of them was published within the last 20 years. Assay technology has improved dramatically over recent decades and the reliability of the relationships must be open to question. Given the known physiology of the vitamin D axis in adults, a positive association between maternal 25(OH)-vitamin D and offspring calcium concentration might not be a surprising finding; however little is known about relationships between 25(OH)-vitamin D and fetal calcium concentrations in utero. Furthermore none of the identified studies addressed postnatal factors such as mode of feeding (breast vs formula) as potential risk modifiers. A positive relationship between maternal 25(OH)-vitamin D status and offspring calcium concentrations does not justify intervention unless the increased calcium concentration brings a benefit. Symptomatic hypocalcaemia did not appear to be found in all studies and is likely to be much more common in high risk populations. It seems reasonable, on the basis of the current evidence, to suggest that maternal vitamin D supplementation is likely to reduce the risk of neonatal hypocalcaemia, but that the dose required, duration and target group is currently unclear (for example by skin colour, ethnicity, or mode of infant feeding), and might usefully form the basis of further investigation.

10.12. Offspring blood pressure

Observational studies (Appendix 6, Table 26)—Two cohort studies were identified which examined the relationship between maternal serum 25(OH)-vitamin D concentration in pregnancy and offspring blood pressure. Both studies were of cohort design and measured maternal serum 25(OH)-vitamin D in late pregnancy. Composite bias score was 4 for both, indicating a medium risk of bias. Gale[25] measured blood pressure in 178 children aged 9 years in the Princess Anne Cohort, UK. No association was observed between maternal 25(OH)-vitamin D and offspring blood pressure. Krishnaveni[102], using a larger Indian cohort of 338 mother-offspring pairs, measured blood pressure in the offspring at two time-points: age 5 and 9.5 years. Similarly, no significant difference in blood pressure was observed in those children born to mothers with vitamin D deficiency (defined by the authors as <37.5 nmol/l) compared with those born to mothers without vitamin D deficiency. Adjustments for offspring sex and age, maternal BMI, gestational diabetes, socioeconomic score, parity and religion made little difference to the results.

Intervention studies—No intervention studies were identified.

Discussion—Neither of the 2 observational studies relating maternal 25(OH)-vitamin D status to offspring blood pressure demonstrated a statistically significant relationship and therefore no treatment recommendation can be made.

10.13. Offspring rickets

Observational studies—No observational studies of maternal vitamin D status and offspring rickets were identified.

Intervention studies—No intervention studies of maternal vitamin D supplementation and offspring rickets were identified. A UK trial, Congdon[22], found no difference in the incidence of offspring craniotabes in the supplemented (n=4) group compared to the unsupplemented group (n=3). This study was assessed to have a high risk of bias, with a composite bias score of −9.

Discussion—It is interesting that there are so few data relating maternal 25(OH)-vitamin D status to offspring rickets. However rickets does not tend to manifest until the first year of life, in contrast to neonatal hypocalcaemia, and therefore it is likely that the determinant is the child's own sun exposure and vitamin D intake. If it is wholly breastfed and receives little sun exposure then increased risk of rickets might be expected. However this scenario does not fall within the remit of the current review.

10.14. Maternal preeclampsia

Observational studies (Appendix 6, Table 27)—Eleven observational studies were identified, comprising six case-control, four cohort and one cross-sectional study. The case-control studies were generally of small size with the minimum number of cases 12 and the maximum 55 and the number of controls ranging from 24 to 220. The definition of preeclampsia was similar across studies: new onset gestational hypertension after 20 weeks (systolic blood pressure persistently (two or more occasions) ≥140mmHg and/or diastolic blood pressure ≥85 or ≥90mmHg) and proteinuria (either 300mg protein excreted in the urine in 24 hours, or a random sample of between 1+ and 2+ protein on urine dipstick or a protein-creatinine ratio more than 0.3). Two of the case-control studies identified cases of severe preeclampsia only, using the American College of Obstetrics and Gynecology 2002 definition (systolic blood pressure ≥160mmHg and/or a diastolic blood pressure ≥110mmHg on at least 2 occasions plus proteinuria (≥300mg in a 24 hour collection or 1+ on urine dipstick), or systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg plus 5g proteinuria in a 24 hour period after 20 weeks gestation). All six case-control studies, the cross-sectional study and three of the five cohort studies used serum 25(OH)-vitamin D concentration as the marker of maternal vitamin D status, with the other two cohort studies using dietary intake. The timing of serum measurements varied across the studies with some measuring in the first trimester and others in the last and one study at three time points. Composite bias scores ranged from 2 to 9 indicating that studies were considered of low to medium risk of bias. Confounding factors were variably included and there was also variation in the criteria for matching to controls.

Of the included studies, three (one case-control, one cross-sectional and one cohort) reported statistically significant inverse associations between maternal vitamin D status and risk of preeclampsia. A further two case-control studies demonstrated a similar association between maternal 25(OH)-vitamin D and risk of severe preeclampsia. A nested case-control study (55 cases and 220 randomly selected, unmatched controls from a cohort of 1198) from Bodnar[124] (composite bias score 8, low risk) measured 25(OH)-vitamin D in nulliparous pregnant women living in Pittsburgh, USA at two time points (before 22 weeks gestation and pre-delivery. A significant inverse relationship was observed at both time points. At <22 weeks gestation a 50 nmol/l reduction in maternal 25(OH)-vitamin D was associated with an over two-fold increased risk of preeclampsia after adjusting for maternal race, ethnicity, pre-pregnant BMI, education, season and gestational age at blood sample. A cross-sectional study from Pakistan (Hossain[120], composite bias score 4, medium risk) measured maternal 25(OH)-vitamin D_3 at delivery in 75 women (76% of whom covered their face, arms, hands and head). Although the number of preeclampsia cases is not given, when the group was divided into thirds, a significantly increased risk of preeclampsia was observed for those in the lowest and middle tertile compared to the highest. The relationship between maternal 25(OH)-vitamin and preeclampsia was only observed in individuals with serum 25(OH)-vitamin D less than 50 nmol/l. Unlike other studies, women were classified as having preeclampsia based on blood pressure alone (systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg). The largest study to date (Haugen[125] (composite bias score 2, medium risk)) followed up a cohort of 23,425 pregnant women enrolled in the Norwegian mother and child cohort. Maternal 25(OH)-vitamin D was not directly measured, but estimated from a food frequency questionnaire at 22 weeks. 1,267 cases of preeclampsia were identified. Lower total vitamin D intake was associated with a significantly increased risk of preeclampsia.

Both studies examining the relationship between severe preeclampsia and maternal 25(OH)-vitamin D demonstrated significant inverse associations. Both were US based case-control studies with a comparable number of cases and controls, and assessed to have a low risk of bias. Baker[126] (composite bias score 9) identified 44 cases and 201 randomly selected controls matched by race/ethnicity from a cohort of 3,992 women. Significantly higher odds of severe preeclampsia were found in those with maternal 25(OH)-vitamin D less than 50 nmol/l compared to those with 25(OH)-vitamin D over 50 nmol/l even after adjusting for season of blood sampling, maternal age, multiparity, BMI, gestational age at blood sample. Similarly, Robinson[127] (composite bias score 5, low risk), in a study of 50 cases and 100 controls matched for race and gestational age at the time of sample, found that the odds of severe preeclampsia significantly reduced as maternal 25(OH)-vitamin D increased even after adjusting for maternal BMI, maternal age, African American race and gestational age at sample collection.

Six studies however found no association between maternal vitamin D status and preeclampsia risk. Seely[128] (composite bias score 2, medium risk) observed no significant difference in late pregnancy mean maternal 25(OH)-vitamin D in 12 cases of preeclampsia compared with 24 controls of similar maternal age, gestation, height, weight, whether primiparous or not and whether Caucasian or not. A second US nested case-control study from Powe[129] (composite bias score 4, medium risk) drew similar conclusions. In this study

of 39 cases and 131 unmatched controls from an overall cohort of 9,930, the odds of preeclampsia were not related to first trimester maternal 25(OH)-vitamin D concentration. Adjusting for maternal BMI, non-white race and summer blood collection made no difference to the results. A significant relationship was still not seen even when the analysis was restricted to mothers with a serum 25(OH)-vitamin D concentration <37.5 nmol/l. A further US nested case-control study from Azar[130] (composite bias score 5, low risk) assessed preeclampsia risk in only white women, all with Type 1 diabetes mellitus, who had serum 25(OH)-vitamin D measured at three time points during their pregnancy (early, mid and late pregnancy). 23 cases were identified and compared to 24 controls, matched for age, diabetes duration, HbA1c and parity, out of a cohort of 151. Again, no statistically significant relationship between maternal 25(OH)-vitamin D, measured at any time-point and preeclampsia risk was observed. A Canadian study of 221 pregnant women with clinical or biochemical risk factors for preeclampsia (Shand[114], composite bias score 6, low risk) found no significantly increased odds of preeclampsia in pregnant women with mid-pregnancy 25(OH)-vitamin D concentrations <37.5, <50 or <75 nmol/l compared to those with 25(OH)-vitamin D concentrations >75nmol/l. However, only 28 cases of preeclampsia were identified. The most recent study by Fernandez-Alonso[115] (composite bias score 3, medium risk) again found no difference in mean early pregnancy maternal 25(OH)-vitamin D in those who developed preeclampsia compared to those with normal pregnancies. This study included the lowest number of cases (seven). Finally, Oken[131] (composite bias score 5, low risk) identified 58 cases of preeclampsia from the US Project Viva cohort of 1,718 women. Maternal serum 25(OH)-vitamin D was not measured directly, but estimated from a food frequency questionnaire at mean 10.4 weeks gestation. No significant relationship between preeclampsia risk and vitamin D intake was seen.

Evidence synthesis—Usable results for meta-analysis of the risk of preeclampsia with increased vitamin D were available from four studies: Bodnar, Powe, Robinson and Azar (early pregnancy visit). All but Bodnar provided unadjusted odds ratios. The unadjusted estimates were synthesised in a random effects model due to statistically significant heterogeneity (I^2=78.4%, p=0.01). The pooled estimate showed no significant risk of preeclampsia with increased vitamin D (pooled OR 0.78, 95% CI 0.59, 1.05; Appendix 7, Figure 10). Synthesising the available adjusted odds ratios from all four studies the result was very similar; there was no statistically significant increased risk of preeclampsia with decreased vitamin D status (pooled OR 0.75, 95% CI 0.48, 1.19; Appendix 7, Figure 11).

Intervention studies (Appendix 6, Table 28)—One clinical trial that included maternal preeclampsia as an outcome measure was identified. Marya[132] randomised 400 pregnant women attending an antenatal clinic in India to either a trial of vitamin D plus calcium (375mg/day calcium plus 1200 IU vitamin D) from 20-24 weeks until delivery or no supplement (n=200 in each arm). Serum 25(OH)-vitamin D concentrations were not measured during the study. There were 12 cases of preeclampsia in the supplemented group versus 18 in the non-supplemented group, a result which did not achieve statistical significance. Systolic and diastolic blood pressure were significantly lower in the supplemented than unsupplemented group at 32 and 36 weeks gestation but no difference was observed at 24-28 weeks gestation. This study had a composite bias score of −2

indicating a high risk of bias, and clearly could not separate an effect of vitamin D from that of calcium supplementation.

Discussion—As with many other outcome measures, results of the various observational studies were conflicting, with some demonstrating an inverse association between maternal vitamin D status and risk of preeclampsia and others no relationship. Both studies looking at the risk of severe preeclampsia found statistically significant inverse relationships with maternal 25(OH)-vitamin D concentration. There was however significant heterogeneity between studies in terms of gestational age at which maternal vitamin D status was assessed, confounding factors adjusted for and the definition of preeclampsia used. Most observational studies were case-control and included only small numbers of cases of preeclampsia (n=7 to 55). Only one intervention study was identified. This was of reasonable size, however was assessed to have a high risk of bias and the supplemented group received calcium and vitamin D together, rather than vitamin D alone. No difference in the risk of preeclampsia was identified in the unsupplemented group. Thus, it is difficult to make any treatment recommendations based on the current evidence. Further high quality intervention studies are needed.

10.15. Maternal gestational diabetes

Observational studies (Appendix 6, Table 29)—Eight observational studies (four case-control, one cross-sectional and three prospective cohort) examined relationships between maternal 25(OH)-vitamin D status and risk of gestational diabetes. One study, Maghbooli[133], found, in a cross-sectional cohort of 741 Iranian women, that mean 25(OH)-vitamin D concentrations (measured at 24-28 weeks) were lower in the 52 subjects who had gestational diabetes (16.5 nmol/l) than in the 527 women who did not (23 nmol/l). There was no adjustment for confounding factors in this analysis and the overall bias score was 3, indicating a medium risk for bias. A further study from Iran, of case-control design (Soheilykhah[134], composite bias score 3, medium risk), found significantly increased odds of gestational diabetes in those with 25(OH)-vitamin D concentrations less than 37.5 nmol/l (measured between 24 and 28 weeks). Thus the mean 25(OH)-vitamin D concentration in those with gestational diabetes was 24 nmol/l and in those without was 32.3 nmol/l. Clifton-Bligh[92], in a prospective cohort of 307 women in New South Wales, Australia, found that mean 25(OH)-vitamin D concentrations (measured at a mean of 28.7 weeks) were 48.6 nmol/l in 81 women with gestational diabetes compared with 55.3 nmol/l in women without. They also found that serum 25(OH)-vitamin D concentration was negatively associated with fasting glucose after adjustment for age, BMI, and season. This study was found to be of low risk of bias with a score of 6. Zhang[135] performed a nested case-control study within a US cohort (n=953), containing 57 women with gestational diabetes (70% white ethnicity) and 114 controls (84% white ethnicity). Controls were frequency matched to cases by the estimated season of conception. After adjustment for maternal age, ethnicity, family history of type II diabetes and prepregnant BMI, 25(OH)-vitamin D concentration less than 50 nmol/l was associated with increased odds of gestational diabetes, compared with women with concentrations greater than 75 nmol/l. This study again achieved a low risk of bias with composite score of 8.

In contrast, an Indian prospective cohort study (Farrant[90], composite bias score 5, low risk) found no difference in 25(OH)-vitamin D concentrations between those with gestational diabetes (n=34, mean 25(OH)-vitamin D concentration 38.8 nmol/l) those without (n=525, mean 25(OH)-vitamin D concentration 37.8 nmol/l), p=0.8. No associations were found by three further studies: Makgoba[136] (composite bias score 7, low risk), in a nested case-control study of 90 women with gestational diabetes and 158 controls, within an overall cohort of 1,200 women, found no difference in serum 25(OH)-vitamin D concentration (47.2 nmol/l in cases versus 47.6 nmol/l in controls, measured at 11-13 weeks gestation). An inverse relationship was found between the serum 25(OH)-vitamin D concentration and fasting glucose, glucose concentration two hours after a glucose tolerance test, and HbA1c at 28 weeks gestation. However, after adjustment for BMI, gestation of blood sampling, smoking, ethnicity, parity, maternal age, conception status, previous gestational diabetes and season, only the relationship with two hour glucose concentration remained statistically significant. A nested case-control study (Baker[137], composite bias score 7, low risk), this time set within a US cohort of 4,225 women in whom serum 25(OH)-vitamin D concentration was assessed at 11-14 weeks gestation, found that amongst the 60 cases of gestational diabetes and 120 controls, after adjustment for maternal age, insurance status, body mass index, gestational age at sample collection and season, there was no association between serum 25(OH)-vitamin D concentration and gestational diabetes. Finally, in a Spanish prospective cohort of 466 women (Fernandez-Alonso[115], composite bias score 3, medium risk) in whom 25(OH)-vitamin D concentrations were measured at 11-14 weeks, there was no statistically significant relationship between baseline 25(OH)-vitamin D concentration and development of gestational diabetes.

Intervention studies—No intervention studies were identified.

Discussion—Several large studies, of low to moderate risk of bias, found no relationship between maternal 25(OH)-vitamin D status and risk of gestation diabetes. Although two Iranian studies did find an increased risk of gestational diabetes in women with low levels of 25(OH)-vitamin D, these seem at odds with the majority of investigations from elsewhere and thus there appears to be no consistent evidence on which to base a recommendation of vitamin D supplementation to prevent gestational diabetes.

10.16. Maternal Caesarean section

Observational studies (Appendix 6, Table 30)—Six observational studies were identified, one of which was case-control and the others cohort designs. Two studies found inverse relationships between 25(OH)-vitamin D status and risk of Caesarean section, with the remaining studies demonstrating no statistically significant associations. Scholl[138] (composite bias score 5, low risk) studied 290 women who delivered by Caesarean section out of a cohort of 1,153 pregnant women. 25(OH)-vitamin D concentration was assessed at a mean of 13.7 weeks gestation. Compared with women who had serum 25(OH)-vitamin D concentrations between 50 and 125 nmol/l in early pregnancy, those who had levels less than 30 nmol/l appeared at increased risk of Caesarean section, and this association persisted after adjustment for age, parity, ethnicity, gestation at entry to study, season and body mass index. Merewood[139] (composite bias score 6, low risk), in a cross-sectional study of US

women, found increased odds of Caesarean section if maternal 25(OH)-vitamin D concentration was less than 37.5 nmol/l in 67 cases of Caesarean section compared with 277 controls, after adjustment for ethnicity, alcohol use in pregnancy, educational status, insurance status and age.

Ardawi[87] (composite bias score 5, low risk) studied a cohort of 264 women in Jeddah, Saudi Arabia. Amongst women with serum 25(OH)-vitamin D status less than 20 nmol/l the frequency of Caesarean section was 12.5% compared with a frequency of 9.6% in those with serum concentrations above this level, a difference which did not achieve statistical significance. A Pakistani study (Brunvand[140], composite bias score 1, medium risk) of nulliparous Pakistani women of low social class found that the median 25(OH)-vitamin D concentration in 37 women who delivered by Caesarean section (measured just before delivery) was 26 nmol/l compared with 19 nmol/l in 80 controls who delivered vaginally. This did not however, achieve statistical significance. A UK cohort study of 1,000 pregnancies yielded 199 Caesarean sections (Savvidou[141], composite bias score 7, low risk) and found no relationship between 25(OH)-vitamin D concentration measured between 11 and 13 weeks gestation and risk of Caesarean section, after adjustment for maternal age, racial origin, smoking, method of conception and season. Finally in the Spanish study of Fernandez-Alonso[115] (composite bias score 3, medium risk), 105 of the cohort of 466 women underwent Caesarean section. There was no relationship between 25(OH)-vitamin D concentration, measured between 11 and 14 weeks gestation, and risk of Caesarean section.

Intervention studies—No intervention studies were identified.

Discussion—The data relating to Caesarean section are all observational and conflicting. Given that many other factors will influence risk of Caesarean section, including physician preference, local policy, pre-existing morbidity, it seems likely that any relationships between maternal 25(OH)-vitamin D concentration and Caesarean section risk will be difficult to extricate from the surrounding noise. The current evidence base does not support use of vitamin D supplementation to reduce risk of Caesarean section and a well designed, prospective observational study is warranted before moving to intervention studies.

10.17. Maternal bacterial vaginosis

Observational studies (Appendix 6, Table 31)—Three studies were identified (two cohort, one cross-sectional) which examined relationships between maternal 25(OH)-vitamin D status and bacterial vaginosis. All three studies elucidated statistically significant relationships although at very different thresholds of 25(OH)-vitamin D concentration. Bodnar[142] (composite bias score 5, low risk) studied 469 women who were all non-Hispanic white or non-Hispanic black. 25(OH)-vitamin D concentration was measured at a mean of 9.5 weeks gestation. Amongst the 192 cases of bacterial vaginosis median 25(OH)-vitamin D concentration was 29.5 nmol/l compared with 40.1nmol/l in the non-diseased women. At 25(OH)-vitamin D concentrations below 80 nmol/l there was an inverse association between frequency of bacterial vaginosis and early pregnancy serum 25(OH)-vitamin D concentration ($p<0.0001$). Above this threshold no relationship was observed. Results were adjusted for the presence of sexually transmitted diseases. Using the National Health and

Nutrition Examination Survey (NHANES) cohort, Hensel[143] (composite bias score 4, medium risk) found a statistically significantly increased risk of bacterial vaginosis in those women whose serum 25(OH)-vitamin D concentration was less than 75 nmol/l. However it is unclear at what stage 25(OH)-vitamin D concentration was measured, and the mean 25(OH)-vitamin D concentrations, together with the unadjusted analyses, are not presented. Dunlop[144] (composite bias score 2, medium risk) sampled 160 non-Hispanic white/non-Hispanic black women from a total of 1547 women participating in the Nashville Birth Cohort. In this cross-sectional analysis, risk of bacterial vaginosis was higher in women whose serum 25(OH)-vitamin D concentration at delivery was less than 30 nmol/l compared with those whose levels were above this threshold, after adjustment for race, age, smoking, BMI, gestational age at delivery, healthcare funding source.

Intervention studies—No intervention studies of maternal vitamin D supplementation on risk of bacterial vaginosis were identified.

Discussion—Although reasonably large, only three studies were identified that reported bacterial vaginosis as an outcome. Each study differed in methodology, using differing thresholds for low serum vitamin D, and there remains a strong possibility of residual confounding which may account for the relationships between bacterial vaginosis and maternal vitamin D. Thus the evidence base does not currently warrant the recommendation of vitamin D supplementation to reduce the risk of bacterial vaginosis, and further high-quality prospective observational studies are required before moving to an intervention study.

11. OTHER STUDY QUESTIONS

Given the altered physiology during pregnancy, it is difficult to define a normal 25(OH)-vitamin D concentration in relation to parathyroid hormone or fractional intestinal calcium absorption, as has been done in non-pregnant individuals. However even in these non-pregnant situations, widely disparate estimates of normality have been obtained[145]. A better approach might be to define a level at which adverse influences on the mother and offspring are minimised. However, it is apparent, from the results presented above, that the evidence base is extremely heterogeneous in this regard; where thresholds have been defined, they differ markedly between studies, and many studies find no relationships at all. Thus, on the basis of the identified studies, it is not possible to answer the study question "*What are the clinical criteria for vitamin D deficiency in pregnant women?*" or to rigorously define an optimal level of serum 25(OH)-vitamin D during pregnancy.

Similarly, the studies are extremely heterogeneous with regard to dose, use of vitamin D2 or D3, route and timing; there is a dearth of high-quality interventional evidence. It was therefore also not possible to answer the study question "*What is the optimal type (D2 or D3), dose, regimen and route for vitamin D supplementation in pregnancy?*" Furthermore, no health economic evaluation was identified. Thus it is not possible to make a rigorously evidence-based recommendation regarding optimal vitamin D supplementation in pregnancy.

12. SUMMARY DISCUSSION

Specific discussion of the findings in relation to each outcome is given in the relevant sections above. There was some evidence to support a positive relationship between maternal vitamin D status and offspring birth weight (meta-analysis of observational studies) and offspring bone mass (observational studies); meta-analysis of randomised controlled trials suggested a positive effect of maternal vitamin D supplementation on neonatal calcium concentrations, but the dose required, duration and target group is currently unclear, and might usefully form the basis of further investigation. Recurring themes in each disease area included marked heterogeneity between studies in terms of design, definition of exposure and outcome, dose, timing, route, statistical analysis and treatment of potential confounding factors. The overall effect of these considerations undoubtedly contributed to the statistically significant measures of heterogeneity in the meta-analyses, but it is difficult to identify individual factors which might predominate. In no single disease area did the evidence base unequivocally support the use of vitamin D supplementation during pregnancy. Although a systematic search for evidence of harm from vitamin D supplementation in pregnancy was not undertaken (as this was not part of the commissioned brief), no studies documenting adverse effects associated with such a strategy were identified. However, it was clear that follow up of participants was almost always of short duration, and the current evidence base is therefore also insufficient to allow the potential identification of more protracted adverse effects.

The strengths of our review include comprehensive coverage of the available literature with exhaustive searching of databases, hand-searching of reference lists and contact with authors. CRD methods were followed with two reviewers executing each stage of the review process. Additionally the review and interpretation of evidence has been based on an understanding of vitamin D physiology, together with possible sources of bias particularly important for this exposure. The overall objectives comprehensively addressed the issue of vitamin D in pregnancy, in terms of normal levels, maternal and child health outcomes, potential interventions and health economic assessments.

Limitations in this review were identified at both study and outcome level, and at the level of the overall review. There was considerable heterogeneity between all of the studies included in the review. Study methodology varied widely in terms of design, population, maternal vitamin D assessment, exposure measures and outcome definition. For example, measures of maternal vitamin D status assessment included serum concentration, estimated dietary intake and UV sunlight exposure. Even when serum 25(OH)-vitamin D concentration was measured, the assay and technique varied widely. Indeed we included comparability and standardisation of assay results in the quality criteria, but these issues were not commonly considered or documented by study authors. Clearly, given the multiplicity of both laboratory techniques (for example, radio-immunoassay, HPLC, LC-MS), and different operators, standardisation of assays across technique and laboratory is essential, and currently the subject of a global initiative by the US National Institutes of Health (http://ods.od.nih.gov/Research/VitaminD.aspx#vdsp). A further issue was the frequent lack of documentation of the gestational age at which sampling occurred, ranging from early pregnancy through to delivery. Confounding factors considered varied widely

from study to study. Only a small number of intervention studies were identified, most of which were not blinded or placebo controlled; all varied in terms of the dose and duration of vitamin D supplementation (for example doses ranged from 800 IU daily to two bolus doses of 600,000 IU in the last trimester). Offspring outcomes were also assessed at varying time-points, ranging from birth through to 9 years of age. The potential for residual confounding and reverse causality in studies of vitamin D is a very important consideration and also difficult to address methodologically. For example, maternal obesity is a risk factor for adverse birth outcomes, and is also associated with reduced 25(OH)-vitamin D concentrations because of sequestration in adipose tissue. Increasing physical activity might be associated with better maternal health, but also greater 25(OH)-vitamin D concentrations because of greater sun expose.

Limitations were also identified at the review level. Although our search strategy was comprehensive, non-English articles were excluded and we were unable to obtain copies of some listed articles, despite requesting them from our local Health Services library and the British library, or direct from authors. There is the possibility that we did not identify all the relevant studies in this field, however, this risk was minimised by a comprehensive electronic search strategy complemented by hand searching and contacting authors and other specialists in this field. Although we did not detect evidence of publication bias, this remains a possibility, such that studies showing null results may not receive priority for publication. In addition, of the studies identified some did not present all necessary summary data, especially if the result was null. In such cases, we did attempt to contact authors for missing data, but this was not possible in all cases.

We set out to answer a number of research questions as described in section 5. The first of these addressed normal levels of vitamin D in pregnancy. Such a value is controversial in non-pregnant adult populations and section 3.7 sets out the reasons why current definitions are lacking in biological support. For many biochemical measurements, the definition of normality may be derived from assessment of a cohort representative of the general population and defining a lower cut off, e.g. the lowest 2.5%. We did not identify any such study in pregnant women, and indeed, for vitamin D, which is largely determined by sunshine exposure and skin colour, such an approach may not be appropriate: one hypothesis is that white skin is an adaptation to low sun exposure in northern hemisphere countries and that this adaptation has not gone far enough to achieve optimal levels. Thus it may be that “normality” (in the sense of what is actually observed in the population) is actually sub-optimal.

It may, therefore, be more appropriate to attempt to define “healthy” levels based on relationships between maternal serum 25(OH)-vitamin D concentration and maternal/offspring disease outcomes. Unfortunately, although there are plenty of studies which attempt to investigate such associations, it is difficult to use them to inform a cut-off below which disease is likely. Typical caveats within studies include small numbers, pre-determined rather than study derived thresholds, poor disease definition, lack of attention to potential confounding and reverse causality. Between studies, these include variable populations, variable ascertainment of vitamin D status and outcome definitions, together with the use of different thresholds. All of these issues make it impossible to make a truly

reliable evidence-based judgement as to the normal (or “healthy”) level of 25(OH)-vitamin D in pregnancy. Furthermore, it is very likely that the optimal level relating to one outcome may not be the same for another; there is also no reason to suppose that increasing levels of 25(OH)-vitamin D will lead to universally positive effects on all diseases. Studies describing the long-term safety of vitamin D supplementation are conspicuous by their non-existence.

We did find evidence of offspring outcomes associated with maternal vitamin D status in pregnancy. Thus there was some evidence to support a positive relationship between maternal vitamin D status and offspring birth weight (meta-analysis of observational studies), neonatal calcium concentrations (meta-analysis of randomised controlled trials) and offspring bone mass (observational studies). However, it was not possible to deduce thresholds at which risk of these outcomes increased, or whether indeed there is a threshold at all.

The next aim was to elucidate whether supplementation with vitamin D in pregnancy would lead to improvements with offspring health, and to identify specific dose requirements. Again, the data do not allow definite conclusions to be made. The majority of the randomised controlled trials of vitamin D supplementation aimed at optimising offspring outcomes are small and of poor methodology and date from around 20 years ago, when assay technology was much less well advanced. In several areas (offspring birth weight, calcium concentration, bone mass) the evidence is sufficient to warrant the instatement of properly conducted large randomised controlled trials, but for other areas, better quality observational evidence should be obtained. A further consideration is how women will feel about potentially taking higher doses of vitamin D during pregnancy than is currently recommended, a subject that is being assessed as part of the MAVIDOS trial. The lack of good evidence linking maternal vitamin D status to offspring disease, and to maternal outcomes, means that it is difficult to obtain a reliable health economic assessment of the potential impact of maternal vitamin D supplementation in pregnancy. Indeed we were unable to identify any studies which attempted to make such an estimate. Clearly it would be appropriate to confirm that maternal vitamin D supplementation actually led to an improvement in maternal and/or offspring health before going on to estimate its health-economic impact.

13. CONCLUSIONS (IMPLICATIONS FOR HEALTH CARE; RECOMMENDATIONS FOR RESEARCH)

The fundamental conclusion is that the current evidence base does not allow the study questions to be definitively answered. It is, therefore, not possible to make rigorously evidence-based recommendations regarding maternal vitamin D supplementation during pregnancy.

