Prenatal vitamin D status and offspring’s growth, adiposity and metabolic health: a systematic review and meta-analysis

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Abstract
In this systematic review and meta-analysis of observational studies, we aimed to estimate the associations between prenatal vitamin D status and offspring growth, adiposity and metabolic health. We searched the literature in human studies on prenatal vitamin D status and offspring growth in PubMed, up to July 2017. Studies were selected according to their methodological quality and outcomes of interest (anthropometry, fat mass and diabetes in offspring). The inverse variance method was used to calculate the pooled mean difference (MD) with 95% CI for continuous outcomes, and the Mantel–Haenszel method was used to calculate the pooled OR with 95% CI for dichotomous outcomes. In all, thirty observational studies involving 35 032 mother–offspring pairs were included. Vitamin D status was evaluated by circulating 25-hydroxyvitamin D (25(OH)D) level. Low vitamin D status was based on each study’s cut-off for low 25(OH)D levels. Low prenatal vitamin D levels were associated with lower birth weight (g) (MD = -100.6; 95% CI = -162.25, -39.13), increased risk of small-for-gestational-age (OR 1.55; 95% CI 1.16-2.07) and an elevated weight (g) in infant at the age of 9 months (g) (MD 119.69; 95% CI 32.97, 206.52). No associations were observed between prenatal vitamin D status and other growth parameters at birth, age 1 year, 4–6 years or 9 years, nor with diabetes type 1. Prenatal vitamin D may play a role in infant adiposity and accelerated postnatal growth. The effects of prenatal vitamin D on long-term metabolic health outcomes in children warrant future studies.

Key words: 25-Hydrovitamin D: Pregnancy: Infant growth: Adiposity: Metabolic health

Barker’s hypothesis about fetal programming stating that adult diseases are partly attributable to insufficient intra-uterine nutrition is now well accepted. Nutrient deficiencies during pregnancy can induce changes in this critical period that will affect physiology and body composition in both fetal and postnatal development. Among those changes, one of the most widely reported is suboptimal infant growth. A common problem with lower birth weight or being born small-for-gestational-age (SGA) is the catch-up growth that follows in early childhood. Indeed, children recover their normal fat mass before they recover their normal height, which can lead to elevated adiposity and hormonal dysregulations that can induce metabolic health problems. Therefore, child growth, adiposity and metabolic health may be partly determined by prenatal nutritional status.

One nutrient of emerging interest is vitamin D, the deficiency of which is a nutritional issue extremely widespread around the globe. There is no universally accepted definition of vitamin D deficiency. On the basis of circulating 25-hydroxyvitamin D (25(OH)D) concentration, different cut-offs have been used to define vitamin D status. The Institute of Medicine states that a serum 25(OH)D concentration <30 nmol/l is vitamin D deficiency, whereas the Endocrine Society defines vitamin D deficiency as 25(OH)D <50 nmol/l. Vitamin D can be absorbed through alimentation or synthesised in the skin with sun exposure. As cutaneous synthesis under sunlight is responsible for the majority of vitamin D in circulation, the problem is alarming in Canada where almost a third of the population has plasma concentrations of 25(OH)D <50 nmol/l.

Vitamin D deficiency is common during pregnancy; almost 40% of pregnant women had plasma 25(OH)D concentrations <50 nmol/l in a prospective multi-centre cohort study in Canada, and it represents a common public health problem. As vitamin D has an important role in placental metabolism and metabolic health during pregnancy, our hypothesis is that low prenatal vitamin D status has an effect on...
infant growth, adiposity and metabolic health. As child growth and metabolic health are important for childhood well-being and long-term health outcomes, this systematic review and meta-analysis aimed to better understand the role of prenatal vitamin D status in child growth, adiposity and metabolic health.

