Effects of maternal vitamin D supplementation on childhood health

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- Intrauterine vitamin D exposure

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Abstract

Vitamin D deficiency during pregnancy is associated with an increased risk of health issues in the offspring. Accordingly, recent Endocrine Society guidelines strongly support supplementation in pregnancy, also underlining that without consensus on optimal maternal vitamin D levels, routine screening is currently irrelevant. Knowledge of organ-specific effects of vitamin D and its association with maternal vitamin D status may aid to optimize vitamin D supplementation. This systematic review outlines the proposed next-generation effects of vitamin D supplementation ≥ 400 IU/d, and explores whether such effects are attributed to a specific maternal vitamin D level obtained during pregnancy.

A systematic literature search was conducted in PubMed and Embase according to the PRISMA guidelines, focusing on health outcomes from ten days post-partum and beyond.

Of the 2,383 screened articles, 39 were included. In 11 of 16 studies, vitamin D supplementation reduced respiratory tract infections in the first years of life. Growth or bone development benefits were observed in six of 12 studies. Positive effects on neurodevelopment and reduced autoimmune risk (diabetes-related antibodies) were noted, although further research is needed to determine the role of vitamin D. Very few studies have measured vitamin D concentrations, but even 1,600 IU/d supplementation was associated with high frequency of infant vitamin D insufficiency.

Current recommendations may not ensure sufficient vitamin D levels at birth, among others, increasing the risk of early-life infections. Further studies linking maternal and infant vitamin D levels to specific outcomes would aid in personalized nutritional advice during pregnancy and improve next-generation health.

Abbreviations

ARI	Acute respiratory infection
BMC	Bone mineral content
BMD	Bone mineral density
DM1	Diabetes mellitus type I
DXA	Dual-energy X-ray absorptiometry
EH	Enamel hypoplasia
GW	Gestational week
IFA	Iron and folic acid
IVF	In-vitro fertilisation
LAZ-score	Length-for-age Z-score

LNS Lipid-based nutrient supplements
NOS Newcastle-Ottawa scale
PUFA Polyunsaturated fatty acids
RCT Randomised controlled trial
RSV Respiratory syncytial virus
VDAART Vitamin D Antenatal Asthma Reduction Trial
VDR Vitamin D receptor
VitD Vitamin D
25(OH)D 25-hydroxyvitamin D = calcidiol

Background

Vitamin D deficiency - a global health problem in pregnancy

Vitamin D (vitD) deficiency is a global health issue estimated to affect around one billion people worldwide(1-4). From an obstetric perspective, a high prevalence of maternal vitD deficiency is disturbing, as it is associated with a multitude of complications, including recurrent pregnancy loss(5,6), gestational diabetes(7-12), preeclampsia(13,14), preterm birth(7-9,11,15), and postpartum depression(16,17), thereby increasing the morbidity and mortality of the mother and child.

The main natural source of vitD is the conversion of cutaneous 7-dehydrocholesterol to pre-vitD$_3$ following exposure to sunlight(18). Notably, vitD production is dependent on the degree of skin pigmentation. Therefore, people with dark complexion require up to 10-50 times more sun exposure to produce the same amount of vitD(19). Clothing habits(2), sunscreen use(2,20), and seasonal differences in sun exposure(21,22) also affect vitD production. In countries at high latitudes, such as Northern Europe, the angle of the sun inhibits vitD production in the skin from October to April, increasing the prevalence of vitD deficiency in this period(13,23-25).

VitD occurs naturally in foods such as fish, eggs, milk, and legumes and may also be obtained through dietary supplements. To ameliorate the potential consequences of inadequate vitD supply during pregnancy, many national health authorities recommend daily vitD supplementation, which is also in line with the recently updated (June 2024) guidelines from the Endocrine Society *(Figure 1)*(26). VitD-fortified foods may also be a solution, and several countries use the fortification of food objects, such as milk, cereal grains, and margarine, to improve the vitD status within their population(27-31).

VitD levels below 25-30 nmol/L are associated with an increased risk of rickets and osteomalacia(32) and have often been used as the definition of vitD deficiency(33,34). With increasing awareness of the physiological importance of vitD(13,35,36), definitions have changed, and the US Institute of Medicine currently defines vitD deficiency as a 25(OH)D concentration <50 nmol/L(37,38). According to this guideline, vitD deficiency is highly prevalent in Asia (e.g., 60% in India and 45% in Pakistan) but also common in Europe (e.g., 35% of the pregnant population in the United Kingdom (UK) and 23% in the Netherlands)(37,39). Most current recommendations regarding vitD supplementation during pregnancy are 25(OH)D concentration >50 nmol/L(3). Similarly, the recommendations for vitD intake in childhood are aimed at maintaining a 25(OH)D concentration >50 nmol/L(13). However, an increasing volume of research suggests that a maternal 25(OH)D level between 50 and 75 nmol/L are insufficient. In contrast to the lack of consensus, the latest guidelines of the Endocrine Society do not suggest screening for specific 25(OH)D levels to define vitD sufficiency or deficiency. Instead, the focus should be on increasing vitD levels in vulnerable populations such as the elderly and pregnant women, as data strongly indicate that low levels are common in these groups(26). However, vitD plays an important role in sensitive prenatal development; for example it plays an important role in brain development(40) and pancreatic development(41). This underlines that individual vitD status during pregnancy may have life-long effects on offspring that are solely dependent on pre-natal vitD exposure.

Foetal vitD status depends on maternal supply(7,42,43), and it is estimated that only about 60-80% of maternal 25(OH)D reaches the foetus bound to the vitD binding protein (VDBP)(44,45). Therefore, the need for a higher cutoff value to determine maternal vitD sufficiency is still debated(44,45). In this respect, knowledge of maternal vitD levels in the presence of other risk factors affecting the intra-uterine life could provide insights into organ-specific roles of vitD in human development, as several studies point toward long-term health risks for children born to mothers with vitD deficiency(4,8,15,23,46-52).

Vitamin D - in human health and development

VitD plays a vital role in bone(53-55), tooth formation(56,57), and the regulation of muscle strength(13,21), underpinning its crucial effect on calcium phosphate homeostasis during pregnancy. The activation of vitD is feedback-regulated by calcium, and vitD maintains plasma calcium levels with the help of the parathyroid hormones(15,21,58). Additional calcium is needed for foetal growth; hence, the need for vitD increases during pregnancy(15). Thus, pregnant women and their unborn children are at greater risk of vitD deficiency than the background population.

In addition to calcium phosphate homeostasis, vitD plays an essential role in a variety of central body functions such as glycaemic control(59), immunomodulation(15,59), blood pressure control(60), and mood regulation(19,61) (*Figure 2*). Many studies have highlighted a decreased immunity with increased risk of infection(15,47) and a higher risk of asthma(62) in children who had inadequate exposure to vitD during prenatal development(62,63). Some studies have also suggested a link between vitD deficiency in foetal life and an increased risk of obesity and diabetes among children(62-65). Furthermore, high intrauterine vitD exposure has been associated with higher muscle strength in

children(66), and vitD may increase the number of type II muscle cells and inhibit muscle cell apoptosis(66,67).

In recent years, the potential role of vitD in brain development has received increased attention. VitD exposure during pregnancy is thought to affect the risk of neurodevelopmental disorders(8,68), autism, and schizophrenia(15,69). Furthermore, low vitD levels in pregnancy have been linked to an increased risk of neurodegenerative diseases, such as multiple sclerosis, later in life(70).

Overall, existing knowledge strongly suggests that suboptimal vitD status during pregnancy has long-term effects on offspring health. So far, much research has focused on how vitD supply may be beneficial in reducing the risk of pregnancy-related complications(5-12,15). However, as emphasized by the widely recognized Developmental Origins of Health and Disease (DOHaD) Hypothesis (71-74) we need a deeper understanding of how vitD supplementation during pregnancy could support human development and the health of the next generation.

To ensure adequate vitD supply in all pregnancies, it is crucial to identify the organ systems that are sensitive to vitD and clarify the sufficient levels of maternal vitD needed to promote optimal foetal development in terms of later health risks.

We therefore systematically searched the existing literature for studies that examined how maternal use of vitD supplements of at least 400 IU/d (10 µg/d) during pregnancy affects child health, with a focus on organ-specific effects of relevance both in the first years of life and later. We also aimed to investigate the current knowledge on how higher doses of vitD and differences in the timing and duration of supplementation affect the health of the exposed children.

Methods

Search strategy

Prior to initiation, this study was registered in the international PROSPERO database (ID: CRD42022385495). A literature search was conducted in the medical databases PubMed and Embase according to the PICO approach(75), including papers published from database inception until January 17, 2023.

Inclusion and exclusion criteria

The study population consisted of pregnant women receiving a minimum of 400 IU/d (10 µg/d) of vitD supplements during pregnancy, as well as studies comparing this exposure to a placebo condition with no supplementation (vitD doses of 0 IU/d) during pregnancy. The eligible studies had to include a follow-up examination of the health and development of the children ten days or more postpartum. Studies that focused solely on the effects of vitD on maternal serum or birth outcomes were excluded. Reviews, systematic reviews, commentaries, preprints and letters are excluded. Only human experimental randomized and observational studies were included, and the inclusion was limited to papers written in English, Danish, Swedish, and Norwegian.

Screening of articles and data extraction

The screening process was performed according to the guidelines for systematic reviews and meta-analyses (PRISMA)(76). This process was performed in the review management program Covidence (Melbourne, Australia), which also ensured the removal of duplicates. All titles and abstracts of the papers were independently screened by two reviewers and excluded if they did not meet the inclusion

criteria. The remaining full texts were independently assessed for content, analysis, and data extraction, which included year of publication, country of origin, population size, study design, dose and time of vitD supplementation, ethnicity of participants, inclusion of twins, season of birth, and birth outcomes. Any conflicts of interest were resolved by agreement between the two reviewers *(Figure 4)*.

Quality assessment

The quality of the studies was assessed using the JADAD scale for randomized studies(77) and Newcastle–Ottawa Scale (NOS) for non-randomized studies(78). Within the JADAD score, the studies were assessed based on the randomization procedure, blinding, and dropout of participants, whereas the NOS score relies on the procedure of participant selection, information retrieval, comparability of the study design, and control of confounders. In addition, the valuation of exposure or outcome was assessed, as the studies were either cohort or case-control studies.

Results

Study selection

Of the 2,383 found articles, 1,311 studies were eligible for screening after removing of duplicates. Based on titles and abstracts, 266 studies underwent full-text screening of which 219 studies were excluded because they did not fulfil the inclusion criteria. After excluding randomized controlled trials (RCT) with a JADAD rating of less than three *(n=3)*(79-81) and cohort- and case-control studies with a NOS rating of less than seven *(n=5)*(68,82-84), a total of 39 articles were included in the systematic review *(Figure 2)*.

Quality assessment of the articles included

As many as 18(85-102) of 31(51,85-114) RCT studies were rated as the highest quality, with a JADAD score of five, and the remaining 13 RCTs were rated with good quality with a JADAD score of four (*n=9*)(103,105-107,109-111,113,114) or three (*n=4*)(51,104,108,112). A JADAD score of four was mainly caused by the lack of double blinding. The six cohort studies included were of good quality with NOS scores between seven and eight (*n=6*)(22,115-118) (maximal points are nine), and both case-control studies included also received a NOS score of seven (*n=2*)(119,120). However, it should be noted, that although we only included studies with a high score in their quality assessment, many of them lacked information on the maternal vitD concentration in the blood during pregnancy.

Study characteristics

Population size and geography

The 39 included studies were categorized into eight different outcomes (*Figure 3*), and their geographical location and whether they had significant outcomes are shown in *Figure 4*.

Overall, the included studies varied considerably in size from 31 to 3,000 participants in the RCT studies, from 156 to 16,070 participants in the cohort studies, and from 245 to 738 participants in the case-control studies (*Figure 4).* Altogether, they provided information about 30,384 pregnancies and 30,357 children. Most of the studies (*n=13*) were conducted in Europe (26,645 children)(51,85-88,92,96,99,102,105,106,112,115-117). Eleven studies were conducted in North America (7,373 children)(22,91,100,101,103,113,114,119-121) and two studies (520 children) were conducted in New Zealand(89,90). Of the remaining studies, nine studies were performed in Asia (10,704 children), seven in Bangladesh(94,98,104,108-111) and two in India(95,107). Only two studies were performed in

Africa (2,468 children), Ghana(93), and Tanzania(97) (*Figure 4)*. Finally, one study was conducted in multiple countries (8,676 children)(118).

It should be noted that these studies largely included healthy women who gave birth at term. Thus, we lack information about mothers with pregnancy related diseases and have little knowledge on the effect of vitD in preterm children.

Vitamin D supplementation – timing and dose

The maternal vitD supplement regimes used in the studies were heterogeneous in terms of both dosage and duration. In 28 studies vitD supplementation was initiated during the second trimester(51,85-99,102,104-113,119), while five studies(100,101,103,114,120) examined the effect of supplementation initiated in the first trimester. Lastly, six of the studies collected information on supplementation habits in pregnancy from the participants postpartum(22,115-118,121), either a few weeks postpartum (*n=2*)(22,115), a few months postpartum (*n=2*)(117,118), and two studies collected this information as late as one year postpartum (*n*=2)(116,121). In the majority of the studies (*n=29*)(22,85-93,96,97,99-106,108,112-116,118-120), women received a daily oral vitD supplement ranging from 400 IU/d to 4,400 IU/d *(Figure 5)*. Among the six studies in which the women received a weekly dose of oral vitD, the exposure was either 28,000 IU/week(98,109-111) or 35,000 IU/week(94), and in one Indian study, 60,000 IU was administrated every fourth week(95), which did not show a significant effect on child health outcomes. Finally, two studies examined the effect of a single oral dose administrated in the second trimester as 120,000 IU(107) and 200,000 IU(51) (*Figure 5*).