Further high-quality research is needed: In many areas well designed large prospective cohort studies are most appropriate as the next step. In others (e.g. birth weight, serum calcium concentration, bone mass), the evidence base is sufficient to suggest randomised controlled trials. Additionally, a critical underlying issue is to ensure that 25(OH)-vitamin D

measurements are comparable between studies, through global standardisation programmes. Specific recommendations are given below:

- Long-term follow-up of mothers and children who have taken part in the vitamin D supplementation trials is required. Although vitamin D supplementation at modest doses appears safe in the short term, the long-term effects are unknown.
- Key issues for all vitamin D research are the requirement for standardisation of exposures and outcomes, inclusion and standardisation of potential confounding factors, and adequate length of follow up. Work aimed at standardising 25(OH)-vitamin D measurements across the globe should be supported, such as the programme led by the US National Institutes of Health (http://ods.od.nih.gov/Research/VitaminD.aspx#vdsp), and which incorporates UK centres.
- There is a need to optimize the biochemical assessment of vitamin D status, whether this is simply 25(OH)-vitamin D concentration, or should incorporate other indices such as vitamin D binding protein, albumin, and be related to parathyroid hormone or calcium concentrations.
- 25(OH)-vitamin D concentrations should be surveyed in a large population-based pregnancy cohort representative of the UK as a whole to enable acquisition of high-quality descriptive epidemiological data on the prevalence of low levels of circulating 25 (OH)-vitamin D. This work would need to take into account potential confounding factors, particularly season, latitude and skin pigmentation/covering/ethnicity.
- High-quality large prospective cohort studies are required to investigate the relationship between maternal 25 (OH)-vitamin D status and the following outcomes: maternal Caesarean section and bacterial vaginosis, and offspring birth length, anthropometric measures, and risk of low birth weight. These studies should take account of potential confounding factors and include measures of vitamin D status early in pregnancy as well as at delivery. Such studies should be performed in several different populations of varying ethnicity, and outcomes and exposures should be standardised, as should potential confounding factors.
- Large well-designed randomised controlled trials with double-blind, placebo-controlled methodology are warranted to investigate the relationship between maternal vitamin D supplementation during pregnancy and the following outcomes: offspring birth weight, calcium concentrations, bone mass, with a weaker recommendation (compared with the appropriateness of high quality prospective observational studies) for offspring asthma and type I diabetes, and maternal pre-eclampsia. There are currently several large randomised controlled trials underway which may help address the study questions. Examples of these include MAVIDOS[146] (ISRCTN 82927713, which is investigating the effects of maternal vitamin D supplementation on offspring bone mass), VDAART (ISRCTN 00920621) and ABCvitaminD (ISRCTN 00856947) (both of which are investigating the effects of maternal vitamin D supplementation on asthma and wheeze).

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Without such a rigorous approach, there is a risk that public health policy will be made on the basis of optimistic evaluations of conflicting and heterogeneous studies. Although modest doses of vitamin D in pregnancy might well be relatively safe, at least in the short term, there are no long-term data to inform their potential long-term effects on offspring health. As with most interventions, it is probably optimistic to expect that there will be no risk of adverse events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix 1: Search strategy

Sources

Completed studies (systematic reviews):

- DARE (CRD)
- Cochrane Database of Systematic Reviews (CDSR)
- HTA database (CRD)

Completed studies (other study types):

- Cochrane Register of Controlled Trials (CENTRAL)
- Medline
- Embase
- Biosis
- Google scholar
- AMED

Hand searching of reference lists from papers identified

Ongoing studies:

- National Research Register archive
- UKCRN Portfolio
- Current Controlled Trials
- ClinicalTrials.gov

Grey literature:

- Conference Proceedings Citation Index-Science (1990-present)
- Zetoc conference search
- Scientific Advisory Committee on Nutrition website
- Department of Health website
- King's Fund Library database
- Trip database
- HTA website
- HMIC (Health Management Information Consortium database)

Databases and years searched	Terms	Number retrieved	Number of relevant hits
Systematic reviews			
Cochrane Library: CDSR, current Issue, 2010 http://www.thecochranelibrary.com/view/0/index.html			
DARE (CRD) 2000-2010 http://www.crd.york.ac.uk/crdweb/			
HTA Database (CRD) http://www.crd.york.ac.uk/crdweb/			
National Coordinating Centre for Health Technology Assessment website http://www.hta.nhsweb.nhs.uk			
Other study types			
Cochrane Library: CENTRAL, current Issue, 2010 http://www.thecochranelibrary.com/view/0/index.html			
Medline (OVID) 1950-2010, June Week 1 (15/6/10)	**1** Pregnan$.ti,ab. 295057 **2** Preconception $.ti,ab. 1752 **3** preconceptual.ti,ab. 135 **4** pre-concept$.ti,ab. 250 **5** Fetal.ti,ab. 157883 **6** Foetal.ti,ab. 11957 **7** Fetus.ti,ab. 43868 **8** Foetus.ti,ab. 4543 **9** Newborn$.ti,ab. 104312	6501 hits	First 500 refs saved (Ref Ids: 82-581 in Ref Man database)

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Databases and years searched	Terms	Number retrieved	Number of relevant hits
	10 Neonat$.ti,ab. 154612 **11** Baby.ti,ab. 21290 **12** Babies.ti,ab. 22884 **13** Infant.ti,ab. 99951 **14** Infancy.ti,ab. 29601 **15** Premature.ti,ab. 68207 **16** Toddler$.ti,ab. 3913 **17** Offspring.ti,ab. 33494 **18** Child$.ti,ab. 770655 **19** Postnatal.ti,ab. 61090 **20** Postpartum.ti,ab. 25159 **21** Maternal.ti,ab. 126587 **22** Maternity.ti,ab. 10210 **23** Mother.ti,ab. 58088 **24** small-for-gestational age.ti,ab. 4212 **25** pre-natal.ti,ab. 573 **26** prenatal.ti,ab. 52711 **27** ante-natal.ti,ab. 267 **28** post-partum.ti,ab. 6959 **29** post-natal.ti,ab. 3777 **30** puerperium.ti,ab. 4552 **31** childbear$.ti,ab. 6830 **32** birthweight.ti,ab. 9667 **33** 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 1557322		

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Databases and years searched	Terms	Number retrieved	Number of relevant hits
	34 Pregnancy/ 609281 **35** Prenatal Nutritional Physiological Phenomena/ 695 **36** Pregnancy, High-Risk/ 3586 **37** Maternal Nutritional Physiological Phenomena/ 988 **38** Pregnancy Complications/ 62603 **39** Pregnancy Outcome/ 29721 **40** Maternal Fetal exchange/ 26212 **41** Prenatal Exposure Delayed Effects/ 14989 **42** exp "Embryonic and Fetal Development"/ 163222 **43** Child Development/ 28583 **44** Preconception Care/ 981 **45** Prenatal Care/ 16979 **46** Postpartum Period/ 14439 **47** exp infant/ 817413 **48** Postnatal Care/ 3095 **49** exp Pregnancy Trimesters/ 27623 **50** 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 2155617 **51** exp Vitamin D/ 34004		

Databases and years searched	Terms	Number retrieved	Number of relevant hits
	52 "1406-16-2 (Vitamin D)".rn. 15518		
	53 "25(OH)-vit D".ti,ab. 15		
	54 25OHD.ti,ab. 424		
	55 hypovitaminosis D.ti,ab. 440		
	56 "19356-17-3 (Calcifediol)".rn. 2398		
	57 "32222-06-3 (Calcitriol)".rn. 11536		
	58 "64719-49-9 (25-hydroxyvitamin D)".rn. 1333		
	59 Vitamin D deficiency/ 5668		
	60 Vitamin D.ti,ab. 25020		
	61 Vitamin D2.ti,ab. 862		
	62 Vitamin D3.ti,ab. 5527		
	63 Cacidiol.ti,ab. 0		
	64 calciol.ti,ab. 12		
	65 "67-97-0 (Cholecalciferol)".rn. 4441		
	66 Ergocalciferol.ti,ab. 288		
	67 Cholecalciferol.ti,ab. 1086		
	68 Colecalciferol.ti,ab. 21		
	69 Calciferol.ti,ab. 330		
	70 Calcitriol.ti,ab. 2923		
	71 Hydroxycholecalciferol.ti,ab. 1111		
	72 dihydroxycholecalciferol$.ti,ab. 1366		
	73 dihydroxyvitamin d.ti,ab. 3858		
	74 dihydrotachysterol$.ti,ab. 294		
	75 doxercalciferol$.ti,ab. 48		
	76 alfacalcidol$.ti,ab. 297		

Databases and years searched	Terms	Number retrieved	Number of relevant hits
	77 paricalcitol$.ti,ab. 180 **78** Calcitriol/ 11536 **79** 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 45279 **80** 49 and 79 67 **81** 50 and 79 8116 **82** Animals/ 4579351 **83** Humans/ 11255304 **84** 82 and 83 1175867 **85** 82 not 84 3403484 **86** **81 not 85 6501**		
Embase (OVID) 2000-2004, Week 21	Figure 1		
BIOSIS 1985-			
Ongoing studies			
NRR archive (National Research Register) https://portal.nihr.ac.uk/Pages/NRRArchiveSearch.aspx (14/6/10)	"Vitamin D" and pregnancy [All fields]	20	0
UKCRN Portfolio http://public.ukcrn.org.uk/Search/Portfolio.aspx (14/6/10)	Pregnancy [Title] Pregnancy vitamin [research summary]	41 2	1, poss 2 1
Current Controlled Trials including MRC Trials dB http://controlled-trials.com/ (14/6/10)	vitamin d AND pregnancy	207	13 (slight overlap with UKCRN)
ClinicalTrials.gov http://clinicaltrials.gov/			
Conferences and grey literature			
Conference Proceedings Citation Index-Science (1990-present)			
Trip database http://www.tripdatabase.com/search/advanced			
King's Fund database http://www.kingsfund.org.uk/library/ (14/6/10)	Pregnancy Vitamin d	528 15	Poss 2
Scientific Advisory Committee on Nutrition website http://www.sacn.gov.uk/reports_position_statements/index.html (14/6/10)	Browse reports and position statements section	Figure 2 2 report	2 reports
Department of Health website http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005936 (14/6/10)	Browse reports	Figure 3	
Zetoc (general & conferences) http://zetoc.mimas.ac.uk/wzgw?id=23685659			

Databases and years searched	Terms	Number retrieved	Number of relevant hits
Guidelines			
SIGN http://www.sign.ac.uk			
NICE http://www.nice.org.uk			
National Guidelines Clearinghouse http://www.ahcpr.gov/clinic/assess.htm			

Appendix 2: Data extraction forms

DATA EXTRACTION FORMS – CASE CONTROL STUDIES

a. Study basic details	
UIN / AN	
Title	
Reviewer	
Date reviewed	
Author	
Journal & year	
Source	

b. Study description	
1. Setting	
2. Study design	
3. Outcome measured	
4. Statistical techniques used	
5. Confounding factors adjusted for	
6. Cohort size	
7. Number of subjects studied for outcome	
8. %follow-up (5 ÷ 6)	

c. Inclusion criteria	d. Exclusion criteria

e. Quality assessment – enter a rating and justify with a brief comment.		
Criterion	**Score**	**Comment**
1.Case definition explicit and appropriate?		

e. Quality assessment – enter a rating and justify with a brief comment.		
Criterion	**Score**	**Comment**
2.How is maternal vitamin D measured?		
3. Participants grouped according to Vitamin D status?		
4. Measurements of outcomes reliably ascertained?		
5. Measurement of later outcomes objective?		
6. Control selection appropriate?		
7. Measures of vitamin D intake/25(OH)-Vitamin D level, outcomes rounded?		
8. Setting and population appropriate?		
9. Outcome assessment blind to Vitamin D status?		
10. Analysis rigorous and appropriate?		
11. Response rates for: **a.** cases **b.** controls (a separate score for each should be given)		
12. Info on representativeness and non-participants		
13. Sample sizes **a.** cases **b.** controls (a separate score for each should be given)		
14. Adequate consideration for important confounding factors? (eg season, sunlight exposure, calcium intake, maternal compliance, infant feeding)		
Overall quality rating (sum of scores):		
f. Study results – free text, to consider cohort details, associations found, any additional quality comments		

g. Screen of references – any additional studies listed which have not already been reviewed?

DATA EXTRACTION FORMS – INTERVENTIONAL STUDIES

a. Study basic details	
UIN / AN	
Title	
Reviewer	
Date reviewed	
Author	
Journal & year	
Source	

b. Study description	
1. Setting	
2. Study design	
3. Outcome measured	

b. Study description	
4. Statistical techniques used	
5. Intention to treat analysis. Patients analysed according to the group they were randomized to?	
5. Confounding factors adjusted for	
6. Cohort size	
7. Number of subjects studied for outcome	
8. %follow-up (5 ÷ 6)	
9. Age range (mean age + SD)	
10. Treatment given/ dose/ route of admin/ duration of treatment	
11. Duration of follow-up	

c. Inclusion criteria	**d. Exclusion criteria**

e. Quality assessment – enter a rating and justify with a brief comment		
Criterion	**Score**	**Comment**
1. Study design appropriate?		
2.Are CONSORT guidelines followed		
3. Adequate description of study participants?		
4. is randomisation adequate?		
5. Is there placebo control and is blinding adequate?		
6. Are details of the study medication given		
7. Is change in maternal vitamin D status measured?		
8.Are details of the assay given?		
9. Measurements of outcomes reliably ascertained?		
10. Measurements of later outcomes objective?		
11. Measures of vitamin D intake/ 25(OH)-vitamin D, bone outcomes eg BMD rounded		
12. Consideration for the effects of important confounding factors? (e.g. season, sunlight exposure, calcium intake, maternal compliance, infant feeding)		
13. What proportion of the cohort completed the trial		
14. info on non-participants		
15. Analysis rigorous and appropriate?		
16. Sample size		
Overall quality rating (sum of scores):		
f. Study results – free text, to consider cohort details, associations found, any additional quality comments		

g. Screen of references – any additional studies listed which have not already been reviewed?

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DATA EXTRACTION FORMS – CASE CONTROL STUDIES

a. Study basic details	
UIN / AN	
Title	
Reviewer	
Date reviewed	
Author	
Journal & year	
Source	

b. Study description	
1. Setting	
2. Study design	
3. Outcome measured	
4. Statistical techniques used	
5. Confounding factors adjusted for	
6. Cohort size	
7. Number of subjects studied for outcome	
8. %follow-up (5 ÷ 6)	

c. Inclusion criteria	**d. Exclusion criteria**

e. Quality assessment – enter a rating and justify with a brief comment		
Criterion	**Score**	**Comment**
1.Case definition explicit and appropriate?		
2.How is maternal vitamin D measured?		
3. Participants grouped according to Vitamin D status?		
4. Measurements of outcomes reliably ascertained?		
5. Measurement of later outcomes objective?		
6. Control selection appropriate?		
7. Measures of vitamin D intake/25(OH)- Vitamin D level, outcomes rounded?		
8. Setting and population appropriate?		
9. Outcome assessment blind to Vitamin D status?		
10. Analysis rigorous and appropriate?		
11. Response rates for: **a.** cases		

e. Quality assessment – enter a rating and justify with a brief comment		
Criterion	**Score**	**Comment**
b. controls (a separate score for each should be given)		
12. Info on representativeness and non-participants		
13. Sample sizes for: **a.** cases **b.** controls (a separate score for each should be given)		
14. Adequate consideration for important confounding factors? (eg season, sunlight exposure, calcium intake, maternal compliance, infant feeding)		
Overall quality rating (sum of scores):		
f. Study results – free text, to consider cohort details, associations found, any additional quality comments		

g. Screen of references – any additional studies listed which have not already been reviewed?

Appendix 3: Study Quality Assessment System

Table 2

Summary of case-control study quality assessment system

	Risk of Bias (score)		
Criterion	**High (−1)**	**Medium (0)**	**Low (+1)**
1. Case definition explicit and appropriate?	Definition and/or incl/ excl criteria not given, ambiguous, or clearly unsuitable	Basic definition given; enough to satisfy that chosen cases (and the criteria used to select them) are suitable	Detailed definition and explanation; all suitable cases included
2. How is maternal vitamin D status measured?	Dietary intake only or insufficient information	Blood levels of 25(OH)-vitamin D	Blood levels of circulating 25(OH)-vitamin D, with details of precision, pick up of D_2 and D_3 and assay used
3. Participants grouped according to Vitamin D status?	Subjects divided and analysed in groups based on pre-existing vitamin D thresholds	Subjects divided and analysed in groups according to Vitamin D level based on group characteristics	Subjects not divided into groups according to Vitamin D level/ or grouped according to at threshold generated from the study
4. Measurements of outcomes reliably ascertained?	Inadequately explained or obviously unsuitable	Adequate description and reliability/suitability of at least one of the following: instruments, technique/ definition/protocol, people, place	Detailed description and reliability of one and at least adequate description of the others
5. Measurements of later outcomes objective?	Subjective measure, eg bone or muscle pain, wheezing	Ascertained from researcher examination	Objective measure e.g. DXA, bone biopsy, lung function tests
6. Control selection appropriate?	No information at all, ambiguous, or not selected from population of cases or otherwise clearly	Selection is from population of cases, and is basically appropriate and similar to cases for all factors other than the	Selection is from population of cases in a manner wholly appropriate to the study objectives, and in such a way as to make

	Risk of Bias (score)		
Criterion	**High (−1)**	**Medium (0)**	**Low (+1)**
	inappropriate to the study objectives	outcome of interest, but not optimally, or with incomplete information	them as similar as possible to cases in all respects except the outcome of interest
7. Measures of vitamin D intake/ 25(OH)-vitamin D level, bone outcomes rounded?	Categorisation or very rough rounding, or if any clear evidence of rounding exists without explanation in the text	Measures are rounded, but not by much	No information given, and no obvious reason to suspect rounding has occurred. Or: explicitly stated that measurements were not rounded.
8. Setting and population appropriate?	Ambiguously described, obviously bias inducing or unsuitable for the objectives and stated conclusions	Possibly restricting but reflected in the scope of the objectives and the stated conclusions	Planned to minimise bias and allow generalisability beyond the immediate scope of the objectives
9. Outcome assessment blind to vitamin D status?	N/A	No details given	Some details or statement given
10. Analysis rigorous and appropriate?	No statistical analyses carried out (just tables or description), or analysis badly carried out	Tables of means and differences given with statistical tests (e.g. t-tests), or some regression but without clear/valid measure of association	Regression (or similar technique) is used which gives a valid measure of association (e.g. odds ratios, hazard ratios, relative risks)
11. Response rates for: **e.** cases **f.** controls (a separate score for each should be given)	Low (<70%)	Medium (70-90%) or not given	High (>90%)
12. Info on representativeness and non-participants	Cases obviously unrepresentative of wider population alluded to in text	Some information on cases and controls lost or excluded, or no information but with no reason to suspect a detrimental lack of representativeness	Detailed information on cases and controls lost or excluded, with numbers and reasons.
13. Sample sizes for: **e.** cases **f.** controls (a separate score for each should be given)	Extremely ambiguous, not given, or small (under 100)	Average (100 to 1000)	Large (over 1000)
14. Adequate consideration of important confounding factors? (e.g. season, sunlight exposure, calcium intake, maternal compliance, infant feeding)	One factor matched on or controlled for in tables; nothing for the others (NB whether they were *measured* or not is irrelevant)	Most factors matched on or controlled for in tables, or fewer if one or more is adjusted for in regression	Most factors adjusted for in regression

Table 3
Summary of cohort/ cross-sectional study quality assessment system

	Risk of Bias (score)		
Criterion	**High (−1)**	**Medium (0)**	**Low (+1)**
1. Study design appropriate?	Ambiguously described, obviously bias inducing or unsuitable for the objectives and stated conclusions	Possibly restricting but reflected in the scope of the objectives and the stated conclusions	Planned to minimise bias and allow generalisability beyond the immediate scope of the objectives
2. Adequate description of study participants?	Little or no information given	Incl/excl and other criteria such as term/ pre-term/ small for gestational age baby given in some way; at least two useful measures including measure of vitamin D status, ethnicity	Incl/excl and other criteria such as term/ pre-term/ small for gestational age baby given in some way; at least three useful measures including measure of vitamin D status, ethnicity with measures of precision
3. How is maternal vitamin D status measured?	Dietary intake only or insufficient information	Blood levels of circulating 25(OH)-vitamin D	Blood levels of circulating 25(OH)-vitamin D, with details of precision, pick up of D2 and D3 and assay used
4. Participants grouped according to Vitamin D status?	Subjects divided and analysed in groups based on pre-existing vitamin D thresholds	Subjects divided and analysed in groups according to Vitamin D level based on group characteristics	Subjects not divided into groups according to Vitamin D level/ or grouped according to at threshold generated from the study
5. Measurements of outcomes reliably ascertained?	Inadequately explained or obviously unsuitable	Adequate description and reliability/suitability of at least one of the following: instruments, technique/ definition/protocol, people, place	Detailed description and reliability of one and at least adequate description of the others
6. Measurements of later outcomes objective?	Subjective measure, eg bone or muscle pain, wheezing	Ascertained from researcher examination	Objective measure e.g. DXA, bone biopsy, lung function tests
7. Measures of vitamin D intake/25(OH)-vitamin D level, bone outcomes rounded?	Measures categorised or rounded very roughly, or if any clear evidence of rounding exists without explanation in the text	Yes, but not by much	No information given and no obvious reason to suspect rounding has occurred; or explicitly stated that measurements were not rounded
8. Consideration for the effects of important confounding factors? (e.g. season, sunlight exposure, calcium intake, maternal compliance, infant feeding)	One factor controlled for in tables, nothing for the others (NB whether they were *measured* or not is irrelevant)	Most factors controlled for in tables, or fewer if one or more is adjusted for in regression	Most factors adjusted for in regression
9. Outcome assessment blind to maternal vitamin D status?	N/A (cannot score −1 in this category)	No details given	Some details or statement given
10. What proportion of the cohort was followed up?	% FU is not given, unclear, or low (below 70%)	% FU is low to average (70-90%)	% FU is high (over 90%)
11. Info on non-participants	Very little or no information, or information given that is adequate but suggests a serious potential for bias	Adequate information given, or information given that is very clear but suggests a moderate potential for bias	Above average information given, none of which suggests a potential for bias

	Risk of Bias (score)		
Criterion	**High (−1)**	**Medium (0)**	**Low (+1)**
12. Analysis rigorous and appropriate?	No statistical analyses carried out (just tables or description)	Tables of means & differences given with statistical tests (e.g. t-tests), or some regression but without clear/valid measure of association	Regression (or similar technique) used which gives a valid measure of association (e.g. odds ratios, hazard ratios, relative risks)
13. Sample size	Extremely ambiguous, not given, or small (under 100)	Average (100 to 1000)	Large (over 1000)

Table 4

Summary of intervention study quality assessment system

	Risk of Bias (score)		
Criterion	**High (−1)**	**Medium (0)**	**Low (+1)**
1. Study design appropriate?	Ambiguously described, obviously bias inducing or unsuitable for the objectives and stated conclusions	Possibly restricting but reflected in the scope of the objectives and the stated conclusions	Planned to minimise bias and allow generalisability beyond the immediate scope of the objectives
2. Are CONSORT guidelines followed?	Not described, not followed or poorly adherent	CONSORT report presented but some data missing	Full adherence to CONSORT guidelines
2. Adequate description of study participants?	Little or no information given	Incl/excl and other criteria such as term/ pre-term/ small for gestational age baby given in some way; at least two useful measures including measure of vitamin D status, ethnicity	Incl/excl and other criteria such as term/ pre-term/ small for gestational age baby given in some way; at least three useful measures including measure of vitamin D status, ethnicity with measures of precision
4. Is randomisation adequate?	No randomisation or not discussed	Some attempt at randomisation	Robust randomisation
5. Is there placebo control and is blinding adequate?	Not controlled, not adequate or not discussed	Placebo control, either not blinded or single blinded	Placebo control, double-blinded
6. Are details of the study medication given?	No details	Some detail e.g. “vitamin D 1000 iu per day”	Full details including D_2 or D_3, manufacturer, GMP compliant, full regimen.
7. Is change in maternal vitamin D status measured?	N/A	No	Yes
8. Are details of the assay given?	No details	Some details e.g. Diasorin RIA	Fully detail-type, manufacturer, precision, D_2/D_3 pick up.
9. Measurements of outcomes reliably ascertained?	Inadequately explained or obviously unsuitable	Adequate description and reliability/ suitability of at least one of the following: instruments, technique/ definition/protocol, people, place	Detailed description and reliability of one and at least adequate description of the others

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	Risk of Bias (score)		
Criterion	**High (−1)**	**Medium (0)**	**Low (+1)**
10. Measurements of later outcomes objective?	Subjective measure, eg bone or muscle pain, wheezing	Ascertained from researcher examination	Objective measure e.g. DXA, bone biopsy, lung function tests
11. Measures of vitamin D intake/ 25(OH)-vitamin D level, bone outcomes, e.g. BMC rounded?	Measures categorised or rounded very roughly, or if any clear evidence of rounding exists without explanation in the text	Yes, but not by much	No information given and no obvious reason to suspect rounding has occurred; or explicitly stated that measurements were not rounded
12. Consideration for the effects of important confounding factors? (e.g. season, sunlight exposure, calcium intake, maternal compliance, infant feeding)	One factor controlled for in tables, nothing for the others (NB whether they were *measured* or not is irrelevant)	Most factors controlled for in tables, or fewer if one or more is adjusted for in regression	Most factors adjusted for in regression
13. What proportion of the cohort completed the trial?	% FU is not given, unclear, or low (below 70%)	% FU is low to average (70-90%)	% FU is high (over 90%)
14. Info on non-participants	Very little or no information, or information given that is adequate but suggests a serious potential for bias	Adequate information given, or information given that is very clear but suggests a moderate potential for bias	Above average information given, none of which suggests a potential for bias
15. Analysis rigorous and appropriate?	No statistical analyses carried out (just tables or description)	Appropriate statistical techniques but no mention of whether intention to treat or pre protocol	Appropriate statistical techniques and intention to treat primary analysis
16. Sample size	Extremely ambiguous, not given, or small (under 100)	Average (100 to 250)	Large (over 250)

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Appendix 4: PRISMA Flow Diagram of Study Selection

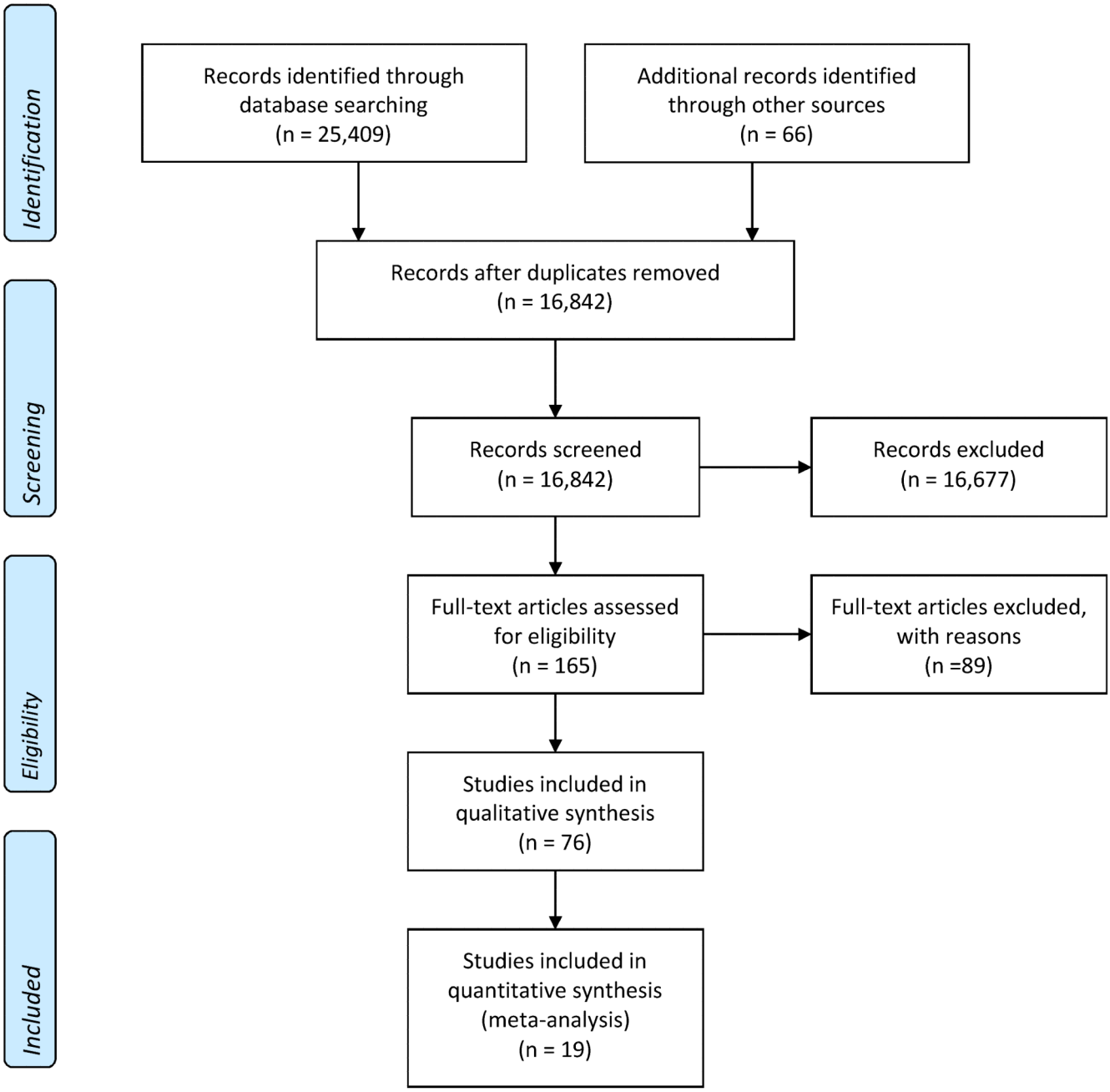

Figure 1.