**Methods**

**Electronic literature search**

To evaluate the overall effects of prenatal vitamin D status on child's growth, adiposity and related metabolic disorders, literature searches on prenatal vitamin D status and newborn anthropometry, SGA, child’s growth and metabolic health disorders were conducted on electronic databases of the human literature in PubMed, up to July 2017 using ‘vitamin D’ and ‘pregnancy’ as keywords. All 2550 studies have been screened by their title and abstract and initially selected if they reported an association between prenatal vitamin D status and newborn anthropometry, more specifically birth weight, length, head circumference and SGA, as well as child’s growth, adiposity and metabolic health, more specifically child weight, length, BMI, fat mass or diabetes type 1. Additional articles have been searched through reviewing the reference lists of relevant articles. Only articles in English have been considered. When only the abstract was available, the author was contacted to provide the data.

**Selection of studies**

After screening the titles and abstracts, sixty articles were fully read. Twenty-three of them were excluded because they met at least one exclusion criterion: (a) they were reviews, case reports or comments; (b) maternal vitamin D levels were estimated according to their nutrient intake; or (c) the data are incomplete or impossible to merge with other studies. Of the remaining thirty-seven studies, seven were further excluded because they did not meet all the inclusion criteria. The inclusion criteria were as follows: (a) study design was a prospective or retrospective cohort study; (b) there were data on child growth, adiposity or metabolic health, such as weight, length, BMI, head circumference, SGA, skinfold thickness, fat mass (g or %) and diabetes type 1; (c) study population was pregnant women without pre-existing chronic disease; (d) vitamin D status was indicated by 25(OH)D assays in maternal or cord blood samples taken before or at delivery; and (e) the study met the predefined methodological quality assessment criteria for non-randomised observational studies. When data were incomplete, authors were contacted and asked to provide the needed data. Crozier et al., Gale et al., Josefson et al. and Leffelaar et al. provided us with additional useful data.

Two reviewers (C. S. and W. G. B.) independently searched the electronic literature, screened titles and abstracts and read full-length articles in order to make final inclusion or exclusion decisions. The most complete version of an article was selected when there were two different publications from the same study. Any disagreements were resolved by discussion with a third reviewer (S. Q. W.).

We evaluated the methodological quality of each study using Newcastle–Ottawa Scale (NOS). The NOS is a method recommended by the Cochrane Non-Randomized Studies Methods Working Group to evaluate the quality of the study. Points are assigned based on the selection process of cohorts (0–4 points), the comparability of the cohorts (0–2 points) and the identification of the exposures and the outcomes of research participants (0–3 points). A score of at least 7 out of 9 was defined as high quality.

**Data collection and analysis**

The primary exposure variable was vitamin D deficiency. The dependent variables were offspring growth and adiposity outcomes. Some outcomes were continuous variables, such as birth weight, birth length, head circumference, BMI and fat mass, and other outcomes were dichotomous variables, such as SGA and diabetes type 1. To merge the results from various studies in meta-analysis, we constructed two-by-two tables of prenatal vitamin D status vs. the presence or absence of adverse offspring outcomes for dichotomous outcomes. For continuous outcomes, the mean values and standard deviations and number of subjects were extracted based on prenatal vitamin D status.

No universal consensus exists in the scientific community concerning the definition of vitamin D deficiency. When different cut-offs were presented in a study, we decided to use the lowest cut-off point as we were interested in studying the effects of vitamin D deficiency. In this meta-analysis, for any outcome with different cut-offs, subgroup analysis was performed. All individual studies reporting the same outcome were pooled to calculate the overall effect.

To merge data for continuous outcomes, the mean values and standard deviations and the number of subjects were needed from each group (vitamin D deficiency and vitamin D non-deficiency) in each study. The mean difference (MD) was calculated using the inverse variance method. To merge dichotomous outcomes, the number of patients with the outcome (SGA and diabetes type 1) and the total in each group (vitamin D deficiency and vitamin D non-deficiency) were needed. The Mantel–Haenszel method was then used to present the effect as OR and 95% CI. For both continuous and dichotomous outcomes, when the heterogeneity was significant, defined as I² of >50%, the analysis model was changed from fixed effect to random effects. Forest plots were used to illustrate the point estimate with 95% CI. Data meta-analysis was performed using the Review Manager (RevMan) 5.3.

Two independent reviewers (C. S., W. G. B.) went through the process of data extraction and calculation. We followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.