Notably, in all six cohort studies(22,115-118,121), individual information regarding vitD supplementation during pregnancy was self-reported and did not include information regarding the

consistency of supplementation. In as many as 32 studies, intake of supplements were reported until delivery(51,85-96,98-114,119,120) and in one study they reported intake until one year postpartum(97), potentially affecting vitD supply during breastfeeding(122,123).

Variation in follow-up time

The follow-up time of the individual studies can be seen in *Figure 6*, with most studies focusing on the first three years.

Respiratory infections in early life

Intrauterine vitD deficiency has been associated with decreased immunity and an increased risk of infection(15,47). Here, we identified four studies(90,98,109,115) that investigated the association between the maternal use of vitD supplements and the risk of respiratory infections among children *(Table 1)*.

The prevalence of respiratory syncytial virus (RSV) infections among children at the age of 12 months was examined by Belderbos *et al.*(115) based on parent-reported symptoms and nose-throat swap specimens during the first year of life. This small cohort study (*n=156*) found no association between the women's retrospective self-reported use of vitD supplements of 400 IU/d and children's risk of RSV. This study did not describe the duration or consistency of 400 IU/d supplementation during pregnancy. However, the children developing RSV had a 1.3-fold lower vitD level at birth compared to those not affected by RSV (65 ± 7 vs. 84 ± 11 nmol/L, *p=0.009*)(115).

In addition, three RCT studies examined the risk of infection by comparing different doses of maternal vitD supplements with placebo exposure. Two of these studies estimated the risk of acute respiratory infection (ARI) in children(90,109). Grant *et al.*(90) found that, the children of women taking a supplement of either 1,000 or 2,000 IU/d vitD from gestational week (GW) 27 until birth had a statistically significantly lower number of ARI episodes within the first six months compared to the offspring from the placebo group (placebo=79; 1,000 IU/d =76; 2,000 IU/d=67) ($p=0.03$)(90). On the contrary, the study by Morris *et al.*(109) (*n=1,174*) did not find any association between the risk of ARI in children in the first six months of age and maternal use of weekly vitD supplements from GW 17-24 until birth when comparing three dosing regimens, that is, 4,200 IU/week, 16,800 IU/week, 28,000 IU/week, with placebo. In the same cohort, Taghivand *et al.*(98) examined the risk of pneumococcal disease in children, known to cause meningitis, pneumonia, and sepsis, and found no relationship between maternal vitD supplementation and pneumococcal acquisition among children at six months of age.

Asthma and wheezing during the first years of life

Fifteen studies(22,51,86,87,89,99-101,103,106,112,114,119-121) investigated the association between vitD supplementation in pregnancy and the risk of asthma, croup, and wheezing, i.e. the presence of airflow turbulence causing a high-pitched sound during breathing *(Table 2)*.

The largest RCT identified, the Vitamin D Antenatal Asthma Reduction Trial (VDAART)(100) (*n=810*), reported a reduced risk of asthma and recurrent wheezing in genetically predisposed children at the age of three years if a maternal supplement of 4,400 IU/d vitD was initiated from GW 10-18 until birth instead of the typical 400 IU/d supplement. The VDAART cohort was subsequently used for several further studies(101,103,114,119,120), finding that maternal plasma levels of vitD prior to

supplementation also affected health risk (as judged by parental reports and wheezing verified by trained professionals). In contrast to the children with the lowest intrauterine exposure (offspring from women with an initial maternal vitD level <75 nmol/L and receiving a 400 IU/d supplement), these further studies on VDAART children reported a beneficial effect regardless of genetic background for those born to pregnancies receiving a high dose vitD supplement with an initial maternal vitD level above 75 nmol/L. Further studies also found a significant association between maternal vitD measured at GW 10-18, and a decrease in the risk of asthma/recurrent wheezing in children at the age of three years(114). However, at six years of age, this association with maternal vitD status was no longer evident(101).

In addition, a possible association between maternal vitD supplementation and allergic rhinitis in children was examined in a subset of the VDAART cohort (*n=414*). Chen *et al.*(103) found a statistically significantly reduced risk of allergic rhinitis at the age of six.

Supporting the beneficial effect of vitD supplementation in pregnancy, Blighe *et al.*(119) found evidence of a vitD linked reduction in susceptibility to allergic airway diseases based on the presence of inflammatory fatty acids in the blood metabolome. In this study, maternal plasma vitD concentration in late pregnancy was statistically significantly correlated with the inflammatory profile at the age of three years(119). The results remained significant after adjusting for sample storage time, maternal age, education, and known asthma status in the children. In addition, exploring the effect of vitD on risk factors for asthma development, Hjelmsø *et al.*(106) examined the association between the airway microbiome in Danish children and their intrauterine vitD exposure from GW 24 until birth.

Comparing, a maternal vitD intake of 400 IU/d to an intake of 2,800 IU/d the increased vitD intake exhibited a beneficial effect on the airway microbiome at six years of age, with a significant decrease in firmicutes and a corresponding increase in proteobacteria such as Moraxella(106).

In contrast, Omand *et al.*(121) did not find any statistically significant association between vitD intake and the frequency of childhood asthma. Notably, mothers were questioned about vitD supplementation during their pregnancies postpartum. Therefore, neither the duration of vitD intake nor the dosage was specified in this study(121). Similarly, Brustad *et al.*(112) found no beneficial effects of vitD in their RCT study (*n=736*), comparing the health effects of a maternal vitD supplement of 2,800 IU/d from GW 24 onwards to the effects of the 400 IU/d standard treatment in a Danish population(124). Based on asthma diagnoses made by a paediatrician (following a predefined, validated diagnostic algorithm), this study found no association between maternal dose of vitD supplementation and asthma development at the age of six years(112).

The effects of vitD on wheezing are not unanimous. Camargo *et al.*(22) found a reduced risk of parent-reported wheezing in children at the age of three in an American cohort when comparing a (self-reported) maternal vitD intake of 160 IU/d with 421 IU/d in pregnancy (*n=1,194*). In contrast, the RCT study by Chawes *et al.*(87) (*n=623*) did not find a significant reduction in the risk of wheezing at this age when comparing the effects of a 2,800 IU/d vitD supplement during pregnancy to a 400 IU/d vitD regime. In this study, vitD supplementation was provided from GW 24 onwards, and a previously validated quantitative algorithm was used to standardize wheezing(87). Furthermore, the RCT study by Goldring *et al.*(51) (*n=180*) did not find that a single high dose vitD exposure of 200,000 IU during GW 27 resulted in a significant reduction in the number of parents reporting at least one incidence of "*wheezing ever"* among children at the age of three. However, their control group included pregnancies in which a daily supplement of 800 IU/d was used from GW 27 and onwards(51).

Croup, allergy, and vitamin D

Using data from their previously described Danish cohort, Brustad *et al.*(86) found that by the age of three, an increased vitD supplement of 2,800 IU/d from GW 24 onwards reduced the risk of croup (diagnosed by a clinician) by 7% compared to the standard vitD supplementation regime of 400 IU/d vitD. These results remained significant after adjustment for persistent wheezing and lower respiratory tract infections(86).

Based on IgE antibodies in the blood and clinically detectable allergies, two studies found that the maternal use of vitD supplements in pregnancy decreased the risk of disease(89,99). Grant *et al.*(89) (*n=260*) found that compared to placebo treatment, supplements of 2,000 IU/d vitD initiated at GW 27 reduced the risk of allergy, measured as a positive test for house dust mites and mite antigen sensitization in children aged 18 months. Furthermore, El-Heis *et al.*(99) (*n=703*) found a significant protective effect of maternal vitD supplementation against the development of atopic eczema at the age of 12 months when studying the benefits of maternal intake of 1,000 IU/d compared to placebo. However, this protective effect weakened as children grew older, and the association was not statistically significant at the age of 24 or 48 months(99).

Vitamin D and the risk of Diabetes Mellitus type I

We identified three studies(116-118) that examined the possible associations between vitD intake during pregnancy and the development of diabetes mellitus type I (DM1) among the offspring *(Table 3)*. The DM1-related outcomes measured were the initial immunological signs of disease activity, that is, autoantibodies against insulin, glutamic acid decarboxylase, and islet antigen 2. These autoantibodies are highly associated with DM1, as only a few diagnosed patients have autoantibody-

negative DM1(125,126). All three studies were cohort studies in which maternal vitD intake was self-reported and recalled after birth and did not include information on the initiation of supplementation. Focusing on the very early debut of DM1, Brekke *et al.*(116) found that maternal intake of a 400 IU/d vitD supplement reduced the prevalence of diabetes-related autoantibodies among children at the age of one year (*n=16,070*) (adjusted OR=0.71 [95% CI 0.52–0.96], *p=0.028*); however, this protective effect of maternal vitD supplementation was no longer present when the children reached 2.5 years of age. The effect at one year of age remained significant after adjustment for DM1 in the family, duration of breastfeeding, timing of the introduction of cow's milk protein, and fish intake(116).

The two remaining cohort studies(117,118) examined only children with genetic risk factors, that is, HLA-conferred susceptibility to DM1. These studies found no association between maternal vitD intake, and DM1 as judged by the presence of autoantibodies in blood samples at the age of two or ten years of age. However, it must be mentioned that the cohort study by Marjamäki *et al.*(117) was based solely on self-reported information, comparing consumption to non-consumption of vitD and Silvis *et al.*(118) only compared vitD supplementation >2,030 IU/d with all doses of vitD supplementation below 2,030 IU/d.

Teeth – enamel hypoplasia and enamel defects

We identified two RCT studies(102,113) that investigated the association between vitD and tooth development *(Table 4).* Nørrisgaard *et al.*(102) (*n=623*) found that, compared to children of women following the 400 IU/d vitD standard supplementation advice, the prevalence of enamel defects in permanent teeth at the age of six was lower in children from pregnancies in which the mother received a 2,800 IU/d vitD supplement from GW 24 until birth (15.1% vs. 27.5%, respectively, *p<0.05).* Reed *et*

al.(113) (*n=145*) examined the risk of enamel hypoplasia in children, comparing the effects of maternal vitD intake of 4,000 IU/d from GW 12 until birth to 400 IU/d, and found no significant association between vitD exposure and enamel hypoplasia in their small sample size. However, they did find a tendency towards a protective effect of vitD, as children with enamel hypoplasia at the age of four were 1.29 times more likely to belong to low-dose pregnancies(113).

Vitamin D and bone strength and mineralization

Six studies(85,88,92,95,105,111) investigated the effect of maternal vitD on bone strength and bone mineralization at different time points within a time span of 16 months to 8 years *(Table 5).* All outcomes of bone mineralization were measured by whole-body dual-energy X-ray absorptiometry (DXA) scans, and all of the studies were RCTs in which the vitD supplement varied from 1,000 IU/d(88,92,105) to 2,800 IU/d(85) or was given as a weekly oral dose of 28,000 IU(111). Three studies(85,88,105) found a statistically significant positive association between vitD and bone health at the age of four-six years.

Among the studies that did not find statistically significant effects, two focused on the Asian population receiving weekly dosing regimens. The first being O'Callaghan *et al.*(111) investigated BMC and BMD at the age of four years in children born to mothers who received either a placebo or a vitD supplement of 4,200 IU/week, 16,800 IU/week, or 28,000 IU/week from GW 17-24 until birth, and found no difference. Similarly, the second study by Sahoo *et al.*(95) found no difference in bone mineralization at 16 months when comparing a maternal vitD intake of 60,000 IU every fourth week to a placebo from GW 20 until birth.

In contrast, the UK-based RCT study by Curtis *et al.*(88) (*n=1,123)* found a beneficial, statistically significant effect on BMD in children at the age of four years, if the mothers had supplemented their diet with 1,000 IU/d vitD from GW 14 until birth compared to placebo, although no statistically significant effects were seen on BMC(88). However, in the Danish cohort by Brustad *et al.*(85), a maternal vitD intake of 2,800 IU/d from GW 24 until birth significantly increased the children's BMC and BMD at the age of six years compared to the children of women with a vitD intake of 400 IU/d. Moreover, Gopal-Kothandapani *et al.*(105) found that a maternal vitD intake of 1,000 IU/d from GW 14 until birth significantly increased metabolic activity in the bones at the age of four years compared to a placebo group. In this study, blood samples were collected from children to investigate the blood markers for bone turnover, P1NP, before and after exposure to a mechanical stimulus(105).

On the other hand, the UK-based RCT study by Moon *et al.*(92) (*n=965)* found no statistically significant effect on BMC at the age of eight, when comparing maternal vitD supplementation of 1,000 IU/d from GW 14 until birth to placebo.

Vitamin D and growth in early life

Five studies(94,104,107,110,127) investigated the association between maternal vitD intake and growth in early childhood, and three identified significant positive results *(Table 6).* The outcomes were anthropometric measurements performed by trained study professionals or physicians during clinical visits. All studies were RCTs comparing a specific vitD dose with either placebo (*n=4*)(94,97,107,110) or vitD doses of 200 IU/d (*n=1*)(104) (*Figure 6*), albeit initiating the vitD supplementation at various time points from GW 12(97), 17(110), 20(104), 26(94), or unspecified between GW 12-24(107). Moreover, none of the five studies stratified the results according to ethnicity or skin tone of the participants.