Appendix 5: Summary of quality assessment scores

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Table 5

Summary of scoring results in terms of risk of bias (low, medium or high) of all case-control studies included in the review

First Author	1. Design	2. Vitamin D m'ment	3. Grouping of participants by vitamin D status	4. Outcomes reliably ascertained	5. Outcomes objective	6. Controls	7. Rounding	8. Setting	9. Blinding	10. Analysis	11. Response rates		12. Non-participants	13. Sample size		14. Confounding	Overall total	Reviewers' judgement
											Cases	Controls		Cases	Controls			
Azar 2011	Low	Low	Low	Med	Low	Med	Med	Med	Med	Low	Low	Low	High	High	High	Low	5	**Low**
Baker 2010	Low	Low	Low	Med	Low	Low	Med	Low	Med	Low	Med	Low	Low	High	Med	Low	9	**Low**
Baker 2011	Low	Low	High	Med	Low	Med	Med	Low	Med	Low	Low	Low	Med	High	Med	Low	5	**Low**
Baker 2012	Low	Low	Med	Low	Low	Med	Med	Med	Med	Low	Low	Low	Med	High	Med	Low	7	**Low**
Bodnar 2007	Low	Low	Low	Med	Low	Med	Med	Low	Med	Low	Low	Low	Med	High	Med	Low	8	**Low**
Bodnar 2010	Med	Low	Low	Med	Low	Med	Med	Low	Med	Low	Low	Low	Med	Med	Med	Low	7	**Low**
Brunvand 1998	Med	Low	Low	Low	Med	High	Med	Med	Med	Low	Med	Med	Med	High	High	Med	1	**Medium**
Delmas 1987	High	Med	Low	High	Med	High	Med	Low	Med	Med	Med	Med	Med	High	High	High	−4	**High**
Makgoba 2011	Low	Low	Med	Low	Low	Med	Med	Low	Med	Low	Med	Med	Med	High	Med	Low	6	**Low**
Powe 2010	Low	Low	Low	Med	Low	Med	Med	Low	Med	Low	High	High	Med	High	Med	Low	4	**Medium**
Robinson 2010	Low	Low	Low	Med	Low	High	Med	Low	Med	Low	Med	Med	,ed	High	Med	Low	5	**Low**
Robinson 2011	Med	Low	Med	Med	Med	Med	Med	Med	Med	Med	Med	Med	Med	Med	Med	Med	1	**Medium**
Seely 1992	Low	Med	Low	Medlow	Low	Med	Med	Med	Med	Low	Med	High	Med	High	High	Med	2	**Medium**
Soheilykkah 2010	Low	Low	High	Low	Low	Med	Med	Med	Med	Low	Med	Med	Med	High	Med	Med	3	**Medium**
Sorensen 2012	Low	Low	Low	Med	Med	Med	Med	Low	Med	Low	Low	Low	Med	Med	Med	Low	8	**Low**
Stene 2003	Low	High	High	Med	Low	Med	Med	Med	Med	Low	Med	High	Med	Med	Low	Low	2	**Medium**
Zhang 2008	Low	Low	Low	Low	Low	Med	Med	Med	Med	Low	Low	Low	Med	High	Med	Low	6	Low

* Numbers represent an estimate of the overall risk of bias, totalling the risk for each question defined as −1 for a "high" risk of bias, 0 for a "medium" risk of bias, and +1 for a "low" risk of bias

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Health Technol Assess. Author manuscript; available in PMC 2014 August 07.

Table 6

Summary of scoring results in terms of risk of bias (low, medium or high) of all cohort/ cross-sectional studies included in the review

First Author	1. Design	2. Participant	3. Vitamin D m'ment	4. Grouping of participant by vitamin D status	5. Outcomes reliably ascertained	6. Outcomes objective	7. Rounding	8. Confounding	9. Blinding	10. % FU	11. Non-participants	12. Analysis	13. Sample size	Overall total	Reviewers' judgement
Akcakus 2006	Med	Low	Low	Low	Med	Low	Med	High	Med	Med	Med	Low	Med	4	**Medium**
Amirlak 2009	Med	Low	Med	Low	Med	Low	Med	Med	Med	High	High	Low	High	2	**Medium**
Ardawi1997	Med	Low	Low	Low	Low	Low	Med	High	Med	Low	Med	Med	Med	5	**Low**
Bodnar 2009	High	Low	Low	Low	Low	Low	Med	High	Med	Low	Med	Low	Med	5	**Low**
Bowyer 2009	Low	Low	Low	High	Med	Low	Med	Med	Med	High	Low	Low	Med	4	**Medium**
Camargo 2007	Low	Low	High	Low	Med	High	Med	Low	Med	High	High	Low	Low	2	**Medium**
Camargo 2011	Low	Low	Low	High	High	High	Med	Low	Med	Low	Med	Low	Med	3	**Medium**
Clifton-Bligh 2008	Med	Low	Low	Low	Low	Low	Med	Low	Med	Med	High	Low	Med	6	**Low**
Cremers 2011	High	Low	Med	Med	Low	Low	Med	Low	Med	High	Med	Low	Med	3	**Medium**
Crozier 2012	Low	Low	Low	Low	Low	Low	Med	Low	Med	High	Low	Low	Med	8	**Medium**
Devereux 2007	Med	Med	High	Med	Med	High	Med	Low	Med	High	High	Low	Low	−1	**High**
Dror 2012	Low	Med	Med	Low	Low	Low	Med	Low	Med	Med	Low	Low	Med	7	**Low**
Dunlop 2011	Med	Med	Med	High	Low	Low	Med	Low	Med	High	Med	Low	Med	2	**Medium**
Erkkola 2009	Med	Med	High	Med	Med	High	Med	Med	Med	High	Med	Low	Low	−1	**High**
Farrant 2009	Med	Low	Low	Low	Low	Low	Med	Med	Med	High	Med	Low	Med	5	**Low**
Fernandez-Alonso, 2012	Low	Med	Low	High	Low	Low	Med	High	Med	Low	Med	Med	Med	3	**Medium**
Gale 2008	Med	Low	Low	High	Low	Low	Med	Med	Med	Med	Med	Low	Med	4	**Medium**
Hensel 2011	Med	High	Low	High	Low	Low	Med	Low	Med	Low	Med	Low	Med	4	**Medium**
Haugen 2009	Med	Low	High	High	Med	Low	Med	Low	Med	Med	High	Low	Low	2	**Medium**
Hossain 2011	Med	Low	Low	Low	Med	Med	Med	Med	Med	Med	Med	Low	Med	4	**Medium**
Javaid 2006	Low	Low	Low	Med	Low	Low	Med	Med	Med	High	Med	Low	Med	5	**Low**
Krishnaveni 2011	Med	Med	Low	Low	Low	Low	Med	Med	Med	Med	High	Low	Med	4	**Medium**
Leffelaar 2010	Low	Low	Low	High	Med	Low	Med	Low	Med	High	Med	Low	Low	5	**Low**
Maghbooli 2007	Med	High	Low	Low	Med	Med	Low	High	Med	Low	High	Med	Med	1	**Medium**
Maghbooli 2008	Med	Low	Low	Med	Low	Low	High	High	Med	Low	High	Med	med	3	**Medium**
Mannion 2006	Med	Low	High	Low	Med	Med	Med	Med	Med	High	High	Low	Med	1	**Medium**
Marjameki 2010	Med	Low	High	Low	Low	Low	Med	Med	Med	Med	Low	low	Low	6	**Low**

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First Author	1. Design	2. Participant	3. Vitamin D m'ment	4. Grouping of participant by vitamin D status	5. Outcomes reliably ascertained	6. Outcomes objective	7. Rounding	8. Confounding	9. Blinding	10. % FU	11. Non-participants	12. Analysis	13. Sample size	Overall total	Reviewers' judgement
Mehta 2009	Med	Med	Med	Med	Med	Med	Med	Med	Med	Med	Low	Low	Med	2	**Medium**
Merewood 2009	Med	Low	Med	High	Low	Low	Med	Low	Med	Low	Low	Low	Med	6	**Low**
Miyake 2010	Med	Med	High	Med	Med	High	Med	Low	Med	Med	High	Low	Med	−1	**High**
Morales 2012	Low	Low	Med	Low	High	High	Med	Low	Medium	High	Med	Low	Low	3	**Medium**
Morley 2006	Med	Low	Low	Low	Low	Low	Med	Low	Med	Med	Low	Low	Med	8	**Low**
Nwaru 2010	Med	Med	High	Low	Low	Low	Med	Low	Med	Med	High	Low	Med	3	**Medium**
Oken 2007	Med	Low	High	Low	Med	low	Med	Low	Med	Med	Low	Low	Low	6	**Low**
Prentice 2009	Med	Low	Low	Low	Low	Low	Med	Low	Med	High	High	low	med	5	**Low**
Rothers 2011	Low	Med	Med	High	Low	Low	Med	Med	Med	High	Med	Low	Med	2	**Medium**
Sabour 2006	Med	Low	High	High	Med	Med	Med	High	Med	Med	High	Low	Med	−2	**High**
Savvidou 2012	Low	Low	Low	Med	Low	Low	Med	Low	Med	Low	Med	Med	Med	7	**Low**
Sayers 2009	Low	Med	High	Low	Low	Low	Low	High	Med	High	High	Low	Low	3	**Medium**
Scholl 2008	Med	Low	High	Med	Low	Med	Low	Med	Med	High	High	Low	Low	2	**Medium**
Scholl 2012	Med	Low	Low	High	Low	Low	Med	Low	Med	High	Med	Low	Low	5	**Low**
Shand 2010	Med	Low	Low	High	Med	Low	Med	low	Med	Low	Low	Low	Med	6	**Low**
Shibata 2011	Low	Med	Low	Low	Med	Med	Med	Med	Med	Med	Med	Low	Med	4	**Medium**
Viljakainen 2010	Med	Low	Low	Med	Low	Low	Med	Med	Med	High	High	Low	Med	3	**Medium**
Viljakainen 2011	Med	Med	Low	Med	Low	Low	Med	Low	Med	High	Low	Low	High	4	**Medium**
Watson 2010	Med	Low	High	Low	Med	Low	Med	Low	Med	Med	High	Low	Med	3	**Medium**
Weiler 2005	Low	Med	Low	High	Low	Low	Med	Low	Med	High	Med	Low	High	3	**Medium**

*Numbers represent an estimate of the overall risk of bias, totalling the risk for each question defined as −1 for a "high" risk of bias, 0 for a "medium" risk of bias, and +1 for a "low" risk of bias

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Table 7

Summary of scoring results in terms of risk of bias (low, medium or high) of all intervention studies included in the review

First Author	1. Design	2. CONSORT guidance followed	3. Participant	4. Randomisation	5. Placebo control and blinding	6. Study med details	7. Maternal 25(OH) D	8. Assay detail	5. Outcomes reliably ascertained	6. Outcome objective	7. Rounding	8. Confounding	10. % FU	11. Non-participant	12. Analysis	13. Sample size	Overall total	Reviewers' judgement
Brooke 1980	Med	High	Med	Med	Low	Med	Low	Med	Med	Med	Med	Med	High	High	Med	High	−2	**High**
Cockburn 1980	Med	High	High	High	Med	Med	Low	Med	Low	Low	Med	Low	High	High	Med	Med	−1	**High**
Congdon 1983	Med	High	High	High	High	Med	High	Med	High	Med	Med	Med	High	High	Med	High	−9	**High**
Delvin 1986	Low	High	High	Med	High	Med	Low	Med	Low	Low	Med	Med	High	High	Med	High	−2	**High**
Hollis 2011	Low	Low	Med	Med	Med	Low	Low	Low	Low	Low	Med	Low	Low	Med	Low	Med	10	**Low**
Kaur 1991	Med	High	Med	Med	High	Med	Med	Med	High	Med	Med	High	High	High	Med	High	−7	**High**
Marya 1981	Med	High	High	Med	High	Med	Med	High	Med	Low	Med	High	High	High	Med	Med	−6	**High**
Marya 1987	Med	High	High	Med	High	Med	Med	Med	Med	Low	Med	High	Low	High	Med	Low	−2	**High**
Marya 1988	Med	High	Low	Med	High	Med	Med	High	Med	Med	Low	Low	High	High	Med	Med	−2	**High**
Mallet 1986	Med	High	High	Med	High	Med	Med	Low	Med	Low	Med	Med	High	High	Low	high	−3	**High**
Yu 2009	Low	Low	Med	Low	High	Med	Low	High	Med	Low	Med	High	Low	Med	Med	Med	3	**Medium**

*Numbers represent an estimate of the overall risk of bias, totalling the risk for each question defined as −1 for a "high" risk of bias, 0 for a "medium" risk of bias, and +1 for a "low" risk of bias

Appendix 6: Study assessments

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Table 8

The effect of maternal Vitamin D status in gestation on offspring birth weight (BW) - Observational studies

First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l)	Birth weight (g) mean (SD) or median (IQR)					Unadjusted regression co-efficient β (95% CI) for BW (g) per 1nmol/l increase in 25(OH)D	Adjusted regression co-efficient β (95% CI) for BW (g) per 1 nmol/l increase in 25(OH)D	Conclusion
Ardawi, 1997 [87]	5 (low)	Jeddah, Saudi Arabia Cohort size=264 women	Cohort	nil	Delivery	47.71 (15.77) 25(OH)D <20 nmol/l in 23% 25(OH)D >20 nmol/l in 77%		25(OH)D <20 nmol/l (n=24)	25(OH)D >20 nmol/l (n=240)			Not given	Not given	No difference in offspring BW in mothers with 25(OH)D <20 nmol/l at delivery compared to those with 25(OH)D >20 nmol/l
							BW	3323 (439)	3481 (410)					
Weiler, 2005 [86]	3 (med)	Winnipeg, Canada Sample size for analysis=50 women	Cross-section al	Nil, but no significant difference in terms of offspring sex, season of birth, gestational age at birth in mothers with 25(OH)D >37.5 nmol/l compared with those with 25(OH)D <37.5 nmol/l Significant difference in race between the 2 groups (p=0.010)	Within 48 hours of delivery	Overall mean not given Mean in adequate 25(OH)D group (>37.5 nmol/l, n=32)= 61.6 (24.7) Mean in the deficient group (<37.5 nmol/l, n=18)=28.6 (7.8)		25(OH)D <37.5 nmol/l (n=18)	25(OH)D ≥37.5 nmol/l (n=32)			Not given	Not given	Offspring BW in mothers with 25(OH)D ≥37.5 nmol/l significantly lower than in mothers with 25(OH)D <37.5 nmol/l p=0.022
							BW	3698 (380)	3399 (451)					
Mannion, 2006 [83]	1 (med)	Calgary, Canada n=279 women, 207 women restricted milk intake (≤250ml milk) which equates to ≤90 IU vitamin D and 72 did not restrict milk intake	Cohort	Gestational weight gain, maternal age, height, education, BMI put into regression	Not measured directly Repeat 24 hour dietary telephone recall. 3 or 4 times during pregnancy (1 cup of milk = 90 IU vitamin D)	In those not restricting milk, Vitamin D intake= 524 (180)IU/day In those restricting milk, <2.25mcg/day per day, vitamin D intake=316 (188)IU/day	In those not restricting milk, BW=3530 (466) In those restricting milk, BW=3410 (475) p (diff. between groups) =0.07					Not given	Not given β for each 40 IU/day increase in vitamin D intake = 10.97 (1.19, 20.75) p=0.029	Vitamin D intake in pregnancy is positively associated with offspring BW
Morley, 2006 [91]	8 (low)	Melbourne, Australia n=374 women (232 recruited in winter, 127 in summer)	Cohort	Sex, maternal height, whether first child, smoking, season of blood sample	11 weeks and 28-32 weeks	Winter recruitment, geometric mean at 11 wks= 49.2; 26-32 wks=48.3 Summer recruitment geometric mean at 11 weeks= 62.6; 26-32 wks=68.9	3540 (520)					At 28-32 wks β for every Log2 increase in 25(OH)D = 40 (−39−119)	At 28-32 wks β for every Log2 increase in 25(OH)D = 31 (−51, 112)	No significant association seen between Log 25(OH)D at 11 wks (data not given) or 28-32 wks and offspring birth weight
								25(OH)D <28 nmol/) at 28-32 wk	25(OH) D >28 nmol/l at 28-32 wk	Diff	Adj Diff			
							BW	3397 (57)	3555 (52)	−157	−153			
Sabour, 2006 [88]	−2 (high)	Tehran, Iran n=449 women	Cross-section al	Nil	Not measured directly Estimated from validated dietary FFQ at delivery (unclear when assessed)	Not measured Mean vitamin D intake =90.4(74.8) IU/day	Overall group mean (SD)		3190 (450)			Not given	Not given	No significant association seen between vitamin D intake and birth weight p=0.53
							Vit D intake <200 IU/day		3150 (480)					

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First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l)	Birth weight (g) mean (SD) or median (IQR)	Unadjusted regression co-efficient β (95% CI) for BW (g) per 1nmol/l increase in 25(OH)D	Adjusted regression co-efficient β (95% CI) for BW (g) per 1 nmol/l increase in 25(OH)D	Conclusion
							Vit D intake >200 IU/day: 3190 (440)			
Magbooli, 2007 [89]	1 (med)	Tehran, Iran n=552 women	Cross-sectional	None	Delivery*	27.82 (10.86)*	3190 (225)	Not given	Not given	No significant association seen between serum 25(OH)D3 and birth weight. p not given
Clifton-Bligh, 2008 [92]	6 (low)	New South Wales, Australia n=307 women (included 81 women with GDM)	Cohort	Gestational age	Mean (SD) 28.7 (3.3) weeks	53.8 (23.9)	Not given	Not given	Not given	No association between maternal 25(OH)D and offspring birth weight p>0.4
Harvey, 2008 [64]		Southampton Women's Survey n=604 women	Cohort	Gestational age, maternal age, maternal BMI, parity	34 weeks		3506 (441)	β per Log 25(OH)D increase = 31.59 (−44.19, 107.36) p=0.42	β per Log 25(OH)D increase = 68.27 (−7.16, 143.71) p=0.08	No significant association seen between maternal serum Log 25(OH)D and offspring birth weight
Gale, 2008 [25]	4 (med)	Princess Anne Cohort, Southampton, UK n=466 women	Cohort	Gestational age, maternal age, maternal BMI, ethnicity and parity	Late pregnancy (median (IQR) 32.6 (32-33.4) weeks	50 (30, 75.3) 50.4% had 25(OH)D >50 nmol/l 28.3% had levels 27.5-50 nmol/l 21.1% had levels <27.5 nmol/l	Divided into quartiles according to maternal 25(OH)D (nmol/l) <30: 3380 (460) 30-50: 3400 (560) 50-75: 3490 (570) >75: 3430 (510)	β per Log 25(OH)D increase = 1.45 (−31.4, 21.7) p=0.247	β per Log 25(OH)D increase = 52.9 (−14.4, 120.3) p=0.123	No significant association seen between maternal serum Log 25(OH)D and offspring birth weight
Farrant, 2009 [90]	5 (low)	Mysore Parthenon Study, India n=559 women (included 34 women with GDM)	Cohort	Maternal age, fat mass, diabetes status	30 (+/− 2) weeks	37.8 (24.0, 58.5) 60% of women had 25(OH)D <50 nmol/l, 31% had 25(OH)D < 28 nmol/l	Geometric mean (IQR) = 2900 (400)	β per Log 25(OH)D increase= −26.82 (−79.28, 25.65) p=0.32	β per Log 25(OH)D increase= −72.47 (−195.82, 50.88) p=0.25	No association seen between late pregnancy maternal Log serum 25(OH)D and offspring birth weight when data analysed both continuously or dividing the group into categories using 25(OH)D <50nmol/l as a threshold (p=0.8)
Scholl, 2009 [84]	2 (med)	The Camden Study, New Jersey, USA n=2251 low income minority pregnant women (47% Hispanic, 37% African American, 15% White)	Cohort	Energy intake, calcium, folate, iron, zinc, protein, age, parity, BMI, ethnicity and gestational age	Not measured directly. Estimated from FFQ at 20 and 28 weeks to calculate daily intake during pregnancy	412.4 (3.56) IU/day	3196 (12.77) Vitamin D intake (IU/day) — BW <285 — 3163(21) 285-368 — 3187(20) 368-440 — 3193(19)	Not given	Not given	Positive association seen between vitamin D intake and birthweight p for trend = 0.043 (after adjustments) When comparing birth weight in those with

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First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l)	Birth weight (g) mean (SD) or median (IQR)			Unadjusted regression co-efficient β (95% CI) for BW (g) per 1nmol/l increase in 25(OH)D	Adjusted regression co-efficient β (95% CI) for BW (g) per 1 nmol/l increase in 25(OH)D	Conclusion
							440-535		3207(19)			intake of <200 IU /day (inadequate intake) to those >200 IU/day (adequate intake , p=0.0270 (after adjustments)
							>535		3228(23)			
Amirlak, 2009 [80]	2(med)	UAE n=84 healthy Arab and South Asian women with uncomplicated term deliveries	Cross-sectional	Cord blood vitamin A, Maternal ferritin	Delivery	18.5(11.0, 25.4)	3317 (510)			Unadjusted β not given Unadjusted r= 0.23; p<0.05	11.6 (3.0-20.1) P=0.009	Positive correlation seen between maternal 25(OH)D at delivery and birthweight. For every 1 unit increase in 25(OH)D, birth weight increased by 11.6 g
Bowyer, 2009 [81]	4 (med)	Sydney, Australia n=971 women	Cohort	Gestation, maternal age, overseas maternal birth place	30-32 weeks	52.0 (17, 174) Median Vit D concentration according to group: Vit D ≤25 nmol l (n=144)= 18 (17, 22) Vit D 26-50 (n=317) = 39 (32, 45) Vit D >50 (n=510) = 73 (60-91)	25(O H)D nmol/l	Unadjusted birth weight	Adjusted birth weight	Not given	Not given	Offspring birth weight significantly lower in women with 25(OH)D deficiency (≤25 nmol/l) p<0.001
							≤25	3254 (545)	Not given			
							>25	3453 (555)	Not given			
							Difference (95% CI)	195 (90-305)	151 (50-250)			
Prentice, 2009 [95]	5 (low)	Gambia, Africa Subset of pregnant Gambian women participating in a calcium supplementation trial n=125 women	Cohort	Season, mat height, weight, weight gain, infant sex and whether received calcium supplement	20 weeks and 36 weeks	20 weeks=103 (25) 36 weeks=111 (27)	2990 (360)			At 36 weeks= −0.70(+/ −2.35) P=0.55	At 36 weeks= −0.12 (+/ −2.16) p=0.91	No significant association seen between maternal 25(OH)D and offspring birth weight when analysed both continuously and categorically (25(OH)D >80 nmol/l vs <80 nmol/l)
Sayers, 2009 [42]	3 (med)	Avon Longitudinal Study of Parents and Children (ALSPAC), UK n=13904 women		Nil	Not directly measured Ambient UVB measured during 98 days preceding birth		Boys (n=7192)=3429 (608) Girls (n=6722) =3327 (550)			1.46(−8.14, 11.06) p=0.77		No association between UVB exposure in 3rd trimester and birth weight
Leffelaar, 2010 [82]	4 (med)	Amsterdam Born Children and their development (ABCD) study cohort=3730 women , all term offspring (37 wks)	Cohort	Gestational age, season of blood sampling, sex, maternal height, maternal age, smoking, pre-pregnancy BMI, educational level, ethnicity,	Early pregnancy (mean 13 weeks)	54.4 (32-78) Group divided by serum vitamin D concentration as follows: >50 nmol/l (median 73.3); 30-49.9 (median 40.4); <29.9 (median 19.9)	Overall=3515.6 (489.1)			1.404 (0.893, 1.916)	0.068 (−0.483, 0.619)	When analysed continuously, no significant relationship observed between maternal early pregnancy 25(OH)D and offspring birth weight.
							≤29.9 nmol/l		3418.4 (510.3)			
							30-49.9 nmol/l		3505.6 (496.2)			
							>50 nmol/l		3559.8 (471.3)			
					Early pregnancy (mean 13 weeks)	54.4 (32-78) Group divided by serum vitamin D concentration as follows: >50 nmol/l (median 73.3); 30-49.9 (median 40.4); <29.9 (median 19.9)	Overall=3515.6 (489.1)			1.404 (0.893, 1.916)	0.068 (−0.483, 0.619)	When analysed continuously, no significant relationship observed between maternal early pregnancy 25(OH)D and offspring birth weight.

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First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l)	Birth weight (g) mean (SD) or median (IQR)				Unadjusted regression co-efficient β (95% CI) for BW (g) per 1nmol/l increase in 25(OH)D	Adjusted regression co-efficient β (95% CI) for BW (g) per 1 nmol/l increase in 25(OH)D	Conclusion
				smoking, parity smoking, parity									When analysed according to categories of 25(OH)D status, deficient vitamin D status (<29.9 nmol/l) was significantly associated with a lower birth weight. Adjusted —64 (−107.1, −20.9) Insufficient vitamin D (30-49.9 nmol/l)was not significantly associated with birthweight Adjusted β= 1 (−35.1, 37.2) (all β adjusted)
Watson, 2010 [85]	3 (med)	Northern New Zealand n=439 women European (75%), Maori (18%) and Pacific Polynesian (7%) women	Cohort	Gestational age, sex, maternal height, weight, smoking, number of pre-schoolers, number of other adults in the house	Not measured directly 24 hour recall and 3 day dietary FFQ at 4 months and 7 months	Mean vitamin D intake at 4 and 7 months = 84 IU/day	3332 (944)			3418.4 (510.3)	Not given	Not given	Vitamin D intake at 4 months is positively associated with Log (Vitamin D). pP=0.015 No significant association seen at 7 months p value not given
							30-49.9 nmol/l			3505.6 (496.2)			
							≥50 nmol/l			3559.8 (471.3)			
Viljakainen, 2010 [94]	3 (med)	Helsinki, Finland n=125 women recruited during last trimester (Oct-Dec). All Caucasian, non-smokers, primiparous	Cohort	Parental size, maternal wt gain in pregnancy, solar exposure, total intake of vitamin D and initial 25(OH)D conc.	First trimester (8-10 weeks) and 2 days post-partum. Mean of 2 values used to calculate “vitamin D status”	At 8-10 weeks=41.0 (13.6) Postpartum=45.1 (11.9) Overall mean=44.8 (11.9) Overall median “vitamin D status” used to categorise group=42.6		25(OH) D below median (42.6 nmol/l)	25 (OH) D above median (42.6 nmol/l)	P (diff. between means)	Not given	Not given	No significant difference in offspring birth weight or z-score birth weight if maternal 25(OH)status below median compared to above (median=42.6 nmol/l) A weak inverse correlation was observed with postpartum 25(OH)D and birth weight z-score (r= −0.193, p=0.068). This was further weakened after adjustment for
							BW (g)	3700 (400)	3520 (440)	0.052			
							BW z-score	0.12 (0.81)	−0.23 (1.09)	0.082			

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First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l)	Birth weight (g) mean (SD) or median (IQR)				Unadjusted regression co-efficient β (95% CI) for BW (g) per 1nmol/l increase in 25(OH)D	Adjusted regression co-efficient β (95% CI) for BW (g) per 1 nmol/l increase in 25(OH)D	Conclusion
													confounders (p= 0.07)
													confounders (p= 0.07)
							BW (g)	3700 (400)	3520 (440)	0.052			
Dror, 2012 [93]	7 (low)	Oakland California n=120 women	Cross-sectional	Gestational age, maternal age, maternal BMI, maternal height, ethnicity, parity, GDM	Peri-natal	75.5 (32.3)	BW z-score 3420 (542)	0.12 (0.81)	−0.23 (1.09)	0.082	−0.63 (−3.68−2.43) p=0.69	−1.79 (−4.57−0.98) p=0.20	No association seen between maternal serum 25(OH)D and offspring birth weight

*Measured 25(OH)D3

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Table 9

The effect of Vitamin D supplementation in gestation on offspring birth weight (BW) – Intervention studies

First Author, year	Risk of bias	Setting	Randomisation	Adjustments/ confounders accounted for	Number of weeks gestation when 25(OH)D was measured	Mean (SD)/ Mean (SE)* or median (IQR) maternal 25(OH)D concentration (nmol/l)	Mean (SD) or Mean (SE)* birth weight (g) in un-supplemented group	Mean (SD) or Mean (SE)* birth weight (g) in supplemented group	Conclusion
Brooke, 1980 [4]	−2 (high)	London, UK, n=126, all Asian women	Double-blinded Randomised to either placebo (n=67) or 1000 IU/day of vitamin D2 in last trimester (n=59)	Nil, but groups of similar age, height, parity, offspring sex, length of gestation	28-32 weeks and at birth	At allocation 25(OH)D=20.1 (1.9)* At term, Controls 25(OH)D=16.2 (2.7)* At term, supplemented group 25(OH)D =168.0 (12.5)*	3034 (64)	3157 (61)	No significant difference in BW between groups p>0.05
Marya, 1981 [5]	−6 (high)	Rohtak, India n=120 women	3 arms: Randomised to either no supplement (n=75) or 1,200 IU vitamin D + 375 mg calcium/ day$^{\Delta}$ 3 throughout the 3rd trimester (n=25); or oral 600,000 IU vitamin D2; 2 doses in 7th and 8th months gestation (n=20)	Nil	Not measured	Not measured	2730 (360)	1200IU/+ ca=2890 (320) 600,000 IU=3140 (450)	BW significantly higher in those taking supplements and highest in the 600,000 IU group p=0.05 for un-supplemented vs. 1200 IU group p=0.001 for non-supplemented vs. 600,000 IU group
Congdon, 1983 [22]	−9 (high)	Leeds, UK n=64, all Asian women	Either 1000 IU vitamin D plus calcium (calcium dose not given) daily in the 3rd trimester (n=19) or no supplement (n=45)	Nil, but groups similar in terms of maternal age, infant sex, gestation length, birth weight	Not measured	Not measured	3056 (59)*	3173 (108)*	No significant difference in BW between the two groups (p value not given)
Delvin, 1986 [7]	−2 (high)	Lyon, France n=40 women	Randomised to either no supplement (n=20) or 1000 IU vitamin D3/day during 3rd trimester (n=20)	Nil Groups similar in terms of maternal age and parity. All deliveries occurred in the same month (June)	At recruitment and at delivery	Mean (SD) 25(OH)D in suppl. group / Mean (SD) 25(OH)D in un-sup group At recruitment: 54.9 (10.0) / 27.5 (10.0) Delivery: 64.9 (17.5) / 32.4 (20.0)	Not given	Not given	No significant difference in BW between the 2 groups (p value not given)
Mallet, 1986 [8]	−3 (high)	Rouen, France n=77, all white women	3 arms: Randomised to either no supplement (n=29) or 1,000 IU vitamin D/day$^{\Delta}$ in last 3 months of pregnancy (n=21), or single oral dose of vitamin D$^{\Delta}$ 200,000 IU in 7th month (n=27)	Nil, but groups of similar maternal age, parity, calcium intake and frequency of outdoors outings	During labour (February and March)	Overall mean not given According to group: Un-supplemented=9.4 (4.9) 1000 IU/day=25.3 (7.7) 200,000 IU=26.0 (6.4)	3460 (70)	1000 IU/day = 3370 (80) 200,000 IU = 3210 (90)	No significant difference in BW between the 3 groups p value not given
Marya, 1988 [6]	−2 (high)	Rohtak, India n=200 women	Randomised to either no supplement (n=100) or oral 600,000 IU vitamin D3; 2 doses in 7th and 8th months gestation (n=100)	Nil, but groups had similar maternal age, maternal height, maternal height, parity, haemoglobin, calcium intake and vitamin D intake	Not measured	Not measured directly, but mean daily vitamin D intake given as follows: Un-supplemented=35.71 (6.17) IU/day Supplemented group=35.01 (7.13) IU/day	2800 (370)	2990 (360)	BW significantly higher in the supplemented group p<0.001
Kaur, 1991 [98]	−7 (high)	Rohtak, India n=50 women	Randomised to either no supplement (n=25) or oral 60,000 IU vitamin D3; 2 doses in 6th and 7th month gestation (n=25)	Nil, but groups had similar maternal age, maternal weight, length of gestation, parity and haemoglobin	Not measured	Not measured	2756 (60)*	3092 (90)*	BW significantly higher in the supplemented group p<0.001
Yu, 2009 [96]	5 (low)	London, UK n=179 women	3 arms Randomised to either no supplement (n=59) or oral	Nil	Measured at 26-27 weeks	27 wks / Delivery	Not given	Not given	No significant difference in BW

