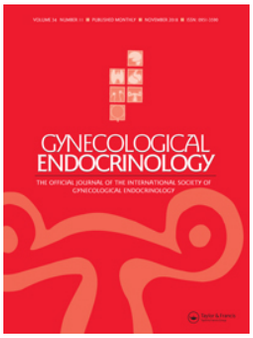

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ASSOCIATION BETWEEN MATERNAL 25-HYDROXYVITAMIN D LEVELS AND PERINATAL OUTCOMES

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# Systematic review and meta-analysis of Spanish studies regarding the association between maternal 25-hydroxyvitamin D levels and perinatal outcomes

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**ABSTRACT**

**Objective:** This systematic review and meta-analysis of Spanish studies assessed the association of maternal 25-hydroxyvitamin D [25(OH)D] levels on perinatal outcomes.

**Methods:** PubMed, Cochrane Library, Embase, Scielo, Scopus, and Web of Science research databases were searched from inception through December 30 2017 using the terms 'vitamin D', 'pregnancy', and 'Spain'. Studies that compared first or second half of pregnancy normal 25(OH)D (≥30.0 ng/mL) versus insufficient (20.0–29.9 ng/mL) or deficient (<20.0 ng/mL) circulating levels and perinatal outcomes were systematically extracted. Data are presented as pooled odds ratios and their 95% confidence intervals (CIs) for categorical variables or mean differences and CIs for continuous variables. Risk of bias was evaluated with the Newcastle–Ottawa Scale.

**Results:** Five cohort studies met inclusion criteria. The risk of gestational diabetes mellitus, preeclampsia, preterm birth, and small-for-gestational-age infants, and birthweight was not influenced by first half of pregnancy maternal 25(OH)D levels. In addition, second half of pregnancy 25(OH) levels did not affect birthweight.

**Conclusion:** Maternal 25(OH)D levels during pregnancy did not affect studied perinatal outcomes and birthweight.

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**KEYWORDS**
Preeclampsia; gestational diabetes mellitus; preterm birth; small-for-gestational-age; vitamin D; 25-hydroxyvitamin D; birthweight

## Introduction

Vitamin D has been related to fertilization, implantation, and placental and fetal maturation and growth [1–3]. In addition to maintain calcium and phosphorus homeostasis and to promote fetal bone mineralization, vitamin D regulates trophoblastic function, glucose homeostasis, inflammatory response, and antimicrobial barrier mechanisms [4–9].

During the first trimester of pregnancy a significant proportion of women display low circulating 25-hydoxyvitamin D [25(OH)D] levels; and as gestation continues these levels progressively decrease, reaching lower levels than those found at the beginning of pregnancy [10]. These observed differences seem to depend on prenatal care supplementation guidelines, geographical location, lifestyle, and dietary habits [10–12]. Cord blood and maternal 25(OH)D levels correlate; indeed, 66% of mothers with levels <20 ng/mL have newborns with levels below 10 ng/mL [13].

A systematic review and meta-analysis of cross-sectional, case-control, and cohort studies reported that maternal 25(OH)D levels were associated with an increased risk for gestational diabetes mellitus (GDM), preeclampsia, preterm birth, and small-for-gestational age infants (SGA) [14]. On the other hand, a meta-analysis of randomized controlled trials (RCTs) regarding the effects of vitamin D supplementation during pregnancy, did not report clinical benefits on obstetrical outcomes [15,16]. Both meta-analyses were based on heterogeneous populations. The present systematic review and meta-analysis aimed at exploring the association of maternal vitamin D status and perinatal outcomes as reported in cohort studies performed in Spain.

## Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [17]. Formal institutional review board approval was not required because this analysis consisted of the pooling of published studies.

### Pre-specified outcomes

Perinatal outcomes included GDM, preeclampsia, preterm birth (<37 weeks), SGA infants, infant birthweight (g), and low birthweight (<2500 g) as defined by the authors. Tentative secondary outcomes included birth Apgar score, cesarean delivery rate, and rate of admissions to the Neonatal Intensive Care Unit (NICU).

### Search strategies

Two investigators independently conducted a systematic literature search of the PubMed, Cochrane Library, Embase, Scielo, Scopus, and Web of Science databases from inception through December 30 2017. The following search terms were

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used: ('vitamin D' or 'ergocalciferol' or 'cholecalciferol') and ('pregnancy'), and ('Spain').

### Inclusion and exclusion criteria

Studies were included if (i) these were prospective cohorts, without language limitation, that had data of the circulating levels of 25(OH)D in pregnant women living in Spain; (ii) 25(OH)D levels during pregnancy were reported as sufficient (≥30.0 ng/mL), insufficient (20.0–29.9 ng/mL), and deficient (<20.0 ng/mL); (iii) they reported perinatal outcomes endpoints of the second half of pregnancy (i.e. GDM, preeclampsia, preterm birth, SGA, infant birthweight, low birthweight, 5-min Apgar scores, and NICU admissions); (iv) study data be presented as effect estimates: odds ratios (ORs) for categorical variables or mean differences (MD) for continuous variables, and their corresponding 95% confidence intervals (CIs), or the article reported data that enabled the calculation of these.

Exclusion criteria were (i) non-maternal measurement of 25(OH)D; (ii) pregnant women living in countries other than Spain; or (iii) no predefined perinatal outcomes. When data from a given cohort was repeatedly reported, the paper with more detailed information was chosen.

### Data extraction and assessment for the risk of bias

Two authors independently extracted the data from each study to a standard registration form. Discrepancies were solved *via* review of the original articles and group discussion. From each study, we extracted information regarding the first author, year of publication, North latitude of the study location, season of blood sampling, method used to measure 25(OH)D, maternal age and body mass index (BMI), gestational age at blood sampling, parity and plurality, obstetric characteristics, and vitamin D supplementation (yes/no). In addition, perinatal outcomes were ascertained (Table 1).