Dewey *et al.*(104) found that weight-, height- and head circumference were significantly increased in the offspring at the age of 6-24 months if the pregnant women took a daily multivitamin supplement (GW 20 onwards) including 400 IU of vitD compared to findings from the control group in which the supplements only included iron and folic acid. Likewise, in an Indian cohort, Kalra *et al.*(107) (*n=300*) found a statistically significant weight and growth improvement at the age of nine months (judged by weight, length, increased head circumference, and a smaller diameter of the anterior fontanelle) when a maternal vitD supplement of 120,000 IU was introduced as a single oral dose in the second trimester.

In three of the RCTs(94,97,110), the World Health Organization (WHO) child growth standards and the length-for-age Z-score (LAZ-score) were used to depict the influence of maternal vitD. Using these parameters, Sudfeld *et al.*(97) (*n=1,148*) defined children with a LAZ score under -2, as having a stunted growth potential. However, their study did not find a statistically significant association between maternal vitD intake and stunting at the age of one year, when comparing the effects of an intake of 3,000 IU/d from GW 12 until one year postpartum to placebo in a group of HIV-positive women(97). Furthermore, the RCT study by Roth *et al.*(110) (*n=1,300*) did not find a vitD-induced improvement of the LAZ score at the age of one when comparing the effects of a maternal vitD intake of doses of 4,200, 16,800, or 28,000 IU/week from week GW 17-24 onwards to placebo. However, a later study(94) found a statistically significant higher LAZ-score at the age of one in the offspring of women taking a weekly supplement of 35,000 IU from GW 26-30 until birth.

Language and motor skills

Three studies investigated the association between maternal vitD intake in pregnancy and neuromotor development determined by the evaluation of language or motor skills among children aged 18 months to six years(93,96,108)*(Table 7)*.

To examine motor skills at the age of 18 months, Matias *et al.*(108) (*n=3,000)* examined the cohort previously investigated by Dewey *et al.*(104) in which the effects of a maternal vitD intake of 400 IU/d, iron, and folic acid were compared with a placebo containing only iron and folic acid. At this time point, vitD supplementation exhibited a statistically significant positive effect on motor milestones, but a comparison of the two groups only revealed a non-significant improvement in similar parameters at the age of 24 months(108). Regarding language, assessed using the Family Care Indicators scale(128,129) (performed by community health workers), no effect of maternal vitD intake on language development was observed in children aged 18 months. However, at 24 months of age, language development was statistically significantly superior in offspring of the vitD-exposed group(108). On the other hand, Prado *et al.*(93) (*n=1,320)* found no significant association between maternal vitD exposure and parental reports on motor- or language skills at the age of 18 months when comparing children from pregnant women, taking multivitamins including 400 IU/d vitD from GW 20 until birth, to the children of women in a placebo group. However, the ability to walk at the age of 12 months was more pronounced among children whose mothers had consumed multivitamins with vitD during pregnancy(93). Targeting the overall development as reported by both parents and trained clinicians, the RCT study performed by Sass *et al.*(96) (*n=623*) found no significant effects on motor skills, emotion, or neurodevelopment during the first six years of life when comparing a maternal vitD intake of 2,800 IU/d from GW 24 until birth to the standard 400 IU/d.

Infant 25(OH)D status

A single study(91) (*n=226*) was identified, that investigated the relationship between maternal intake of vitD supplements and the infant's serum concentration of vitD, determining 25(OH)D at eight weeks postpartum *(Table 8)*. The vitD status of the infant was compared based on the maternal intake of either 400 IU/d, 1,000 IU/d, or 1,600 IU/d from GW 13-24 until birth. Here, a significantly higher vitD concentration was found in the offspring of pregnancies exposed to the highest dose of supplementation. VitD sufficiency, a serum level of vitD >75 nmol/L, was seen in 44% of the children exposed to 1,600 IU/d during pregnancy, whereas only 15% of the children in the other two groups (400 or 1,000 IU/d) were vitD sufficient.

Discussion

This review highlights the need for greater attention on intrauterine and infant vitD status and the public health benefits of vitD supplementation in pregnancy. Beneficial effects of vitD were found in 21 of 39 studies(22,85,86,88-91,94,99,100,102-108,114,116,119,120), showing statistically significant outcomes from maternal vitD supplementation at a minimum dosage of 400 IU/d. The positive effects of vitD were widespread and included a reduced risk of respiratory infections, asthma, early life reduction of DM1 risk, improving teeth- and bone development as well as language and motor skill enhancements suggesting beneficial effects on brain development and muscle function. However, the results were inconsistent, suggesting that the vitD need of the offspring might not be fulfilled solely by a maternal vitD intake of 400 IU/d during pregnancy(130).

Notably, no deleterious effects of vitD supplementation were reported. As vitD is a fat-soluble vitamin, with accumulation potentially leading to intoxication (serum level of 25(OH)D >375)(21,131-137), safety should be considered. However, vitD supplementation at doses up to 4,100 IU/d or even 35,000

IU/week has been tested and proven safe for pregnant women and their children(138-140). Overall, the potentially favorable effects on the health of children exceed the low risk of intoxication, whereas a higher recommended dose of vitD supplementation may be beneficial. From the authors' own experience, data from a yet unpublished clinical trial in a Danish population demonstrates that 3,600 IU/d vitD doses are safe and do not cause maternal intoxication(140). However, this dose remarkably reduced vitD insufficiency at birth(141).

When contemplating increased vitD supplementation, the possibility of a ceiling effect of vitD is often suggested if increased vitD intake does not increase benefits(142,143). Notwithstanding the possibility that the effect investigated might not be responding to vitD *per see*, a possibility that may always be the case when increasing the search for hitherto unknown developmental benefits of supplementation, the presence of a ceiling effect could indeed hamper interpretation. On the one hand, the absence of significant vitD effects could indicate that though the effect is vitD dependent, the vitD supply was not enough to obtain the effect in all or a subgroup of participants. On the other hand, it might also suggest that sufficient vitD levels were already present in most of the participants, meaning the ceiling was already reached. While a ceiling effect cannot be ruled out, especially in studies in relative wealthy populations, accustomed to vitD supplementation or exposed to many fortified food objects, a dietary factor not taken into consideration in the studies identified in this review, the low infant concentration of vitD found following a supplementation in the 400 IU/d to 1600 IU/d range, strongly suggests that somewhat higher doses of vitD are needed to reach any ceiling effect(91,141) when it comes to vitD effects on human development.

Despite the strong link between recorded maternal intake and the vitD status in offspring, 18 of the 39 identified studies(51,87,92,93,95-98,101,109-113,115,117,118,121) did not find a statistically significant positive effect of vitD supplementation. Notably, six studies were cohort studies where the maternal vitD intake was self-reported and recalled after birth and did not include information on time of initiation during pregnancy(22,115-118,121). This may have affected the results, when it comes to the unmet vitD need in subgroups in whom the average vitD concentrations might be lower due to limited nutritional(144), genetic factors and sun exposure(7,21,22,145). This review also points towards a lack of data on significant vitD deficiency risk factors in many studies. Moreover, public health benefits can be underestimated as important subgroups known to be more prone to vitD deficiency or with an increased need for vitD, as many studies have deliberately excluded risk pregnancies such as those suffering from preeclampsia, foetal growth restriction, obesity or gestational diabetes(7-15). Future studies should address how both dietary and seasonal variation are likely to affect the outcomes measured.

Further, impeding the interpretation of the findings, several studies did not report maternal skin pigmentation(19,146). Together with the differences in seasonal variations in sun exposure(7,21,22,145) and use of covering clothes among the participants, the interpretation of such studies becomes difficult, as expected difference in vitD exposure between groups might not have been present if real life vitD status had been compared. This is also reflected in *Figure 5* which shows that the beneficial effects of vitD cannot, at present be linked to a specific vitD dose during pregnancy. Knowing the actual maternal vitD levels in future studies would combine the effects of the cutaneous and the dietary vitD supply in one measurement. Together, with a more precise timing and duration of the vitD exposure through repeated measurement in pregnancy, this would likely contribute to

identifying organ-specific vitD requirements. Therefore, large-scale studies simultaneously examining the impact on several organ systems over time are needed to make health policy decisions regarding recommendations of vitD for pregnant women, especially those at high risk of vitD deficiency. To achieve this, future studies, rather than excluding women with complicated births, low-weight infants or preterm births, should be of a considerable size and include vulnerable women. In addition, they need a detailed collection of clinical and biological data to allow for analysis to distinguish between different groups of vulnerable women at a high risk of vitD deficiency. Further, we agree with the latest guidelines of the Endocrine Society(26) that simply measuring vitD status in all pregnancies does not necessarily benefit the individual woman at present, it must be concluded that there is still a need for systematic gathering of large dataset for the benefit of improved guidelines.

Given the many non-significant studies identified it is striking that although vitD is among the first nutritional supplements to be initiated after birth(130), and the recommended dose of vitD for both premature and mature infants is as high as 600 IU/d, the typically recommended dose for pregnant women, the only source of vitD during prenatal life, is as low as 400 IU/d in most parts of the world(38,147). Underlining the potential risks of limiting maternal supplementation to a 400 IU/d dose, a study by March *et al.*(91) found that a maternal supplement as high as 1,600 IU/d could be needed to minimize vitD deficiency i.e. a vitD < 75 nmol/L at birth. As mentioned, 60-80% of the maternal vitD will reach the infant(44,45), requiring a maternal level well above 100 nmol/L 25(OH)D, whereas it seems likely that in the majority of studies identified in this review, many women may have been below this level, and investigations of the benefits of maternal levels in the range of at least 100-125 nmol/L 25(OH)D would provide additional knowledge for the future.

As the effects of vitD on prenatal development is likely to include both direct maternal-foetal transfer as well as vitD benefits for the maternal health such as reducing maternal and placental inflammation, a known risk factor for foetal development(148-150), it is also evident that there is currently a massive lack of corresponding vitD measurements from maternal and infant dyads in relation to organ-specific outcomes. Such approach would also be able to consider the role of the placenta in both the maternal-foetal transfer and as part of the developmental effects of vitD, as the role of maternal biology in placental vitD response and vitD transfer is far from understood(150). In line with this, future studies should also consider genetic differences such as VDBP polymorphisms. Circulating vitD in the form of 25(OH)D is bound to VDBP on the passage from the maternal circulation to the placenta through the megalin/cubilin complex, similar to the tubular uptake in the kidneys(151,152). The 1F VDBP allele has been associated with an increased risk of vitD deficiency(153), impacting how much vitD that is transported from the mother to the offspring. Notably, the VDBP polymorphisms are believed to be unevenly distributed among races(154), a factor that deserves further scrutiny. Many of the existing studies were thus performed in a European or North American setting without considering this factor. Although the findings of this review are not conclusive, most studies examining respiratory tract infections in this systematic review (11 out of 16)(22,86,89,90,99,100,103,106,114,119,120) reported a positive effect of maternal vitD supplementation in pregnancy and a reduction in respiratory problems among children, most evidently in very young children. With the current data it cannot be conclude if these effects mainly reflect the benefit of an inborn storage of vitD or the benefits of development programming of the immune system, but it has been shown that intrauterine vitD status may influence immune regulation in early life through an inverse correlation between umbilical blood mononuclear cells and umbilical vitD levels(155). Regardless of the mechanisms, the findings emphasise that alterations in maternal nutrition in pregnancy is an efficient tool to improve overall infant health.

Respiratory diseases are a major problem among newborns, whereas RSV alone is estimated to result in 118,200 annual deaths in children under five years of age worldwide(156). Thus, any positive effects of maternal vitD supplementation seem to be a cheap and easy way to decrease the need for hospitalization and advanced treatment of RSV, especially among newborns, who are at the greatest risk for serious complications of the infection. However, based on the studies identified here, it cannot be excluded that these vitD benefits might also reflect that a higher maternal vitD level will lead to a higher transfer of vitD in the maternal milk in the first months of life(157). This aspect of vitD health should be consider in public health initiatives supporting breast-feeding in order to further improve perinatal health through an even healthier breast milk composition.

After the first years of life, the importance of maternal exposure appeared to be weaning off concurrently with the increasing importance of the children's own uptake of vitD from both diet and supplements and the endogenous production of vitD in the skin. This may be the reason why the beneficial effects on asthma and allergy were more ambiguous in this review. The combination of maternal and child vitD supplementation must be examined in parallel to see the full potential of vitD. Higher levels of vitD at birth have been associated with a lower number of regulatory T-cells and IFN-γ response(155,158). This may suggest that prenatal vitD levels independently may influence the development of the immune system of the offspring, and thereby the vulnerability to infections and asthma in early life(155). VitD-mediated changes in the development of the immune system may also have more long-term effects, as they may inhibit the development of autoimmune diseases by affecting immune modulation(159). Over 30 positive effects of vitD on the immune system in general have been reported, as vitD is involved in regulation and differentiation of immune cells both directly on T- and

B- cells and more indirectly on dendritic cells(15,47,160-170). Interestingly, Brekke *et al.*(116) found a significant association between islet-directed autoimmunity and maternal vitD intake, indicating a potential vitD-protection against DM1 development. Epidemiological studies have shown that autoimmune diseases, in general, seem to cluster among families(171-173), underlining the importance of both environmental and genetic factors. Moreover, the fact that the benefits of vitD did not persist at the age of 2.5(116) underlines the interplay between pre- and postnatal vitD exposure. This is in line with animal studies finding that non-obese diabetic mice showed a delayed progression of DM1 when an active vitD supplement administered to the dams during embryonic development(174,175). However, the supply of vitD was not able to protect the offspring of mice with a strong diabetic phenotype from developing diabetes over their lifetime(175). Studies by Marjamäki *et al.*(117) and Silvis *et al.*(118) focused on children with a genetic DM1 risk and found no significant vitD effects. Notably, their data on vitD exposure were very limited in terms of seasons and actual exposures, whereas they may suffer from a high overlap between groups in terms of the actual exposure. It could also be speculated that genetically susceptible individuals have a higher need for vitD. Interestingly, others have found that vitD metabolism itself may be involved in the autoimmune process of DM1, as antibodies against VDBP, the protein to which vitD is bound when taken up in tissues, are increased in DM1 patients(176). If epigenetic changes in the metabolism and autoimmunity of vitD towards VDBP participates in other autoimmune diseases remains to be seen in the coming years. However, previous reports have linked low vitD levels in pregnancy to multiple sclerosis in the offspring(70), supporting that vitD increase in pregnancy could be beneficial in a broader context.