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First Author, year	Risk of bias	Setting	Randomisation	Adjustments/ confounders accounted for	Number of weeks gestation when 25(OH)D was measured	Mean (SD)/ Mean (SE)* or median (IQR) maternal 25(OH)D concentration (nmol/l)			Mean (SD) or Mean (SE)* birth weight (g) in un-supplemented group	Mean (SD) or Mean (SE)* birth weight (g) in supplemented group	Conclusion
			vitamin D2 800 IU/day vitamin from 27 weeks onwards (n=60), or a single 200,000 IU calciferol at 27 weeks gestation (n=60) Each group contained equal numbers of 4 ethnic groups (Caucasian, Black, Asian, Middle Eastern)	No significant difference in baseline characteristics across the 3 groups	and again at delivery	No sup	25 (21-38)	27 (27-39)			across the 3 groups
						800 IU daily	26 (20-37)	42 (31-76)			
						single sup	26 (30-46)	34 (30-46)			
Hollis, 2011 [97]	10 (low)	Charleston, USA	3 arms Randomised to either oral vitamin D3 400 IU/day (n=111) or 2000 IU/day (n=122) or 4000 IU/day (n=117) from 12-16 weeks gestation until delivery	Nil	Measured at baseline, then monthly and at delivery		Mean of measurements between 20-36 weeks	delivery	No un-supplemented group. All groups received some form of vitamin D3 supplementation	400IU/day = 3221.8 (674.9) 2000 IU/ day=3360.1 (585.0) 4000 IU/ day=3284.6 (597.6)	No significant difference in BW across the 3 groups (p=0.23)
						400 IU daily	79.1 (29.5)	78.9 (36.5)			
						2000 IU daily	94.4 (26.1)	98.3 (34.2)			
						4000 IU daily	110.8 (28.3)	111.0 (40.4)			

△ = not known whether supplementation was vitamin D2 or vitamin D3

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Table 10

The effect of maternal vitamin D status in gestation on offspring birth length– Observational studies

First Author and year	Bias score	Study Details	Study Type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH) D concentration (nmol/l)	Mean (SD) or median (IQR) birth length (cm)					Unadjusted regression co-efficient β (95% CI) for birth length (cm) per 1nmol/l increase in 25(OH)D	Adjusted regression coefficient β (95% CI) for birth length (cm) per 1 nmol/l increase in 25(OH)D	Conclusion
Ardawi, 1997 [87]	5 (low)	Jeddah, Saudi Arabia Cohort size=264 women	Cohort	nil	Delivery	47.71 (15.77) 25(OH)D <20 nmol/l in 23% 25(OH)D >20 nmol/l in 77%		25(OH)D <20 nmol/l (n=24)	25(OH)D >20 nmol/l (n=240)			Not given	Not given	No difference in offspring birth length in mothers with 25(OH)D <20 nmol/l at delivery compared to those with 25(OH)D >20nmol/l
							Birth length (cm)	51.7 (2.9)	51.0 (2.4)					
Sabour, 2006 [88]	−2 (high)	Tehran, Iran n=449 women	Cross-sectional	Nil	Not measured directly Estimated from validated dietary FFQ at delivery (unclear when assessed)	Not measured Mean vitamin D intake = 90.4 (74.8) IU/day	Overall group mean (SD)	34.81 (6.55)				Not given	Not given	Offspring birth length significantly higher in mothers with adequate dietary vitamin D intake compared to those with inadequate intake p=0.03
							Vit D intake <200 IU/day	49.5 (3.77)						
							Vit D intake >200 IU/day	50.37 (2.73)						
Mannion, 2006 [83]	1 (med)	Calgary, Canada n=279 women, 207 women restricted milk intake (≤250ml milk) which equates to ≤90 IU vitamin D and 72 not restricting milk intake	Cohort		Not measured directly Repeat 24 hour dietary telephone recall. 3 or 4 times during pregnanc y (1 cup of milk = 90 IU vitamin D)	In those not restricting milk, Vitamin D intake= 524 (180)IU/day In those restricting milk, <2.25mcg/day per day, vitamin D intake=316 (188)IU/day	In those not restricting milk, unadjusted birth length= 51.4 (3.6) In those restricting milk, unadjusted birth length= 51.1 (3.5) P (diff. between groups)=0.46					Not given	Not given	No difference in offspring birth length in mothers restricting milk intake in pregnancy compared to those with unrestricted intake
Morley, 2006 [91]	8 (low)	Melbourne, Australia n=374 women (232 recruited in winter, 127 in summer)	Cohort	Sex, maternal height, whether first child, smoking, season of blood sample	11 weeks and 28-32 weeks	Winter recruitment, geometric mean at 11 wks=49.2; 26-32 wks=48.3 Summer recruitment geometric mean at 11 weeks=62.6; 26-32 wks=68.9		25(OH)D<28 (nmol/l) at 28-32 wk	25(OH)D >28 (nmol/l) at 28-32 wk	Diff (95% CI)	Adj Diff (95% CI)	At 28-32 wks β for every Log_2 increase in 25(OH)D = −0.3 (−0.08−0.6)	At 28-32 wks β for every Log_2 increase in 25(OH)D = −0.3 (−0.1−0.6))	No significant association seen between Log 25(OH)D at 11 wks (data not given) or 28-32 wks and offspring birth length
							BL	49.8 (2.7)	50.4 (2.4)	−0.6 (−1.5−0.3)	−0.6 (−1.5−0.3)			
Magbooli, 2007 [89]	1 (med)	Tehran, Iran n=552 women	Cross-sectional	None	Delivery*	27.82 (21.71)*	50.02 (1.58)					Not given	Not given	No significant association seen between serum 25(OH)D_3

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First Author and year	Bias score	Study Details	Study Type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH) D concentration (nmol/l)	Mean (SD) or median (IQR) birth length (cm)	Unadjusted regression co-efficient β (95% CI) for birth length (cm) per 1nmol/l increase in 25(OH)D	Adjusted regression coefficient β (95% CI) for birth length (cm) per 1 nmol/l increase in 25(OH)D	Conclusion
										and offspring birth length and offspring birth length and offspring birth length p not given
Clifton-Bligh, 2008 [92]	6 (low)	New South Wales, Australia n=307 women (included 81 women with GDM)	Cohort	Gestational age	Mean (SD) 28.7 (3.3) weeks	53.8 (23.9)	Not given	Not given	Not given	No association between maternal 25(OH)D and offspring birth length p>0.4
Gale, 2008 [25]	4 (med)	Princess Anne Cohort, Southampton , UK n=466 women	Cohort	Gestational age, maternal age, maternal BMI, ethnicity and parity	Late pregnancy Median 32.6 weeks (32.0-31.4)	50 (30-75.3) 50.4% had 25(OH)D >50nmol/l 28.3% had levels 27.5-50 nmol/l 21.1% had levels <27.5 nmol/l	Not given	β per Log 25(OH)D increase = 0.23 (−0.09, 0.54) p=0.150	β per Log 25(OH)D increase = 0.18 (−0.10, 0.46) p=0.215	No association seen between maternal serum 25(OH)D and offspring birth length
Farrant, 2009 [90]	5 (low)	Mysore Parthenon Study, India n=559 women (included 34 women with GDM)	Cohort	Maternal age, fat mass, diabetes status	30 (+/− 2) weeks	37.8 (24.0-58.5) 60% of women ha d 25(OH)D <50 nmol/l, 31% below 28 nmol/l	Geometric mean =48.9 (2.2)	β per Log 25(OH)D increase= −0.07 (−0.34, 0.20) p=0.6	β per Log 25(OH)D increase= −0.27 (−0.80, 0.26) p=0.3	No association seen between late pregnancy maternal Log serum 25(OH)D and offspring birth length when data analysed both continuously or dividing the group into categories using 25(OH)D <50nmol/l as a threshold (p=0.9)
Prentice, 2009 [95]	5 (low)	Gambia, Africa Subset of pregnant Gambian women participating in a calcium supplement trial n=125 women	Cohort	Season, mat height, weight, weight gain, infant sex and whether received calcium supplement	20 weeks and 36 weeks	20 weeks = 103 (25) 36 weeks = 111 (27)	50.5 (1.9) *	0.0634 (0.136) p=0.36	0.0736 (0.138) p=0.30	No significant association seen between maternal 25(OH)D and offspring birth length when analysed both continuously and categorically (25(OH)D >80 nmol/l vs <80 nmol/l)
Sayers, 2009 [42]	3 (med)	ALSPAC, cohort, UK n=10584 women	Cohort	Nil	Not directly measured Ambient UVB measured during 98 days	Not measured	Boys (n=5447)=50.93 (2.61) Girls (n=5140)=50.19 (2.44)	β per 1 SD increase in UVB 0.10 (0.05-0.15) p=0.00004	No adjustments made	Maternal UVB exposure in late pregnancy is positively associated with

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First Author and year	Bias score	Study Details	Study Type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH) D concentration (nmol/l)	Mean (SD) or median (IQR) birth length (cm)				Unadjusted regression co-efficient β (95% CI) for birth length (cm) per 1nmol/l increase in 25(OH)D	Adjusted regression coefficient β (95% CI) for birth length (cm) per 1 nmol/l increase in 25(OH)D	Conclusion
					preceding birth preceding birth								offspring birth length
Leffelaar, 2010 [82] **	4 (med)	Amsterdam Born Children and their development (ABCD) study cohort=3730 women, all term offspring (≥37 wks)	Cohort	Gestational age, season of blood sampling, sex, maternal height, maternal age, smoking, pre-pregnancy BMI, educational level, ethnicity, smoking, parity	Early pregnancy (mean 13 weeks)	54.4 (32-78) Group divided by serum vitamin D concentration as follows: Adequate; ≥50 nmol/l (median 73.3) Insufficient;30 −49.9 (median 40.4) Deficient ≤29.9 (median (19.9)		All	25(OH)D≤29.9	25(OH)D 30-49.9	259OH)D ≥50	Not given	Not given	Infants born to mothers with 25(OH)D ≤29.9 nmol/l (deficient) had lower length at 1 month. No difference between birth length in mothers with insufficient and adequate 25(OH) levels in early pregnancy
							Unadj Length at 1 month	54.8 (0.05)	54.2 (0.09)	54.8 (0.10)	55.1 (0.06)			
Viljakainen,2010 [9]	3 (med)	Helsinki, Finland n=125 women recruited during last trimester (Oct-Dec). All Caucasian, non-smokers, primiparous	Cohort	Parental size, maternal wt gain in pregnancy, solar exposure, total intake of vitamin D and initial 25(OH)D conc.	First trimester (8-10 weeks) and 2 days post-partum. Mean of 2 values used to calculate “vitamin D status”	At 8-10 weeks = 41.0 (13.6) Postpartum = 45.1 (11.9) Overall mean= 44.8 (11.9) Overall median “vitamin D status” used to categorise group=42.6			25(OH)D below median (42.6 nmol/l)	25 (OH)D above median (42.6 nmol/l)	P (diff. between means)	Not given	Not given	No significant difference in offspring birth length or z-score birth length if maternal 25(OH)status below median compared to above (median=42.6 nmol/l) An inverse correlation was observed with postpartum 25(OH)D and birth length z-score (r= −0.261, p=0.013). This relationship was no longer significant after adjustment for confounders
							Unadj. Birth length (cm)		51.0 (1.9)	50.5 (1.8)	0.140			
							Unadj. z-score birth length		0.14 (1.0)	−0.20 (0.96)	0.104			
Dror, 2012 [93]	7 (low)	Oakland Califomia n=120 women	Cross-sectional	Gestational age, maternal age, maternal BMI, maternal height, ethnicity, parity, GDM	Perinatal	75.5 (32.3)	Not given					−0.004 p=0.53	−0.009 (−0.022-0.004) p=0.18	No association seen between maternal serum 25(OH)D and offspring birth length

* Measured 25(OH)D3

** Measured when infant was 1 month old

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Table 11

The effect of vitamin D supplementation in gestation on offspring birth length – Intervention studies

First Author, year	Risk of bias	Setting	Randomisation	Adjustments/ confounders accounted for	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/1)	Mean (SD) or Mean (SE)* birth length (cm) in un-supplemented group	Mean (SD) or Mean (SE)* birth length (cm) in supplemented group	Conclusion
Brooke, 1980 [4]	−2 (high)	London, UK, n=126 women(all Asian)	Double-blinded Randomised to either placebo (n=67) or 1000 IU/day of vitamin D2 in last trimester (n=59)	Nil, but groups of similar age, height, parity, offspring sex, length of gestation	28-32 weeks and at birth	At allocation 25(OH)D = 20.1 (1.9) At term, Controls 25(OH)D= 16.2 (2.7) At term, supplemented group 25(OH)D = 168.0 (12.5)	49.5 (0.4)*	49.7 (0.3)*	No significant difference in birth length between groups p>0.05
Marya, 1988 [6]	−2 (high)	Rohtak, India	Randomised to either no supplement (n=100) or oral 600,000 IU vitamin D3; 2 doses in 7th and 8th months gestation (n=100)	Nil, but groups had similar maternal age, maternal height, maternal height, parity, haemoglobin, calcium intake and vitamin D intake	Not measured	Not measured directly, but mean daily vitamin D intake given as follows Un-supplemented = 35.71 (6.17) IU/day Supplemented group = 35.01 (7.13) IU/day	48.45 (2.04)	50.06 (1.79)	Birth length significantly higher in the supplemented group p<0.001

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Table 12

The effect of maternal vitamin D status in gestation on offspring head circumference (HC) – Observational studies

First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH) D concentration (nmol/l)	Mean (SD) or median (IQR) HC (cm)					Unadjusted regression co-efficient β (95% CI) for HC (cm) per 1nmol/l increase in 25(OH)D	Adjusted regression co-efficient β (95% CI) for HC (cm) per 1 nmol/l increase in 25(OH)D	Conclusion
Ardawi, 1997 [87]	5 (low)	Jeddah, Saudi Arabia Cohort size=264 women	Cohort	nil	Delivery	47.71 (15.77) 25(OH)D <20 nmol/l in 23% 25(OH)D >20 nmol/l in 77%		25(OH)D <20 nmol/l (n=24)	25(OH)D >20 nmol/l (n=240)			Not given	Not given	No difference in offspring HC in mothers with 25(OH)D <20 nmol/l at delivery compared to those with 25(OH)D >20nmol/l
							HC (cm)	34.8 (1.3)	34.11 (1.46)					
Mannion, 2006 [83]	1 (med)	Calgary, Canada n=279women, 207 women restricted milk intake (≤250ml milk) which equates to ≤90 IU vitamin D and 72 not restricting milk intake	Cohort	No adjustments made for HC	Not measured directly Repeat 24 hour dietary telephone recall. 3 or 4 times during pregnancy (1 cup of milk = 90 IU vitamin D)	In those not restricting milk, Vitamin D intake= 524 (180)IU/day In those restricting milk, <2.25mcg/day per day, vitamin D intake=316 (188)IU/day	In those not restricting milk, unadjusted HC= 34.6 (1.5) In those restricting milk, unadjusted HC= 34.3 (1.5) P (diff. between groups)=0.19					Not given	Not given	No difference in offspring HC in mothers restricting milk intake in pregnancy compared to those with unrestricted intake
Morley, 2006 [91]	8 (low)	Melbourne, Australia n=374 women (232 recruited in winter, 127 in summer)	Cohort	Sex, maternal height, whether first child, smoking, season of blood sample	11 weeks and 28-32 weeks	Winter recruitment, geometric mean at 11 wks= 49.2; 26-32 wks=48.3 Summer recruitment geometric mean at 11 weeks= 62.6; 26-32 wks=68.9	HC	25(OH)D <28 (nmol/l) at 28-32 wk	25(OH)D ≥28 (nmol/l) at 28-32 wk	Diff	Adj. Diff	At 28-32 wks β for every Log_2 increase in 25(OH)D = −0.02 (−0.2, 0.2)	At 28-32 wks β for every Log_2 increase in 25(OH)D = −0.05 (−0.3, 0.2)	No significant association seen between Log 25(OH)D at 11 wks (data not given) or 28-32 wks and offspring HC
								34.5 (1.5)	34.7 (1.5)	−0.2	−0.2			
Sabour,2006 [88]	−2 (high)	Tehran, Iran n=449 women	Cross-sectional	Nil	Not measured directly Estimated from validated dietary FFQ at delivery (unclear when assessed)	Not measured Mean vitamin D intake = 90.4 (74.8) IU/day	Overall group mean (SD)			34.81 (6.55)		Not given	Not given	No significant association seen between maternal vitamin D intake and offspring HC P=0.47
							Vit D intake <200 IU/day			34.51 (2.66))				
							Vit D intake >200 IU/day			35.19 (10.38				
Magbooli, 2007 [89]	1 (med)	Tehran, Iran n=552 women	Cross-sectional	None	Delivery*	27.82 (21.71)*	Not given					Not given	Not given	No significant association seen between

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First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH) D concentration (nmol/l)	Mean (SD) or median (IQR) HC (cm)				Unadjusted regression co-efficient β (95% CI) for HC (cm) per 1nmol/l increase in 25(OH)D	Adjusted regression co-efficient β (95% CI) for HC (cm) per 1 nmol/l increase in 25(OH)D	Conclusion
													serum 25(OH)D and offspring HC. p not given
Clifton-Bligh, 2008 [92]	6 (low)	New South Wales, Australia N=307 women (included 81 women with GDM)	Prospective cohort	Gestational age	Mean (SD) 28.7 (3.3) weeks	53.8 (23.9)	Not given				Not given	Not given	No association between maternal 25(OH)D and offspring HC p>0.4
Gale, 2008 [25]	4 (med)	Princess Anne Cohort, Southampton, UK n=466 women	Cohort	Gestational age, maternal age, maternal BMI, ethnicity and parity	Late pregnancy Median 32.6 weeks (32.0−31.4)	50 (30−75.3) 50.4% had 25(OH)D >50nmol/k 28.3% had levels 27.5−50 nmol/l 21.1% had levels <27.5 nmol/l	Not given				β per Log 25(OH)D increase = 0.06 (−0.14, 0.26) p=0.557	β per Log 25(OH)D increase = 0.06 (−0.13, 0.25) p=0.530	No association seen between maternal serum 25(OH)D and offspring HC
Farrant, 2009 [90]	5 (low)	Mysore Parthenon Study, India n=559 women (included 34 women with GDM)	cohort	Maternal age, fat mass, diabetes status	30 (+/− 2) weeks	37.8 (24.0−58.5) 60% of women had 25(OH)D <50 nmol/l, 31% below 28 nmol/l	53.40 (1.53)				β per Log 25(OH)D increase= −0.002 (−0.19-0.19) P=0.98	β per Log 25(OH)D increase= −0.01 (−0.41-0.39) P=0.96	No association seen between late pregnancy maternal Log serum 25(OH)D and offspring HC at birth
Prentice, 2009 [95]	5 (low)	Gambia, Africa Subset of pregnant Gambian women participating in a calcium supplementation trial n=125 women	Cohort	Season, mat height, weight, weight gain, infant sex and whether received calcium supplement	20 weeks and 36 weeks	20 weeks =103 (25) 36 weeks =111 (27)	35.5 (1.6)*				−0.0371 (0.112) p=0.52	−0.0465 (0.113) p=0.42	No significant association seen between maternal 25(OH)D and offspring HC when analysed both continuously and categorically (25(OH)D >80 nmol/l vs <80 nmol/l) Still no association when HC measured again at 13 or 52 weeks
Viljakainen, 2010 [94]	3 (med)	Helsinki, Finland n=125 women recruited during last trimester (Oct-Dec). All Caucasian, non-smokers, primiparous	Cohort	No adjustments made for HC	First trimester (8−10 weeks) and 2 days post-partum. Mean of 2 values used to calculate	At 8-10 weeks = 41.0 (13.6) Postpartum = 45.1 (11.9) Overall median “vitamin D status=” 42.6	HC (cm)	25(OH) below median (42.6 nmol/l)	25 (OH)D above median (42.6 nmol/l)	P (diff. between means)	Not given	Not given	No significant difference in offspring HC if maternal 25(OH) below median compare to above
						At 8-10 weeks = 41.0 (13.6) Postpartum = 45.1 (11.9) Overall median “vitamin D status=” 42.6	HC (cm)	25(OH) below	25.5 (1.6) (OH)D	P (diff. between means)	Not given	Not given	No significant difference in offspring HC if maternal 25(OH) below median compare to above

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First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH) D concentration (nmol/l)	Mean (SD) or median (IQR) HC (cm)				Unadjusted regression co-efficient β (95% CI) for HC (cm) per 1nmol/l increase in 25(OH)D	Adjusted regression co-efficient β (95% CI) for HC (cm) per 1 nmol/l increase in 25(OH)D	Conclusion
					"vitamin D status" "vitamin D status"			median (42.6 nmol/l)	above median (42.6 nmol/l)				(median=42.6 nmol/l)
Dror, 2012 [93]	7 (low)	Oakland California n=120 women	Cross-sectional	Gestational age, maternal age, maternal BMI, maternal height, ethnicity, parity, GDM, infant age in days, infant feeding practice (breast, formula, mixed)	Peri-natal	75.5 (32.3)	Not given*	35.7 (1.4)	35.9 (0.6)	0.511	−0.003 (−0.012, 0.005) p=0.46	0.005 (−0.013, 0.003) p=0.23	No association seen between maternal serum 25(OH)D and offspring HC

*HC measured in infant at 2 weeks

**HC measured in infant between 8-21 days old

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Table 13

The effect of vitamin D supplementation in gestation on offspring head circumference (HC) – Intervention studies

First Author, year	Risk of bias	Setting	Randomisation	Adjustments/ confounders accounted for	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/1)	Mean (SD) or Mean (SE)* HC (cm) in un-supplemented group	Mean (SD) or Mean (SE)* HC (cm) in supplemented group	Conclusion
Brooke, 1980 [4]	−2 (high)	London, UK, n=126 women (all Asian)	Double-blinded Randomised to either placebo (n=67) or 1000 IU/day of vitamin D2 in last trimester (n=59)	Nil, but groups of similar age, height, parity, offspring sex, length of gestation	28-32 weeks and at birth	At allocation 25(OH)D = 20.1 (19) At term, Controls 25(OH)D= 16.2 (2.7) At term, supplemented group 25(OH)D = 168.0 (12.5)	34.3 (0.2)*	34.5 (0.1)*	No significant difference in HC between groups p>0.05
Marya, 1988 [6]	−2 (high)	Rohtak, India n=200 women	Randomised to either no supplement (n=100) or oral 600,000 IU vitamin D3; 2 doses in 7th and 8th months gestation (n=100)	Nil, but groups had similar maternal age, maternal height, maternal height, parity, haemoglobin, calcium intake and vitamin D intake	Not measured	Not measured directly, but mean daily vitamin D intake given as follows Un-supplemented = 35.71 (6.17) IU/day Supplemented group = 35.01 (7.13) IU/day	33.41 (1.11)	33.99 (1.02)	HC at birth significantly higher in the supplemented group p<0.001

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Table 14

The effect of maternal vitamin D status in gestation on offspring bone mass – Observational studies

First Author and year	Bias score	Study Type	Study Details, age at which children were assessed and technique used	Offspring bone outcomes assessed (units)	Confounders/ adjustments	Number of weeks gestation when maternal 25(OH)D 3 was measured	Mean (SD) or median (IQR) maternal 25(OH)D concentration (nmol/l)	Mean (SD) bone outcome according to maternal 25(OH)D category/ Unadjusted correlation co-efficient (r) or regression co-efficient (β) (95% CI)	Adjusted correlation co-efficient (r) or regression co-efficient (B) (95% CI)	conclusion
Weiler, 2005[86]	3 (med)	Cross-sectional	Winnipeg, Canada Overall cohort= 342 women Sample size for analysis=50 Neonates delivered at term and assessed within 15 days of birth by DXA	Lumbar spine (LS) BMC (g) LS BMC/body weight (wt) (g/kg) Femur BMC Femur BMC/wt Whole Body (WB) BMC WB BMC/wt	Infant weight, gestational age at birth, infant weight, gestational age at scan, infant vitamin D status, lean mass Infant sex, infant length and maternal ethnicity not included in the final model since they did not significantly predict infant BMC	Within 48 hours of delivery	Overall mean not given Mean in adequate 25(OH)D group (≥37.5 nmol/l, n=32)= 61.6 (24.7) Mean in the deficient group (≤37.5 nmol/l, n=18)= 28.6 (7.8)	25(OH) D nmol/l: <35 / >35 / P value LS BMC(g): 2.3 (0.5) / 2.3 (0.5) / ≥0.99 LS BMC/wt (g/kg): 0.59 (.14) / 0.66 (.125) / 0.08 Femur BMC (g): 2.8 (0.7) / 2.9 (0.6) / 0.60 Femur BMC/wt (g/kg): 0.71 (.17) / 0.81 (.15) / 0.027 WB BMC (g): 76.4 (12.9) / 75.7 (13.7) / 0.86 WB BMC/wt (g/kg): 19.49 (3.05) / 21.33 (2.03) / 0.017	Not given	No significant difference in lumbar spine BMC or lumbar spine BMC/body weight, femur BMC or whole body BMC was observed between those with adequate and deficient maternal 25(OH)D Significantly higher femur BMC/body weight and WB BMC/ body weight in those with adequate maternal 25(OH)D
Javaid, 2006[2]	5 (low)	Cohort	Princess Anne Cohort, Southampton, UK n=198 women Children assessed at mean 8.9 years by DXA	WB BMC (g) BA (cm^2) BMD (g/cm^2) Lumbar spine (LS) BMC(g), BA (cm^2) BMD(g/cm^2)	Gestational age , offspring age at DXA	34 weeks	25(OH) D conc (nmol/l): n (%) <27.5: 28 (18) 27.5-50: 49 (31) >50: 83 (52)	Not given	Outcome: r for each 2.5 nmol/l increase in maternal 25(OH) D: P value WB BMC: 0.21: 0.0088 WB BA: 0.17: 0.0269 WB BMD: 0.21: 0.0063 LS BMC: 0.17: 0.03 LS BA: 0.07: 0.3788 LS BMD: 0.21: 0.0094	Positive association found between maternal 25(OH)D in late pregnancy and offspring WB and LS BMC, WB BA, WB and LS BMD at aged 9 years
Prentice, 2009[95]	5 (low)	Cohort	Gambia, Africa Subset of pregnant Gambian women participating in a calcium supplementation trial n=125 women Children assessed at 2, 13 and 52 weeks by SPA for radial measurements and DXA for whole body measurements	Radial midshaft BMC (g) and bone width WB BMC (g/cm) WB BA (cm^2)	Season, mat height, weight, weight gain, infant sex and whether received calcium supplement	20 weeks and 36 weeks	20 weeks = 103 (25) 36 weeks = 111 (27)	Not given	Not given	No association between maternal 25(OH)D and infant radial midshaft BMC and bone width, or WB BMC and WB BA at either time point
Sayers, 2009[42]	3 (med)	Cohort	ALSPAC, cohort, UK n=6955 women Children assessed at	WB less head BMC, (g), BA (cm^2) BMD WB less head BMC, (g), BA (cm^2) BMD	BMC adjusted for area BA adjusted for height BMC adjusted for area BA adjusted for height	Not directly measured Ambient UVB measured during 98 days preceding birth Not directly measured Ambient UVB measured during 98 days preceding birth	Not measured Not measured	Outcome: β (change in outcome per 1 SD increase in UVB) (95% CI): p value BMC (g): 9.6 (5.3, 13.8): <0.0001 BA (cm^2): 4.3 (1.3, 7.3): 0.0052 Outcome: β (change in outcome per 1 SD increase in UVB) (95% CI): p value	Not given Not given	Maternal UVB exposure in pregnancy was positively associated with offspring Maternal UVB exposure in pregnancy was positively associated with offspring

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First Author and year	Bias score	Study Type	Study Details, age at which children were assessed and technique used	Offspring bone outcomes assessed (units)	Confounders/ adjustments	Number of weeks gestation when maternal 25(OH)D 3 was measured	Mean (SD) or median (IQR) maternal 25(OH)D concentration (nmol/l)	Mean (SD) bone outcome according to maternal 25(OH)D category/ Unadjusted correlation co-efficient (r) or regression co-efficient (β) (95% CI)			Adjusted correlation co-efficient (r) or regression co-efficient (B) (95% CI)			conclusion
			mean age 9.9 years by DXA, mean age 9.9 years by aBMA	BMC (g), aBMA (g)				BMC (g)	9.6 (5.3, 13.8)	<0.0001				BMC, BA and BMD. This remained with BA even after adjusting for height. No relationship was observed with maternal UV exposure and aBMC
								BMD (g/cm^2)	0.004 (0.001, 0.007)	<0.0001				
								aBMC (g)	0.69 (0.22, 1.60)	0.14				
Akcakus 2009 [100]	4 (med)	Cross-sectional	Turkey Cohort=100 women 3 groups, 30 SGA, 40 AGA, 30 LGA infants Most women veiled Children assessed within 24hour of birth by DXA	WB BMC(g) WB BMD (g/cm^2)	Nil	Delivery	Overall not given SGA= 21.8 (7.5) AGA= 21.5 (7.5) LGA=19.3 (7.0) >90% had 25(OH)D <25 nmol/l	WB BMC; r= −0.055 WB BMD; r=0.042			Not given			No relationship observed between maternal 25(OH)D at delivery and neonatal BMC and BMD
Viljakainen, 2010 [94]	3 (med)	Cohort	Helsinki, Finland n=125 women recruited during last trimester (Oct-Dec). All Caucasian, non-smokers, primiparous Children assessed when newborn by pQCT of tibia	Tibial BMC (g/cm), tibial CSA (mm^2) and tibial BMD (mg/cm^3)	3 models: **1** adjusted for z score birth weight **2** as above + maternal height **3** as above +log(age of newborn at pQCT)	First trimester (8-10 weeks) and 2 days post-partum. Mean of 2 values used to calculate ,vitamin D status-	At 8-10 weeks = 41.0 (13.6) Postpartum = 45.1 (11.9) Overall median ,vitamin D status=- 42.6	Bone outcome	r for log 25(OH) D p value		r after adjust 1	r after adjust 2	r after adjust 3	A positive significant association seen between maternal 25(OH)D status and offspring tibial BMC and tibial CSA. Tibial BMC and CSA significantly higher in those with maternal 25(OH)D above median than those below even after adjustments No association seen with tibial BMD
								Tibial BMC	0.149, p=0.163		0.232 P=0.034	0.230 p=0.036	0.192 P=0.085	
								Log (tibial CSA)	0.197, p=0.05		0.214 p=0.05	0.218 P=0.048	0.226 P=0.042	
Viljakainen 2011 [99]	4 (med)	Cohort	Helsinki, Finland n=68 women Children assessed at 14 months by pQCT of tibia This was a follow-up study of same cohort as Viljakainen, 2010). 55 children had bone data at both time-points	Tibial BMC (g/cm), tibial CSA (mm^2) and tibial BMD (mg/cm^3)	Sex, birth weight z score, walking age, exclusive breast feeding and offspring 25(OH)D at 14 months.	First trimester (8-10 weeks) and 2 days post-partum. Mean of 2 values used to calculate ,vitamin D status-	Not given Overall median "vitamin D status" = 42.6	Not given			Not given			No difference in tibial BMC or BMD in offspring with maternal 25(OH)D above median than those below CSA higher at 14 months in offspring with maternal 25(OH)D above median than those below. This suggest that postnatal vitamin D supplementation only partly improved the differences in bone variables induced by maternal vitamin D