**Results**

In all, thirty studies involving a total of 35,032 mother–offspring pairs were included in this meta-analysis. Among the sixty preselected articles, twenty-three were excluded because they had insufficient data. Then, seven of the remaining thirty-seven
articles were excluded because they did not meet all inclusion criteria: six of them were not observational studies as they used supplementation\(^1\)\(^{21–26}\) and one of them had a population of pregnant women with a chronic disease – diabetes type 2\(^2\)\(^{27}\). The details of the process of literature search and selection of studies are presented in Fig. 1 – study eligibility flow chart. Table 1 shows characteristics of the included studies: study design, study setting (country), sample size, gestational age when the blood sample was taken, season when the blood sample was taken (percentage of winter), assay method used to determine the 25(OH)D level (including chemiluminescent immunometric assay, electrochemiluminescence immunoassay, ELISA, liquid chromatography-tandem MS, RIA and HPLC), 25(OH)D cut-off the authors used (when there were more than one, the lowest one was chosen) and child outcomes. Four studies\(^1\)\(^{17,35,43,51}\) measured cord blood 25(OH)D levels and the remaining studies measured maternal blood 25(OH)D levels. Cord blood vitamin D levels were lower than maternal blood levels, but they were highly correlated\(^5\)\(^{44}\). We also performed sensitivity analysis (excluding the studies with only cord blood data) and similar results were obtained. There was no evidence of publication bias.

Among the finally selected thirty articles, sixteen studies\(^1\)\(^{16–18,28,30,32,35,36,44–46,49,51–53}\) involving 18 096 participants reported birth weight. Vitamin D deficiency definition was different in individual studies. We used a 25(OH)D cut-off of 25 nmol/l in seven studies\(^2\)\(^{29,30,32,35,46,49}\), a cut-off of 27.5 nmol/l in one study\(^5\)\(^{51}\), a cut-off of 28 nmol/l in one study\(^4\)\(^{44}\), a cut-off of 30 nmol/l in three studies\(^1\)\(^{16,18,50}\) and a cut-off of 50 nmol/l in four studies\(^1\)\(^{17,45,52,53}\). Fig. 2 shows the summary MD of the association between low prenatal 25(OH)D levels and birth weight. The overall summary MD of birth weight (g) was \(−100.69 (95\% CI −162.25, −39.13) (P = 0.001)\). There was significant heterogeneity across studies (\(\chi^2 = 123.58, 50; \tau^2 = 21.80, 67; I^2 = 92\%; P < 0.00001\)). Subgroup analysis (online Supplementary Fig. S1) shows a significant association between prenatal 25(OH)D < 30 nmol/l and a lower birth weight (MD = −111.26; 95\% CI −139.60, −82.92; \(P < 0.00001\)). There was no significant heterogeneity. Subgroup analysis also shows significant association between prenatal 25(OH)D < 25 nmol/l and a lower birth weight (MD = −212.43; 95\% CI −408.90, −15.96; \(P = 0.03\)), but this association would become non-significant if accounting for multiple tests. Heterogeneity was significant.

In all, ten studies\(^1\)\(^{16,17,35,36,44–46,49,51,53}\) involving 8191 mother–newborn pairs reported the relationship between prenatal vitamin D and newborn length/height. As some studies had data on the height at birth\(^1\)\(^{16,17,35,36,44–46,49,53}\) while others had data on the length at approximately 2 weeks after birth\(^5\)\(^{45,51}\), the outcome of interest is newborn (0–28 days) length instead of birth length. There was no association between prenatal vitamin D status and newborn length (MD = −0.00; 95\% CI −0.32, 0.31; \(P = 0.98\)). There was significant heterogeneity (\(\chi^2 = 0.18; \tau^2 = 48.89; I^2 = 82\% ; P < 0.00001\)).