This broader benefit of vitD on human development is also seen in other organ systems. We found that maternal vitD intake had a positive effect on children's growth, bones, and teeth health in seven of 13

studies(85,88,94,102,104,105,107). This likely reflects the diversity of the study populations, since vitD, calcium absorption and bone formation have been linked through decades(23,177-181). In general, we found an effect of high doses of vitD among populations from the Western world, whereby theoretically, the effect could be related to the general diet, or it may indicate that the effects of vitD may be hidden if other important vitamins or minerals are lacking in other parts of the world.

The degree of vitD exposure of the foetus may also directly affect brain development(181), as studies on neonatal rats have shown that calcitriol stimulates neurite outgrowth, such as hippocampal explants, and induces the expression of nerve growth factor(182,183). Likewise, low prenatal vitD is associated with altered brain shape and enlarged cerebral ventricles(184). In rodents, maternal vitD deficiency impairs the ability of the offspring(185,186). This is in line with one of the human studies included in this review in which maternal vitD supplementation affected motor milestones and language development(108). These findings support that vitD acts as a neurosteroid(61,181,187,188) and that maternal vitD status may alter the developing brain. While the effect of maternal vitD on motor milestones was significant at the age of 12 months, the effect on language development was observed in children at the age of 24 months(108). These results indicate that maternal vitD intake may influence language development more indirectly, perhaps by having a profound epigenetic effect that becomes evident as the brain continues to mature after birth. As vitD has been shown to have direct effects on pregnancy complications(5-12,15-17), future studies on neurodevelopment may benefit from separating the children in vulnerable pregnancies, as important, positive effects may be hidden when excluding children born before GW 37, such as in the study by Sass *et al.*(96), again underlining the need for inclusion of complicated pregnancies in future studies.

Strengths and limitations

The design of this review with a systematic, transparent, and reproducible literature search based on the PICO search and PRISMA strategy allowed us to identify both well-known and lesser-known associations between vitD during pregnancy and the health of children. Limiting the search to English and Nordic languages only, may however, have limited the inclusion of studies performed in Asia and other parts of the Global South. The databases selected could also potentially impact the findings, however a subsequent surge in Medline did not disclose any additional studies.

Overall, the studies included in this systematic review varied in study design, study population, countries of origin, sample size, and dose and duration of vitD supplementation, and many studies had to rely on self-reports with the risk of recall bias. Together with the differences in pigmentation, diet, and sun exposure(7,21,22,145), the interpretation of many studies is difficult, as the vitD status of many participants might to some degree be determined by factors other than the supplement itself, as measurements of the maternal and infant serum concentrations of vitD are lacking in most studies, despite being studies with a high quality score. Furthermore, very few studies have specifically targeted the vitD needs of women with an increased risk of deficiency, such as dark skin pigmentation, VDBP polymorphism(189), obesity, and smoking.

Heterogeneity among the studies prevented the possibility of performing a meta-analysis that combined multiple datasets. In particular, the diverse initiation periods of vitD supplementation, ranging from the first trimester to the third trimester, and different vitD dosage regimes make it difficult to compare study results and identify organ-specific needs for vitD. Existence of organ-specific difference in the vitD demand may explain the variation in results when different studies with the same exposure are compared. Moreover, evidence from studies on the ceiling effect points towards organ specific findings. Studies have thus reported that increased vitD-related benefits in terms of improved muscle

function (in middle-aged men) wears off at 60 nmol/L(142), whereas the benefits in terms of a reduced stroke risk in a Chinese population wore off at 50 nmol/L(190). At present there is little knowledge on organ-specific vitD needs, and as most studies focus only on one or a few outcomes, there are no data available for comparison between organs in the same individual.

In addition to the next-generation effects discussed, other studies have also focused on later-life outcomes, such as ADHD/autism(8,15), multiple sclerosis(15,46), and neurodegenerative diseases such as Parkinson's disease(191,192). Future studies may support this field by establishing prospective cohorts linking prenatal and postnatal events. However, indications found in human studies may need verification in experimental models to provide evidence of causal relationships within a reasonable timeframe.

Conclusion

Maternal vitD supplementation during pregnancy has postnatal effects on offspring growth patterns and the risk of early life respiratory problems, including infections such as RSV, though it remains to be seen if this is a result of prenatal programming or being born with a high vitD reserve. The development of multiple organ systems is affected and in addition to bone development, maternal vitD supplementation can affect brain development and may play a role in the later development of autoimmune diseases. Therefore, we conclude that the development of several organ systems is affected by maternal vitD status.

As there is currently a gap in knowledge concerning the optimal vitD level during pregnancy, further studies are essential to identify the maternal vitD response to various vitD supplementation regimens. We lack studies examining the actual vitD levels in both mother and offsprings, also taking into

consideration the increased need for vitD in some women e.g., darkly pigmented women, women with obesity, smokers, and those with genetic risk factors such as VDBP polymorphisms. We conclude that larger and higher quality studies are needed to establish appropriate recommended doses for pregnant women especially regarding different vulnerable groups as it is too premature to make health policy decision based on the current available data. To secure the accurate vitD recommendations, and avoid an underestimation of the effects of vitD, we need to measure the vitD concentrations in pregnant women to establish vulnerable groups and examine multiple organ specific effects in the offspring related to different doses of vitD supplementation and the maternal vitD concentration during pregnancy. Systematic studies focused on short-term supplementation may help determine sufficient vitD concentrations until more knowledge is available. Once data is obtained, hopefully, a more personalized approach towards nutrition in pregnancy will be possible, as addressing organ specific needs for vitD during development could ensure well-founded decision about vitD recommendations to improve childhood health of future generations.

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Figures and tables

Figure 1: Overview of the recommended dose of vitamin D supplementation in pregnancy in selected countries(7,51,117,193-197). The zenith angle of 33° latitude during August and March is illustrated in the northern hemisphere (blue) and southern hemisphere (pink), as a zenith angle below 33° inhibits cutaneous vitamin D production(7,21).

Figure 2: PRISMA-diagram of the screening process

Figure 3: The 39 included studies were divided into eight different outcomes. Where n indicates the number of participants, followed by the quality assessment score, either the JADAD score (J) or NOS score (N). The star (*) indicates studies with significant findings. The number in parentheses represents the reference number.

Figure 4: The included studies according to country of origin, study type, and dose of vitamin D supplement. Significant outcomes are marked by stars (*).

Figure 5: Dosage of vitD in the 31 different RCT studies in this review divided into having an effect or not on the children's different outcome.

Figure 6: Follow-up time of each study, displayed by the target organ. The stars indicate the presence of a statistically significant effect of vitD exposure. Overall, 22 studies(22,85,86,88-91,94,99,100,102-108,114-116,119,120) reported a beneficial effect of vitD, while 17 studies(51,87,92,93,95-98,101,109-113,117,118,121) found no association between vitD exposure and health outcomes of the exposed children.

Figure 7: VitD associations with growth, separated according to dose and follow-up time(94,104,107,110,127). The stars (*) indicate significant results of vitD supplementation.

Table 1: Overview of studies on respiratory infections included in this review. The studies with a significant effect are marked in white, while the studies with no significant findings are marked in grey. The season of inclusion was described, although these data were not used in connection with the results. vitD = vitamin D. [1]ARI = acute respiratory infection. [8]GW = gestational week. [14]RSV = respiratory syncytial virus. *Taking a maximum of 200 IU/d vitD before inclusion in the study.

Table 2: Overview of included studies on asthma, croup, wheezing, and allergy. Studies with a significant effect are marked in white, and studies with no significant findings are marked in grey. The season of inclusion was described, although these data were not used in connection with the results. vitD = vitamin D. [8]GW = gestational age. [9]PUFA = polyunsaturated fatty acid. [10]IVF = in vitro fertilization. *Taking a maximum of 200 IU/d vitD before the inclusion in the study. **Taking a maximum of 2,000 IU/d vitD before the inclusion in the study.

Table 3: Studies evaluating vitD effects on DM1 risk. Studies with a significant effect are marked in white, and studies with no significant findings are marked in grey. The season of inclusion is described, although these data were not used in connection with the results. VitD = vitamin D.

Table 4: Overview of studies on tooth development. Studies with a significant effect are marked in white, and studies with no significant findings are marked in grey. The season of inclusion was described, although these data were not used in connection with the results. VitD = vitamin D. [6]EH = enamel hypoplasia. [8]GW = gestational week. *Taking a maximum of 600 IU/d vitD before inclusion in the study.

Table 5: Overview of studies on bones included in this review. Studies with a significant effect is marked in white, whereas studies with no significant findings are marked in grey. The season of inclusion was described, although these data were not used in connection with the results. VitD = vitamin D. [3]BMC = bone mineral content. [4]BMD = bone mineral density, aBMD = areal bone mineral density. [8]GW = gestational week. [11]DXA = dual-energy X-ray absorptiometry.

Table 6: Overview of studies on growth included in this review. Studies with a significant effect are marked in white, and studies with no significant findings are marked in grey. The season of inclusion was described, although these data were not used in connection with the results. VitD = vitamin D. [5]LAZ-score = length-for-age z-score. [8]GW = gestational week. [12]IFA = iron and folic acid. [13]LNS = lipid-based nutrient supplement.

Table 7: Overview of studies on language and motor skills included in this review. Studies with a significant effect are marked in white, and studies with no significant findings are marked in grey. The season of inclusion was described, although these data were not used in connection with the results. VitD = vitamin D. [8]GW = gestational week. [12]IFA = iron and folic acid. [13]LNS = lipid-based nutrient supplements. *Taking a maximum of 600 IU/d vitD before the inclusion in the study.

Table 8: Overview of key parameters in the study on infant vitamin D levels included in this review. The season of inclusion was described, although these data were not used in connection with the results. VitD = vitamin D. [8]GW = gestational week. *Taking a maximum of 400 IU/d vitD before inclusion in the study.

Table 1: Overview of studies on respiratory infections included in this review. The studies with a significant effect are marked in white, while the studies with no significant findings are marked in grey. The season of inclusion was described, although these data were not used in connection with the results. vitD = vitamin D. [1]ARI = acute respiratory infection. [8]GW = gestational week. [14]RSV = respiratory syncytial virus. *Taking a maximum of 200 IU/d vitD before inclusion in the study.

First author, year, country	Study design	*Study population*	JADAD/NOS score	Maternal vitamin D supplementation	Children's outcome	Follow-up time	Results
Respiratory infections in early life							
Grant 2014 (96) New Zealand	RCT n=260	Pregnant women* without pregnancy complications Season: all year	JADAD 5. appropriate randomization and double blinding.	1,000-, 2,000 IU/d or placebo. From GW[8] 27 to birth.	ARI[1]. Parent-reported and primary care visits	6 months	Maternal vitD doses of 2,000 IU/d reduced the risk of ARI[1] in children significant from 99% to 88%, p=0.03
Belderbos 2011(121) Holland	Cohort n=156	Healthy children with an uncomplicated birth Ethnicity: Caucasian, other Season: parted in 4 seasons	NOS 8. No selection bias, comparability in the cohort. Outcome from record linkage.	400 IU/d. Recall after birth.	RSV[14] infection. Parent-reported symptoms and nose-throat swap specimens	1 year	Maternal vitD intake was not significantly associated with reduced risk of RSV[14] in children.
Morris 2021 (115) Bangladesh	RCT n=1,174	Pregnant women in GW 17-24. Age: over 18 years old Season: parted in 4 seasons	JADAD 4. appropriate randomization and mention of blinding.	28,000-, 16,800-, 4,200 IU/week or placebo. From GW[8] 17-24 to birth.	Microbiologically confirmed ARI[1]. Nasal swaps collections	6 months	Maternal vitD intake was not significantly associated with risk of ARI[1] in children. HR=1.12 [95% CI: 0.90-1.40]
Taghivand 2022 (104) Bangladesh	RCT n=1,174	Pregnant women in GW 17-24 Age >18 Season: parted in 4 seasons	JADAD 5. appropriate randomization and blinding.	28,000-, 16,800-, 4,200 IU/week or placebo.	Pneumococcal disease. Routine home visits and nasal swaps.	6 months	Maternal vitD intake was not significantly associated with risk of pneumococcal disease in children. Placebo: Reference 4,200 IU/week: HR=0.87 [95% CI 0.70-1.08]

				From GW[8] 17-24 to birth.			16,800 IU/week: HR=1.16 [95% CI 0.94-1.44] 28,000 IU/week: HR=1.05 [95% CI 0.85-1.30]

Table 2: Overview of included studies on asthma, croup, wheezing, and allergy. Studies with a significant effect are marked in white, and studies with no significant findings are marked in grey. The season of inclusion was described, although these data were not used in connection with the results. vitD = vitamin D. [8]GW = gestational age. [9]PUFA = polyunsaturated fatty acid. [10]IVF = in vitro fertilization. *Taking a maximum of 200 IU/d vitD before the inclusion in the study. **Taking a maximum of 2,000 IU/d vitD before the inclusion in the study.