When data were provided as median and interquartile range (IQR), the mean was calculated by the formula $x = (a + 2m + b)/4$, using median ($m$), P25 and P75 ($a$ and $b$, respectively); and the standard deviation calculated by the formula SD = IQR/1.35 [18].

### Evaluation of the risk of bias

For every eligible study the risk of bias was evaluated by two investigators using the Newcastle–Ottawa Scale (NOS) for assessing cohort studies. Disagreements were solved through discussion among all authors. The NOS evaluates eight items that are categorized into three groups: the selection of exposure and non-exposure groups, the comparability of these groups, and outcome evaluation. An additional star can be given for adjusted exposure or outcome. Therefore, a maximum number of nine stars can be obtained by any or each article. Achieving a total of seven or more stars indicates that the study has a low risk of bias [19]. The score of each individual publication is shown in Table 2.

### Statistical analysis

Data on dichotomous outcomes were combined and effect sizes were presented as OR with 95% CIs. For continuous outcomes, we estimated mean differences (MDs) with 95% CI. Forest plots were generated to illustrate the study-specific effect sizes along with a 95% CI. The significance of the pooled OR was determined using the $Z$ test, with a $p < .05$ considered as significant.

Heterogeneity across studies was assessed using the $Q$-test based on the $\chi^2$ statistic ($p < .1$ was considered statistically significant). To quantify heterogeneity, the $I^2$ value was calculated and values of 40–65% interpreted as moderate level of heterogeneity. A $p$ values of <.1 for $\chi^2$ was used to define the presence of heterogeneity. The between-study variance was estimated using tau-squared ($\tau^2$) statistic [20]. The fixed-effects (Mantel–Haenszel method) were used to calculate pooled effect estimates. If $I^2$ exceeded 65%, results were then pooled using the random effects models using the Der Simonian–Laird method [21].

The leave-one-out sensitivity analysis (omission of a single study at a time) was performed in order to assess whether a particular omission could affect effect sizes and heterogeneity across studies. The extent of publication bias was assessed by the Begg's test and the Egger's regression asymmetry test [22,23].

## Results

### Search results

The search identified 599 publications with 135 duplicates. After the exclusion of 438 articles, based on the title and abstract, 26 full-text articles were reviewed along with one additional record which was a full doctoral thesis identified from online literature. Finally, six publications (five papers + doctoral thesis) were included in qualitative and quantitative synthesis (Figure 1).

### Included studies

Four cohorts reported data according to the inclusion criteria [10,24–27]. In addition, a research doctoral degree thesis was also found online [28]. 25(OH)D measurements were reported either from the first half of pregnancy, from (mean ± SD) 9.5 ± 1.3 to 13.7 ± 2.4 weeks [10,24,27,28], and/or the second half of pregnancy from range 24–28 weeks [26] to 250 days (interquartile range 242–258 days) [28]. 25(OH)D levels were measured either by electrochemiluminescence immunoassay [10,24,26], or high performance liquid chromatography [25,27,28].

Pregnant women were living at Ourense (latitude 42°N) [24]; Almería (latitude 36°N) [10]; Valencia (latitude 39°N), Sabadell (latitude 41°N), Asturias (latitude 43°N), Guipúzcoa (latitude 42°N)[25]; Cartagena (latitude 37°N) [28]; Madrid (latitude 40°N) [26]; and Valencia (latitude 39°N), Sabadell (latitude 41°N), Asturias (latitude 43°N), and Guipúzcoa (latitude 42°N) [27].

Parity, plurality, and maternal characteristics are shown in Table 1. No specific recommendations were given concerning diet containing vitamin D, sun exposure, and vitamin D supplementation. Some women were using, *ad libitum*, polyvitaminics that included a dosage of 200 IU of cholecalciferol or ergocalciferol. The clinical characteristics of the analyzed studies are summarized in Table 1.

### Risk of bias assessment and publication bias

According to the NOS, all studies were identified as of good quality (NOS Score ≥7) (Table 2).

There was no evidence of interdependence of variance and effect size with the Begg–Mazumdar test ($p > .05$); despite this, due to the small number of studies, caution is recommended for the interpretation of results.