Seven studies\(^1\)\(^{16,35,36,44–46,49,53}\) on newborn head circumference involving 5018 participants were included in this meta-analysis (vitamin D deficiency cut-off of 30 nmol/l\(^{10,50}\), 28 nmol/l\(^{14}\), 27.5 nmol/l\(^{51}\) or 25 nmol/l\(^{35,46,49}\)). No association between
Table 1. Characteristics of the included studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>Country</th>
<th>Study design</th>
<th>Sample size (n)</th>
<th>Specimen GA (weeks)</th>
<th>Season</th>
<th>Assay method</th>
<th>25(OH)D cut-off (nmol/l)</th>
<th>Child outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ates et al.</td>
<td>Turkey</td>
<td>Prospective cohort</td>
<td>229</td>
<td>13-2 (11.0–14.0)</td>
<td>51-1</td>
<td>LC-MS</td>
<td>&lt;25 v. ≥25</td>
<td>SGA</td>
</tr>
<tr>
<td>Bodnar et al.</td>
<td>USA</td>
<td>Prospective cohort</td>
<td>412</td>
<td>&lt;22-0</td>
<td>21-1</td>
<td>CLIA</td>
<td>&lt;37.5 v. ≥37.5</td>
<td>SGA</td>
</tr>
<tr>
<td>Bowyer et al.</td>
<td>Australia</td>
<td>Prospective cohort</td>
<td>971</td>
<td>30-0–32.0</td>
<td>NA</td>
<td>CLIA</td>
<td>&lt;25 v. ≥25</td>
<td>SGA</td>
</tr>
<tr>
<td>Boyle et al.</td>
<td>New Zealand</td>
<td>Prospective cohort</td>
<td>1710</td>
<td>30-0–28.0</td>
<td>NA</td>
<td>CLIA</td>
<td>&lt;25 v. ≥25</td>
<td>SGA</td>
</tr>
<tr>
<td>Burris et al.</td>
<td>USA</td>
<td>Prospective cohort</td>
<td>1133</td>
<td>26-0–28.0</td>
<td>NA</td>
<td>CLIA</td>
<td>&lt;25 v. ≥25</td>
<td>SGA</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>China</td>
<td>Prospective cohort</td>
<td>3658</td>
<td>&lt;13 (35.1 %)</td>
<td>20-2</td>
<td>RIA</td>
<td>&lt;25 v. ≥25</td>
<td>Birth weight</td>
</tr>
<tr>
<td>Choi et al.</td>
<td>South Korea</td>
<td>Prospective cohort</td>
<td>220</td>
<td>First trim: 22.3 %</td>
<td>5-9</td>
<td>LC-MS</td>
<td>≤50 v. ≥50</td>
<td>SGA</td>
</tr>
<tr>
<td>Crozier et al.</td>
<td>UK</td>
<td>Prospective cohort</td>
<td>At birth: 574</td>
<td>25-OH D</td>
<td>NA</td>
<td>RIA</td>
<td>≤50 v. ≥50</td>
<td>Fat mass at birth, at ages 4 years and 6 years</td>
</tr>
<tr>
<td>Dalgaard et al.</td>
<td>Denmark</td>
<td>Prospective cohort</td>
<td>1038</td>
<td>Cord blood</td>
<td>NA</td>
<td>LC-MS</td>
<td>≤25 v. ≥25</td>
<td>Birth weight</td>
</tr>
<tr>
<td>Eckhardt et al.</td>
<td>USA</td>
<td>Retrospective cohort</td>
<td>2473</td>
<td>20-7 (15.9, 23.4)</td>
<td>23-0</td>
<td>LC-MS</td>
<td>&lt;30 v. ≥30</td>
<td>Newborn length</td>
</tr>
<tr>
<td>Fernandez-Alonso</td>
<td>Spain</td>
<td>Cross-sectional</td>
<td>466</td>
<td>First trimester</td>
<td>NA</td>
<td>ECLI</td>
<td>≤50 v. ≥50</td>
<td>Newborn head circumference</td>
</tr>
<tr>
<td>Gale et al.</td>
<td>UK</td>
<td>Prospective cohort</td>
<td>Birth: 466</td>
<td>28-O–42.0</td>
<td>NA</td>
<td>RIA</td>
<td>≤30 v. ≥30</td>
<td>Birth weight</td>
</tr>
<tr>
<td>Gernand et al.</td>
<td>US</td>
<td>Retrospective cohort</td>
<td>2416</td>
<td>20-6 (15.7, 23.4)</td>
<td>23-9</td>
<td>LC-MS</td>
<td>&lt;37.5 v. ≥37.5</td>
<td>SGA</td>
</tr>
<tr>
<td>Gould et al.</td>
<td>Australia</td>
<td>Prospective cohort</td>
<td>792</td>
<td>≤26.0</td>
<td>23-9</td>
<td>LC-MS</td>
<td>&lt;50 v. ≥50</td>
<td>SGA</td>
</tr>
<tr>
<td>Josefson et al.</td>
<td>USA</td>
<td>Prospective cohort</td>
<td>316/318</td>
<td>Cord blood</td>
<td>NA</td>
<td>LC-MS</td>
<td>&lt;25 v. ≥25</td>
<td>Newborn head circumference</td>
</tr>
<tr>
<td>Krishnaveni et al.</td>
<td>India</td>
<td>Prospective cohort</td>
<td>505/469</td>
<td>28-O–32.0</td>
<td>NA</td>
<td>RIA</td>
<td>≤50 v. ≥50</td>
<td>Fat mass, BMI, height at age 9 months</td>
</tr>
<tr>
<td>Leffelaar et al.</td>
<td>Netherlands</td>
<td>Prospective cohort</td>
<td>3730</td>
<td>13-S (3.3)</td>
<td>43-6</td>
<td>ELISA</td>
<td>≤50 v. ≥50</td>
<td>Birth weight</td>
</tr>
<tr>
<td>Miettinen et al.</td>
<td>Finland</td>
<td>Retrospective cohort</td>
<td>686</td>
<td>First trimester</td>
<td>NA</td>
<td>CLIA</td>
<td>≤50 v. ≥50</td>
<td>Newborn height</td>
</tr>
<tr>
<td>Morgan et al.</td>
<td>Canada</td>
<td>Nested case-control</td>
<td>1328</td>
<td>Cord blood</td>
<td>NA</td>
<td>CLIA</td>
<td>≤50 v. ≥50</td>
<td>Diabetes type I</td>
</tr>
<tr>
<td>Morley et al.</td>
<td>Australia</td>
<td>Prospective cohort</td>
<td>374</td>
<td>28-O–32.0</td>
<td>NA</td>
<td>RIA</td>
<td>≤28 v. ≥28</td>
<td>Birth weight</td>
</tr>
<tr>
<td>Ong et al.</td>
<td>Singapore</td>
<td>Prospective cohort</td>
<td>910</td>
<td>26-8</td>
<td>NA</td>
<td>LC-MS</td>
<td>≤50 v. ≥50</td>
<td>Newborn head circumference</td>
</tr>
<tr>
<td>Reichetzeder et al.</td>
<td>Germany</td>
<td>Prospective cohort</td>
<td>547</td>
<td>NA</td>
<td>NA</td>
<td>ELISA</td>
<td>≤25 v. ≥25</td>
<td>Birth weight</td>
</tr>
<tr>
<td>Rodriguez et al.</td>
<td>Spain</td>
<td>Prospective cohort</td>
<td>2342</td>
<td>13-S (2.2)</td>
<td>NA</td>
<td>HPLC</td>
<td>≤50 v. ≥50</td>
<td>Newborn head circumference</td>
</tr>
</tbody>
</table>
Table 1. Continued