First author, year, country	**Study design**	*Study population*	**JADAD/NOS score**	**Maternal vitamin D supplementation**	**Children's outcome**	**Follow-up time**	**Results**
Asthma, croup, wheezing and allergy							
Camargo 2007 (22) USA	Cohort n=1,194	Singleton pregnant women in GW[8] <22, English-speaking. Ethnicity: 74% White Season: data not shown	NOS 7. No selection bias, comparability in the cohort. Outcome from record linkage and exposure self-reported.	Between 160 IU/d and 421 IU/d. Recall during pregnancy or after birth.	Wheezing at 3 and 6 years of age. Parent-reported at study visits.	6 years	Higher maternal vitD intake significantly reduced the risk of wheezing in the offspring. OR=0.39 [95% CI 0.25-0.62], p=0.001
Grant 2016 (95) New Zealand	RCT n=260	Pregnant women* in GW[8] <27 without pregnancy complications. Ethnicity: European, Māori, Pacific, other Season: Parted in 4 seasons	JADAD 5. appropriate randomization and double blinding.	2,000 IU/d, 1,000 IU/d or placebo. From GA[8] week 27 to birth.	Allergy, Blood sample at 18 months of age. IgE-antibodies measured in blood samples.	1.5 years	Maternal vitD intake reduced the risk of allergy in children significantly. House dust mites: Placebo: 9% had allergy (reference) 1,000 IU/d vitD: 3% had allergy (p=0.28) 2,000 IU/d vitD: 0% had allergy (p=0.03) Mite antigen sensitization:

							Placebo: (Data not shown) Reference 1,000 IU/d vitD: RR=0.71 [95% CI 0.33-1.52] 2,000 IU/d vitD: RR=0.34 [95% CI 0.12-0.94]
Litonjua 2016 (106) USA	RCT n=881	Singleton pregnant women** in GW[8] 10-18, but without hypertension, diabetes, kidney disorder, sarcoidosis, or IVF[10] treatment. Only pregnancies where at least one of the parents were diagnose, with asthma/atopy were included. Maternal age: 18-39 years old Ethnicity: 44% Afro-American, 26% Caucasian non-Hispanic, 14% Caucasian Hispanic, 29% other. Season: all year	JADAD 5. appropriate randomization and blinding.	4,400 IU/d or 400 IU/d. From GW[8] 10-18 to birth.	Asthma and recurrent wheezing Blood sample at 1 and 3 years of age. Parental report of physician's diagnosis of asthma.	3 years	Maternal vitD intake reduced the risk of asthma and recurrent wheezing in children significantly. 4,400 IU/d vitD: 24.3% [95% CI 18.7-28.5] 400 IU/d vitD: 30.4% [95% CI 25.7-73.1] HR=0.8 [95% CI 0.6-1.0], p=0.051
Blighe 2017 (124) USA	Case-control n=245	Pregnant, non-smoking women in GW[8] 10-18 with a history of asthma, eczema or allergic rhinitis. Alternatively, the father of the child with those diseases. Ethnicity: Asian (n=14), Caucasian (n=78), native Hawaiian (n=3), African American	NOS 7. No selection bias. Same method of ascertainment and comparability between cases and control.	400- or 4,400 IU/d From GW[8] 10-18 to birth	Asthma or recurrent wheezing. Blood sample at 3 years of age. Metabolomics profiles measured by blood samples.	3 years	Maternal vitD intake was a significant predictor of metabolomics profiles in children. OR=1.032 [95% CI 1.0021-1.065], p=0.0014

		(n=117), other (n=33). Season: Data not shown					
Wolsk 2017 (120) USA	RCT n=712	Singleton pregnant women** in GW[8] 10-18, with a history of asthma or atopy but without hypertension, diabetes, kidney disorder, sarcoidosis or IVF[10] treatment. Alternatively, the father of the child with asthma/atopy. Age: 18-39 years old Ethnicity: African American (n=312), non-African American (n=400) Age: 18-39 years. Season: Data not shown	JADAD 4. appropriate randomization and mention of blinding.	400- or 4,400 IU/d. From GW[8] 10-18 to birth	Asthma and recurrent wheezing. Parental report of diagnosis of asthma or recurrent wheeze made by a physician	3 years	Maternal vitD level above 75 nmol/L including vitD supplemental use of 4,400 IU/d decreased the risk of asthma and recurrent wheezing in children significantly. aOR = 0.42 [95% CI 0.19-0-91], p=0.03 Logistic regression of treatment group and the risk of asthma/wheeze in children: aOR (400 IU/d) = 1.0 aOR (4,400 IU/d) = 0.74 (0.53-1.05), p=0.09 Stratified for maternal initial vitD status. Adjusted for clinical site, maternal education, maternal age, adherence to vitD supplement (>80%), and maternal BMI.
Hjelmsø 2020 (112) Denmark	RCT n=695	Pregnant women in GW[8] <24 Ethnicity: Caucasian, other. Season: Parted in 4 seasons	JADAD 4. appropriate randomization and mention of blinding.	2,800 IU/d or 400 IU/d. From GW[8] 24 to birth.	Airway microbiome as a risk factor for asthma and wheezing. Measured in an airway sample from infants.	1 month	Maternal vitD intake positively changed the airway microbiome of children aged 1 month. F=3.740, R^2=0.007, p=0.005
Lee-Sarwar 2020 (125) USA	Case-control n=738	Singleton pregnant women** in GW[8] 10-18 with a history of asthma/allergy but without	NOS 7. No selection bias. Same method of ascertainme	400- or 4,400 IU/d. From GW[8] 10-18 to birth	Asthma and recurrent wheezing.	3 years	Maternal vitD intake significantly reduced the risk of asthma and recurrent wheezing in children.

		hypertension, diabetes, kidney disorder, sarcoidosis, or IVF[10] treatment. Alternatively, the father of the child with asthma/allergy. Age: 18-39 years Ethnicity: Black (41%), White (20%). Season: Data not shown	nt and comparability between cases and control.		Blood sample at 1 and 3 years of age. Parental report of physician-diagnosed asthma, recurrent wheeze, and medications.		PUFA[9] <0.86g/d of the child + 400 IU/d during pregnancy vitD: PUFA[9] <0.86g/d of the child + 4,400 IU/d vitD during pregnancy: OR=0.57 [95% CI 0.24-1.36], p=0.21 PUFA[9] >0.86g/d of the child + 400 IU/d vitD during pregnancy: OR=0.45 [95% CI 0.20-1.00], p=0.05 PUFA[9] >0.86g/d of the child + 4,400 IU/d vitD during pregnancy: OR=0.37 [95% CI 0.16-0.84], p=0.02
Chen 2021 (109) USA	RCT n=414	Pregnant women** in GW[8] 10-18, with a history of asthma. Alternatively, the father of the child with asthma/atopy. Age: 18-39 years old Season: Parted in 4 seasons	JADAD 4. appropriate randomization, and mention of blinding.	4,400 IU/d or 400 IU/d. From GW[8] 10-18 to birth.	Allergic rhinitis Blood samples at 3 and 6 years of age. Aeroallergen sensitization at age 6 years was defined by a positive serum specific IgE.	6 years	Maternal vitD doses of 4,400 IU/d compared to 400 IU/d significantly decreased the risk of allergic rhinitis in children. aOR=0.54 [95% CI 0.32–0.91], p=0.02 Adjusted for maternal education, preterm birth, child sex, child race and ethnicity, parental asthma, and child body mass index at the age of 6 years.
El-Heis 2022 (105) England	RCT n=703	Singleton pregnant women in GW[8] < 17 with a plasma level of 25(OH)D between 25-100 nmol/L, calcium < 2.75 nmol/L and not exceeding a vitD intake >400 IU/d.	JADAD 5. appropriate randomization and blinding.	1,000 IU/d or placebo From GW[8] 14 to birth	Atopic eczema diagnosis at 12, 24 and 48 months of age. Diagnosis by a trained	4 years	Maternal vitD intake decreased the risk of atopic eczema in children significantly. OR (12 months) = 0.55 [95% CI 0.32-0.97], p=0.04 OR (24 months) = 0.76 [95% CI 0.47-1.23], p=0.27

		Without metabolic-, kidney disease, hyperparathyroidism, and major anomalies of foetus. Age: >18 years Ethnicity: >95% White. Season: Adjusted for season			research nurse.		OR (48 months) = 0.75 [95% CI 0.37-1.52], p=0.42 Adjusted for breastfeeding duration.
Brustad 2022 (92) Denmark	RCT n=736	Pregnant women in GW[8] <26 without endocrine-, cardiovascular- or nephrological disorders. Season: Data not shown.	JADAD 5. appropriate randomization and blinding.	2,800- or 400 IU/d. From GW[8] 24 to birth.	Croup and wheezing Diagnosed at clinical visits.	3 years	Maternal intake of 2,800 IU/d vitD reduced children's risk of croup (11% vs 18%) significantly. HR=0.60 [95% CI 0.38-0.93], p=0.02. Remained statistically significant after adjustment for persistent wheezing (p<0.01) and lower respiratory tract infections (p<0.01)
Goldring 2013 (32) England	RCT n=180	Pregnant women in GW[8] 27 without sarcoidosis, osteomalacia, kidney dysfunction, and tuberculosis. In twin pregnancies, only the firstborn child was included. Ethnicity: Asian, Middle Eastern, Black and White. Season: April to November	JADAD 3. appropriate randomization and blinding of researcher, but not participants.	800 IU/d, 200,000 IU x 1 or placebo. From GW[8] 27 to birth.	Wheezing Blood sample at 3 years of age. Parent-reported and measured at clinical visits.	3 years	Maternal vitD intake was not significantly associated with the risk of wheezing in children. RR=0.86 [95% CI 0.49-1.50], p=0.69
Chawes 2016 (93) Denmark	RCT n=623	Pregnant women in GW[8] <26 without endocrine-, cardiovascular- or nephrological disorder.	JADAD 5. appropriate randomization and blinding.	2,800 or 400 IU/d. From GW[8] 24 to birth.	Wheezing Diagnosed according to a previously validated	3 years	Maternal vitD intake was not significantly associated with risk of wheezing in children. HR=0.76 [95% CI 0.52-1.12], p=0.16

		Season: March to November			quantitative algorithm.		
Omand 2018 (126) Canada	Cohort n=2,926	Healthy children aged 0-6 years. Excluded if having chronic diseases (except asthma), developmental delay, born < GW[8] 32. Ethnicity: European (67%), African (7%), Asian (13%), Latin-American (4%). Season: Summer and winter	NOS 7. No selection bias, comparability in the cohort. Outcome from record linkage and exposure self-reported.	Recall after birth.	Asthma Blood sample 7 times during the first 6 years of life. Diagnosis of asthma in different databases.	6 years	Maternal vitD intake was not significantly associated with the risk of asthma in children. Hospital admission: aOR = 0.76 [95% CI 0.54-1.08] Emergency department visits aRR = 0.92 [95% CI 0.81-1.04] Outpatient sick visits aRR = 1.03 [95% CI 0.99-1.08] Adjusted for age, sex, BMI, number of children in the household, day-care/preschool attendance, smoking status, birth weight, and gestational age.
Brustad 2019 (118) Denmark	RCT n=736	Pregnant women in GW[8] <26. Excluded if any endocrine-, cardiovascular- or nephrological disorder. Season: Data not shown	JADAD 3. Appropriate randomization.	2,800- or 400 IU/d. From W[8] 24 to birth.	Asthma at 6 years of age. Diagnosed by a study paediatrician following a predefined, validated diagnostic algorithm.	6 years	Maternal vitD intake was not significantly associated with risk of asthma in children. OR=1.27 [95% CI 0.67-2.42], p=0.46
Litonjua 2020 (107) USA	RCT n=881	Singleton pregnant women** in GW[8] 10-18, with a history of asthma or atopy but without hypertension, diabetes, kidney disorder, sarcoidosis, or IVF[10] treatment. Alternatively, the	JADAD 5. appropriate randomization and blinding.	4,400 or 400 IU/d. From GW[8] 10-18 to birth.	Asthma and recurrent wheezing Blood sample at 1 and 3 years of age. Lung function was measured at clinical visits at 4-6 years of age.	6 years	Maternal vitD intake was not significantly associated with the risk of asthma or recurrent wheezing in children. HR=1.12, p=0.25

		father of the child with asthma/atopy. Age: 18-39 years old Ethnicity: 44% Afro-American, 26% Caucasian non-Hispanic, 14% Caucasian Hispanic, 29% other. Season: All year					

***Table 3**:* Studies evaluating vitD effects on DM1 risk. Studies with a significant effect are marked in white, and studies with no significant findings are marked in grey. The season of inclusion is described, although these data were not used in connection with the results. VitD = vitamin D.