**Table 1.** Baseline characteristics of the studies as reported by authors.

| Study, year [reference] | Study location and North latitude | Study duration month, year–month year | Season at blood extraction | Measurement methods | Maternal age (years) Mean ± SD | Maternal BMI ($kg/m^2$) Mean ± SD | Parity | Plurality | Maternal characteristics | Gestational age (weeks) at blood extraction Mean ± SD | Vitamin D levels first half of pregnancy Mean ± SD | Vitamin D levels second half of pregnancy Mean ± SD | Vitamin D supplementation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Álvarez-Silvares et al., 2016 [24] | Ourense<br>Latitude 42° N | March 2013–June 2014 | Spring ($n = 94$)<br>Summer ($n = 48$)<br>Fall ($n = 94$)<br>Winter ($n = 134$) | ECI | 32.3 ± 5.1 | 24.3 ± 3.8 | Pregnancies: 1.1 ± 0.7 | Singleton | Low obstetric risk | 9.5 ± 1.3 | Between 8 and 14 weeks:<br>13.8 ± 8.5 ng/mL<br>$N = 370$ | Not reported | No calcidiol supplementation (no supplements and no fortification) |
| Fernández-Alonso et al., 2012 [10] | Almería<br>Latitude 36° N | May 2009–April 2010 | At first half of pregnancy blood extraction:<br>Spring ($n = 45$)<br>Summer ($n = 280$)<br>Fall ($n = 110$)<br>Winter ($n = 31$) | ECI | <20 years:<br>$n = 28$<br>20–29 years:<br>$n = 222$<br>≥30 years:<br>$n = 252$ | <25 $kg/m^2$:<br>$n = 307$<br>25–30 $kg/m^2$:<br>$n = 132$<br>≥30 $kg/m^2$:<br>$n = 63$ | 0:<br>$n = 262$<br>1-2:<br>$n = 228$<br>≥3:<br>$n = 12$ | Not reported | No increased risk for intrauterine fetal growth restriction, no hereditary or acquired trombophilias | First half of pregnancy:<br><12 weeks:<br>$n = 175$<br>≥12 weeks:<br>$n = 327$<br>Second half of pregnancy:<br>Range 36–39 weeks | Between 11 and 14 weeks:<br>27.4 (20.9–32.8) ng/mL[a]<br>$N = 466$ | Between 36 and 39 weeks:<br>18.2 ± 8.8 ng/mL<br>$N = 148$ | No vitamin D supplementation upon recruitment or follow-up |
| Morales et al., 2014 [25] | Valencia (39°N), Sabadell (41°N), Asturias (43° N) and Guipúzcoa (42° N) | November 2003–February 2008 | Spring, summer, fall and winter | HPLC | <20 ng/mL:<br>30.2 ± 4.6<br>20–29.9 ng/mL:<br>30.4 ± 4.3<br>≥30 ng/mL:<br>31.0 ± 4.2 | Not extractable | Both nulliparous and multiparous | Singleton | ≥16 years, intention to deliver at the reference hospital, no assisted conception | <20 ng/mL:<br>13.7 ± 2.4<br>20–29.9 ng/mL:<br>13.6 ± 2.2<br>≥30 ng/mL:<br>13.4 ± 2.0 | 14.0 (13.0–15.0)[b] weeks:<br>29.4 (21.9–37.2) ng/mL[a]<br>$N = 2358$ | Not reported | Not reported |
| Moreno Fuentes et al., 2017 [28] | Cartagena (37° N) | First half of pregnancy:<br>November 2014–February 2015<br>Second half of pregnancy:<br>May 2015–August 2015 | First half of pregnancy:<br>Fall and winter<br>Second half of pregnancy:<br>Spring and summer | HPLC | 30.2 ± 5.2 | First half of pregnancy:<br>25.2 (18.8–31.7)[a]<br>Second half of pregnancy:<br>28.9 (26.6–32.0)[a] | 19.5% nulliparous | Singleton | >18 years, no diabetes, no HBP, no severe pathology, no kidney or liver disease, no gestational hypertension previously | First half of pregnancy:<br>75 (67–83)[a] days<br>Second half of pregnancy:<br>250 (242–258)[a] days | Between 9 and 13 weeks:<br>20.9 ± 11.0 ng/mL<br>$N = 215$ | Between 35 and 37 weeks:<br>32.4 ± 17.5 ng/mL<br>$N = 215$ | 24.2%:<br>200 IU/day: 21.9%<br>400 IU/day 2.3% |
| Pérez-Ferré et al., 2012 [26] | Madrid (40° N) | June 2010–September 2010 | Spring, summer and fall | ECI | 33 (29–36)[a] | Before pregnancy:<br>23.1 (20.8–25.6)[a]<br>During pregnancy:<br>25.7 (23.2–27.9)[a] | Nulliparous:<br>$n = 107$<br>Second pregnancy:<br>$n = 64$<br>>2 pregnancies:<br>$n = 95$ | Not reported | Samples were studied coinciding with screening for gestational diabetes mellitus | Range 24–28 weeks | Not reported | Between 24 and 28 weeks:<br>18.9 (11.5-24.7) ng/mL[a]<br>$N = 266$ | Usual practice (5 mcg or 200 IU/day) |
| Rodríguez et al., 2014 [27] | Valencia (39°N), Sabadell (41°N), Asturias (43° N) and Guipúzcoa (42° N) | November 2003–February 2008 | Spring, summer, fall and winter | HPLC | 32.0 ± 4.2 | 27% BMI ≥25 $kg/m^2$ before pregnancy (overweight or obese) | Both nulliparous and multiparous | Singleton | ≥16 years, intention to deliver at the reference hospital, no assisted conception | 13.5 ± 2.2 | 29.4 (21.8–37.2) ng/mL[a]<br>$N = 2382$ | Not reported | Not reported |

BMI: body mass index; ECI: electrochemiluminescence immunoassay; HPLC: high performance liquid chromatography; HBP: high blood pressure.
[a]Median (interquartile range).
[b]Median (range).

**Table 2.** Study quality assessment using Newcastle–Ottawa scale.

| | Selection | | | | | | Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Study, Year | Representativeness of exposed cohort | Selection of non-exposed cohort | Ascertainment of exposure | Outcome not present at baseline | Comparability of cohorts (adjusted for) | Assessment of outcome | Sufficient follow-up duration | Adequate follow-up | Total score |
| Álvarez-Silvares et al., 2016 [24] | * | * | * | * | ** | * | * | * | 9 |
| Fernández-Alonso et al., 2012 [10] | * | * | * | * | (Adjusted for maternal and seasonal variables) * | * | * | * | 8 |
| Morales et al., 2014 [25] | * | * | * | * | (Not adjusted) ** | * | * | * | 9 |
| Moreno Fuentes et al., 2017 [28] | * | * | * | * | (Adjusted for maternal height, age, parity, ethnicity and pregnancy weight, father's height and fetal sex) ** | * | * | * | 9 |
| Pérez-Ferré et al., 2012 [26] | * | * | * | * | (Adjusted for maternal age, ethnicity, education, employment situation, smoking, BMI, sun exposure, vitamin D intake and vitamin supplementation) ** | * | * | * | 9 |
| Rodríguez et al., 2014 [27] | * | * | * | * | (Adjusted for age, ethnicity, family, personal history, BMI and smoking) ** | * | * | * | 9 |
| | | | | | (Adjusted for child sex, gestational age, parity, maternal social class, education, age at delivery, smoking, overweight, alcohol consumption and area of study) | | | | |

*A study can be awarded a maximum of one star for each numbered item within the selection and exposure categories.
**A study can be awarded a maximum of two stars for comparability of cohorts.