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First Author and year	Bias score	Study Type	Study Details, age at which children were assessed and technique used	Offspring bone outcomes assessed (units)	Confounders/ adjustments	Number of weeks gestation when maternal 25(OH)D 3 was measured	Mean (SD) or median (IQR) maternal 25(OH)D concentration (nmol/l)	Mean (SD) bone outcome according to maternal 25(OH)D category/ Unadjusted correlation co-efficient (r) or regression co-efficient (β) (95% CI)	Adjusted correlation co-efficient (r) or regression co-efficient (B) (95% CI)	conclusion
										status during pregnancy status during pregnancy
Dror, 2012 [93]	7 (low)	Cross-sectional	Oakland California, USA n=120 women Children assessed between 8-21 days old by DXA	WB BMC WB aBMC	Maternal height, GDM, infant age at DXA, feeding practice (breast, formula, mixed), infant weight-for-height z score, infant height-for age z score, bone area and size for gestational age	Per-natal	75.5 (32.3)	WB BMC β= −0.02 (p=0.52)	WB aBMC: β= 0.0007 (−0.031, 0.032) P=0.97	No association seen between maternal 25(OH)D and offspring WB BMC or WB aBMC either analysed continuously or categorically

SGA = small for gestational age, AGA = appropriate for gestational age, LGA = large for gestational age

WB BMC= whole body bone mineral content, WB BMD = whole body bone mineral density, WB BA= whole body bone area, aBMC= bone mineral content adjusted for bone area)

DXA= Dual energy X-ray absorptiometry

SPA= Single photon absorptiometry

pQCT= peripheral quantitative computed tomography

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Table 15

The effect of vitamin D supplementation in gestation on offspring bone mass – Intervention studies

First Author, year	Risk of bias	Setting	Randomisation and study Details, Age at which children were assessed and technique used	Offspring bone outcomes assessed (units)	Adjustments /confounders accounted for	Number of weeks gestation when 25(OH)D was measured	Mean (SE) maternal 25(OH)D concentration (nmol/l)	Mean (SE) offspring bone outcome (units) in unsupplemented group	Mean (SE) bone outcome(units) in supplemented group	Conclusion
Congdon, 1983 [22]	−9 (high)	Leeds, UK n=64, all Asian women	Either 1000 IU vitamin D plus calcium (calcium dose not given) daily in the 3rd trimester (n=19) or no supplement (n=45) Offspring assessed within 5 days of birth. Method of bone measurement not given	Forearm BMC (units not given)	Nil, but groups similar in terms of maternal age, infant sex, gestation length, birth weight	Not measured	Not measured	3.10 (0.10)*	3.19 (0.12)*	No difference in forearm BMC between groups p value not given

*Results expressed in arbitrary units proportional to the mineral mass per unit length of the radius and ulna combined

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Table 16

The effect of maternal vitamin D status in gestation on offspring anthropometry and body composition – Observational studies

First Author and year	Bias score	Study type	Study Details, age at which children were assessed and technique used	Offspring outcome assessed (units)	Confounders/ adjustments	Number of weeks gestation when maternal 25(OH)D3 was measured	Mean (SD) or median (IQR) maternal 25(OH)D concentration (nmol/l)	Mean (SD) offspring outcome according to maternal 25(OH)D category/Unadjusted correlation coefficient (r) or regression coefficient (B) (95% CI)			Adjusted correlation coefficient (r) or regression coefficient (B) (95% CI)	Conclusion
Weiler, 2005 [86]	3 (med)	Cross-sectional	Winnipeg, Canada Sample size for analysis=50 women Neonates delivered at term and assessed within 15 days of birth by DXA	Whole body fat (%)	Nil, but no significant difference in terms of offspring sex, season of birth, gestational age at birth in mothers with 25(OH)D >37.5 nmol/l compared with those with 25(OH)D <37.5 nmol/l Significant difference in race between the 2 groups (o=0.010	Within 48 hours of delivery	Overall mean not given Mean in adequate 25(OH)D group (>37.5 nmol/l, n=32)= 61.6 (24.7) Mean in the deficient group (<37.5 nmol/l, n=18)=28.6 (7.8)		Maternal 215(OH)D <37.5 nmol	Maternal 25(OH)D >37.5 nmol	Not given	No significant difference in offspring whole body fat in those with maternal 25(OH)<37.5 nmol/l compared to those with maternal 25(OH)D >37.5 nmol/l
								Mean (SD) neonatal whole body fat (%)	12.7 (4.1)	10.6 (4.1)		
Morley, 2006 [91]	8 (low)	Cohort	Melbourne, Australia n=374 women (232 recruited in winter, 127 in summer) Neonates assessed between 12-72 h of age using calipers/ encircling tape	Subscapular skinfold (mm) Triceps skinfold (mm) Suprailiac skin fold (mm) Mid upper-arm circumference (cm) Calf circumference (cm)	Sex, maternal height, whether first child, smoking, season of blood sample	11 weeks and 28-32 weeks	Winter recruitment, geometric mean at 11 wks=49.2; 26-32 wks=48.3 Summer recruitment geometric mean at 11 weeks=62.6; 26-32 wks=68.9		β (95% CI) for every Log_2 increase in maternal 25(OH)D (i.e. doubling of 25(OH)D at 28-32 wks		Adjusted β (95% CI) for every Log_2 increase in maternal 25(OH)D (i.e. doubling of 25(OH)D) at 28-32 weeks	A weak inverse association seen between maternal 25(OH)D and offspring subscapular and triceps skinfold thickness. No significant association seen with suprailiac skinfold thickness, mid upper arm circumference or calf circumference after adjustment for confounders
								Subscapular skinfold (mm)	−0.2 (−0.4, −0.02)		−0.2 (−0.4, −0.06)	
								Triceps skinfold (mm)	−0.3 (−0.5, −0.02)		−0.1 (−0.4, 0.1)	
								Suprailiac skin fold (mm)	−0.06 (−0.4, 0.1)		−0.06 (−0.4, 0.2)	
								Mid upper arm circumference (cm)	0.08 (−0.07, 0.2)		0.1 (−0.06, 0.3)	
								Calf circumferene (cm)	0.05 (−0.1, 0.2)		0 (−0.2, 0.2)	
Gale, 2008 [25]	4 (med)	Cohort	Princess Anne Cohort, Southampton, UK Children assessed at birth n=466), 9 months (n=440) and 9 years (n=178) using measuring	Mid-upper arm circumference (cm) at birth and 9 months Fat mass (kg) Lean mass (kg) at 9 years	Adjusted for age of child at scan	Late pregnancy (median (IQR) 32.6 (32-33.4) weeks	50 (30-75.3) 50.4% had 25(OH)D >50nmol/k 28.3% had levels 27.5-50 nmol/l 21.1% had levels <27.5 nmol/l	P value for difference in offspring outcome according to quartile of maternal 25(OH)D			Not given	No significant association between maternal 25(OH)D concentration measured in late pregnancy and offspring's mid upper arm circumference at birth and 9 months.
									p value			
								Mid-upper arm circumference at birth	0.080			
								Mid-upper arm circumference at 9 months	0.581			

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First Author and year	Bias score	Study type	Study Details, age at which children were assessed and technique used	Offspring outcome assessed (units)	Confounders/ adjustments	Number of weeks gestation when maternal 25(OH)D3 was measured	Mean (SD) or median (IQR) maternal 25(OH)D concentration (nmol/l)	Mean (SD) offspring outcome according to maternal 25(OH)D category/Unadjusted correlation coefficient (r) or regression coefficient (B) (95% CI)	Adjusted correlation coefficient (r) or regression coefficient (B) (95% CI)	Conclusion
			tape with DXA at 9 years only					Fat mass at 9 years: 0.090 Lean mass at 9 years: 0.090		At 9 years fat mass and lean mass tended to be lower in children born to mothers in the lowest of 25(OH)D distribution but no statistically significant linear trends seen.
Sayers, 2009 [42]	3 (med)	Cohort	ALSPAC, cohort, UK n=6955 women Children assessed at mean age 9.9 years by DXA	Lean mass (kg) fat mass (kg)	Nil	Not directly measured Ambient UVB measured during 98 days preceding birth	Not measured	Lean mass (kg): β (95% CI) change in outcome per 1 SD increase in UVB: 163 (89, 237); P value: 0.00002 Fat mass (kg): 73.9 (−44.2, 191.9); 0.22	Not given	Maternal UVB exposure in pregnancy is positively associated with offspring lean mass at age 9 years. No significant association seen with fat mass.
Krishnaveni, 2011 [102]	4 (med)	Cohort	Mysore Parthenon Study, Mysore, India Children assessed at 5 years (n=506) and 9.5 years (n=469) using measuring tape, calipers and bioimpedence	Arm muscle area (AMA; cm^2) Subscapular skinfold, thickness (mm), Triceps skinfold thickness (mm), Waist circumference, Fat mass (kg), Percent body fat (%), Fat-free mass (kg), Percent fat-free mass (%)	Offspring sex and age, maternal BMI, gestational diabetes, socioeconomic score, parity and religion	28-32 weeks (at study entry)	39.0 (24-58) 67% of women had 25(OH)D <50 nmol/l (the authors definition of deficiency)	Not given	Comparing offspring of mothers with and without 25(OH)D deficiency (deficient=0, non-deficient=1) 5 yr: β / P Value AMA: 0.4 / 0.01 Subsca p: .004 / 0.86 Triceps: 0.01 / 0.55 Waist: 0.07 / 0.81 Fat mass: −0.01 / 0.92 %Fat: −0.4 / 0.48 Fat-free mass: 0.1 / 0.33 %fat free mass: 0.3 / 0.51 9.5 yr AMA: 0.7 / 0.02 Subscap: −.009 / 0.80 Triceps: .004 / 0.88 Waist: 0.3 / 0.62 Fat mass: −0.07 / 0.77	At ages 5 and 9.5 years offspring born to women with 25(OH)D <50 nmol/l in late pregnancy had significantly reduced arm-muscle area in comparison to those children born to mothers without deficient. No significant difference seen in any of the other anthropometric or body composition measurements

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First Author and year	Bias score	Study type	Study Details, age at which children were assessed and technique used	Offspring outcome assessed (units)	Confounders/ adjustments	Number of weeks gestation when maternal 25(OH)D3 was measured	Mean (SD) or median (IQR) maternal 25(OH)D concentration (nmol/l)	Mean (SD) offspring outcome according to maternal 25(OH)D category/Unadjusted correlation coefficient (r) or regression coefficient (B) (95% CI)			Adjusted correlation coefficient (r) or regression coefficient (B) (95% CI)			Conclusion
											%Fat mass	−0.6	0.34	
											Fat free mass	0.2	0.50	
											%Fat free mass	0.6	0.33	
Crozier, 2012 [103]	8 (low)	Cohort	Southampton Women's Survey, UK Children assessed at birth (574), 4 years (565) and 6 years (447) using DXA	Fat mass (kg) Fat free mass (kg)	Offspring sex, gestation, age at measurement, length/ height, maternal educational attainment, smoking in pregnancy, pre-pregnancy BMI, maternal height, parity, social class, Institute of Medicine weight gain category, breastfeeding duration, vitamin D intake at 3 years, physical activity at 3 years	34 weeks	62 (43-89)	Outcome	Unadjusted β (95% CI)	P Value	Adjusted β (95% CI)	P value		Positive association between late pregnancy maternal 25(OH)D and offspring fat mass at birth after adjusting for confounders. Negative association late pregnancy maternal 25(OH)D and fat mass at 6 years after adjusting for confounders. No significant association seen at 4 years after adjustments for confounders.
								Birth fat mass (SD)	0.06 (−0.01, 0.12)	0.09	0.08 (0.02, 0.15)	0.02		
								Birth fat-free mass (SD)	0.02 (−0.03, 0.07)	0.44	0.04 (−0.02, 0.09)	0.17		
								4-y fat mass (SD)	−0.09 (−0.16, 0.02)	0.02	−0.01 (−0.08, 0.07)	0.81		
								4-y fat-free mass (SD)	0.03 (−0.02, 0.08)	0.21	0.03 (−0.02, 0.08)	0.30		
								6-y fat mass (SD)	−0.16 (−0.23, −0.08)	<0.001	−0.10 (−0.17, −0.02)	0.01		
								6-y fat-free mass (SD)	0.01 (−0.04, 0.06)	0.65	0.02 (−0.03, 0.07)	0.43		

DXA = Dual energy X-ray absorptiometry

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Table 17

The effect of vitamin D supplementation in gestation on offspring anthropometry and body composition – intervention studies

First Author, year	Risk of bias	Setting	Randomisation and study Details, Age at which children were assessed and technique used	Offspring outcome assessed (units)	Adjustments/ confounders accounted for	Number of weeks gestation when 25(OH)D was measured	Mean (SE) maternal 25(OH)D concentration (nmol/l)	Mean (SD)/ Mean (SE)* offspring outcome (units) in un-supplemented group		Mean (SD)/ Mean (SE)* offspring outcome(units) in supplemented group		Conclusion
Brooke 1980 [4]	−2 (high)	London, UK, n=126, all Asian women	Double-blinded Randomised to either placebo (n=67) or 1000 IU/day of vitamin D2 in last trimester (n=59) Offspring assessed within 48 hours of birth. Method of measurement not given	Triceps skinfold (mm) Forearm length (cm) Fontanelle area (cm^2)	Nil, but groups of similar age, height, parity, offspring sex, length of gestation	28−32 weeks and at birth	At allocation 25(OH)D =20.1 (1.9)* At term, Controls 25(OH)D=16.2 (2.7)* At term, supplemented group 25(OH)D=168.0 (12.5)*	Triceps skinfold (cm)	3.6 (0.1)*	Triceps skinfold (cm)	3.8 (0.1)*	Significantly greater fontanelle area in the supplemented group ($p<0.05$). No significant difference in forearm length or triceps skinfold thickness
								Forearm length (cm)	8.1 (0.1)*	Forearm length (cm)	8.1 (0.1)*	
								Fontanelle area	6.1 (0.7)*	Fontanelle area	4.1 (0.4)*	
Marya, 1988 [6]	−2 (high)	Rohtak, India N=200 women	Randomised to either no supplement (n=100) or oral 600,000 IU vitamin D3; 2 doses in 7th and 8th months gestation (n=100) Offspring measured within the first 24 hours of birth using calipers and measuring tape	Mid-arm circumference (cm) Triceps skinfold thickness (mm) Infrascascapular skinfold thickness (mm)	Nil, but groups had similar maternal age, maternal height, maternal height, parity, haemoglobin, calcium intake and vitamin D intake	Not measured	Not measured directly, but mean daily vitamin D intake given as follows: Un-supplemented = 35.71 (6.17) IU/day Supplemented group = 35.01 (7.13) IU/day	Mid-arm circum (cm)	9.44 (0.85)	Mid-arm circum (cm)	9.82 (0.72)	Significantly higher mid-arm circumference, triceps skinfold and infrascapular skinfold in the supplemented group (all $p<0.01$)
								Triceps skinfold (mm)	7.30 (0.83)	Triceps skinfold (mm)	7.72 (0.67)	
								Infrascap skinfold (mm)	7.49 (0.89)	Infrascap skinfold (mm)	7.82 (0.67)	

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Table 18

The effect of maternal vitamin D status in gestation on offspring asthma and atopy— Observational studies

First Author and year	Bias score	Cohort details	Study type	Adjustments	When was maternal serum 25 OH D measured	Mean (SD) or median (IQR) 25OHD3 concentration (nmol/l-unless other stated)	Risk of Asthma/Wheeze/ Eczema	Conclusion
Camargo, 2007 [106]	2 (med)	Massachusetts, USA Cohort = 2128 women 1194 (56%) studied for outcome	Cohort	Sex, birth weight, income, maternal age, pre-pregnancy BMI, passive smoking exposure, breastfeeding duration, number of children in household, maternal and paternal history of asthma, dietary intake of fish, fruit and vegetables	Not measured Based on modification to validated food frequency questionnaire at initial prenatal visit and 26-28 weeks gestation.	Not measured Mean vitamin D intake (mean of early pregnancy and 26-28 week for each participant) was 548 (167) IU/ day.	In comparison to the lowest quartile, mothers in the highest quartile of daily vitamin D intake had a lower risk of having a child with recurrent wheeze at 3years (OR 0.38; 95%CI 0.22−0.65).	A higher maternal intake of vitamin D during pregnancy was associated with a lower risk of recurrent wheeze in children at 3 years of age
Devereux, 2007 [27]	−1 (high)	Aberdeen, Scotland Cohort = 1924 mother-offspring pairs 1212 (63%) children included in questionnaire follow up at 5 years; 797 (41%) children had lung function assessment and skin prick testing at 5 years	Cohort	Adjusted for maternal atopy, age, smoking, education, social class, deprivation index based on area of residence, breastfeeding, infant sex, infant antibiotic use in first year, birth weight, birth order, season of last menstrual period, maternal intakes of vitamin E, zinc and calcium.	Not measured Estimated from food frequency questionnaire at 32 weeks gestation.	Not measured Median maternal vitamin D intake 131 (102-173)IU/day	In models adjusted for potential confounders, including the children's vitamin D intake, compared to the lowest quintile, the highest quintile of maternal vitamin D intake displayed lower risk of "ever wheeze" (OR: 0.48; 95%CI: 0.25-0.91), and "wheeze in the previous year" (OR: 0.35; 95%CI 0.15-0.83) at 5years determined by parental questionnaire. No differences in atopic sensitization or spirometry.	Low maternal vitamin D intakes during pregnancy are associated with increased wheezing symptoms in children at 5 years.
Gale, 2008 [25]	4 (med)	Princess Ann Cohort, Southampton, UK n= 440 at 9 months n=178 at 9 years	Cohort	Nil	Late pregnancy Median (IQR)= 32.6 (33-33.4) weeks	50 (30-75.3) 50.4% had 25(OH)D >50nmol/k 28.3% had levels 27.5-50 nmol/l 21.1% had levels <27.5 nmol/l	OR (95% CI) for eczema or asthma 25(OH)D: <30 / 30-50 / 50-75 / >75 Visible eczema on examination at 9 months: 1.0 / 0.59 (0.14-2.50) / 0.79 (0.21-3.00) / 3.26 (1.15-9.29) Atopic eczema at 9 months (UK working party criteria): 1.0 / 1.11 (0.43-2.84) / 1.75 (0.73-4.17) / 1.62 (0.67-3.89) Reported eczema at 9 years: 1.0 / 0.71 (0.15-3.39) / 0.49 (0.08-2.68) / 1.89 (0.51-6.99)	

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First Author and year	Bias score	Cohort details	Study type	Adjustments	When was maternal serum 25 OH D measured	Mean (SD) or median (IQR) 25OHD3 concentration (nmol/l-unless other stated)	Risk of Asthma/Wheeze/ Eczema					Conclusion
							Reported asthma at 9 years	1.0	2.05 (0.36-11.80)	2.05 (0.36-11.80)	5.40 (1.09-26.65)	
Erkkola, 2009 [104]	−1 (high)	Finland — 3 university hospitals Cohort = 4193 women 1669 (40%) studied for outcome	Cohort	Adjusted for sex, area of birth, gestation, maternal age, maternal education, smoking during pregnancy, siblings, parental asthma, atopic eczema, pets in house before 1 years, maternal intake of vitamin C, vitamin E, selenium and zinc	Not measured Estimated from food frequency questionnaire. Completed retrospectively after delivery for 8th month of pregnancy.	Not measured Mean total maternal vitamin D intake 260 (152)IU/day.	After adjustment, maternal total vitamin D intake associated with reduced risk of asthma (HR 0.76; 95%CI 0.59-0.99) and allergic rhinitis (HR 0.84; 95% CI 0.72-0.98) but not atopic eczema (OR 0.94; 95% CI 0.83-1.07) at 5 years					Maternal vitamin D intake during pregnancy inversely associated with the development of asthma and allergic rhinitis
Miyake, 2010 [105]	−1 (high)	Osaka, Japan Cohort = 1002 women 763 (76%) studied for outcome	Cohort	Adjusted for maternal age, gestation at baseline, residential municipality during pregnancy, family income, maternal and parental education, history of asthma, atopic eczema and allergic rhinitis, season, changes in diet, smoking, older siblings, sex, birth weight, age at child assessment.	Not measured Self administered validated questionnaire of dietary intake. Measured between 5 and 39 weeks of pregnancy.	Not measured Mean intake of vitamin D= 248 (148) IU/day	Consumption of ≥4.309 mcg/day vitamin D associated with a decreased risk of wheeze (adjusted OR 0.64; 95% CI 0.43-0.97) and eczema (adjusted OR 0.41-0.98) at 16-24 months of age.					Higher consumption of vitamin D in pregnancy was associated with a lower risk of wheeze and eczema in infancy.
Nwaru, 2010 [111]	3 (med)	Finland Cohort = 1175 women 931 (79%) studied for outcome	Cohort	Place and season of birth, sex, siblings, gestational age at birth, parental asthma and allergic rhinitis, maternal age at delivery, maternal smoking, and maternal education.	Not measured Estimated from food frequency questionnaire. Completed retrospectively after delivery for 8th month of pregnancy.	The mean daily intake of vitamin D during pregnancy by the mothers was 208(112) IU/day. Of the women, 28% had taken vitamin D supplements during pregnancy with a mean intake of 44 (96) IU/day.	Increasing maternal intake of vitamin D was inversely association with sensitization (specific IgE≥0.35KU/l) to food allergens (adjusted OR 0.56 (95%CI 0.35-0.91, p<0.026) but not inhaled allergens (adjusted OR 0.76 (95%CI 0.50-1.17) at 5 years of age.					Increasing maternal intake of vitamin D was inversely associated with sensitization to food allergens.
Camargo, 2011 [107]	3 (med)	Wellington and Christchurch, New Zealand Cohort = 922 women	Cohort	Season of birth, study site, maternal age, parental history of asthma,	Not measured Cord blood 25(OH)D were measured	Not measured Median cord blood 25(OH)D= 44nmol/L (IQR 29−78).	Adjusting for season, the OR for cumulative wheeze at 5 years increased across categories of 25(OH)D (1.00 [reference] for ≥75 nmol/L, 1.63 [95% CI: 1.17-2.26] for 25−74 nmol/L, and 2.15 [95% CI: 1.39−3.33] for <25 nmol/L). No association with incident asthma at 5 years					Cord-blood levels of 25(OH)D had inverse associations with

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First Author and year	Bias score	Cohort details	Study type	Adjustments	When was maternal serum 25 OH D measured	Mean (SD) or median (IQR) 25OHD3 concentration (nmol/l-unless other stated)	Risk of Asthma/Wheeze/ Eczema	Conclusion
		823 (89%) studied for outcome 823 (89%) studied for outcome 823 (89%) studied for outcome		gestational age, birth weight, child's gender and ethnicity, smoking, number of children in household, during of exclusive breastfeeding.				childhood wheezing but no association with incident asthma.
Cremers, 2011 [110]	3 (med)	Netherlands Cohort = 2834 women (2343 women with a conventional lifestyle; 491 women with an alternative lifestyle with regards to child rearing practices, diet an vaccination programmes) 415 (14.6%) studied for outcome	Cohort	Recruitment group (conventional or alternative lifestyle), maternal age, maternal education, maternal smoking, alcohol consumption, pre-pregnancy BMI, child's BMI at 2 years, birth weight, exposure to tobacco smoke, season of blood sampling, physical activity	36 weeks gestation	46.0(18.2) nmol/l	No association between maternal plasma 25(OH)D at 36weeks gestation and offspring FEV_1 (p=0.99) nor FVC p=0.59) at 6-7 years	No association between maternal late pregnancy 25-hydroxyvitamin D levels and lung function in children aged 6-7 years.
Rothers, 2011 [108]	2 (med)	Tucson, Arizona, USA Cohort = 482 women 219 (45%) studied for outcome	Cohort	Maternal ethnicity, household smoking, birth season	Not measured Plasma levels of 25(OH)D measured in cord blood specimens	Not measured Median cord blood 25(OH)D = 64 nmol/L (IQR 49-81)	Both total and inhalant allergen specific IgE showed non-linear associations with cord blood 25(OH)D in that levels were highest in those with cord blood 25(OH)D<50nmol/l and >100nmol/l. Greater risk of skin-prick testing positivity to aeroallergens at 5 years in children with cord 25(OH)D ≥100nmol/l compared with reference group (25(OH)D 50-74.9nmol/l): OR3.4; 95%CI 1.0-11.4, p=0.046)	Non-linear relationship between vitamin D status at both and markers of atopy at 5 years
Morales 2012 [109]	3 (med)	Spain, Cohort=2860 women enrolled in the INMA project (Infancia y Medio Ambiente) 1233 (43%) children studied for outcome	Cohort	Offspring sex, maternal pre-pregnancy BMI, maternal history of asthma, maternal educational level, maternal smoking in pregnancy, breastfeeding duration, day-care attendance in the first year of life, and area of study	Between 12-23 weeks gestation Mean (SD) =12.6 (2.5) weeks	Median= 73.6 (56.2-92.6) nmol/l	No significant association seen between maternal 25(OH)-vitamin D and: wheeze at 1 year (unadjusted p=0.453, adjusted p=0.441 wheeze at 4 years (unadjusted p=0.559, adjusted p=0.708 asthma at 4-6 years (unadjusted p=0.339; adjusted p=0.481	No association seen between maternal 25(OH)-vitamin D and offspring wheeze at 1 year and 4 years, or offspring asthma at 4-6 years

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Table 19

The effect of maternal vitamin D status in gestation on risk of offspring being born small for gestational age – Observational studies

First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Maternal mean (SD) 25(OH)D concentration (nmol/l) in cases of SGA infants	Maternal mean (SD) 25(OH)D concentration (nmol/l) in infants appropriate for GA (AGA)	Odds ratio (95% CI) of offspring being SGA from univariate analysis	Odds ratio (95% CI) of offspring being SGA from multivariate analysis	Conclusion
Akcakus, 2006 [100]	4 (med)	Turkey Cohort=100 women Cases of SGA*=30 Most women veiled	Cross-sectional	NIl	Delivery	21.75 (7.5)	21.5 (7.5)	Not given	Not given	No difference in maternal 25(OH)D at delivery in SGA infants compared to AGA infants
Mehta, 2009 [118]	3 (med)	Tanzania Overall Cohort=1078. Women all HIV infected taking part in a clinical trial of vitamin use Cases of SGA*=74 Cohort for analysis= 675	Prospective cohort	Multivitamin supplementation, maternal age at baseline, CD4 count at baseline, HIV disease stage at baseline	12-27 weeks (at enrolment to trial)	Mean not given 44.6% had 25(OH)D <80 nmol/l 55.4% had 25(OH) D >80 nmol/l	Mean not given	1.25 (0.81, 1.91) p=0.31	1.25 (0.82, 1.90) p=0.31	No relationship between SGA risk and maternal 25(OH)D amongst women with HIV
Leffelaar, 2010 [82]	5 (low)	Amsterdam Born Children and their development (ABCD) study, Netherlands Cohort=3730 women Cases of SGA*=9.2% (approx. 343)	Prospective cohort	2 models OR1 adjusted for gestational age, season of collection, sex, maternal parity, maternal age, smoking, pre-pregnancy BMI, educational level OR2 additional adjustment for ethnic group and vitamin D status	Early pregnancy (mean 13 weeks)	Not given	Not given	Crude OR adjusted for season of blood sample and gestational age 25(OH)D nmol/l — Crude OR (95% CI) <30 — 2.4 (1.0-3.2) 30-49.9 — 1.5 (1.1-2.0) 50+ — 1.0 (Ref)	 25(OH)D nmol/l — OR1 (95% CI) — OR2 (95% CI) <30 — 1.8 1.3-2.5 — 1.9 (14-2.7) 30-49.9 — 1.2 0.9-1.7 — 1.2 (0.9-1.3) 50+ — 1.0 (Ref) — 1.0 (Ref)	After adjusting for confounders, women with 25(OH)D <30 have a significantly increased risk of SGA infant
Bodnar, 2010 [112]	7 (low)	Pittsburg, USA Overall cohort size=1198 women Cases of SGA*=111 Controls=301	Nested case-control	Pre-pregnancy BMI, smoking during pregnancy, socioeconomic score. Additional adjustments for season, maternal age, gestational age at blood sampling, marital status, insurance status, smoking pre=pregnancy, pre conceptual multivitamin use, preconception physical activity had no	<22 weeks <22 weeks	Geometric mean (95% CI) according to race White= 73.2 (69.7, 76.8) Black=39.8 (36.7, 43.2) Geometric mean (95% CI) according to race White= 73.2 (69.7, 76.8) Black=39.8 (36.7, 43.2)	Geometric mean (95% CI) according to race White= 71.5 (64.0, 79.9) Black= 39.8 (33.6, 47.0) Geometric mean (95% CI) according to race White= 71.5 (64.0, 79.9) Black= 39.8 (33.6, 47.0)	OR broken down according to race 25(OH)D Nmol/l — White — Black <37.5 — 10.6 (2.6, 42.5) — 1.4 (0.5, 3.1) 37.5-75 — 1.0 (ref) — 1.0 (Ref) >75 — 1.0 (ref) — 1.9 (1.1, 3.4) OR broken down according to race	Adjusted OR broken down according to race White — Black 7.5 (1.8, 31.9) — 1.5 (0.6, 3.5) 1.0 (ref) — 1.0 (ref) 2.4 (1.2, 4.8) — 2.0 (0.5, 5.5) Adjusted OR broken down according to race	No relationship between SGA risk and maternal 25(OH)D amongst black mothers No sig. difference in relationship between geometric means of 25(OH)D in white amongst black and without mothers No sig. difference in shaped the relation was geometric means of 25(OH)D in white women with and without SGA infants. A u-shaped relation was