First author, year, country	**Study design**	*Study population*	**JADAD/NOS score**	**Maternal vitamin D supplementation**	**Children's outcome**	**Follow-up time**	**Results**
Diabetes							
Brekke 2007 (122) Sweden	Cohort n= 16,070	Children born from 1996 to 1999. Season: Parted in 2 seasons	NOS 7. No selection bias, comparability in the cohort. Outcome from record linkage and exposure is self-reported.	400 IU/d. Recall after birth.	Diabetes-related autoimmunity at 1 and 2.5 years of age. Blood sample at 1 and 2.5 years of age. Antibodies measured in blood samples.	2.5 years	Maternal vitD intake reduced the risk of diabetes-related autoimmunity in children at 1 year significantly, but not 2.5 year. 1 year: aOR=0.71 [95% CI 0.52–0.96], p=0.028 2.5 years aOR=1.25 [95% CI 0.91-1.73]) Adjusted for familial type 1 diabetes, maternal education, maternal age, delivery mode, weight increase from birth, breast-feeding duration,

							introduction of cow's-milk protein, fish intake.
Marjamäki 2010 (38) Finland	Cohort n= 3,723	Children with an HLA-type with risk of diabetes type 1. Exclusion of children with anomalies, immune system-disorders, or language-difficulties. Season: Data not reported	NOS 8. No selection bias, comparability in the cohort. Outcome from record linkage and exposure self-reported.	Yes/no intake. Recall after birth.	Beta cell autoimmunity and type 1 diabetes Blood sample at 3, 6, 12, 18 and 24 months of age. Antibodies measured in blood samples.	2 years	Maternal vitD intake was not significantly associated with beta cell autoimmunity in children. HR=1.05 [95% CI 0.95-1.16]
Silvis 2018 (123) Finland, Germany, Sweden, and USA	Cohort n= 8,676	Children with an HLA-type with risk of diabetes type 1. Season: All year	NOS 7. No selection bias, comparability in the cohort. Outcome from record linkage and exposure self-reported.	>2,030, <2,030 IU/d vitD or no vitD. Recall after birth.	Islet autoimmunity and progression to diabetes type 1 Blood samples every 3 months until 4 years of age. Antibodies measured in blood samples.	10 years	Maternal vitD intake was not significantly associated with the risk of islet autoimmunity in children. HR=1.11 [95% CI 0.94-1.31]

Table 4*:* Overview of studies on tooth development. Studies with a significant effect are marked in white, and studies with no significant findings are marked in grey. The season of inclusion was described, although these data were not used in connection with the results. VitD = vitamin D. [6]EH = enamel hypoplasia. [8]GW = gestational week. *Taking a maximum of 600 IU/d vitD before inclusion in the study.

First author, year, country	**Study design**	*Study population*	**JADAD/NOS score**	**Maternal vitamin D supplementation**	**Children's outcome**	**Follow-up time**	**Results**
Teeth							
Nørrisgaard 2019 (108) Denmark	RCT n=623	Healthy pregnant women* in GW[8] <24. Without endocrine, cardiovascular, or kidney disorders.	JADAD 5. appropriate randomization and blinding.	400- or 2,800 IU/d From GW[8] 24 to birth	Enamel defects and caries	6 years	Only 15.1% of children exposed to maternal vitD dose of 2,800 IU/d have enamel defects compared to 27.5% of children exposed to

		Ethnicity: >94% was White Twins included: yes Season: Data not reported			Measured at a dental examination at 6 years of age performed by a dental professional.		maternal vitD dose of 400 IU/d OR=0.47, [95% CI 0.27-0.81], p<0.05 No association between supplementation and caries.
Reed 2018 (119) USA	RCT n=145	Singleton pregnant women in GW[8] > 16 without calcium/parathyroid conditions, diuretic intake, cardiac medication or active thyroid disease Age: above 16 years Ethnicity: 45% White, 31% Hispanic, and 24% Black. Season: Data not reported	JADAD 4. Appropriate blinding and mention of randomization.	400-, 1,000- or 4,000 IU/d vitD. From GW[8] 12-16 to birth.	EH[6] Measured by two examiners at digital images of the buccal surfaces of the maxillary central incisors in the children.	4 years	Maternal vitD intake was not significantly associated with EH[6] in children. OR=1.29 [95% CI 0.143-1.543]).

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2

3 ***Table 5****:* Overview of studies on bones included in this review. Studies with a significant effect is marked in white, whereas
4 studies with no significant findings are marked in grey. The season of inclusion was described, although these data were not
5 used in connection with the results. VitD = vitamin D. [3]BMC = bone mineral content. [4]BMD = bone mineral density, aBMD
6 = areal bone mineral density. [8]GW = gestational week. [11]DXA = dual-energy X-ray absorptiometry.

First author, year, country	**Study design**	*Study population*	**JADAD/NOS score**	**Maternal vitamin D supplementation**	**Children's outcome**	**Follow-up time**	**Results**
Bones							
Brustad 2020 (91) Denmark	RCT n=623	Pregnant women in GW[8] <24 Ethnicity: White Caucasian Twins included: Yes Season: All year	JADAD 5: appropriate randomization and blinding.	2,800 or 400 IU/d. From GW[8] 24 to birth.	Bone mineralization (BMC[3] + BMD[4]). Whole body DXA[11] scans at 3 and 6 years of age.	6 years	Maternal vitD intake of 2,800 IU/d compared to 400 IU/d significantly increased BMC[3] and BMD[4] in children. **3 year** BMD[4], mean: 0.007

							[95% CI -0.003-0.017], p=0.16 BMC[3], mean: 9.9 [95% CI 0.3-19.6], p=0.04 **6 year** BMD[4], mean: 0.009 [95% CI 0.001-0.017], p=0.04 BMC[3], mean: 13,9 [95% CI 3.2-24.7], p=0.01 Adjusted for age, sex, height, and weight.
Gopal-Kothandapani 2020 (111) England	RCT n=31	Children aged 4-5 years without balance problems, fractures, bone-, liver- or kidney diseases, Age: 4-5 years Ethnicity: Caucasian or other. Season: Data not reported	JADAD 4. appropriate randomization and mention of blinding.	1,000 IU/d or placebo. From GW[8] 14 to birth.	Post-natal bone formation after mechanical stimuli measured by the bone formation marker P1NP. Blood sample before and after full-body vibrations.	4 years	Maternal vitD intake significantly increased metabolic activity in the bones after mechanical stimuli in children. ΔP1NP, 1,000 IU/d: 40.6 ng/mL ΔP1NP, placebo: -92.6 ng/mL Difference in ΔP1NP between the two groups: 133.2 ng/mL [95% CI 0.4-266.0], p=0.049
Curtis 2022 (94) England	RCT n=1,123	Pregnant women coming for their first pregnancy scan between 06. October 2008 and 11. February 2014. Age: above 18 years Ethnicity: White Caucasian or other. Twins included: Yes	JADAD 5. appropriate randomization and blinding.	1,000 IU/d or placebo. From GW[8] 14 to birth.	Bone mineralization. Whole body DXA[11] scan.	4 years	Maternal vitD intake of 1,000 IU/d significantly increased bone mineralization in children. aBMD[4]: 1,000 IU/d: mean 0.477 g/cm2 [95% CI 0.472–0.481] Placebo: mean 0.470 g/cm2 [95% CI 0.466–0.475], p = 0.048.

		Season: Parted in 4 seasons					
Sahoo 2017 (101) India	RCT n=300	Singleton pregnant women in GW[8] 14-20 without metabolic disorder, kidney- or liver disease, tuberculosis or epilepsy. Age: >18 years Ethnicity: Non-White population. Season: Data not shown	JADAD 5. appropriate randomization and blinding.	60,000 IU every fourth week, 60,000 IU every eight week or 400 IU/d From GW[8] 20 to birth.	BMC[3] and BMD[4]. Whole body DXA[11] scan.	16 months	Maternal vitD intake was not associated with better bone health in the children, at the age of 16 months.
Moon 2021 (98) England	RCT n=965	Singleton pregnant women taking <400 IU/d vitD and having 25(OH)D at 25-100 nmol/L Ethnicity: 94% was White Caucasian. Season: Parted in 4 seasons	JADAD 5. appropriate randomization and blinding.	1,000 IU/d or placebo. From GW[8] 14 to birth.	Bone mineralization. Whole body DXA[11] scan.	8 years	Maternal vitD intake was not significantly associated with bone mineralization in children. Whole body BMC[3]: Intervention: mean 61.6 g [95% CI 60.3-62.8 g] Placebo: mean 60.5 g [95% CI 59.3-61.7 g] p=0.21
O'Callaghan 2021 (117) Bangladesh	RCT n=1,300	Healthy singleton pregnant women in GW[8] 17-24. Season: All year	JADAD 4. appropriate randomization and mention of blinding.	4,200-, 16,800-, 28,000 IU/week or placebo From GW[8] 17-24 to birth.	Bone mineralization (BMC[3] and BMD[4]). Whole body DXA[11] scan. Blood sample from the children 4 years of age.	4 years	Maternal vitD intake was not significantly associated with BMC[3] or BMD[4] in children. Association between placebo and 28,000 IU/week: BMC[3]: mean difference 0.61 g [95% CI–10.90-12.13], p=0.92 Placebo: mean=276.2 g, SD 48.5 g

							28.00 IU/week: mean = 276.8 g., SD 52.8 g. BMD[4]: mean difference 0.0004 g/cm2 [95% CI –0.0089-0.0097], p=0.93 Placebo: mean = 0.438 g/cm2, SD 0.039 g/cm2. 28.000 IU/week: mean = 0.439 g/cm2, SD 0.043 g/cm2.

Table 6*:* Overview of studies on growth included in this review. Studies with a significant effect are marked in white, and studies with no significant findings are marked in grey. The season of inclusion was described, although these data were not used in connection with the results. VitD = vitamin D. [5]LAZ-score = length-for-age z-score. [8]GW = gestational week. [12]IFA = iron and folic acid. [13]LNS = lipid-based nutrient supplement.

First author, year, country	**Study design**	*Study population*	**JADAD/NOS score**	**Maternal vitamin D supplementation**	**Children's outcome**	**Follow-up time**	**Results**
Growth							
Kalra 2011(113) India	RCT n=300	Pregnant women in GW[8] 12-24 not taking vitD or calcium. Without kidney or liver disorders. Season: Data not reported	JADAD 4. appropriate randomization and mention of blinding.	60,000 IU x1, 120,000 IU x2 or placebo. Dose given in the 2. /3. trimester.	Weight, length, head circumference, and diameter of anterior fontanelle. Measured at study visits.	9 months	Maternal vitD intake significantly increased growth in children at 9 months of age. Head circumference (cm) 60,000 IU x1: mean 42.9 (±SD 0.7), 120,000 IU x2: mean 42.4 (±SD 2.6), Placebo: mean 41.8 (±SD 2.2), p=0.012 Anterior fontanelle (cm) 60,000 IU x1: mean 0.9 (±SD 0.4) 120,000 IU x2: mean 0.9 (±SD 0.3), Placebo: mean 1.5 (±SD 0.5), p<0.001 Length (cm):

							60,000 IU x1: mean 69.3 (±SD 1.9), 120,000 IU x2: mean 69.9 (±SD 1.4), Placebo: mean 67.4 (±SD 1.7), p<0.001 Weight (kg): 60,000 IU x1: mean 8.4 (±SD 0.6), 120,000 IU x2: mean 8.5 (±SD 0.5), Placebo: mean 7.7 (±SD 0.4), p<0.001
Dewey 2022 (110) Bangladesh	RCT n=2,011	Pregnant women in GW[8] <20 without plans to move. In twin pregnancies, only one child was included. Season: Data not reported	JADAD 3. appropriate randomization and blinding of researcher, but not participants.	200- or 400 IU/d vitD From GW[8] 20 to birth.	Weight, height and head circumference. Measured by anthropometrics at study visits.	2 years	Maternal vitD intake significantly increased growth in children at 6-24 months of age. <u>0-6 months:</u> Lengths gain: LNS[13]= mean 16.1, ±SD 1.8 IFA[12]=mean 16.1, ±SD 1.9, p=0.38 Head circumference gain: LNS[13]= mean 8.1, ±SD 1.2 IFA[12]= mean 8.1 ±SD 1.2, p=0.15 Weight gain: LNS[13]= mean 4055, ±SD 742 IFA[12]=mean 4086, ±SD 739, p=0.39 <u>6-24 months:</u> Lengths gain: LNS[13]= mean 5.9, ±SD 0.6 IFA[12]= mean 5.8, ±SD 0.6, p=0.01 Head circumference gain: LNS[13]= mean 1.41, ±SD 0.24 IFA[12]=mean 1.37, ±SD 0.24, p=0.009 Weight gain: LNS[13]= mean 1009, ±SD 225 IFA[12]= mean 981, ±SD 211

Roth 2022 (100) Bangladesh	RCT n=145	Pregnant women in GW[8] 26-30 Age: 18-35 years old. Twins included: yes. Season: Parted in 4 seasons	JADAD 5. appropriate randomization and blinding.	35,000 IU/week or placebo. From GW[8] 26-30 to birth	Anthropometry and LAZ-score[5] Blood sample at 8 and 24 weeks of age. Measured at visits by study personnel using a standardized method and supervised by study physicians.	1 year	Maternal vitD intake significantly enhanced early postnatal linear growth in children. <u>Birth</u> Lengths: p=0.18 Placebo: mean 48.0 ± SD 2.0 VitD: mean 48.0 ± SD 1.9 Weight: p=0.32 Placebo: mean 2.8 ± SD 0.4 VitD: mean 2.9 ± SD 0.4 Head circumference: p=0.97 Placebo: mean 33.0 ± SD 1.5 VitD: mean 33.0 ± SD 1.5 LAZ[5]: p=0.14 Placebo: mean 0.82 ± SD 1.0 VitD: mean 0.56 ± SD 1.0 <u>1 year</u> Length: p=0.14 Placebo: mean 71.8 ± SD 3.0 VitD: mean 72.6 ± SD 3.0 Weight: p=0.57 Placebo: mean 8.4 ± SD 1.0 VitD: mean 8.5 ± SD 1.2 Head circumference: p=0.95 Placebo: mean 44.4 ± SD 1.4 VitD: mean 44.4 ± SD 1.4 LAZ[5]: p=0.02 Placebo: mean -133 ± SD 1.2 VitD: mean -0.89 ± SD 1.2
Roth 2018(116) Bangladesh	RCT n=1,300	Pregnant women in GW[8] 17-24. Season: Data not reported	JADAD 4. appropriate randomization and mention of blinding.	4,200-, 16,800-, 28,000 IU/week or placebo From GW[8] 17-24 to birth	LAZ-score[5] Blood sample from the children 3 and 6 years of age.	1 year	Maternal vitD intake was not significantly associated with LAZ-score[5] in children. LAZ[5]: Placebo: mean −0.93± SD 1.05

					Measured at a clinical examination by trained personnel according to standardized procedures.		4,200 IU/d: mean −1.11 ± SD 1.11 16,800 IU/d: mean −0.98 ± SD 0.97 28,000 IU/d: mean −1.06 ± SD1.07 p=0.25
Sudfeld 2022 (103) Tanzania	RCT n=1,148	Pregnant women in GW[8] 12-27 with an HIV infection and normal serum albumin-adjusted calcium level. Age: above 18 years old Twins included: yes. Season: Data not reported	JADAD 5. appropriate randomization and blinding.	3,000 IU/d or placebo. From GW[8] 12-27 to 1 year postpartum.	Infant stunting at 1 year of age defined by a LAZ-score[5] Measured at study visits by study physicians and nurses.	1 year	Maternal vitD intake was not significantly associated with infant stunting. RR=1.00 [95% CI 0.92-1.10], p=0.95

Table 7: Overview of studies on language and motor skills included in this review. Studies with a significant effect are marked in white, and studies with no significant findings are marked in grey. The season of inclusion was described, although these data were not used in connection with the results. VitD = vitamin D. [8]GW = gestational week. [12]IFA = iron and folic acid. [13]LNS = lipid-based nutrient supplements. *Taking a maximum of 600 IU/d vitD before the inclusion in the study.