### *Meta-analyses*

Maternal 25(OH)D levels during the first half of pregnancy were unrelated to the risk of GDM (OR =0.93, 95% CI: 0.70–1.25, $I^2 = 27\%$, $p = .64$, Figure 2), preeclampsia (OR =0.73, 95% CI: 0.35–1.51, $I^2 = 0\%$, $p = .39$, Figure 3), preterm birth (OR =1.01, 95% CI: 0.76–1.34, $I^2 = 0\%$, $p = .95$, Figure 4), SGA infants (OR =1.02, 95% CI =0.83–1.27, $I^2 = 0\%$, $p = .84$, Figure 5), and birthweight (MD =9.6 g, 95% CI: −21.7 to 40.9, $I^2 = 35\%$, $p = .55$, Figure 6).

Maternal 25(OH)D levels during the second half of pregnancy were unrelated to differences in infant birthweight for two studies assessing vitamin D insufficiency (MD = −1.9 g, 95% CI: −99.3 to 95.5 g, $I^2 = 55\%$, Figure 7). Other tentative outcomes were not available for the analyzed studies.

## Discussion

The present systematic review and meta-analysis was based on Spanish studies reporting on pregnant women attended at the National Public Health System with standard care and fairly similar common lifestyle conditions. The present study found that the risk of GDM, preeclampsia, preterm birth, and SGA infants did not increase in relation to 25(OH)D status in the first half of pregnancy. In addition, neonatal birthweight did no differ when several 25(OH)D cutoffs were considered either in the first or second half pregnancy.

A previous systematic review and meta-analysis of 24 observational studies from different world regions reported that pregnant women with 25(OH)D levels below 20 ng/mL had a higher risk of GDM, preeclampsia, preterm birth, and SGA infants [14]. Our systematic review and meta-analysis of five cohorts of pregnant women living in the European continental part of Spain showed that perinatal outcomes and infant birthweights were not influenced by baseline first trimester or second half of pregnancy maternal 25(OH)D levels. Despite this, vitamin D supplementation during pregnancy has been associated with higher birthweight [15,16].

Despite the fact that all women were living in a very close latitude with different weather conditions, maternal 25(OH)D levels were not influenced by temperature or cloudiness differences which in theory would alter the skin synthesis of vitamin D. On the other hand, dietary and lifestyle habits are very similar all over Spain, suggesting common patterns (i.e. sun exposure, skin protection, and diet content of vitamin D). Of interest is to mention the fact that the National Spanish Society of Obstetrics and Gynecology has no recommendation regarding vitamin D supplementation during gestation; although women may receive during some periods of their pregnancy multivitamin supplements that contain small amounts of vitamin D (usually 200 IU/pill). This amount does not seem to prevent the natural and spontaneous decline of vitamin D levels observed from the first to the third trimester of pregnancy [10].

Due to the small number of included studies in our analysis, it was not possible to assess the potential influence that the season of the year, cloudiness, BMI, and weight gain could have over 25(OH)D levels and perinatal outcomes. A previous systematic review and meta-analysis of randomized controlled trials of vitamin D supplementation did not report significant benefits over pregnancy outcomes [15,16].

Low vitamin D has been related to inflammatory alterations that may be related to negative perinatal outcomes [29–31]. However, it seems that the benefits of high maternal vitamin