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First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Maternal mean (SD) 25(OH)D concentration (nmol/l) in cases of SGA infants	Maternal mean (SD) 25(OH)D concentration (nmol/l) in infants appropriate for GA (AGA)	Odds ratio (95% CI) of offspring being SGA from univariate analysis	Odds ratio (95% CI) of offspring being SGA from multivariate analysis	Conclusion
				meaningful impact on results meaningful impact on results						seen between SGA risk and maternal 25(OH)D amongst white mothers with the lowest risk between 6080 nmol/l
Shand, 2010 [114]	6 (low)	Vancouver, Canada All women had either clinical or biochemical risk factors for preeclampsia△ Cohort=221 women Cases of SGA**=13	Cohort	Maternal age, ethnicity, parity, BMI, season, multivitamin use, smoking	Between 10 and 20 weeks 6 days (mean 18.7 (1.88) weeks)	Not given	Not given	25(OH)D Nmol/l Unadjusted values not given <37.5 37.5-75 >75	White Black 10.6 (2.6, 42.5) 1.4 (0.5, 3.1) 1.0 (ref) 1.0 (Ref) 1.9 (1.1, 3.4) 1.9 (1.1, 3.4)	25(OH)D conc OR (95% CI) 7.5 (1.8, 31.9) 1.78 (0.65, 5.03) <50 1.0 (ref) 50-75 2.94 (0.55, 8.49) >75 2.76 (0.26, 18.2) 7.5 (1.2, 6.8) 3.2 (0.6, 5.5)	No significant relationship seen between maternal 25(OH)D and risk of infant being SGA
Robinson 2011 [113]	1 (med)	South Carolina, USA All women has early onset preeclampsia (EOSPE)△△ Cases=33 Controls=23	Case-control	No significant differences between cases and controls in terms of maternal age, nulliparity, African-American race, mean arterial blood pressure, BMI. Cases had significantly higher age at gestation, therefore all birth weights converted to percentile growth for gestational age	Not given	41.9 (22.2-57.4)	63.1 (39.9-82.4)	Not given	Not given	Serum 25(OH)D significantly lower in women with EOSPE and SGA offspring compared to EOSPE controls with normal sized offspring p=0.02
Fernandez-Alonso, 2012 [115]	3 (med)	Almeria, Spain Cohort=466 women Cases of SGA*=46	Cohort	Nil	Between 11-14 weeks	Overall mean not given	Not given	Not given	Not given	No significant relationship seen between maternal 25(OH)D and risk of infant being SGA p=0.78

*SGA defined as infants born <10th percentile of birth weight according to nomograms based on gender and gestational age

**SGA defined as infants born <3rd percentile of birth weight according to nomograms based on gender and gestational age

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△Defined as past obstetric history of early-onset or severe preeclampsia, unexplained elevated α-fetoprotein ≥ 2.5 multiples of the median (MoM), unexplained elevated human chorionic gonadatrophin, or low pregnancy-associated plasma protein A ≤ 0.6 MoM

△△Defined as meeting the American College of Obstetrics and Gynecology criteria for severe preeclampsia and having this diagnosis at <34 weeks gestation

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Table 20

The effect of vitamin D supplementation in gestation on risk of offspring being born small for gestational age in the offspring – Intervention studies

First Author, year	Risk of bias	Setting	Randomisation	Adjustments/ confounders accounted for	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l)			Percentage of infants SGA* in un-supplemented group	Percentage of infants SGA* in supplemented group	Conclusion
Brooke, 1980 [4]	−2 (high)	London UK, n=126 women (all Asian)	Double-blinded Randomised to either placebo (n=67) or 1000 IU/day of vitamin D2 in last trimester (n=59)	Nil, but groups of similar age, height, parity, offspring sex, length of gestation	28-32 weeks and at birth	At allocation 25(OH)D = 20.1 (1.9) At term, Controls 25(OH)D= 16.2 (2.7) At term, supplemented group 25OHD3 = 168.0 (12.5)			28.6% (19 out of 67)	15.3% (9 out of 59)	No significant difference in risk of SGA between groups p>0.05; X^2 = 3.1
Yu, 2009 [96]	5 (low)	London, UK n=119 women	3 arms Randomised to either no supplement (n=59) or oral vitamin D2 800 IU/day vitamin from 27 weeks onwards (n=60), or a single 200,000 IU D2l at 27 weeks gestation (n=60) Each group contained equal numbers of 4 ethnic groups (Caucasian, Black, Asian, Middle Eastern)	Nil No significant difference in baseline characteristics across the 3 groups	Measured at 26-27 weeks and again at delivery		27 wks	Delivery	17%	15% in daily dose group 13% in stat dose group	No significant difference in rate of SGA across the 3 groups p=0.7
						No sup	25 (21-38	27 (27-39)			
						Daily sup	26 (20-37)	42 (31-76)			
						Single sup	26 (30-46)	34 (30-46)			

*SGA defined as infants born <10th percentile of birth weight

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Table 21

The effect of maternal vitamin D status in gestation on preterm birth of the offspring – Observational studies

First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Maternal mean (SD) 25(OH)D concentration (nmol/l) in cases of infants born preterm	Maternal mean (SD) 25(OH)D concentration (nmol/l) in full-term infants	Odds ratio (95% CI) of offspring being preterm from univariate analysis	Odds ratio (95% CI) of offspring being preterm from multivariate analysis	Conclusion
Delmas, 1987 [117]	-4 (high)	Lyon, France. n=9 women (controls) n=10 women (cases of preterm)* None of the women were taking supplemental vitamin D	Case-control	None	Delivery	44.9 (17.5)	47.4 (7.5)	Not given	Not given	No difference in matemal 25(OH)D at delivery in preterm compared to full-term births p value not given
Mehta, 2009 [118]	2 (med)	Tanzania Overall Cohort=1078 women Women all HIV infected taking part in a clinical trial of vitamin use Cases of preterm birth=204** Cases of severe preterm birth=70*** Cohort for analysis=758	Prospective cohort	Multivitamin supplementation, maternal age at baseline, CD4 count at baseline, HIV disease stage at baseline	12-27 weeks (at enrolment to trial)	Mean not given 34% of preterm, 37% of severe preterm had 25(OH)D <80 nmol/l 66% of preterm, 63% of severe preterm had 25(OH) D>80 nmol/l	Not given	RR if matemal 25(OH)D <80 nmol/l compared to >80 nmol/l Preterm= 0.83 (0.65, 1.07) p=0.14 Severe preterm=0.77 (0.49, 1.19) p=0.24	Adjusted RR if maternal 25(OH)D <80 nmol/l compared to >80 nmol/ Preterm= 0.84 (0.65, 1.07). p=0.15 Severe preterm=0.77 (0.50, 1.18). p=0.23	No increased risk of preterm or severe preterm birth if maternal 25(OH)D <80nmol/l compared with > 80nmol/l
Baker, 2011 [119]	5 (low)	North Carolina, USA Overall cohort size= 4225 women Cases of preterm birth #=40 Controls=120	Nested case-control	Controls matched by race ethnicity in a 3:1 ratio No significant difference in terms of matemal age, ethnicity, parity, private insurance, BMI, gestational age at delivery between cases and controls. Season of blood draw did differ but not significantly (p=0.06) Results adjusted for matemal age, insurance status, BMI, gestational age at serum collection, season of blood draw	11-14 weeks	25(OH)D (nmol/l) / n (%) <50 / 3 (7.5) 50-74.9 / 8 (20) ≥75 / 29 (72.5)	25(OH)D (nmol/l) / n (%) <50 / 8 (6.7) 50-74.9 / 24 (20) ≥75 / 88 (73.3)	25(OH)D (nmol/l) / OR (95% CI) p value <50 / 1.14 (0.31, 4.26) p=0.61 50-74.9 / 1.01 (0.42, 2.46) p=0.99 ≥75 / 1 (Ref)	25 (OH)D (nmol/l) / Adj OR (95% CI) p value <50 / 0.82 (0.19, 3.57) p=0.79 50-74.9 / 0.87 (0.34, 2.25) p=0.77 ≥75 / 1 (Ref)	No significant association seen between maternal 25(OH)D and risk of preterm birth
Shand, 2010 [114]	6 (low)	Vancouver, Canada All women had either clinical or biochemical risk factors for preeclampsia△ Cohort=221 women	Cohort	Matemal age, ethnicity, parity, BMI, season, multivitamin use, smoking	Between 10 and 20 weeks 6 days (mean 18.7 (1.88) weeks)	Not given	Not given	Unadjusted values not given	25(OH)D conc (nmol/l) / OR (95% CI) <37.5 / 0.97 (0.43, 2.21) <50 / 1.02 (0.48, 2.17) ≥50 / 0.89 (0.31, 2.06)	No significant relationship seen between maternal 25(OH)D and risk of preterm birth using 3 different maternal
			Cohort	Matemal age, ethnicity, parity, BMI, season, multivitamin use, smoking	Between 10 and 20 weeks 6 days (mean 18.7 (1.88) weeks)	Not given	Not given	Unadjusted values not given	25(OH)D conc (nmol/l) / OR (95% CI) <50 / 1.29 (0.51, 3.27) ≥50 / 1 (Ref)	No significant relationship seen between maternal 25(OH)D and risk of preterm birth using 3 different maternal

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First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Maternal mean (SD) 25(OH)D concentration (nmol/l) in cases of infants born preterm		Maternal mean (SD) 25(OH)D concentration (nmol/l) in full-term infants	Odds ratio (95% CI) of offspring being preterm from univariate analysis	Odds ratio (95% CI) of offspring being preterm from multivariate analysis		Conclusion
		Cases of preterm birth Cases of preterm birth Cases of preterm birth										25(OH)D cut offs
Hossain, 2011 [120]	4 (med)	Karachi, Pakistan Cohort=75 women Cases of preterm birth** = not given 26% of women covered their arms, hands and head; 76% also covered their face	Cross-sectional	None	At delivery	42.2 (19.5)+		32.9 (16.8)+	Not given	Not given		Maternal 25(OH)D tended to be higher in those who delivered preterm but did not achieve statistical significance (p=0.057)
										>37.5	0.97 (0.43, 2.21)	
										<50	1.02 (0.48, 2.17)	
										<75	0.79 (0.31, 2.06)	
Shibata, 2011 [116]	4 (med)	Toyoake, Japan Cohort size=93 women. Deliveries spread equally across seasons) Cases of threatened premature delivery △△=14	Cross-sectional	Matemal age, serum albumin, serum corrected calcium, serum bone specific ALP, serum Type 1 collagen N-terminal telopeptide, serum phosphate	At recruitment (>30 wks)	30.0 (8.0)		37.9 (12.7)	Not given	β=−0.019 (p=0.023)		Significantly lower maternal 25(OH)D in women with threatened premature delivery compared to normal deliveries. p for difference in means=0.002
Fernandez-Alonso, 2012 [115]	3 (med)	Almeria, Spain Cohort= 466 women Cases of preterm birth** = 33	Cohort	Nil	Between 11-14 weeks	25(OH)D conc (nmol/l)	n (%)	Not given	Not given	Not given		No significant relationship seen between maternal 25(OH)D and risk of preterm birth P=0.86
						<50	7 (21)					
						50-74.9	15 (45)					
						>75	11 (33)					

*No threshold for preterm birth given. Gestational age determined by the scoring system of Dubowitz (based on examination of the neonate and scored on neurological and physical examination features

**Preterm birth defined as delivery at <37 weeks gestation

***Severe preterm birth defined as delivery at <34 weeks gestation

#Preterm birth defined as delivery at >23 weeks and <35 weeks gestation

+25(OH)D3 measured

△Defined as past obstetric history of early-onset or severe preeclampsia, unexplained elevated a-fetoprotein ≥ 2.5 multiples of the median (MoM), unexplained elevated human chorionic gonadatrophin, or low pregnancy-associated plasma protein A ≤ 0.6 MoM

△△This study assessed risk of threatened premature delivery. Defined as progressive shortening of cervical length (<20 mm) as detected by transvaginal ultrasound before the 34th week of gestation, and/or elevation of granulocyte elastase level in the cervical mucus before 32 weeks gestation; AND the number of uterine contractions equal to or more than twice per 30 minutes (before the 32nd week of gestation)

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Table 22

The effect of maternal vitamin D status in gestation on risk of Type 1 Diabetes Mellitus (DM) in the offspring – Observational studies

First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Maternal mean (SD) 25(OH)D concentration (nmol/l) in cases of offspring DM	Maternal mean (SD) 25(OH)D concentration (nmol/l) in offspring without DM	Odds ratio (95% CI) of offspring developing Type 1 Diabetes from univariate analysis		Odds ratio (95% CI) of offspring developing Type 1 Diabetes from multivariate analysis		Conclusion
Stene, 2003 [122]	2 (med)	Norway Cases of offspring Type 1 DM=545 (mean age 10.9 (3.4) years) Controls=1668	Case-control	Controls matched for period of birth (between 1/1/1985 – 31/12/1999) Maternal use of cod liver oil in pregnancy, child's use of cod liver oil or other vitamin D supplement during the first year of life, duration of exclusive breastfeeding, child's age at introduction of solids, maternal education, smoking in pregnancy, maternal age at delivery, child number of siblings, type 1 DM amongst child's siblings or parents, child's age, child's sex	Not measured. Retrospective questionnaire of maternal use of vitamin D supplements during pregnancy. Grouped into either ,no supplements-; ,yes, 1-4 times per week- or ,yes, 5+ times per week-	Not measured	Not measured	Vit D suppl. in pregnancy	OR (95% CI)	Vit D suppl in pregnancy	Adjusted OR (95% CI)	Maternal use of vitamin D supplements in pregnancy were not associated with an increased risk of type 1 DM in the offspring
								No	1 (ref)	No	1 (Ref)	
								Yes, 1-4 times per week	0.86 (0.63, 1.18)	Yes, 1-4 times per week	1.09 (0.77, 1.56)	
								Yes, 5+ times per week	0.89 (0.69, 1.13)	Yes, 5+ times per week	0.98 (0.73, 1.31)	
								p for trend	0.28	p for trend	0.94	
Marjamaki, 2010 [123]	6 (low)	Diabetes Prediction and Prevention study (DIPP), Finland Cohort size=3723 women and their children with increased genetic risk of diabetes* Cases of offspring Type 1 DM=74 (children observed for mean 4.3 (range 0.2-8.9) years	Prospective cohort	2 models: HR1 adjusted for genetic risk and familial type 1 DM HR2 adjusted for genetic risk, familial Type 1 diabetes, sex, gestational age,maternal age, maternal education, delivery hospital, route of delivery, number of earlier deliveries, smoking	Not measured. Estimated from FFQ completed 1-3 months after delivery – focused on food taken in the 8th month of pregnancy and the use of supplements	Not given	Not given	Not given		HR given HR1=1.18 (0.74 p=0.187) p=0.49 HR2=1.08 (0.65 p=1.79) p=0.77		Maternal intake of vitamin D, either from food or supplements is not associated with type 1 DM or advanced B cell autoimmunity in the offspring

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First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Maternal mean (SD) 25(OH)D concentration (nmol/l) in cases of offspring DM	Maternal mean (SD) 25(OH)D concentration (nmol/l) in offspring without DM	Odds ratio (95% CI) of offspring developing Type 1 Diabetes from univariate analysis		Odds ratio (95% CI) of offspring developing Type 1 Diabetes from multivariate analysis			Conclusion
				during pregnancy during pregnancy									
Sorensen, 2012 [121]	8 (low)	Norway Overall cohort=29072 women Cases of offspring type 1 DM= 109 (mean age at diagnosis 9.0 (3.6) years Controls=219	Nested case-control	No significant difference between cases and controls in terms of maternal age, parity, gestational week of blood sample, frequency of C-section or maternal diabetes pre-pregnancy. Significantly more female offspring in cases than controls. Adjustments: 2 models: OR1 adjusted for sex of child and season of blood sample OR2 adjusted for age of child at diagnosis, offspring sex, mothers age at delivery, parity, gestational week of blood sample, pregestational diabetes, season of blood sample, region of residence, percentage undergoing C-section	Median (IQR) cases=37 (22-38) wks Median (IQR) controls=37(24-38) wks	65.8 (26.5))	73.1 (27.2)	25(OH)D conc	OR	25(OH)D conc	OR1	OR2	Trend towards higher risk of type 1 diabetes in the offspring with lower levels of maternal 25(OH)D in late pregnancy, especially in those with 25(OH)D under 54 nmol/l
								>89	1.0 (ref)	>89	1.0 (ref)	1.0 (ref)	
								>69-89	1.32 (0.63, 2.76)	>69-89	1.35 (0.63, 2.89)	Not given	
								>54-69	1.73 (0.86, 3.48)	>54-69	1.78 (0.85, 3.74)	Not given	
								≤54	2.25 (114, 4.46)	≤54	2.38 (1.12, 5.07)	2.39 (1.07-5.11	
								Test for trend Cont.	P=0.022	Test for trend Cont.	0.031	0.032	

* Increased genetic risk defined by genotype HLA DQB1*02*0302 for high risk and HLA-DQB1*0302/x, where x=other than *03, *0301 or *0602 for moderate risk

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Table 23

The effect of maternal vitamin D status in gestation on risk of low birth weight (LBW)* in the offspring – Observational studies

First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Maternal mean (SD) 25(OH)D concentration (nmol/l) in cases of LBW infants	Maternal mean (SD) 25(OH)D concentration (nmol/l) in infants without LBW	Odds ratio (95% CI) of offspring having LBW from univariate analysis	Odds ratio (95% CI) of offspring having LBW from multivariate analysis	Conclusion
Sabour, 2006 [88]	-2 (high)	Tehran, Iran n=449 women Cases of LBW* - not given	Cross-sectional	Nil	Not measured directly Estimated from validated dietary FFQ at delivery (unclear when assessed)	Not given	Not given	Not given	Not given	Incidence of LBW significantly lower with adequate maternal calcium and vitamin D intake (1000mg ca, 200 IU vitamin D) p=0.007
Maghbooli, 2007 [89]	1 (med)	Tehran, Iran n=552 women Cases of LBW*=5.4% (30)	Cross-sectional	None	Delivery**	Not given	Not given	Not given	Not given	No significant association seen between serum 25(OH)D_3 and LBW p not given
Mehta, 2009 [118]	3 (med)	Tanzania Overall Cohort=1078. Women all HIV infected taking part in a clinical trial of vitamin use Cases of LBW*=80 Cohort for analysis=675	Prospective cohort	Multivitamin supplementation, maternal age at baseline, CD4 count at baseline, HIV disease stage at baseline	12-27 weeks (at enrolment to trial)	Mean not given 35% of LBW had 25(OH)D <80 nmol/l 65% had 25(OH) D>80 nmol/l	Not given	0.85 (0.55, 1.32)	0.84 (0.55, 1.28)	No relationship between LBW risk and maternal 25(OH)D amongst women with HIV p=0.42

* LBW defined as infants born <2500g

** Measured 25(OH)D_3

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Table 24

The effect of maternal vitamin D status in gestation and offspring serum calcium (Ca) concentration – Observational studies

First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH) D concentration (nmol/l)	Mean (SD) offspring serum Ca (mmol/l)		Unadjusted regression co-efficient β (95% CI) or correlation coefficient r (95% CI) for offspring serum Ca (mmol/) per 1nmol/l increase in 25(OH)D	Adjusted regression co-efficient β (95% CI) or correlation coefficient r (95% CI) for offspring serum Ca (mmol/) per 1nmol/l increase in 25(OH)D	conclusion
Ardawi, 1997 [87]	5 (low)	Jeddah, Saudi Arabia Cohort size=264 women	Cross-sectional	nil	Delivery	47.71 (15.77) 25(OH)D <20 nmol/l (inadequate) in 23% 25(OH)D>20 nmol/l (adequate) in 77%	Mean cord Ca =2.49 (0.19)		r=0.02 (p=0.40)	No adjustments made	No significant correlation between maternal 25(OH)D measured at delivery and offspring cord Ca No difference in cord Ca if group divided according to maternal 25(OH)D using 20 nmol/l as a threshold (p>0.05)
							Maternal 25(OH)D	Mean (SD) cord calcium concentration (mmol/l)			
							<20 (n=24)	2.48 (0.18)			
							>20 (n=240)	2.40 (0.22)			

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Table 25

The effect of Vitamin D supplementation in gestation on offspring serum calcium (Ca) concentration – Intervention studies

First Author, year	Risk of bias	Setting	Randomisation	Adjustments/ confounders accounted for	Number of weeks gestation when 25(OH)D was measured	Mean (SD)/ Mean (SE)* or median (IQR) 25(OH)D concentration (nmol/l)			Mean (SD) or Mean (SE)* offspring serum calcium conc (mmol/l) in un-supplemented group		Mean (SD) or *Mean (SE) serum calcium conc (mmol/l) in supplemented group		Conclusion
Brooke, 1980 [4]	−2 (high)	London, UK, n=126 women (all Asian)	Double-blinded Randomised to either placebo (n=67) or 1000 IU/day of vitamin D2 in last trimester (n=59)	Nil, but groups of similar age, height, parity, offspring sex, length of gestation 27% of control group and 22% of treatment group bottle fed their infants	28-32 weeks (allocation) and at birth	At allocation 25(OH)D = 20.1 (1.9)* At term, placebo group= 25(OH)D= 16.2 (2.7*) At term, supplemented group 25(OH)D = 168.0 (12.5)*			cord	2.65 (0.02)*	Cord	2.71 (0.02)*	No significant difference in cord Ca between groups at birth , but significantly higher levels in the treatment group at day 3 and 6, but higher rates of breast feeding in the treatment group, which in itself was positively associated with offspring calcium conc. Compared to bottle feeding) When groups considered separately, a weak correlation see between maternal 25(OH)D and cord Ca in the treatment group. r= 0.31, p<0.05 5 cases of symptomatic hypocalcaemia in control group, 0 in treatment group (X^2 = 4.6, p<0.01)
									Day 3	2.18 (0.04)*	Day 3	2.30 (0.04)*	
									Day 6	2.29 (0.02*	Day 6	2.49 (0.04)	
Cockburn, 1980 [21]	−1 (high)	Edinburgh, UK n=1139 women	Either given placebo (n=633) or 400 IU vitamin D_2 (n=506) from week 12 of gestation Deliveries on one ward given placebo, deliveries on another ward given supplement.	Nil, but groups similar in terms of social class, parity, and maternal age. All deliveries between September to May. Maternal age, parity, type of delivery, offspring Apgar score at birth, social class, maternal preeclampsia, birth weight and gestational age were not associated with offspring 6 day Ca concentration	24, 34 weeks and delivery		25(OH)D in placebo	25(OH)D in supp	Cord	2.69 (0.26) (n=452)	Cord	2.66 (0.27) (n=262)	No significant difference in cord blood serum Ca at delivery. Significantly higher serum Ca in infants at day 6 in the supplemented group, independent of infant sex and effects of type of feeding (breast vs. formula) 6% of infants in thesupplemented group were hypocalcaemic at day 6 (Ca<1.85 mmol/l) compared with 13% in the placebo group.
						24 wks	32.5 (n=82)	39.0 (n=82)					
						34 wks	38.5 (n=80)	44.5 (n=80)	Day 6	2.25 (0.3) (n=394)	Day 6	2.34 (0.2) (n=233)	
						delivery	32.5 (n=84)	42.8 (n=80)					
Marya, 1981 [5]	−6 (high)	Rohtak, India n= 120 women	3 arms: Randomised to either no supplement (n=75) or 1,200 IU vitamin D +	Nil	Not measured	Not measured			2.52 (0.23) (value represents cord blood at delivery)		1200IU/+ ca= 2.55 (0.17) 600,000 IU = 2.67 (0.12) (values represents cord blood at delivery)		No difference in cord calcium between un-supplemented and 1200 IU+ 375 mg Ca/ day

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First Author, year	Risk of bias	Setting	Randomisation	Adjustments/ confounders accounted for	Number of weeks gestation when 25(OH)D was measured	Mean (SD)/ Mean (SE)* or median (IQR) 25(OH)D concentration (nmol/l)			Mean (SD) or Mean (SE)* offspring serum calcium conc (mmol/l) in un-supplemented group		Mean (SD) or *Mean (SE) serum calcium conc (mmol/l) in supplemented group		Conclusion
			375mg calcium/ day 375mg calcium/ day throughout the 3rd trimester (n=25); or oral 600,000i IU vitamin D2; 2 doses in 7th and 8th months gestation (n=20)										supplementation Cord Ca significantly higher in those taking 600,000iu supplement compared to un-supplemented (p=0.001)
Congdon, 1983 [22]	−9 (high)	Leeds, UK n=64, all Asian women	Either 1000 IU vitamin D plus calcium (calcium dose not given) daily in the 3rd trimester (n=19) or no supplement (n=45)	Nil, but groups similar in terms of maternal age, infant sex, gestation length, birth weight	Not measured	Not measured			2.50 (0.03)		2.64 (0.05)		Cord Ca significantly higher in the supplemented group P<0.025
Mallet, 1986 [8]	−3 (high)	Rouen, France n=77 women	3 arms: Randomised to either no supplement (n=29) or 1,000 IU vitamin D/day△ in last 3 months of pregnancy (n=21), or single oral dose of vitamin D△ 200,000iu in 7th month (n=27)	Nil, but groups of similar maternal age, parity, calcium intake and frequency of outdoors outings	During labour (February and March)	Overall mean not given According to group: Un-supplemented = 9.4 (4.9) 1000IU/day = 25.3 (7.7) 200,000 IU= 26.0 (6.4)			2.37 (0.11) (value represents cord blood at delivery)		1000 IU/day =2.44 (0.14) 200,000 IU = 2.41 (0.21) (values represents cord blood at delivery)		No significant difference in serum Ca between the 3 groups 1 case of neonatal hypocalcaemia observed in the un-supplemented group (serum Ca 1.69 mmol/l)
Delvin, 1986 [7]	−2 (high)	Lyon, France n=40 women	Randomised to either no supplement (n=20) or 1000 IU vitamin D3/day during 3rd trimester (n=20)	Nil Groups similar in terms of maternal age and parity. All deliveries occurred in the same month (June) All infants of similar gestational age and breast fed from the 6th hour of life	At recruitment (n=50) and at delivery		25(OH)D in suppl. group	25(OH)D in unsuppl group	When measured	Mean infant serum Ca (SE) (mmol/l)	When measured	Mean infant serum Ca (SE) (mmol/l)	Significant correlation between maternal 25(H)D and cord blood total Ca concentration (p<0.005) No significant difference in cord blood total Ca concentration at delivery between groups. At day 4, infant Ca levels were significantly higher in those in the supplemented group (p<0.025) Infant Ca fell significantly more from delivery to day 4 in the un-supplemented group compared to the supplemented group (p<0.05)
						At recruitment (185 days gest)	54.9 (10.0)*	27.5 (10.0)*	Cord at delivery n=15	2.63 (0.025)*	Cord at delivery n=15	2.55 (0.5)*	
						Delivery	64.9 (17.5)*	32.4 (20.0)*	Infant day 6 n=12	2.1 (0.05)*	Infant day 6 n=13	2.28 (0.5)*	
Marya, 1988 [6]	−2 (high)	Rohtak, India n=200 women	Randomised to either no supplement (n=100) or oral 600,000 IU vitamin D3; 2	Nil, but groups had similar maternal age, maternal height, maternal	Not measured	Not measured directly, but mean daily vitamin D intake given as follows Un-supplemented = 35.71 (6.17) IU/day Supplemented group = 35.01 (7.13) IU/day			2.57 (0.26) (value represents cord blood at delivery)		2.77 (0.18) (value represents cord blood at delivery)		Cord serum Ca concentration significantly higher in the supplemented group (P<0.001)

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First Author, year	Risk of bias	Setting	Randomisation	Adjustments/ confounders accounted for	Number of weeks gestation when 25(OH)D was measured	Mean (SD)/ Mean (SE)* or median (IQR) 25(OH)D concentration (nmol/l)	Mean (SD) or Mean (SE)* offspring serum calcium conc (mmol/l) in un-supplemented group	Mean (SD) or *Mean (SE) serum calcium conc (mmol/l) in supplemented group	Conclusion
			doses in 7th and 8th months gestation (n=100)	height, parity, haemoglobin, calcium intake and vitamin D intake					

Table includes any studies that measured maternal vitamin D status in pregnancy and either cord calcium concentration of offspring serum calcium concentration.