First author, year, country	**Study design**	*Study population*	**JADAD/NOS score**	**Maternal vitamin D supplementation**	**Children's outcome**	**Follow-up time**	**Results**
Language and motor skills							
Matias 2017 (114) Bangladesh	RCT n=3,000	Pregnant women in GW[8] <20 without plans to move. In twin pregnancies,	JADAD 3. appropriate randomization, and blinding of researcher, but not	400 IU/d or IFA[12] (placebo) From GW[8] 20 to birth.	Motor milestones and language. Measured by home stimulation at 12, 18, and 24 months of age by	2 years	Maternal vitD intake was significantly associated positively with motor milestones at the age of 18 months and language in children at the age of 24 months.

		only one child was included. Season: Data not reported	participants .		using the Family Care Indicators scale.		Motor milestones, 18 months LNS[13]-LNS[13]: OR=0.74 [95% CI 0.56-0.99] IFA[12]-LNS[13]: OR=0.66 [95% CI 0.49-0.89] IFA[12]-MNP: OR=0.75 [95%CI 0.56-1.00] p=0.004 Language, receptive: 24 months LNS[13]-LNS[13]: OR=0.70 [95% CI 0.53-0.94] IFA[12]-LNS[13]: OR=0.74 [95% CI 0.55-1.00] IFA[12]-MNP: OR=0.77 [95%CI 0.58-1.02] p=0.009 Milestones, 24 months: (data not shown), p=0.141 Language, receptive, 18 months: (data not shown), p=0.415
Prado 2016 (99) Ghana	RCT n=1,320	Pregnant women in GW[8] <20 without infections, HIV, asthma, epilepsy, tuberculosis, allergies or planning to move. Age: above 18 years old. Season: Data not reported	JADAD 5. appropriate randomization and blinding.	400 IU/d or placebo. From GW[8] 20 to birth.	Motor milestones and language. Reported by parents in specific checklists.	18 months	Maternal vitD intake was not significantly associated with motor milestones and language in children. Motor milestones: difference in mean z-scores ranged from 0.03 to 0.13, p=0.84 Language: difference in mean z-scores ranged from 0.01 to 0.08, p=0.46 Walking at 12 months: RR=1.23 [95% CI 1.02–1.49], p=0.025
Sass 2020 (102) Denmark	RCT n=623	Pregnant women* in GW[8] <24 without endocrine-, heart-, neuro or	JADAD 5. appropriate randomization and blinding.	2,800- or 400 IU/d. From GW[8] 24 to birth.	Cognitive development assessed at 2.5 years of age. Motor milestone achievement,	6 years	Maternal vitD intake was not significantly associated with cognitive development in children. Motor milestones:

	kidney diseases, child born < GW 37, or child with a birthweight <2,500 g. Danish-speaking. Ethnicity: 96% White Twins included: yes. Season: Parted in 4 seasons	language development, and general neurodevelopment at 3 years of age, and emotional and behavioural problems at 6 years of age. Data from both parents and trained clinicians in specific checklists.	β = 0.08 [95% CI −0.26-0.43], p=0.64 Cognitive development: score difference: 0.34 [95% CI −1.32-1.99], p=0.70 Neurodevelopment: (data not shown), p=0.62 Emotional and behavioural problems OR=0.76 [95% CI 0.53-1.09], p=0.14

Table 8: Overview of key parameters in the study on infant vitamin D levels included in this review. The season of inclusion was described, although these data were not used in connection with the results. VitD = vitamin D. [8]GW = gestational week. *Taking a maximum of 400 IU/d vitD before inclusion in the study.

First author, year, country	Study design	*Study population*	JADAD/NOS score	Maternal vitamin D supplementation	Children's outcome	Follow-up time	Results
Infant 25(OH)D status							
March 2015 (97) Canada	RCT n=226	Pregnant women* in GW[8] 13-24 without metabolic-, inflammatory or genetic disorders (hypertension, tuberculosis, heart- and kidney diseases), bowl-disorders or complicated pregnancy. Age: 18-45 years Ethnicity: 72% Caucasian, 28% non-Caucasian. Season: Parted in 4 seasons	JADAD 5. appropriate randomization and double blinding.	400-, 1,000-, 1,600 IU/d vitD. From GW[8] 13-24 to birth	VitD levels in infants Blood sample at 8 weeks of age. Measured in blood samples.	8 weeks	44% of children exposed to maternal vitD 1,600 IU/d had a 25(OH)D level above 75 nmol/L, compared to less than 15% in the two other groups (p=0.05). Serum 25(OH)D at the age of 8 weeks: 400 IU/d: mean=45 [95% CI 38-52] 1,000 IU/d: mean=52 [95 % CI 45-58] 1,600 IU/d: mean=75 [95 % CI 67-83]

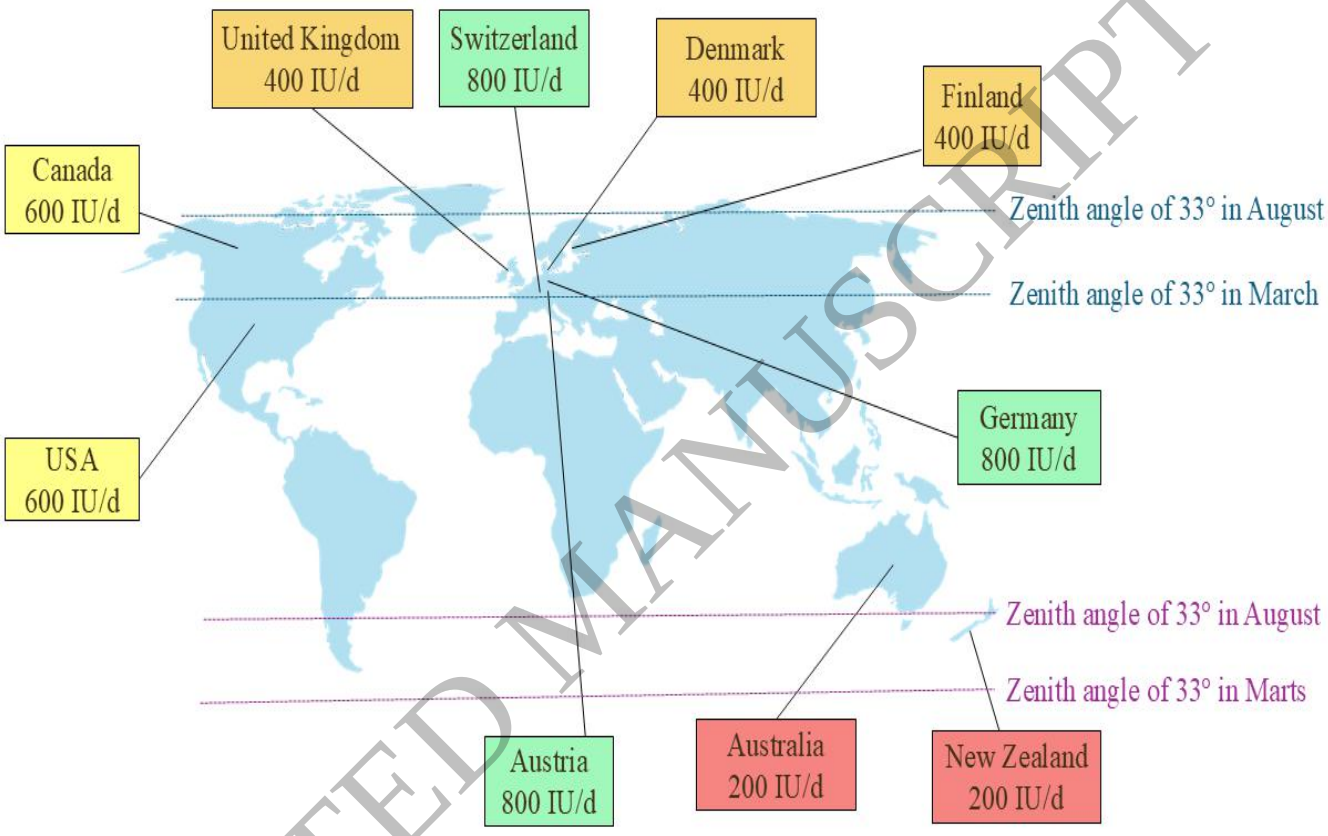

Figure 1
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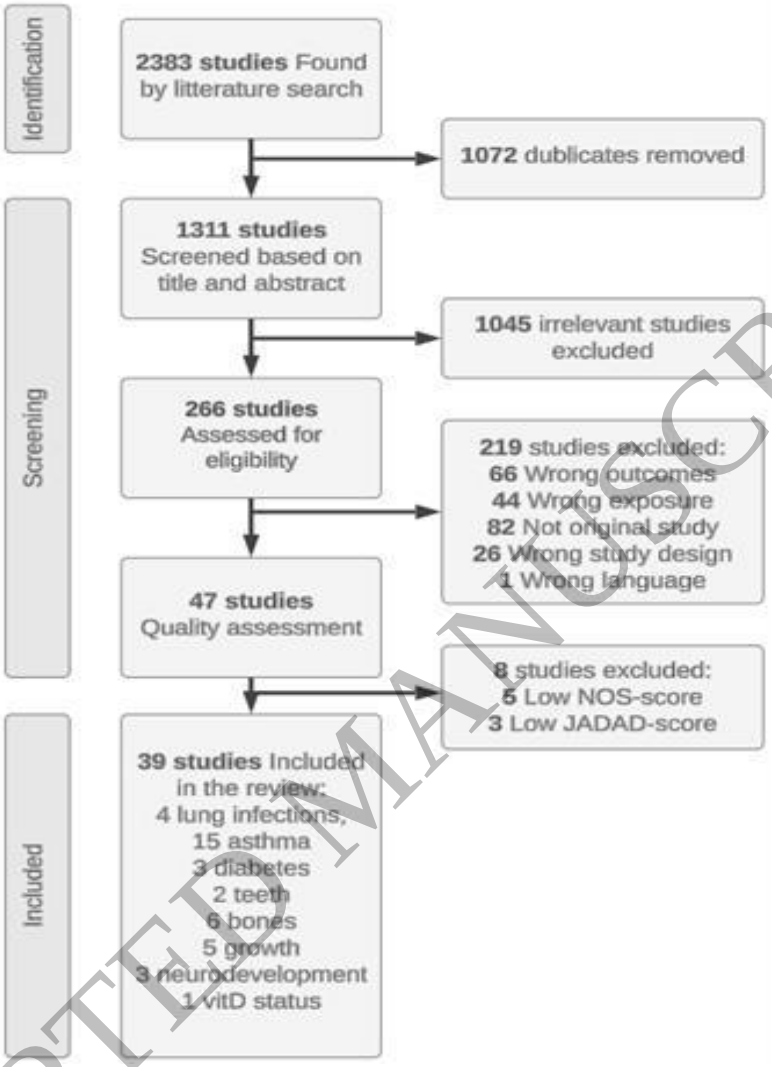