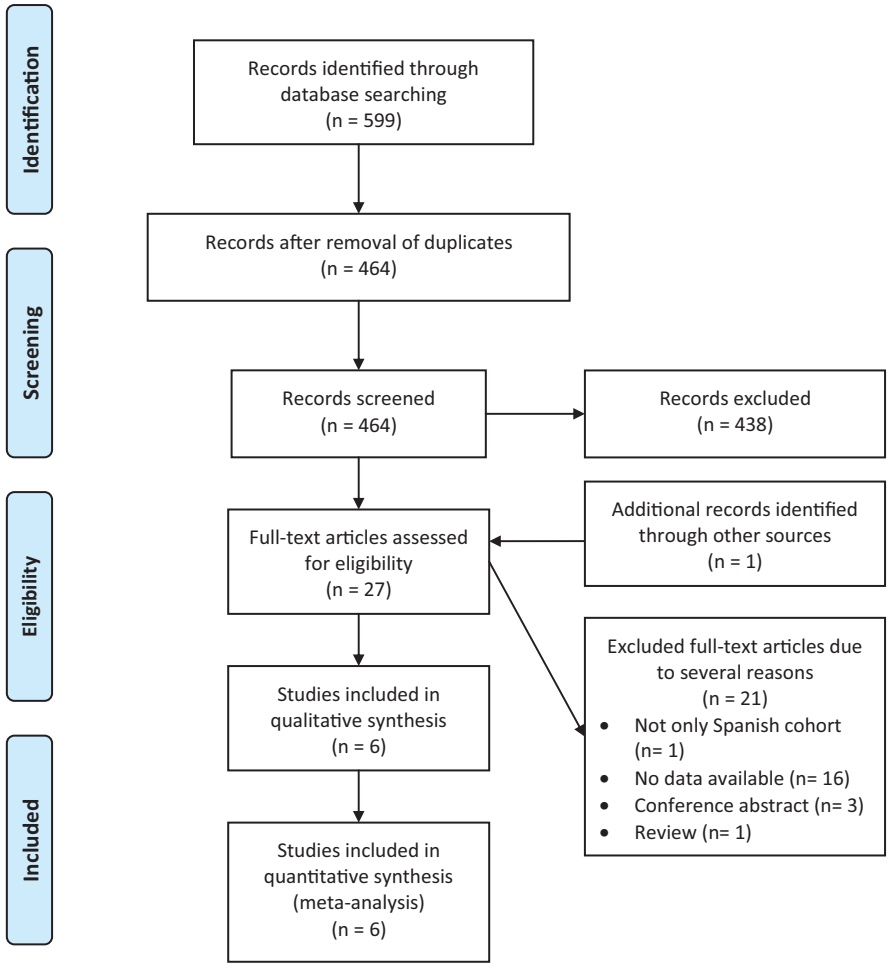


**Figure 1.** Flow diagram of included studies.

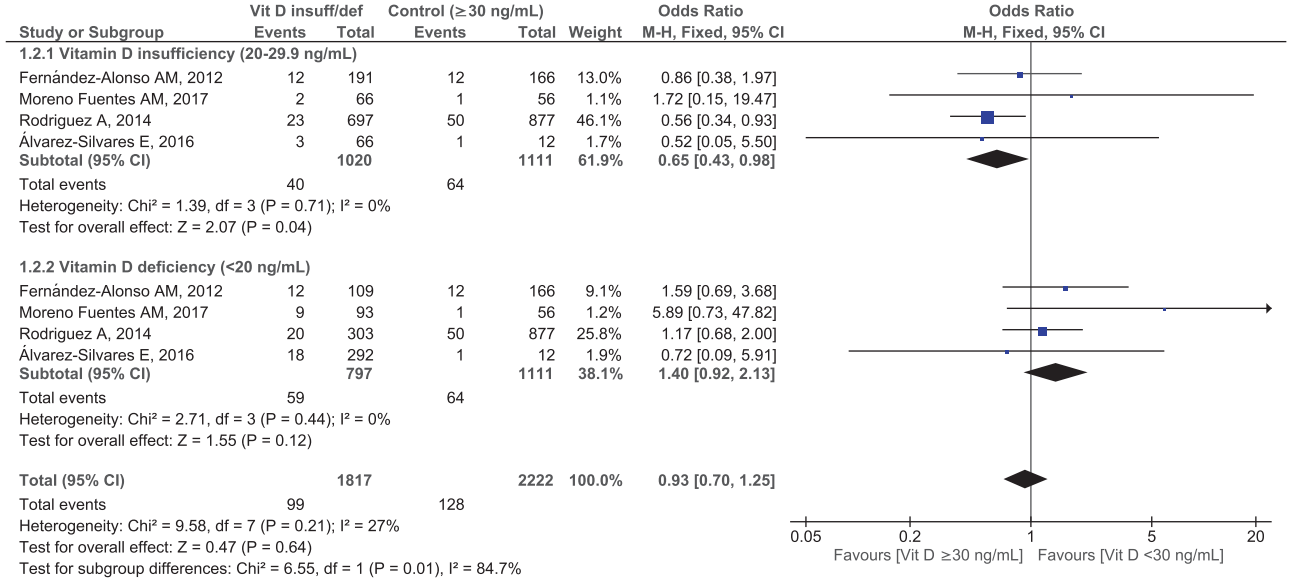


**Figure 2.** Maternal insufficient (20.0–29.9 ng/mL, top) and deficient (<20.0 ng/mL, bottom) 25(OH)D levels during the first half of pregnancy as compared to sufficient levels (≥30.0 ng/mL) and gestational diabetes risk.

D levels (>40 ng/mL) have rarely been reported in supplemented or non-supplemented pregnancies [32]. Despite this, high dose of vitamin D supplementation has been associated to the reduction of the rate of GDM [33], preeclampsia, low birthweight [34], preterm birth [32,35], and SGA infants [36]. There is a need for more well-designed studies using high vitamin D dosages in order to confirm or deny these possible benefits. Future studies should also include the study of inflammatory markers

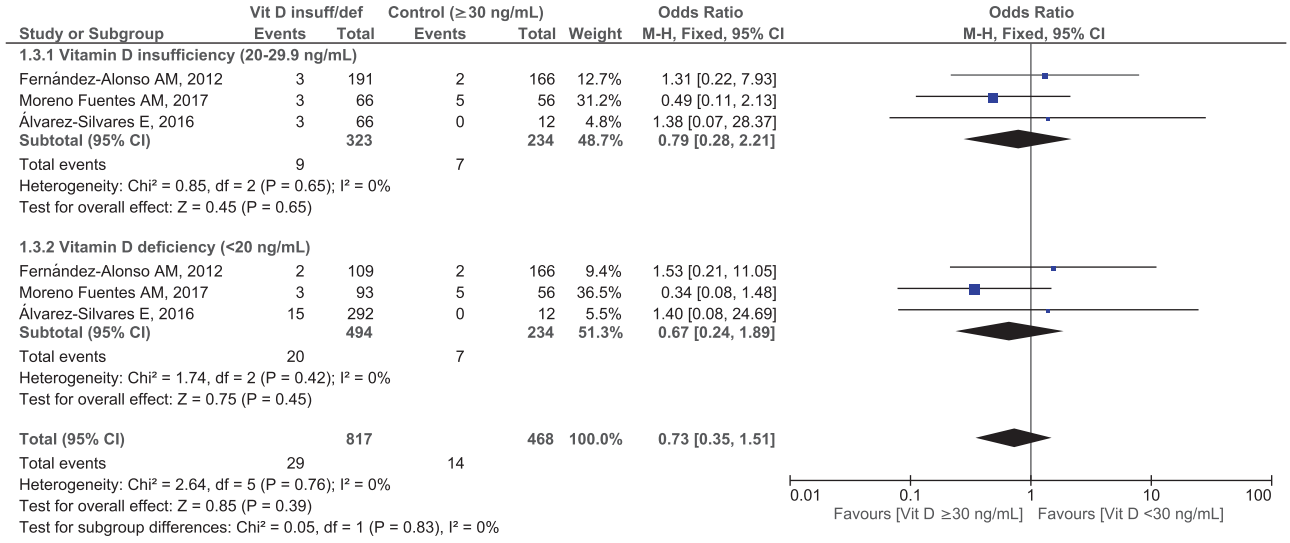


**Figure 3.** Maternal insufficient (20.0–29.9 ng/mL, top) and deficient (<20.0 ng/mL, bottom) 25(OH)D levels during the first half of pregnancy as compared to sufficient levels (≥30.0 ng/mL) and preeclampsia risk.