| Studies | County | Specimen GA (weeks) | Assay method | 25(OH)D cut-off \( \text{nmol/l} \) | GA, gestational age at the time of specimen sampling; 25(OH)D, 25-hydroxyvitamin D; LC-MS, liquid chromatography-tandem MS; SGA, small-for-gestational-age; NA, not available; CLIA, chemiluminescent immunometric assay; ECLI, enzyme-linked immunometric assay.

| C. Santamaria et al. | Schneuer et al. | (49) China Cross-sectional 70 Before labour NA ELISA \( <50 \text{nmol/l} \) | NEWBORN LENGTH | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBORN HEAD CIRCUMFERENCE | NEWBON...
The risk of diabetes type 1 in prenatal vitamin D-deficient mother–child pairs has been compared with vitamin D-non-deficient mother–child pairs in two studies, including 1014 mother–child pairs. Sørensen et al. showed that low maternal 25(OH)D level was associated with increased risk of diabetes type 1 in children (the mean age at diabetes diagnosis was 9 years), whereas Miettinen et al. did not observe any difference between 25(OH)D levels of the case and control mothers (the mean age at diabetes diagnosis was 3 years). The meta-analysis results show that low maternal vitamin D status during pregnancy was not associated with risk of diabetes type 1 in the offspring. The summary crude OR was 1.25 (95% CI 0.78, 2.02). There was significant heterogeneity ($\chi^2 = 2.92, P = 0.05$).