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Table 26

The effect of maternal vitamin D status in gestation on offspring blood pressure – Observational studies

First Author and year	Bias score	Study type	Study Details, age at which offspring blood pressure children was measured	Confounders/ adjustments	Number of weeks gestation when maternal 25(OH)D3 was measured	Mean (SD) or median (IQR) maternal 25(OH)D concentration (nmol/l)	Mean (SD) offspring blood pressure according to maternal 25(OH)D category/ Unadjusted correlation co-efficient (r) or regression co-efficient (B) (95% CI)	Adjusted correlation co-efficient (r) or regression coefficient (B) (95% CI)	Conclusion
Gale, 2008 [25]	4 (med)	Cohort	Princess Anne Cohort, Southampton, UK n=178 women, and Children assessed at 9 years	Nil	Late pregnancy (median (IQR) 32.6 (32-33.4) weeks	50 (30-75.3) 50.4% had 25(OH)D >50nmol/k 28.3% had levels 27.5-50 nmol/l 21.1% had levels <27.5 nmol/l	Maternal 25(OH)D (nmol/l) <30 / −50 / −75 / >75 / p value Systolic BP (mm Hg): 103.4 (7.94) / 102.2 (7.26) / 101.9 (8.18) / 102.9 (8.10) / 0.47 Diastolic BP (mm Hg): 59.8 (5.25) / 60.1 (5.49) / 60.2 (5.7) / 59.9 (6.2) / 0.75	Not given	No significant association between maternal 25(OH)D concentration measured in late pregnancy and offspring blood pressure at age 9
Krishnaveni 2011 [102]	4 (med)	Cohort	Mysore Parthenon Study, Mysore, India Children assessed at 5 years (n=338) and 9.5 years (n=312)	Offspring sex and age, maternal BMI, gestational diabetes, socioeconomic score, parity and religion	28-32 weeks (at study entry)	39.0 (24-58) 67% of women had 25(OH)D <50 nmol/l (the authors definition of deficiency)	Maternal 25(OH)D < 50 nmol/l (deficient) / >50 nmol/l (non-deficient) / p value Systolic BP at 5 yr (mm Hg): 96.7 (8.4) / 97.0 (8.1) / 0.67 Diastolic BP at 5 yr (mm Hg): 58.3 (6.8) / 57.9 (6.6) / 0.54 Systolic BP at 9.5 yr (mm Hg): 101.6 (8.7) / 100.5 (8.3) / 0.2 Diastolic BP at 9.5 yr (mm Hg): 58.3 (6.5) / 58.7 (7.2) / 0.5	Comparing offspring of mothers with and without 25(OH)D deficiency (deficient=0, non-deficient=1) 5 yr systolic BP β=0.3 (−1.32, 1.89; p=0.72) 5 yr diastolic BP β= −0.3 (−1.67, 0.98; p=0.61) 9.5 yr systolic BP β=− 1.2 (−2.87, 0.42;p=0.15) 9.5 yr diastolic BP β=0.4 (−0.90, 1.74; p=0.53)	No significant difference in offspring BP at 5 and 9.5 years in those born to mothers with 25(OH)D deficiency in late pregnancy compared to those born to mothers without vitamin D deficiency

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Table 27

The effect of maternal vitamin D status in gestation on maternal preeclampsia – Observational studies

First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or Mean (sEM) * or median (IQR) 25(OH)D concentration (nmol/l) in cases	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l) in controls	Odds ratio/ Relative risk of preeclampsia from univariate analysis	Odds ratio/ relative risk of pre-eclampsia from multivariate analysis	Conclusion
Seely, 1992 [128]	2 (med)	Boston, USA 12 cases 24 controls	Case-control	No adjustments, but cases and controls similar for age, gestation, number Caucasian, height, weight, no. primiparous	Mean 35.5 (0.6) weeks for cases and 36 (0.4) wks for controls	73.9 (7.5) *	89.3 (11.7) *	Unadjusted OR not given	OR not given	No statistically significant relationship seen
Bodnar, 2007 [124]	8 (low)	Pittsburgh, USA Cohort size=1198 women 55 cases 220 controls All women nulliparous	Nested case-control	Controls randomly selected and un-matched Adjusted for: Maternal race/ ethnicity, pre-pregnant BMI, education, season, gestational age at collection	2 occasions: Before 22 weeks Pre-delivery	Adjusted geometric mean (<22 weeks): 45.4 (38.6-53.4) Adjusted geometric mean at delivery 54.4 (45.1-65.7)	Adjusted geometric mean (<22 weeks): 53.1 (47.159.9) Adjusted mean at delivery 64.7 (56.4-74.2)	Unadjusted OR not given	**At <22 weeks:** Adjusted OR for pre-eclampsia Serum 25(OH)D OR (95% CI) <37.5 5 (1.7, 14.1) 50 nmol/l reduction in 25(OH)D increased risk of pre-eclampsia OR 2.4; (95% CI 1.1-5.4) **At delivery :** 25(OH)D significantly lower in cases (15% reduction; p<0.05)	At <22 weeks a strong inverse relationship between preeclampsia and 25(OH)D was observed (p=0.02)
Oken, 2007 [131]	5 (low)	Project Viva, Eastern Massachusetts, USA n=1718 women Cases= 59	Cohort	Maternal age, BMI, first trimester systolic BP, ethnicity, education, parity, total energy intake	Not measured FFQ at mean 10.4 weeks	Not measured Mean intake (IU/day)= 466 (183)	Not measured Mean intake (IU/day)= 492 (210)	Unadjusted OR not given	OR (per 100 IU increase in Vitamin D intake per day) of developing preeclampsia = 0.99 (0.87, 1.13)	No significant relationship seen
Azar, 2011 [130]	5 (low)	Oklahoma, USA All white women with Type 1 diabetes Cohort = 151 women 23 cases 24 controls	Nested case-control	Cases and controls matched for age, diabetes duration, HbA1c and parity. Higher BMI and lower HDL cholesterol in the cases Adjusted for parameters that differed between groups (BMI and HDL cholesterol)	3 visits Mean 12.2 (1.9) wks Mean 21.6 (1.5) wks Mean 31.5 (1.7 weeks)	Visit 1: 44.4 (32.9-51.4) Visit 2: 44.2 (35.7-58.2) Visit 3: 47.2 (23.5-55.4)	Visit 1: 47.2 (37.4-58.2) Visit 2: 43.4 (30.0-61.4) Visit 3: 44.9 (33.2-65.9)	Visit 1 (early pregnancy): 0.91 (0.88-0.95) Visit 2 (mid-pregnancy): 1.02 (0.98-1.06) Visit 3 (late pregnancy): 0.90 (0.73-1.11)	Visit 1: 0.99 (0.77-1.30) Visit 2: 1.02 (0.78-1.33) Visit 3: 0.92 (0.75-1.14)	No statistically significant relationship seen at any time point (after adjusting for confounders)
Baker, 2010 [126] **	9 (low)	Boston, USA, cohort size =3992 women 44 cases 201 controls	Nested case-control	Controls matched by race/ethnicity Adjusted for: Season of blood sampling, maternal age, multiparity, BMI, gestational age at serum collection	Between 15 and 20 weeks	75 (47-107)	98 (680- 114)	OR for severe pre-eclampsia 25(OH)D (nmol/l) / OR (95% CI) / p value >75: 1 (Ref) / - 50-74.9: 1.53 v(0.67,3.49) / 0.31 <50: 3.63 (1.52,8.65) / 0.004	Adjusted OR for severe pre-eclampsia 25(OH)D (nmol/l) / Adjusted OR (95% CI) / p value >75: 1 (Ref) / - 50-74.9: 2.16 (0.86,5.40) / 0.10 <50: 5.41 (2.02,14.52) / 0.001	Lower 25(OH)D3 was associated with increased risk of severe pre-eclampsia
Haugen, 2009 [125]	2 (med)	Norwegian mother and child cohort,	Cohort	BMI, height, maternal age, maternal	Not measured Estimated from FFQ at 22 weeks	Median (5^{th}, 95^{th} percentile) total vitamin D intake (IU/day): Cases= 308 (60,1200)	Median (5^{th}, 95^{th} percentile) total	OR for pre-eclampsia	OR for pre-eclampsia	Lower total vitamin D intake

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First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or Mean (sEM) * or median (IQR) 25(OH)D concentration (nmol/l) in cases	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l) in controls	Odds ratio/ Relative risk of preeclampsia from univariate analysis		Odds ratio/ relative risk of pre-eclampsia from multivariate analysis		Conclusion
		Norway n=23,425 women Cases= 1267		education, season of childbirth			vitamin D intake (IU/ day): 336 (68, 1256)	Total Vit D intake (IU/day)	OR	Total Vit D intake (IU/day)	OR	associated with an increased risk of pre-eclampsia (p<0.001)
								<200	1	<200	1	
								200-399	0.93 (0.81,1.07)	200-399	0.99 (0.85,1.14)	
								400-599	0.81 (0.67,0.97)	400-599	0.87 (0.73,1.05)	
								600-799	0.69 (0.55,0.87)	600-799	0.77 (0.61,0.96)	
								>800	0.78 (0.65,0.92)	>800	0.89 (0.89,1.06)	
Powe, 2010 [129]	4 (med)	Massachusetts General Hospital Obstetric maternal Study, Massachusetts, USA Cohort size=9930 women Cases=39 Controls=131	Nested case control	Controls unmatched Adjusted for: BMI, non-white race and summer blood collection	first trimester	68.5 (0.48) * nmol/l	72.0 (2.0) * nmol/l	OR per 25 nmol/l increase in 25(OH)D = 0.86 (0.60,1.25) If Vit D <37.5 nmol/l OR=2.49 (0.89,6.90)		OR per 25 nmol/l inrease in 25(OH)D = 1.24 (0.78,1.98) If Vit D <37.5 nmol/l OR=1.35 (0.4,4.5)		No significant relationship seen (p=0.435)
Robinson, 2010 [127] **	5 (low)	South Carolina, USA Cases=50 Controls=100	Case-control	Controls matched by race and gestational age at sample collection Adjusted for: BMI, maternal age, African American race, gestational age at sample collection	Time of diagnosis <34 weeks	45 (32.5-77.5)	80 (50-110)	OR per 25 nmol/l increase in 25(OHD = 0.58 (0.43,0.77)		OR per 25 nmol/l increase in 25(OH)D = 0.37 (0.22,0.62)		Lower 25(OH)D associated with increased risk of severe early preeclampsia p<0.001
Shand, 2010 [114]	6 (low)	Vancouver, Canada All women had either clinical or biochemical risk factors for preeclampsia Δ Cohort=221 women Cases=28	Cohort	Maternal age, ethnicity, parity, BMI, season, multivitamin use, smoking	Between 10 and 20 weeks 6 days (mean 18.7 (1.88) weeks)	42.6 (32.7-72.4)	50.4 (35.8-68.0)	Unadjusted values not given		25(OH)D (nmol/l)	OR for pre-eclampsia	No significant relationship seen
										<37.5	0.91 (0.31,2.62)	
										<50	1.39 (0.54,3.53)	
										<75	0.57 (0.19,1.66)	
Hossain, 2011 [120]	4 (med)	Karachi, Pakistan Cohort=75 women Cases= not given 26% of women covered their arms, hands and head; 76% also covered their face	Cross-sectional	Maternal age, level of exercise, attire, duration of gestation, newborn weight	At delivery	29.7 + (13.7)	36.2 + (18.4)	Not given		25(OH)D3 tertile	Adjusted OR(95% CI) for preeclampsia (systolic BP>140, and/or diastolic BP>90mmHg	Women in the lowest and middle tertile for 25(OH)D3 more likely to meet criteria for Preeclampsia compared to those in the highest tertile. 25(OH)D3 of 50nmol/l maximum identified as the threshold relating to increased risk for preeclampsia
										Highest tertile	1.0 (Ref)	
										Middle tertile	11.05 (1.15,106.04)	
										Lowest tertile	3.38 (0.40,28.37)	

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First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or Mean (sEM) * or median (IQR) 25(OH)D concentration (nmol/l) in cases		Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l) in controls	Odds ratio/ Relative risk of preeclampsia from univariate analysis	Odds ratio/ relative risk of pre-eclampsia from multivariate analysis	Conclusion
Fernandez-Alonso, 2012 [115]	3 (med)	Almeria, Spain Cohort=466 women Cases=7	Cohort	Nil	Between 11-14 weeks	Overall mean not given		Not given	Not given	Not given	No significant association between development of preeclampsia as a function of first trimester 25(OH)D status (p=0.51)
						25(OH)D conc	n				
						<50	2				
						50-75	3				
						>75	2				

*Mean (SEM)

**Severe preeclampsia

+25(OH)D3 measured

△Defined as past obstetric history of early-onset or severe preeclampsia, unexplained elevated α-fetoprotein ≥ 2.5 multiples of the median (MoM), unexplained elevated human chorionic gonadatrophin, or low pregnancy-associated plasma protein A ≤ 0.6 MoM

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Table 28

The effect of Vitamin D supplementation in gestation on preeclampsia – Intervention studies

First Author, year	Risk of bias	Setting	Randomisation	Adjustments/ confounders accounted for	Number of weeks gestation when 25(OH)D3 measured	Mean (SD) 25(OH)D concentration (nmol/1-unless other stated)	No. of cases in un-supplemented group	No. of cases in supplemented group	Conclusion
Marya, 1987 [132]	−2 (high)	Rohtak, India	Randomised to either no supplement (n=200) or 375 mg/day calcium + 1200 IU Vitamin D given at 20-24 weeks until birth (n=200)	Nil	Not measured	Not measured	18	12	No significant difference in rates of pre-eclampsia in the 2 groups (p>0.05) Significantly reduced diastolic and systolic BP in the supplemented group at 32 and 36 weeks (p<0.001). No significant difference at 24 or 28 weeks (p value not given)

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Table 29

The effect of maternal vitamin D status in gestation on risk of gestational diabetes (GDM) – Observational studies

First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l) in cases of GDM	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l) in unaffected controls	Odds ratio (95% CI) of GDM from univariate analysis		Odds ratio of GDM from multivariate analysis			Conclusion
Maghbooli, 2008 [133]	3 (med)	Tehran, Iran Overall cohort size=741 women Cases of GDM=52 Controls=527	Cross-sectional	Nil. Cases significantly older, higher parity and higher BMI.	24-28 weeks**	16.49 (10.44)**	22.97 (18.25)**	Not given		Not given			25(OH)D3 significantly lower in individuals with GDM p=0.009
Clifton-Bligh, 2008 [92]	6 (low)	New South Wales, Australia Cases of GDM= 81 women Normal pregnancies=183 women	Prospective cohort	Age, BMI, ethnicity, season	Mean (SD) 28.7 (3.3) weeks	48.6 (24.9)	55.3 (23.3)	Not given		OR if 25(OH)D <50 nmol/l= 1.92 (0.89,4.17)			Significant difference in mean 25(OH)D between cases and controls (p=0.04). However no significant association between GDM and 25(OH)D deficiency (25(OH)D <50 nmol/l) 25(OH)D significantly negatively associated with fasting glucose, fasting insulin and insulin resistance in unadjusted analysis. After adjustments however only significant relationship remaining was with fasting glucose (r= −0.11 (−0.26, −0.01)
Zhang, 2008 [135]	8 (low)	Omega Study, Seattle and Washington, USA Overall cohort size=953 women Cases of GDM=57 women (70% white) Controls=114 women (84% white)	Nested case-control	Controls frequency matched to cases for the estimated season of conception OR1 = Maternal age, race/ethnicity, family history of type 2 DM OR2 = as above plus pre-pregnant BMI Physical activity measured but not included in the analysis as did alter the OR by >10%	16 weeks	24.2 (8.5)	30.1 (9.7)	25(OH)D conc	Unadjusted OR (95% CI)	25(OH)D conc	OR1 (95% CI)	OR2 (95% CI)	25(OH)D is early pregnancy is significantly associated with an elevated risk of GDM
								75+	1 (reference)	75+	1 (ref)	1 (ref)	
								50-74	1.86 (0.86,4.01)	50-74	1.86 (0.84,4.09)	1.56 (0.69,3.52)	
								<50	4.33 (1.78,10.5)	<50	3.74 (1.47,9.50)	2.66 (1.01,7.02)	
								P for trend	0.001	P for trend	0.006	0.05	
								Per 12.5 nmol/l reduction	1.44 (1.16,1.69)	Per 12.5 nmol/l reduction	1.36 (1.11,1.69)	1.29 (1.05,1.60)	

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First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l) in cases of GDM	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l) in unaffected controls	Odds ratio (95% CI) of GDM from univariate analysis		Odds ratio of GDM from multivariate analysis	Conclusion
Farrant, 2009 [90]	5 (low)	Mysore Parthenon Study, India Cases of GDM=34 women Normal pregnancies=525 women	Prospective cohort	Maternal age, fat mass, diabetes status	30 weeks	38.8	37.8	Not given		Not given	No significant association between serum 25(OH)D at 30 weeks and GDM. (p=0.8 for difference in mean between GDM and normal) 25(OH)D positively related to fasting 32-33 split proinsulin concentration. Negative association between 30 minute glucose concentration following GTT and 25(OH)D in those with 25(OH)D <50 nmol/l
Soheilykhah, 2010 [134]	3 (med)	Iran Cases of GDM=54 women Controls=111 women	Case-control	Nil Controls matched for gestational age, maternal age, maternal BMI	24-28 weeks	24.05 (20.65)**	32.25 (35.8)**	25(OH)D3 conc	OR (95% CI) of GDM	No multivariate analysis performed	Significantly increased risk of GDM if 25(OH)D3 <37.5 nmol/l.<50
								<50	2.02 (0.88,4.6)		
								<37.5	2.66 (1.26,5.6)		
Makgoba, 2011 [136]	7 (low)	London, UK Overall cohort size=1200 women Cases of GDM=90 women Controls=158 women	Nested case-control	Unclear how cases and controls were matched Cases had higher BMI, prior history of Type 2 DM and a family history of Type 2 DM, higher blood pressure. No difference in parity, smoking, method of conception Adjusted for: BMI, gestation age at blood sampling, smoking, ethnicity, parity, maternal age, conception status, previous GDM, month of blood sampling	11-13^{+6} weeks	47.2 (26.7)	47.6 (26.7	Not given		Not given	No significant association between serum 25(OH)D in first trimester and GDM. P=0.863 in univariate analysis; 0.782 in multivariate analysis 25(OH)D negatively associated with fasting glucose (p=0.0009), 2 hour glucose following GTT (p=0.002) and HbA1c (0.002) at 28 weeks in univariate analysis. After adjustments however the only significant relationship remaining was with 2 hour glucose (p=0.048)

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First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l) in cases of GDM		Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l) in unaffected controls		Odds ratio (95% CI) of GDM from univariate analysis	Odds ratio of GDM from multivariate analysis	Conclusion
Baker, 2012 [137]	7 (low)	North-Carolina, USA Overall cohort=4225 women Cases of GDM=60 women Controls=120 women	Nested case-control	Controls matched by race/ethnicity Adjusted for: Maternal age, insurance status, BMI, gestational age at serum collection, season of blood test	11-14 weeks	Mean not given		Mean not given		1.25 (0.39,4.05) if 25(OH)D <50 compared with those with 25(OH)D >75	0.78 (0.22,2.78) if 25(OH)D <50 compared with those with 25(OH)D >75	No significant association between serum 25(OH)D in early pregnancy and GDM
						25(OH)D conc	N (%)	25 (OH)D conc	N (%)			
						<50	5 (8.3)	<50	8 (6.7)			
						50-74.9	11 (18.3)	50-74.9	24 (20)			
						75+	44 (73.3)	75+	88 (73.3)			
Fernandez-Alonso, 2012 [115]	3 (med)	Almeria, Spain Cohort=466 women Cases of GDM=36	Prospective cohort	Nil	11-14 weeks	Overall mean not given		Not given		Not given	Not given	No significant association between serum 25(OH)D in early pregnancy and GDM (p=0.84 for difference in mean between GDM and normal
						25(OH)D conc	N					
						<50	109					
						50-75	191					
						>75	166					

** Measured 25(OH)D3

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Table 30

The effect of maternal vitamin D status in gestation on Caesarean section (C-section) – Observational studies

First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l) in cases of C-section	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l) in vaginal deliveries	Odds ratio/Relative risk of C-section from univariate analysis			Odds ratio of C-section from multivariate analysis	Conclusion
Ardawi, 1997 [87]	5 (low)	Jeddah, Saudi Arabia Cohort size=264 women	Cohort	nil	Delivery	Not given C-section incidence of 12.5% (n=3) if 25(OH)D <20 nmol/l c-section rate of 9.59% (n=23) if 25(OH)D >20 nmol/l	Not given	Not given			Not given	25(OH) <20 nmol/l was associated with an increased rate of C-section but results not significant (p>0.05).
Brunvand, 1998 [140]	1 (med)	Pakistan Cases=37 women Controls=80 women All nulliparous Pakistani women of low social class Cases all had emergency C-sections due to mechanical dystocia	Case-control	Cases had higher maternal age, lower maternal height, lower maternal weight , longer length of gestation and higher neonatal birth weight. Maternal height and birth weight included in logistic regression model	Just before delivery**	26 (15-37)**	19 (11-27)**	Not given	1.03 (0.99,1.06)			No significant association seen between maternal 25(OH)D concentration and risk of emergency C-section due to obstructed labour
Merewood, 2009 [139]	6 (low)	Boston, USA Cohort=277 women Cases=67 women All cases were women having primary C-sections	Cross-sectional	No significant difference in season of birth, maternal age, maternal BMI, maternal education, maternal insurance status, marital status, prenatal vitamin use and calcium supplementation, milk in pregnancy or sunscreen in pregnancy. Race/ethnicity, alcohol in pregnancy (yes/ no), maternal educational status, maternal insurance status and maternal age included in multivariate analysis	Within 72 hours of delivery	Unadjusted = 45.0 (36.5-62.0)	Unadjusted = 62.5 (57.4-68.2)	If 25(OH)D <37.5 nmol/l, OR= 2.43 (1.20,4.92)	If 25(OH)D <37.5 nmol/l, adjusted OR= 3.84 (1.71,8.62)			25(OH)D <37.5 nmol/l is significantly associated with an increased risk of primary C-section
Scholl, 2012 [138]	5 (low)	Camden cohort, New Jersey, USA	Cohort	Age, parity, ethnicity, gestation at	At entry to study. Mean (SD) 13.73 (5.6) weeks	Not given	Overall mean not given	Not given	25(OH)D conc.	OR1 (95% CI)	OR2 (95% CI)	Serum 25(OH)D <30 was
									<30	1.70 (1.12,2.58)	1.66 (1.09,2.52)	

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First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l) in cases of C-section	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l) in vaginal deliveries	Odds ratio/Relative risk of C-section from univariate analysis			Odds ratio of C-section from multivariate analysis	Conclusion
		Cohort=1153 women Cases=290 women (173 primary C-sections)		entry to study, season at entry to study used to calculate adjusted OR1. Adjusted OR2 used the same confounders with the addition of maternal BMI					30-49.9	0.89 (0.63,1.25)	0.83 (0.59,1.17)	associated with a significantly increased risk of overall C-section in both regression models. Regarding primary C-section, if BMI is not included in the model (OR1), serum 25(OH)D <30 was associated with a significantly increased risk of primary C-section, When maternal BMI is included (OR2) in the model the trend remains but the relationship no longer remains significant (p=0.054) Risk of overall C-section and primary C-section due to prolonged labour was significantly higher iif 25(OH)D <30 nmol/l even after adjusting for maternal BMI (OR2 = 2.24 (1.17,3.98) for primary C-section)
									50-125	Ref	Ref	
									>125	0.59 (0.17,2.08)	0.90 (0.49,1.66)	
Savvidou, 2012 [141]	7 (low)	London, UK Cohort=1000 women Cases=199 women (111 emergency)	Cohort	Maternal age, racial origin, smoking, method of conception, season of blood sampling	Between 11-13 weeks	Elective= 58.40 (28.12-78.89) Emergency=42.53 (22.91-72.1)	46.4 (28.25-69.01)	Not given	OR not given. Result presented as multiples of the median after adjustments			No significant association seen between maternal 25(OH)D concentration and risk of
									Indication		MoM (IQR)	
									Vaginal		0.99 (0.71,1.33)	

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First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l) in cases of C-section		Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l) in vaginal deliveries	Odds ratio/Relative risk of C-section from univariate analysis		Odds ratio of C-section from multivariate analysis	Conclusion
										Elective	0.96 (0.73,1.27)	either elective or emergency C-section
										Emergency (total)	0.99 (0.71,1.46)	
										Emergency due to failure to progress	0.95 (0.71,0.25)	
										Emergency due to fetal distress in labour	0.95 (0.71,1.27)	
Fernandez-Alonso, 2012 [115]	3 (med)	Almeria, Spain Cohort=466 women Cases=105 women (61 emergency)	Cohort	Nil	Between 11-14 weeks**	Overall mean not given		Not given	Not given	Not given		No significant association between C-section rates as a function of first trimester 25(OH)D status Overall C-section, p=0.65 Emergency C-section p=0.47 Elective C=section p=0.06
						25(OH)D conc	N					
						<50	23					
						50-75	41					
						>75	41					

** Measured 25(OH)D3

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Table 31

The effect of maternal vitamin D status in gestation on risk of bacterial vaginosis – Observational studies

First Author and year	Bias score	Study details	Study type	Confounders/ adjustments	Number of weeks gestation when 25(OH)D was measured	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l) in cases of bacterial vaginosis	Mean (SD) or median (IQR) 25(OH)D concentration (nmol/l) in unaffected controls	Odds ratio of bacterial vaginosis from univariate analysis	Odds ratio of bacterial vaginosis from multivariate analysis	Conclusion
Bodnar, 2009 [142]	5 (low)	Pittsburgh USA Cohort=469 women all nonHispanic white or non-Hispanic black) Cases=192 (approx.)	Cohort	Presence of other sexually transmitted disease. Other confounders maternal age, parity, education, employment status, season, family income, pre-pregnant BMI, gestational age at enrolment, number of sexual partners and frequency of vaginal intercourse were not included as they did not satisfy the priori change-in-estimate criterion (>10% change in PR)	Mean (SD) 9.5 (3.2 weeks	Unadjusted geometric mean = 29.5 (27.1-32.0)	Unadjusted geometric mean = 40.1 (37.0-43.5)	Not given	Prevalence ratio (PR) given 25(OH) conc nmol/l: Adjusted PR (95% CI) 20 (25th centile): 1.65 (1.01,2.69) 50 (75th centile): 1.26 (1.10,1.57) 75 (90th centile: Referent 90 (97th centile): 1.32 (0.84,2.09)	A significant relationship observed between serum 25(OH)D and risk of bacterial vaginosis. Prevalence of bacterial vaginosis declined as 25(OH)D increased until a plateau at 80 nmol/l was reached (p<0001). At doses higher this this, no significant relationship was observed
Hensel, 2011 [143]	4 (med)	National Health and Nutrition Examination Survey (NHANES), USA Cohort n=440 women	Cohort	Maternal age, race/ ethnicity, education, poverty index, marital status, age at first sex, number of lifetime partners, ever had a female sex partner, unprotected sex in the last 30 days, current oral contraceptive use, douching frequency, active smoking, BMI	Unclear	Not given	Not given	Not given	Adjusted odd ratio (95% CI) if Vitamin D deficient (<75 nmol/l) = 2.87 (1.13,7.28). p=0.03	Serum 25(OH)D <75 nmol/l is significantly associated with an increased risk of bacterial vaginosis
Dunlop, 2011 [144]	2 (med)	Sample of the Nashville Birth Cohort Total cohort size=1547 women Sample size=160 women (all non-Hispanic white or non-Hispanic black) Cases=14	Cross-sectional	Race, age, smoking, BMI, gestational age at delivery, payer source	At delivery	45.0 (20.35)	60.85 (29.93)	25(OHD cone (nmol/1) / OR (95% Cl) <30: 7.58 (2.13,27.03) <50: 1.4 (0.79,14.93)	25 (OH)D con (nmol/1) / Adjusted OR (95% Cl) <30: 5.11 (1.19,21.97) <50: 1.2 (0.39,3.85)	A significant risk of bacterial vaginosis seen if 25(OH)D <30 nmol/1 No significant association seen if 25(OH)D <50 nmol/1

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Appendix 7: Forest plots

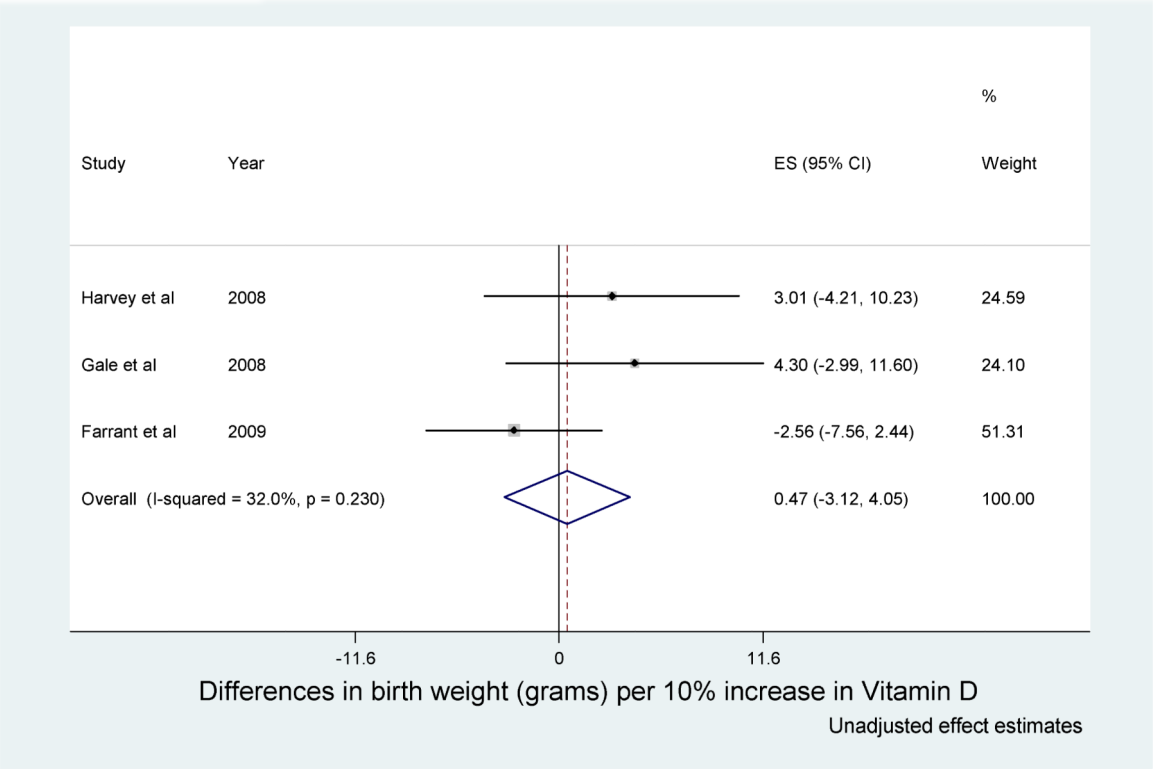

Figure 2.
Forest plot of the effect of maternal vitamin-D on offspring birth weight – observational studies using log-transformed 25(OH)-D (unadjusted)