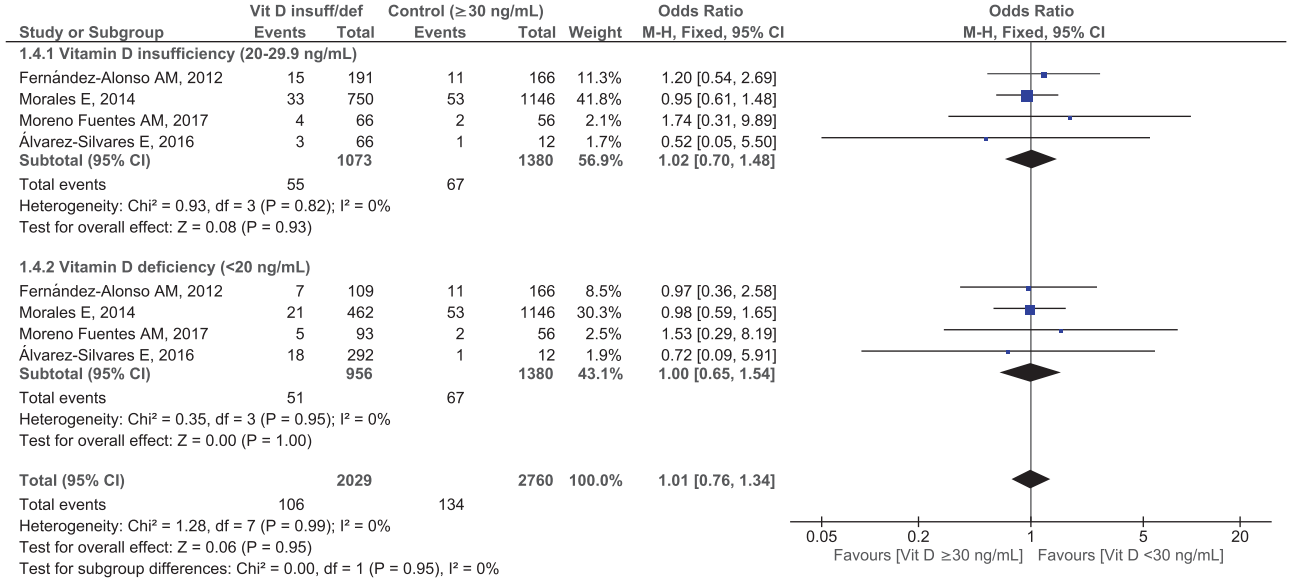


**Figure 4.** Maternal insufficient (20.0–29.9 ng/mL, top) and deficient (<20.0 ng/mL, bottom) 25(OH)D levels during the first half of pregnancy and preterm birth risk.

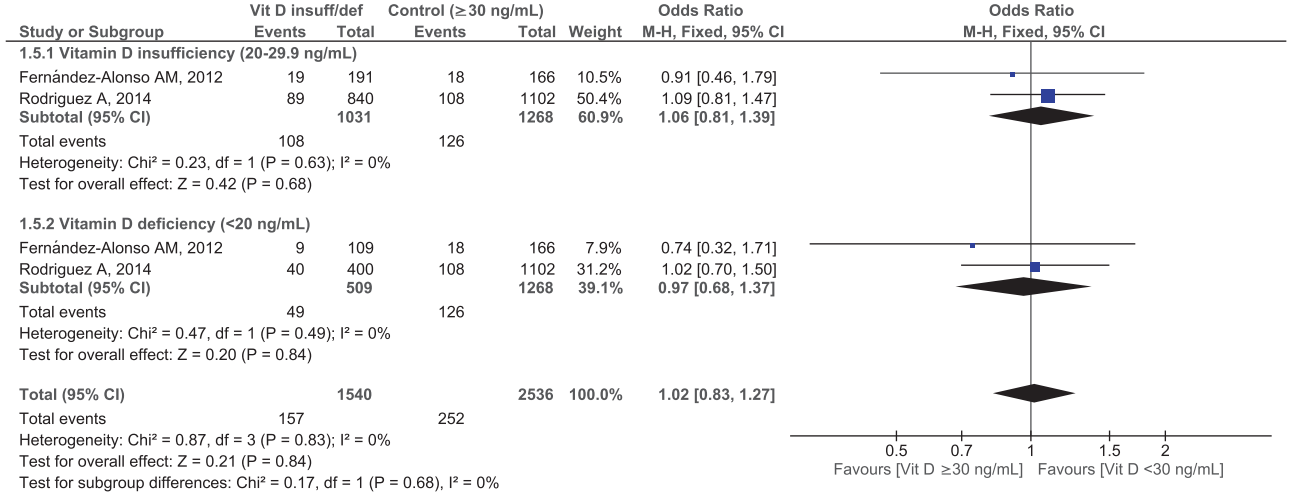


**Figure 5.** Maternal insufficient (20.0–29.9 ng/mL, top) and deficient (<20.0 ng/mL, bottom) 25(OH)D levels during the first half of pregnancy and small for gestational infant risk.