### Discussion

The main findings of this systematic review and meta-analysis were that low prenatal vitamin D status was associated with lower birth weight and increased risk of SGA. Interestingly, low prenatal vitamin D status was associated with greater weight in infants at the age of 9 months, but no significant difference was observed in length, indicating that low prenatal vitamin D status may be linked to accelerated growth and adiposity in early postnatal life. However, prenatal vitamin D deficiency was not related with risk of childhood diabetes type 1.

Previous systematic reviews of observational studies mainly focused on vitamin D during pregnancy and maternal and neonatal outcomes. Aghajari's meta-analysis found an association between prenatal vitamin D deficiency and lower birth weight and elevated risks of SGA, as well as other maternal health outcomes.
C. Santamaria et al.

### (a) Vitamin D deficiency versus Vitamin D non-deficiency

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vitamin D deficiency</th>
<th>Vitamin D non-deficiency</th>
<th>MD SD Mean Total</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-12/2 25(OH)D cut-off: 30 nmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gale 2008</td>
<td>9100</td>
<td>1070</td>
<td>110</td>
<td>9113.3 1185-76</td>
</tr>
<tr>
<td>Subtotal (95 % CI)</td>
<td>971</td>
<td>3199</td>
<td>100-0</td>
<td>119.75 32.97</td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 1.39$, df = 1 ($P = 0.24$); $I^2 = 28%$ Test for overall effect: $Z = 2.70$ ($P = 0.007$) Test for subgroup differences: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95 % CI)</td>
<td>971</td>
<td>3199</td>
<td>100-0</td>
<td>119.75 32.97</td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 1.39$, df = 1 ($P = 0.24$); $I^2 = 28%$ Test for overall effect: $Z = 2.70$ ($P = 0.007$) Test for subgroup differences: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### (b) Vitamin D deficiency versus Vitamin D non-deficiency

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Vitamin D deficiency</th>
<th>Vitamin D non-deficiency</th>
<th>MD SD Mean Total</th>
<th>IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-14/2 25(OH)D cut-off: 30 nmol/l</td>
<td></td>
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</tr>
<tr>
<td>Gale 2008</td>
<td>71.2</td>
<td>2.85</td>
<td>110</td>
<td>71.4</td>
</tr>
<tr>
<td>Subtotal (95 % CI)</td>
<td>971</td>
<td>3199</td>
<td>100-0</td>
<td>119.75 32.97</td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 0.15$, df = 1 ($P = 0.69$); $I^2 = 0%$ Test for overall effect: $Z = 0.79$ ($P = 0.43$)</td>
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<tr>
<td>Total (95 % CI)</td>
<td>971</td>
<td>3199</td>
<td>100-0</td>
<td>119.75 32.97</td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 0.15$, df = 1 ($P = 0.69$); $I^2 = 0%$ Test for overall effect: $Z = 0.79$ ($P = 0.43$)</td>
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<tr>
<td>Test for subgroup differences: not applicable</td>
<td></td>
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### Fig. 4. Forest plots of summary mean difference (MD) of anthropometry in infants at the age of 9 months between prenatal vitamin D deficiency and vitamin D non-deficiency. (a). The association between prenatal vitamin D deficiency and infant weight (g) at the age of 9 months. (b). The association between prenatal vitamin D deficiency and infant length (cm) at the age of 9 months. 25(OH)D, 25-hydroxyvitamin D.