Figure 2
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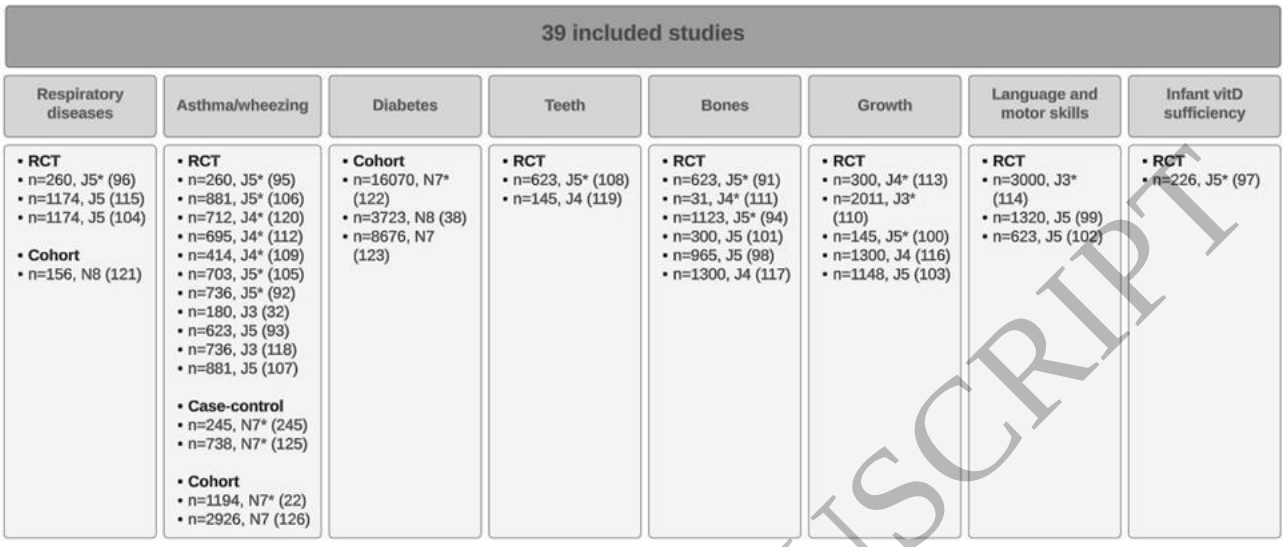

Figure 3
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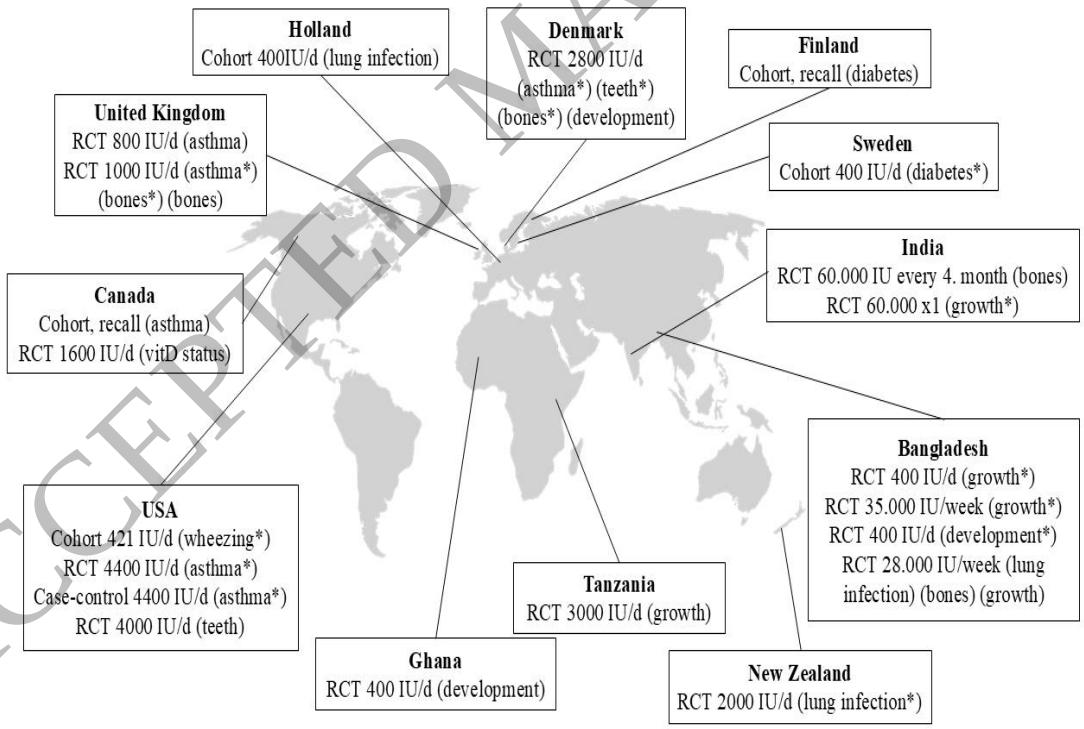

Figure 4
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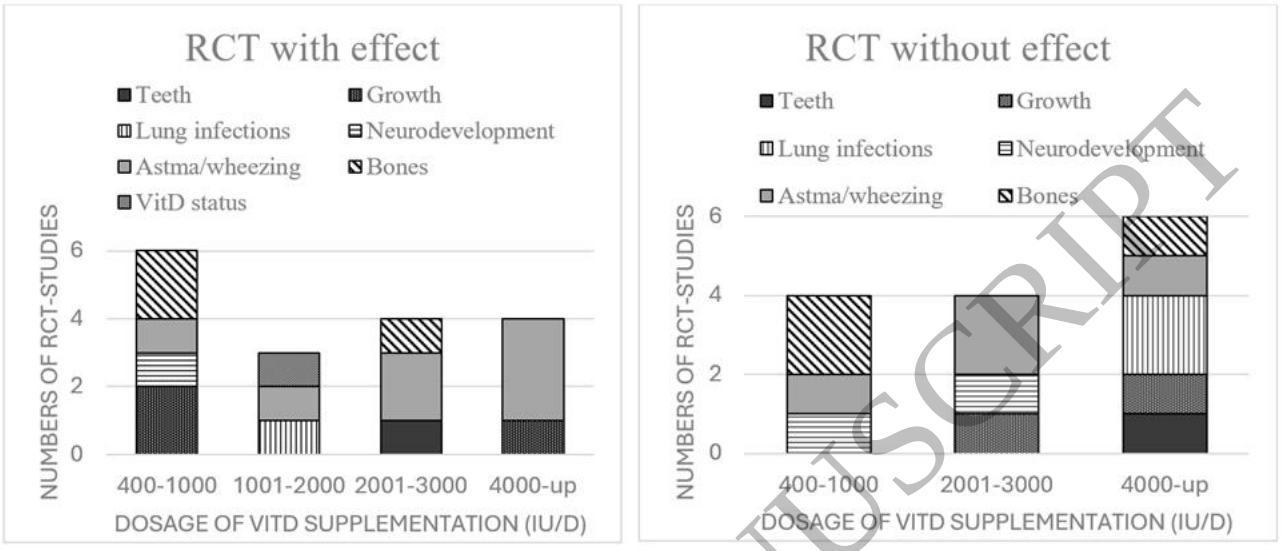

Figure 5
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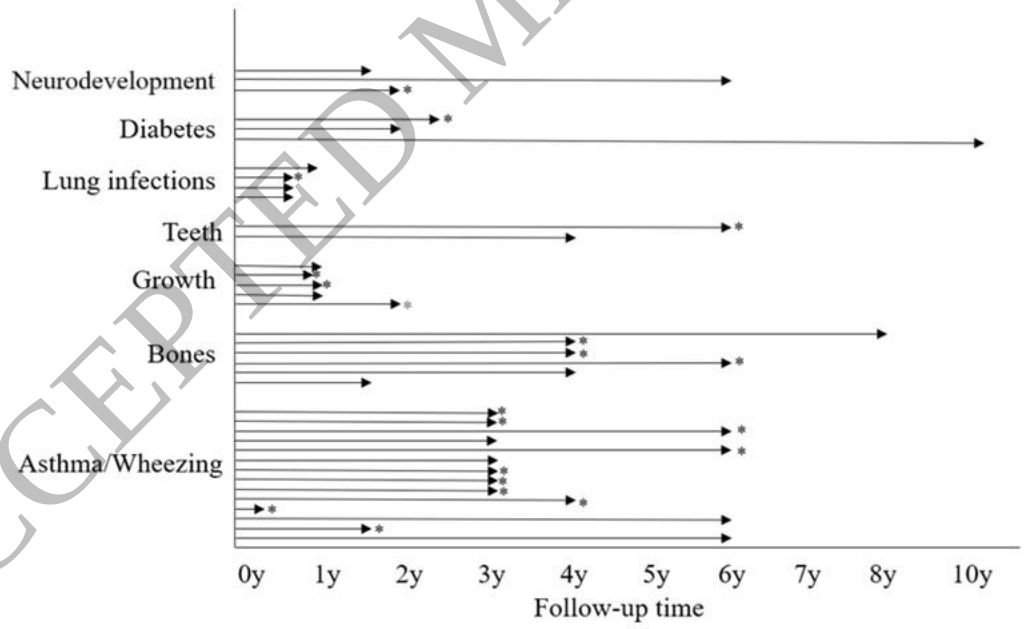

Figure 6
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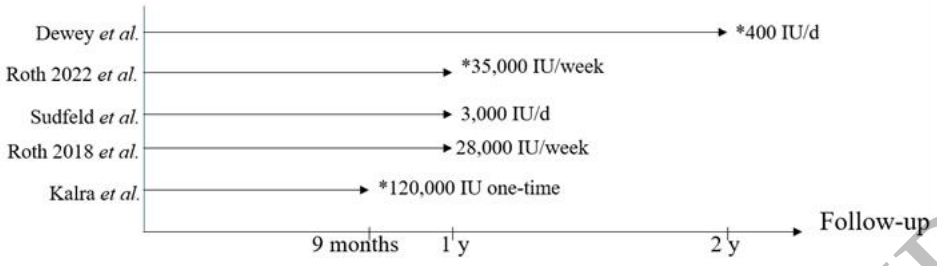

Figure 7
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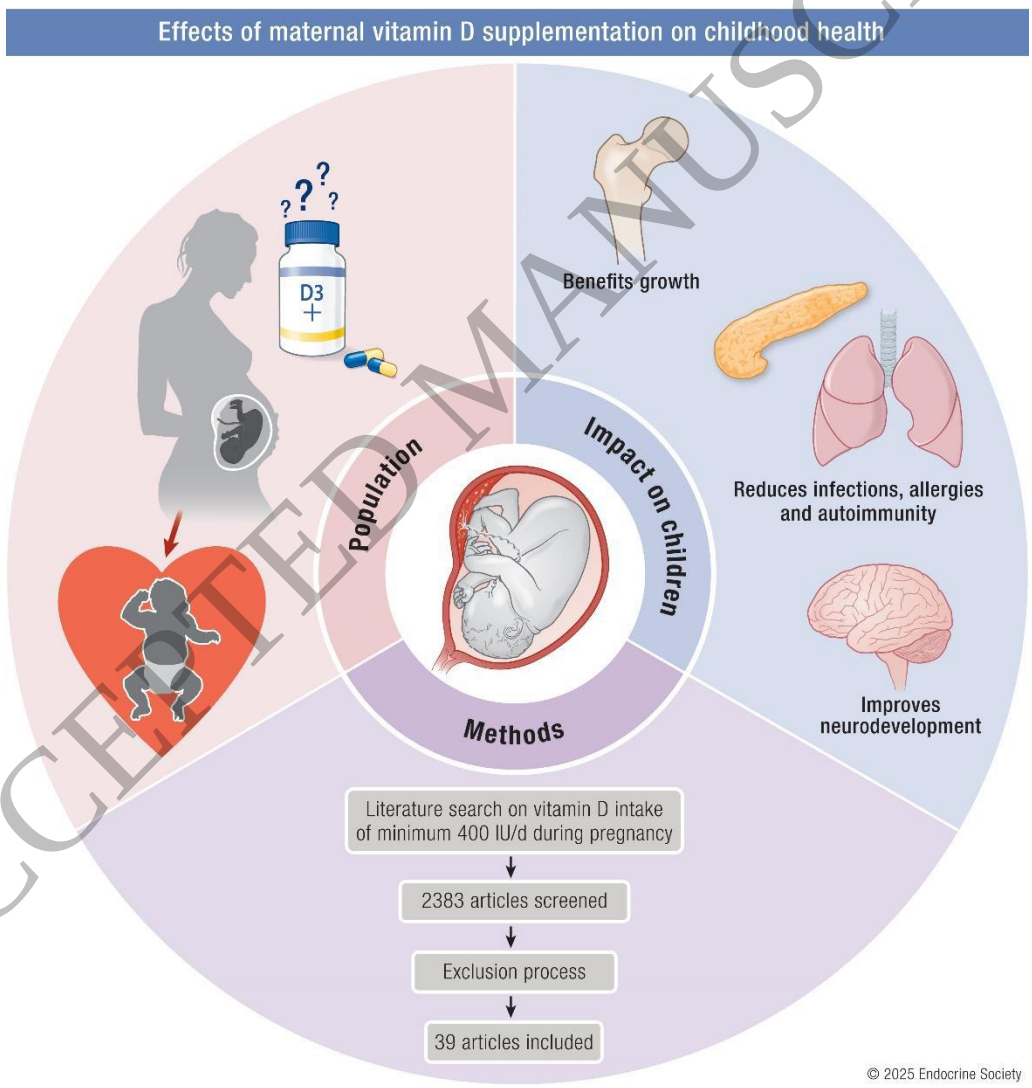

Graphical Abstract
135x142 mm (x DPI)

Essential points

- Early exposure to maternal vitamin D supplements ≥ 400 IU/day has a positive effect on growth, bone development, and the risk of early life respiratory problems, including respiratory syncytial virus infection.
- Existing knowledge is challenged by a lack of data on maternal and infant vitamin D levels in relation to both supplementation regime used, maternal response and the impact of maternal biology on vitamin D status and the actual effect on offspring health
- Available data on infant levels does however suggest that a 400 IU daily supplement is associated with a high prevalence of vitamin D sufficiency in newborns
- Maternal vitamin D supplementation has beneficial effects on brain development and autoimmune diseases, such as asthma in the newborn.
- Vitamin D seems to have an ameliorating effect on autoimmune activity in pancreatic islands in the first year of life.
- Further studies are needed to determine organ-specific vitamin D needs and the duration of the effects of intrauterine exposure.