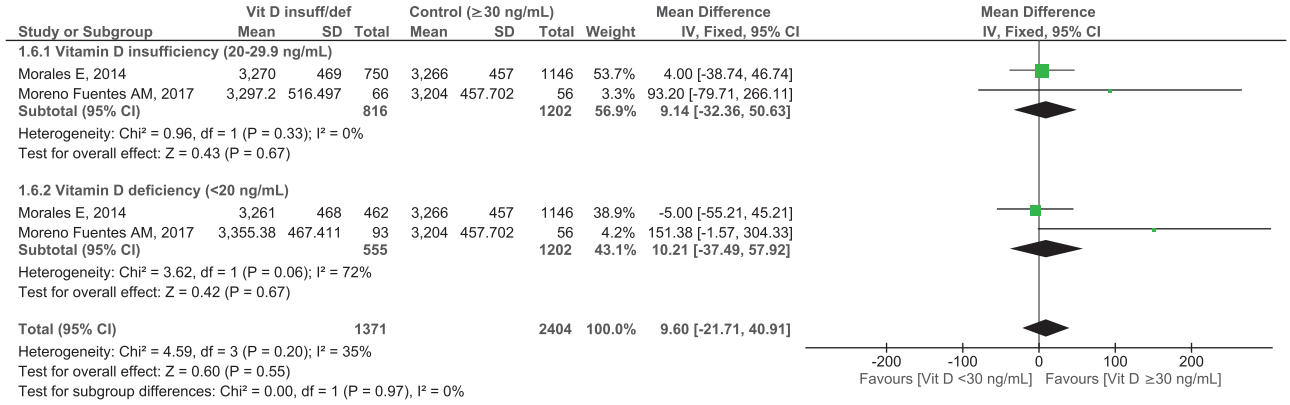


**Figure 6.** Maternal insufficient (20.0–29.9 ng/mL, top) and deficient (<20.0 ng/mL, bottom) 25(OH)D levels during the first half of pregnancy and mean difference birthweight in grams.

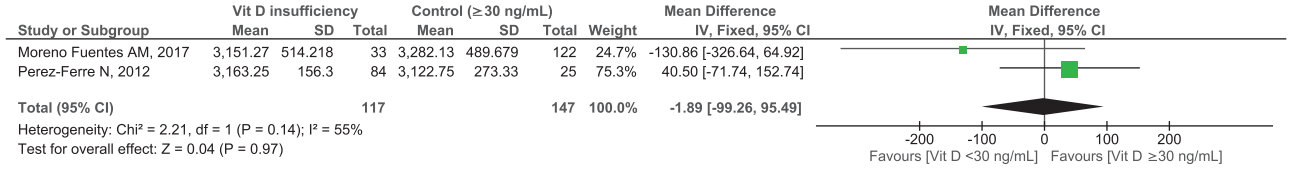


**Figure 7.** Maternal insufficient (20.0–29.9 ng/mL) 25(OH)D levels during the second half of pregnancy and mean difference in infant birthweight in grams.

[29,31,35], insulin endocrinology and body weight changes [37], and the measurements of other vitamin D metabolites that might be more representative of the endogenous vitamin D status [38].

On the other hand, there is also a need for controlled studies that analyze the intake of a significant cholecalciferol supplementation (2000 IU/day or adjusted according to maternal circulating 25(OH)D levels at the beginning of pregnancy) in order to analyze the effect that of achieving maternal vitamin D levels >40 ng/mL would have over maternal and fetal outcomes.

Finally, regarding the limitations of our study one can mention the reduced number of available publications and that not all analyzed studies reported on geographic climatological temperature and humidity variations found throughout the year. Also, there is a lack of information regarding maternal body weight gain during pregnancy and lack of a sufficient vitamin D supplementation. The strengths of the present meta-analysis are (1) the inclusion of women of a homogeneous health care system subject to similar diagnostic and complementary tests and perinatal diagnostic criteria; and (2) the very low to moderate statistic heterogeneity found among studies.

It can be concluded that maternal 25(OH)D levels during pregnancy of women living in Spain were not associated to adverse perinatal outcomes or lower birthweight. However, it remains to be confirmed if adequate (enough) vitamin D supplementation may be able to reduce obstetric, neonatal, and postnatal adverse outcomes [32,35,39–42].

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## Disclosure statement

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## References

[1] Pérez-López FR. Vitamin D: the secosteroid hormone and human reproduction. Gynecol Endocrinol. 2007;23:13–24.
[2] Mulligan ML, Felton SK, Riek AE, Bernal-Mizrachi C. Implications of vitamin D deficiency in pregnancy and lactation. Am J Obstet Gynecol. 2010;202:429.e1.
[3] Brannon PM, Picciano MF. Vitamin D in pregnancy and lactation in humans. Annu Rev Nutr. 2011;31:89–115.
[4] Shin JS, Choi MY, Longtine MS, Nelson DM. Vitamin D effects on pregnancy and the placenta. Placenta. 2010;31:1027–1034.
[5] Young BE, Cooper EM, McIntyre AW, et al. Placental vitamin D receptor (VDR) expression is related to neonatal vitamin D status, placental calcium transfer, and fetal bone length in pregnant adolescents. FASEB J. 2014;28:2029–2037.
[6] Tamblyn JA, Hewison M, Wagner CL, et al. Immunological role of vitamin D at the maternal–fetal interface. J Endocrinol. 2015; 224:R107–R121.
[7] Knabl J, Hüttenbrenner R, Hutter S, et al. Gestational diabetes mellitus upregulates vitamin D receptor in extravillous trophoblasts and fetoplacental endothelial cells. Reprod Sci. 2015; 22:358–366.
[8] Ganguly A, Tamblyn JA, Finn-Sell S, et al. Vitamin D, the placenta and early pregnancy: effects on trophoblast function. J Endocrinol. 2018;236:R93–R103.
[9] von Websky K, Hasan AA, Reichetzeder C, et al. Impact of vitamin D on pregnancy-related disorders and on offspring outcome. J Steroid Biochem Mol Biol. 2017. DOI:10.1016/j.jsbmb.2017.11.008
[10] Fernández-Alonso AM, Dionis-Sánchez EC, Chedraui P, Spanish Vitamin D and Women's Health Research Group, et al. First-trimester maternal serum 25-hydroxyvitamin $D_3$ status and pregnancy outcome. Int J Gynaecol Obstet. 2012; 116:6–9.