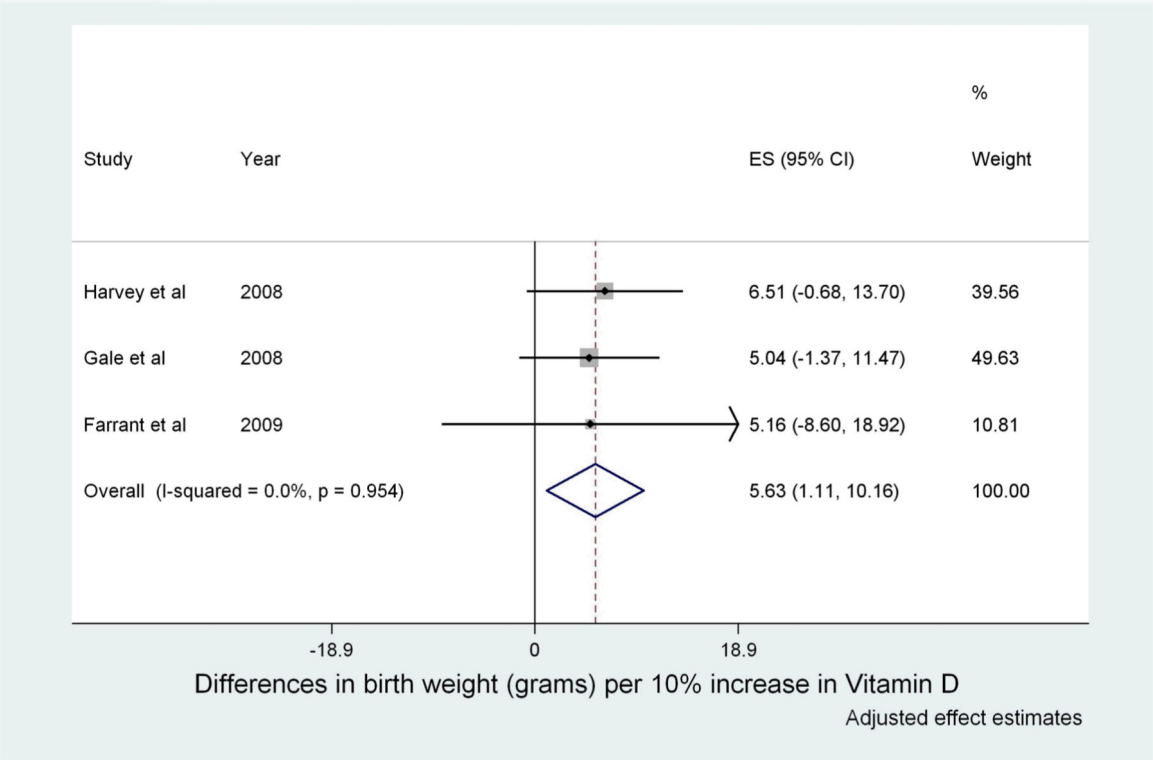

Figure 3.
Forest plot of the effect of maternal vitamin-D on offspring birth weight – observational studies using log-transformed 25(OH)-D (adjusted)

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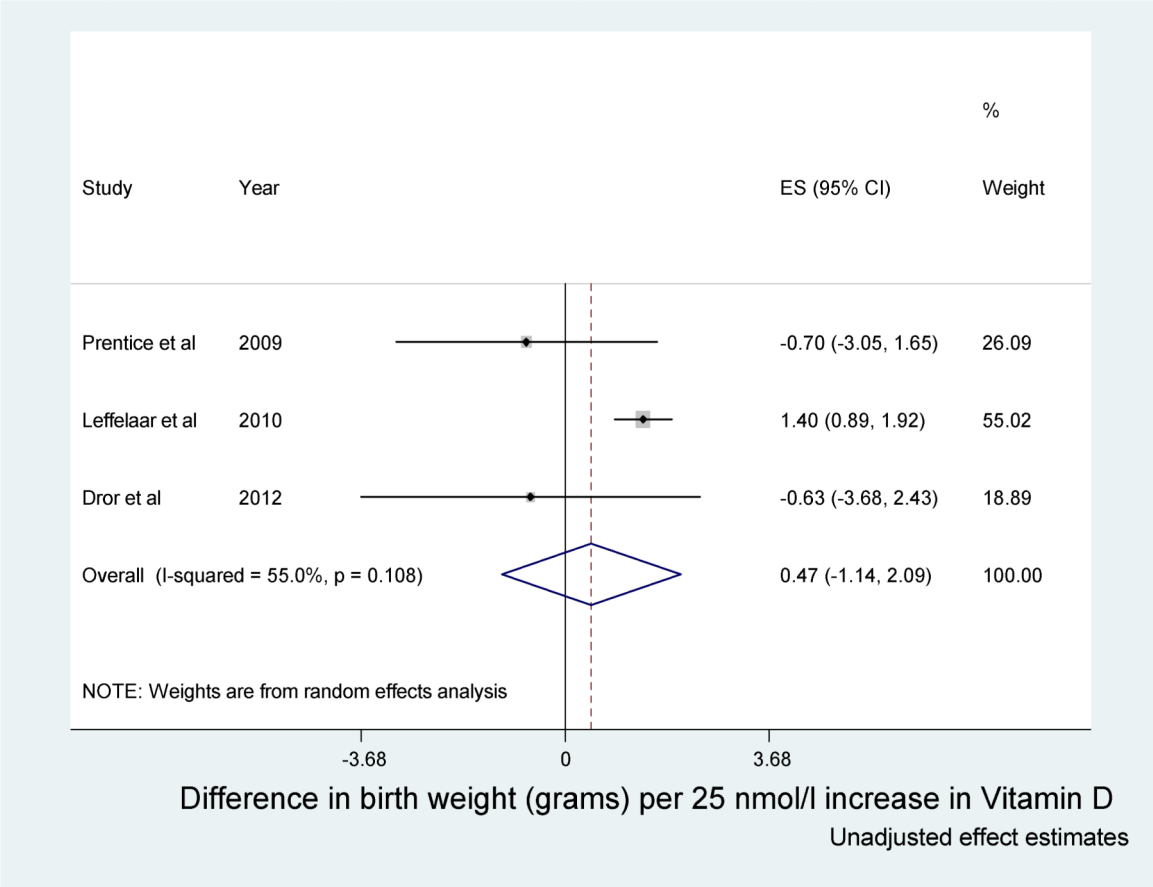

Figure 4.
Forest plot 3 of the effect of maternal vitamin-D on offspring birth weight – observational studies (unadjusted)

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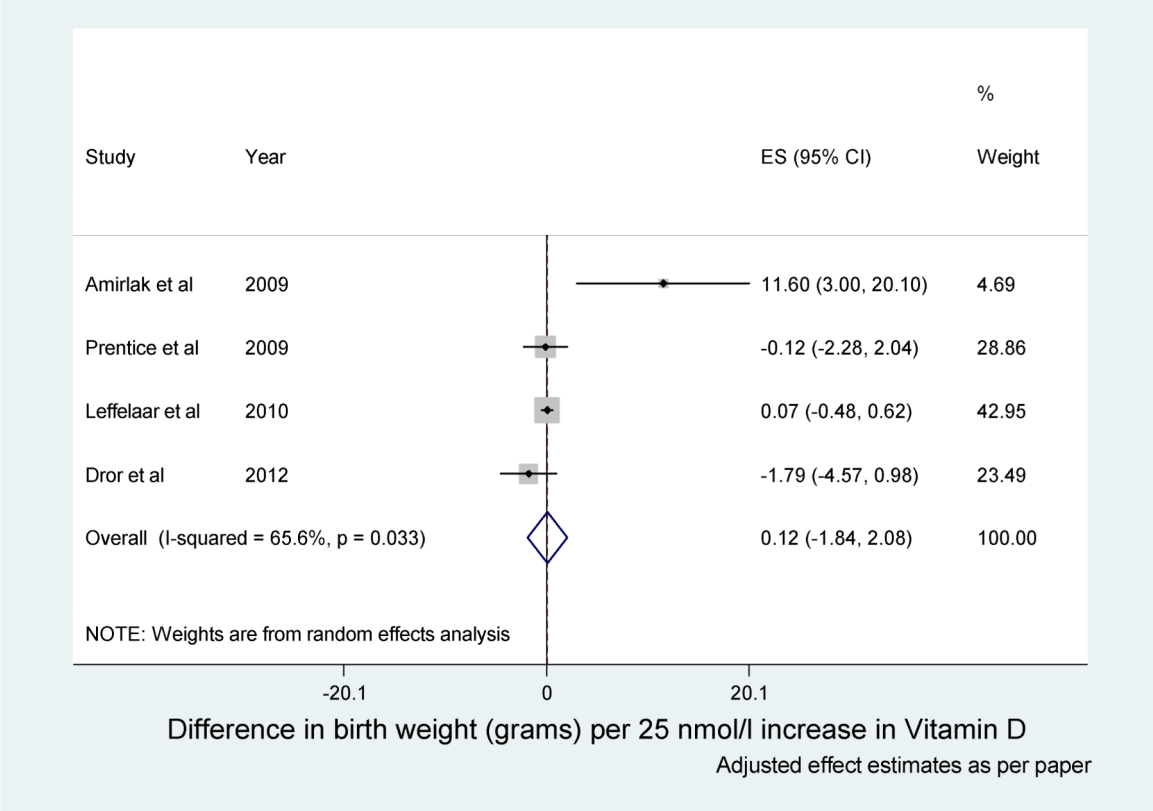

Figure 5.
Forest plot of the effect of maternal vitamin-D on offspring birth weight – observational studies (adjusted)

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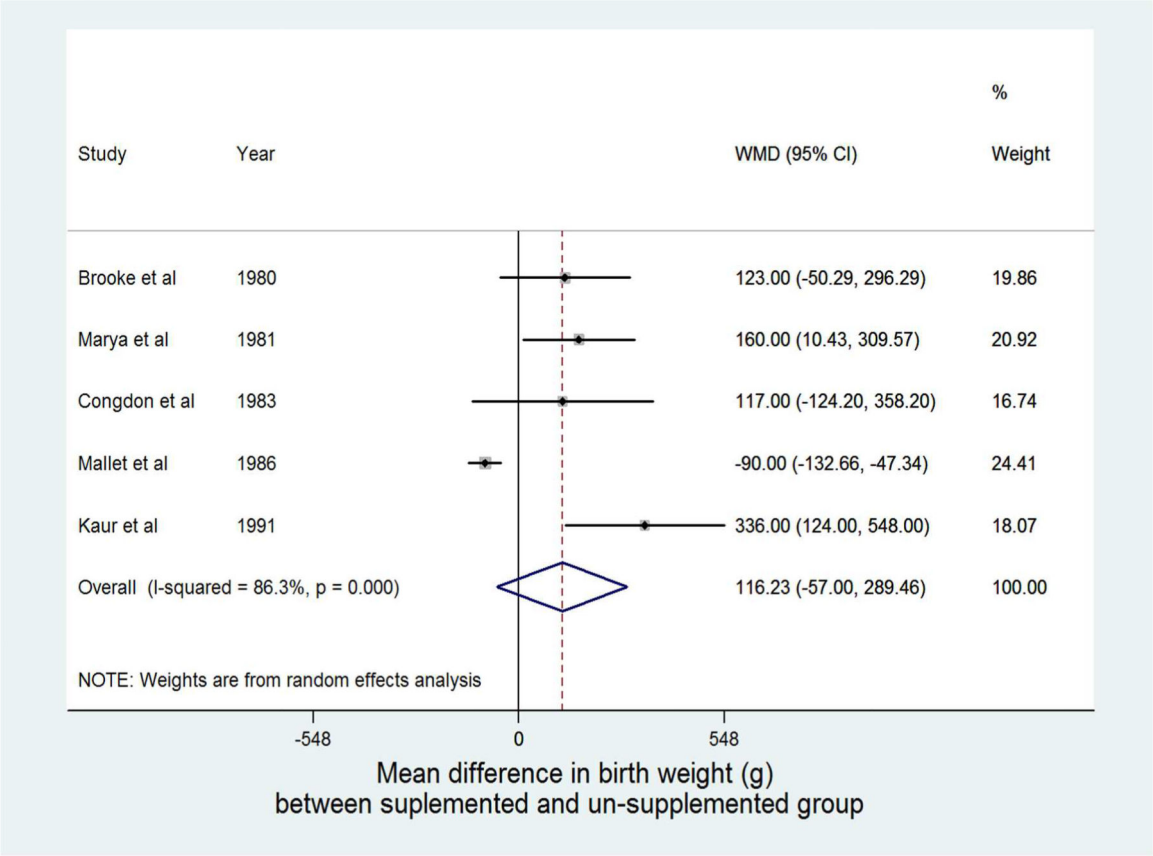

Figure 6.
Forest plot of the effect of maternal vitamin-D supplementation on offspring birth weight – intervention studies (low dose)

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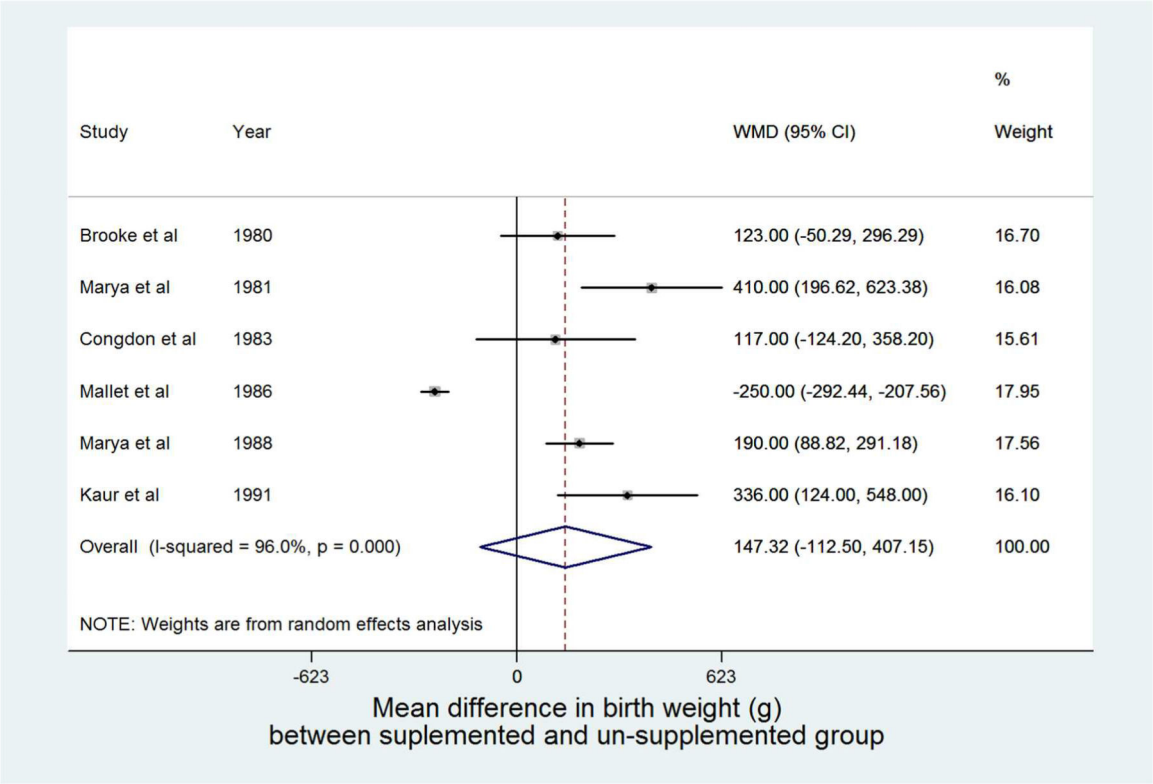

Figure 7.

Forest plot of the effect of maternal vitamin-D supplementation on offspring birth weight – intervention studies (high dose)

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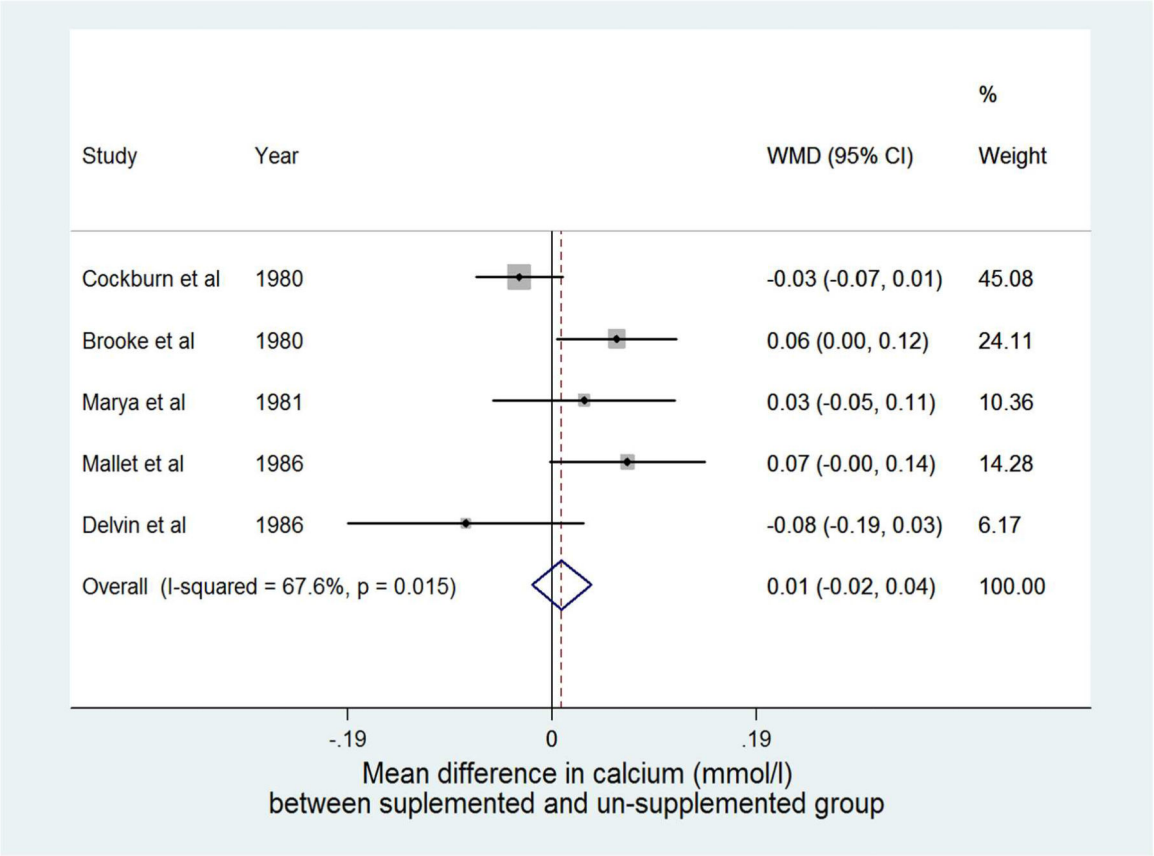

Figure 8.

Forest plot of the effect of maternal vitamin-D supplementation on offspring calcium concentration – intervention studies (low dose)

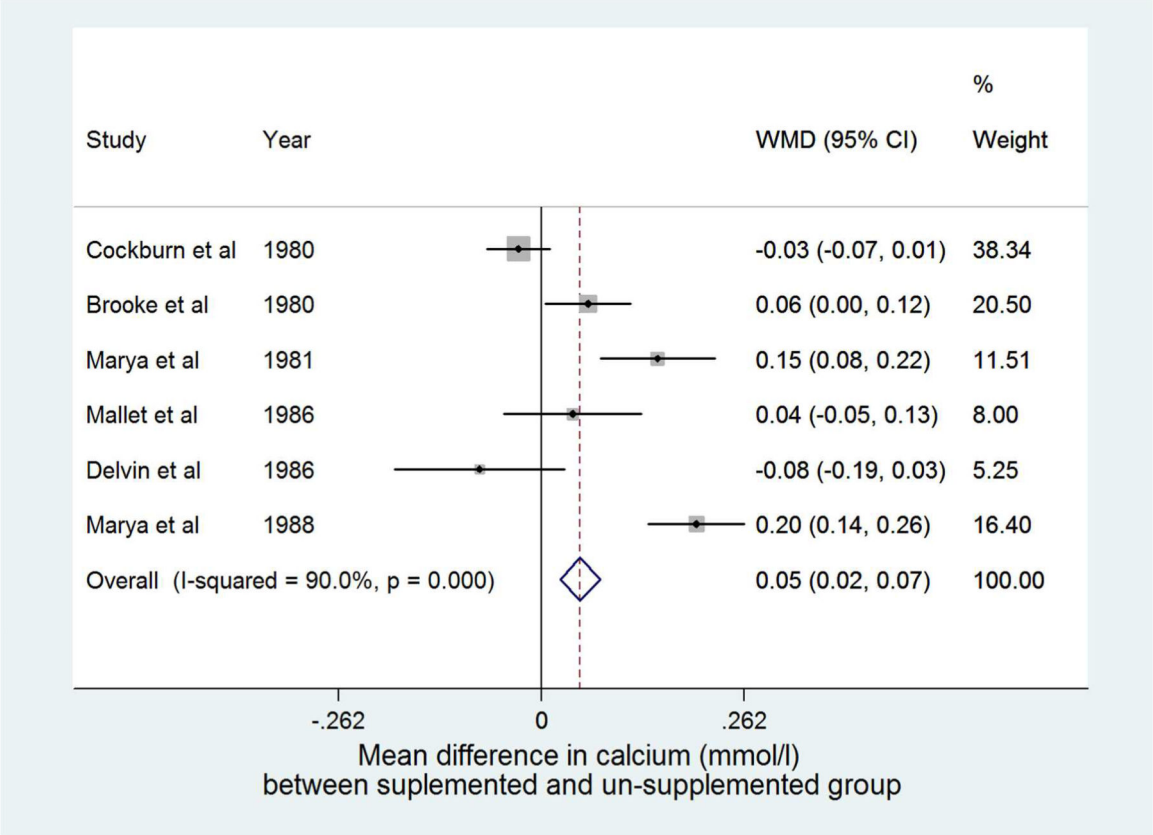

Figure 9.
Forest plot of the effect of maternal vitamin-D supplementation on offspring calcium concentration – intervention studies (high dose)

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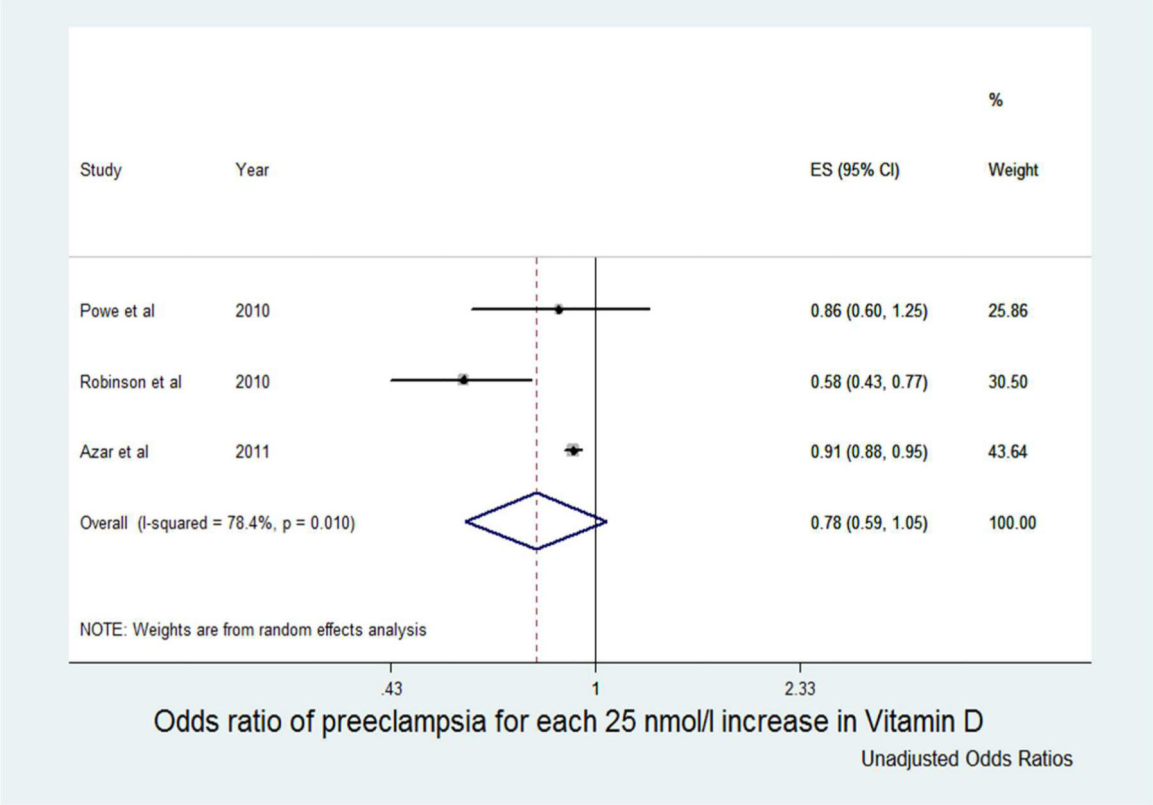

Figure 10.
Forest plot of the effect of maternal vitamin-D on risk of preeclampsia – observational studies (unadjusted)

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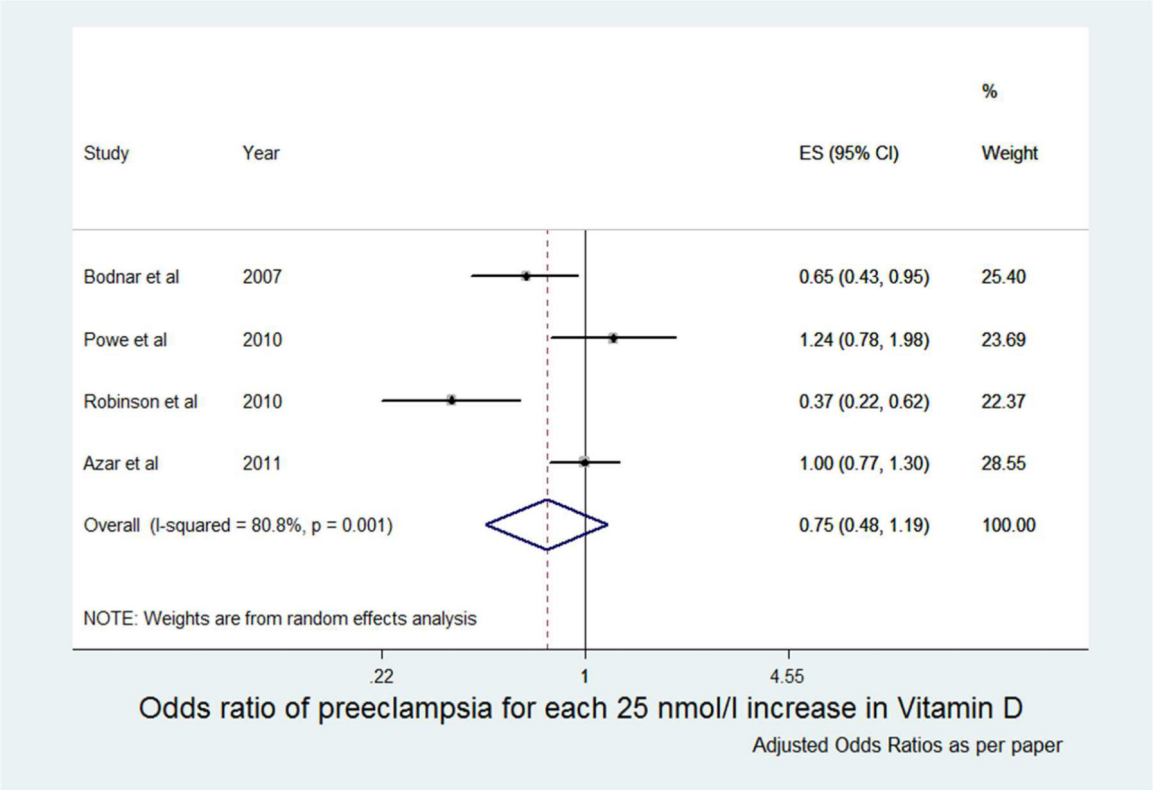

Figure 11.
Forest plot of the effect of maternal vitamin-D on risk of preeclampsia – observational studies (adjusted)

LIST OF ABBREVIATIONS

Alb	Albumin
aBMC	Areal Bone Mineral Density
ABCVitamin D	Vitamin D Supplementation During Pregnancy for Prevention of Asthma in Childhood trial
ALP	Alkaline Phosphatase
ALSPAC	Avon Longitudinal Study of Parents and Children
AMED	Allied and Complementary Database
ATP	Adenosine Tri-Phosphate
BA	Bone Area
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BMUS	British Medical Ultrasound Society

BRU	Biomedical Research Unit
BW	Birth weight
Ca	Calcium
COMA	Committee on Medical Aspects of Food and Nutrition Policy
CSA	Cross sectional Area
CD4	Cluster Differentiation 4
CDSR	Cochrane Database of Systematic Reviews
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
DBP	Vitamin D Binding Protein
DEQAS	Vitamin D External Quality Assessment Scheme
DNA	Deoxyribonucleic Acid
DMC	Data Monitoring Committee
DXA	Dual-Energy X-ray Absorptiometry
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GC-MS	Gas Chromatography-Mass Spectroscopy
GMP	Good Manufacturing Practice
GnRH	Gonadotrophin Releasing Hormone
HIV	Human Immunodeficiency Virus
HLA	Human Leucoctye Antigen
HMIC	Health Management Information Consortium
HMSO	Her Majesty’s Stationery Office
HPLC	High Performance Liquid Chromatography
HTA	Health Technology Assessment
ISRCTN	International Standard Randomised Controlled Trial Number
IMP	Investigational Medicinal Product
IOV	Inter-Operator Variation
IQ	Intelligence Quotient
ITT	Intention to Treat
LMP	Last Menstrual Period

MAVIDOS	Maternal Vitamin D Osteoporosis Study
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
mRNA	messenger Ribonucleic Acid
NHS	National Health Service
NIHR	National Institute for Health Research
RCT	Randomised Controlled Trial
RIA	Radio-Immuno Assay
pQCT	Peripheral Quantitative Computed Tomography
PTH	Parathyroid Hormone
NICE	National Institute for Health and Clinical Excellence
SACN	Scientific Advisory Committee on Nutrition
SGA	Small for Gestational Age
SPA	Single Photon Absorptiometry
SWS	Southampton Women's Survey
UK	United Kingdom
UKCRN	United Kingdom Clinical Research Network
UHS	University Hospital Southampton NHS Foundation Trust
USA	United States of America
UVB	Ultra-Violet B
VDARRT	Vitamin D Antenatal Asthma Reduction Trial
VDR	Vitamin D Receptor
WMD	Weighted Mean Difference

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Table 1
Trials of vitamin D supplements in pregnancy

Trial	No.	Location	Intervention	Outcome	
Cockburn (1980)	1139	Scotland	400 IU/day or	25(OH)D maternal	↑
			or placebo	Cord	↑
				Infant	↑
Brooke (1980)	126	UK Asian	1,000 IU/day	Ca maternal	↑
			or placebo	Cord	→
				Neonatal	↑
				Maternal weight	↑
Marya (1981)	120	Asian	600,000 IU (×2);	Ca maternal	↑
		Indian	1,200 IU/day	Cord	↑
			or placebo	ALP maternal	↓
				Cord	↓
Marya (1988)	200	Asian	600,000 IU (×2);	Ca/P maternal	↑
		Indian	or placebo	Cord	↑
				ALP maternal	↓
				Cord	↓
Delvin (1986)	34	France	1,000 IU/day;	25(OH)D cord	↑
			or no vit D	Neonatal	↑
Mallet (1986)	68	France	200,000 IU (×1); 1,000 IU/day; or no vit D	25(OH)D maternal with both regimes	↑

↑ elevation; → no change; ↓ decrease; ALP alkaline phosphatase