The results of this meta-analysis show that low maternal vitamin D status was associated with higher weight at the age of 9 months, indicating that maternal low vitamin D status may be associated with an accelerated postnatal growth. Accelerated growth during infancy has been reported to be associated with childhood adiposity and the risk of subsequent overweight or obesity. However, results have to be interpreted cautiously. The mean weight difference in infants at the age of 9 months was only 119.75 g (1.3 % of infant weight), which may not be clinically relevant. Although there is a lack of data on what percentage of weight difference during infancy can increase odds of overweight or obesity in later life, further research is needed in this area. In addition, confounding factors such as dietary intake and breast-feeding during infancy may have affected this relationship. Adiposity was observed to be elevated at child at age 6 years in prenatally vitamin D-deficient mother–offspring pairs.

An association between maternal vitamin D deficiency and risk of diabetes type 1 in children was not observed in this meta-analysis. However, there were only two studies that examined the link between maternal vitamin D status and diabetes in offspring. A nested case–control study showed the association, whereas another study did not. However, the mean age at diagnosis for diabetes was too young (only about 3-4 years) in the Miettinen study, whereas the peak incidence for diabetes in children is at age 10-14 years, and thus this study cannot exclude the possibility that maternal vitamin D deficiency may contribute to the risk of diabetes type 1. More longitudinal cohort studies with longer follow-up of children (age 10-14 years) are needed to clarify this association.

The underlying mechanisms in the association between maternal vitamin D during pregnancy and infant growth and adiposity are biologically plausible. Indeed, vitamin D promotes Ca and P absorption, which is essential for the mineralisation process during fetal bone formation. During pregnancy, the placenta synthesises vitamin D to help achieve a higher concentration in circulation. As Ca reaches fetal circulation by crossing the placental barrier, the mineralisation of fetus bones depends on the mother’s Ca absorption. Therefore, vitamin D deficiency in the mother can induce Ca deficiency in the fetus, which may affect bone formation in the fetus. In addition, intra-uterine exposure to low vitamin D status negatively affects fetal skeletal muscle and adiposity development.

The adverse effects of prenatal vitamin D deficiency on fetal bone, muscle and fat development might be responsible for lower birth weight or SGA. Vitamin D also helps to reduce inflammatory response during pregnancy and contributes to embryo implantation. Moreover, it is widely accepted that vitamin D is mainly stored in adipose tissue. Numerous studies have reported a correlation between vitamin D deficiency and obesity. However, the causal relationship between vitamin D status and
obesity remains unclear. Vitamin D deficiency might play a role in the development of obesity because decreased circulating 25(OH)D levels could result from a modification in vitamin D metabolism occurring during obesity development\(^66\). Indeed, modifications in the expression of genes encoding key enzymes of vitamin D metabolism have been reported in the adipose tissue from the animal model\(^67\), indicating that prenatal vitamin D status may affect adiposity in offspring.

Some limitations of this review should be noted. First, there is no universal definition of vitamin D deficiency, and various definitions were used in individual studies. However, we performed overall analysis based on vitamin D deficiency and non-deficiency, as well as subgroup analysis according to the specific cut-off of 25(OH)D level, and the findings were similar. Second, the observed associations between prenatal vitamin D status and offspring outcomes could be affected by potential confounding factors. However, most adjusted OR were similar to the crude estimates. Third, the variability in the assay methods for 25(OH)D may have affected the results. Finally, loss to follow-up may be an issue for cohort studies on child long-term health outcomes.

This systematic review has strengths. It was the first to summarise the evidence on prenatal vitamin D status on offspring growth, adiposity and metabolic health. It included the most recent studies and followed the MOOSE guidelines\(^68\). The quality of the review data in this review depends on the methodological quality of the included studies. Each study was evaluated using the NOS, and only high-quality observational studies were included in the meta-analysis.

The evidence from this systematic review indicates that low prenatal 25(OH)D status has an impact on fetal growth and low prenatal vitamin D status may be associated with infant adiposity. Further confirmation of these findings in large longitudinal cohorts is warranted. Carefully defined large multi-centre randomised clinical trials of vitamin D supplementation in pregnancy for improving infant growth need to be implemented to better define the risks and benefits. Given the high prevalence of vitamin D deficiency in pregnant women, the findings could have substantial public health implications.

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The authors declare that there are no conflicts of interest.

**Supplementary material**

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114517003646

**References**