[11] Sachan A, Gupta R, Das V, et al. High prevalence of vitamin D deficiency among pregnant women and their newborns in northern India. Am J Clin Nutr. 2005;81:1060–1064.
[12] Haggarty P, Campbell DM, Knox S, et al. Vitamin D in pregnancy at high latitude in Scotland. Br J Nutr. 2013;109:898–905.
[13] Saraf R, Morton SM, Camargo CA Jr, Grant CC. Global summary of maternal and newborn vitamin D status – a systematic review. Matern Child Nutr. 2016;12:647–668.
[14] Wei SQ, Qi HP, Luo ZC, Fraser WD. Maternal vitamin D status and adverse pregnancy outcomes: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2013;26:889–899.
[15] Pérez-López FR, Pasupuleti V, Mezones-Holguin E, et al. Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril. 2015;103:1278–1288.e4.
[16] Pérez-López FR, Pasupuleti V, Mezones-Holguin E, et al. Erratum. Fertil Steril. 2016;105:1649–1650.
[17] Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8:336–341.
[18] Cheng JM, Corstiaan A, Hoeks SE, et al. Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. Eur Heart J. 2009;30:2102–2108.
[19] Wells GA, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non randomised studies in meta-analyses. Ottawa, Canada: Ottawa Health Research Institute; 2017.
[20] Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions, Version 5.1.0. The Cochrane Collaboration [updated 2011 Mar]. Available from: http://handbook.cochrane.org
[21] Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–1558.
[22] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test 339 for publication 340 bias. Biometrics. 1994;50:1088–1101.
[23] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–634.
[24] Álvarez-Silvares E, Vilouta-Romero M, Borrajo-Hernández E, et al. [Maternal serum 25-hydroxy vitamin D levels in the first trimester and adverse gestational outcomes]. Ginecol Obstet Mex. 2016;84:150–163.
[25] Morales E, Rodriguez A, Valvi D. Deficit of vitamin D in pregnancy and growth and overweight in the offspring. Int J Obes. 2015;39:61–68.
[26] Perez-Ferre N, Torrejon MJ, Fuentes M. Association of low serum 25-hydroxyvitamin D levels in pregnancy with glucose homeostasis and obstetric and newborn outcomes. Endocr Pract. 2012;18:676–684.
[27] Rodriguez A, García-Esteban R, Basterretxea M, et al. Associations of maternal circulating 25-hydroxyvitamin D3 concentration with pregnancy and birth outcomes. BJOG. 2015;122:1695–1704.
[28] Moreno Fuentes AM. Asociación de los niveles maternos de 25-hidroxivitamina D con la aparición de eventos adversos durante el embarazo, parto y en el neonato. RIUCAM [cited 2018 Jan 3]. Available from: http://repositorio.ucam.edu/handle/10952/2360
[29] Yates N, Crew RC, Wyrwoll CS. Vitamin D deficiency and impaired placental function: potential regulation by glucocorticoids? Reproduction. 2017;153:R163–R171.
[30] Liu NQ, Larner DP, Yao Q, et al. Vitamin D-deficiency and sex-specific dysregulation of placental inflammation. J Steroid Biochem Mol Biol. 2018;177:223–230.
[31] Akoh CC, Pressman EK, Cooper E, et al. Low vitamin D is associated with infections and proinflammatory cytokines during pregnancy. Reprod Sci. 2018;25:414–423.
[32] McDonnell SL, Baggerly KA, Baggerly CA, et al. Maternal 25(OH)D concentrations ≥40 ng/mL associated with 60% lower preterm birth risk among general obstetrical patients at an urban medical center. PLoS One. 2017;12:e0180483.
[33] Zhang Y, Gong Y, Xue H, et al. Vitamin D and gestational diabetes mellitus: a systematic review based on data free of Hawthorne effect. BJOG. 2017. DOI:10.1111/1471-0528.15060
[34] De-Regil LM, Palacios C, Lombardo LK, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. Sao Paulo Med J. 2016;134:274–275.
[35] Mohamed SA, El Andaloussi A, Al-Hendy A, et al. Vitamin D and corticotropin-releasing hormone in term and preterm birth: potential contributions to preterm labor and birth outcome. J Matern Fetal Neonatal Med. 2017. DOI:10.1080/14767058.2017.1359534
[36] Chen Y, Zhu B, Wu X, et al. Association between maternal vitamin D deficiency and small for gestational age: evidence from a meta-analysis of prospective cohort studies. BMJ Open. 2017;7:e016404.
[37] Santamaria C, Bi WG, Leduc L, et al. Prenatal vitamin D status and offspring's growth, adiposity and metabolic health: a systematic review and meta-analysis. Br J Nutr. 2018;119:310–319.
[38] Papapetrou PD. The interrelationship of serum 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D and 24,25-dihydroxyvitamin D in pregnancy at term: a meta-analysis. Hormones. 2010;9:136–144.
[39] Li W, Green TJ, Innis SM, et al. Suboptimal vitamin D levels in pregnant women despite supplement use. Can J Public Health. 2011;102:308–312.
[40] Pérez-López FR, Fernández-Alonso AM, Chedraui P, Women's Health Research Group, et al. Hypovitaminosis D during pregnancy: are we ready to recommend vitamin D supplementation? Gynecol Endocrinol. 2012;28:856–858.
[41] Tabatabaei N, Auger N, Herba CM, et al. Maternal vitamin D insufficiency early in pregnancy is associated with increased risk of preterm birth in ethnic minority women in Canada. J Nutr. 2017;147:1145–1151.
[42] Rodda CP, Benson JE, Vincent AJ, et al. Maternal vitamin D supplementation during pregnancy prevents vitamin D deficiency in the newborn: an open-label randomized controlled trial. Clin Endocrinol. 2015;83:363–368.