# Vitamin D during pregnancy in relation to childhood growth, overweight and obesity

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“The greatest gift we could give the next generation is to improve the nutrition and growth of girls and young women”
David Barker

# Abstract

The aim of this thesis is to investigate the association between maternal vitamin D intake and status in pregnancy and the child´s growth and risk of overweight and obesity in childhood. Data from the Norwegian Mother, Father and Child Cohort Study (MoBa) and the Swedish GraviD study were used in **Paper I-IV** and **Paper III-IV**, respectively.

**Paper I** include investigations of vitamin D status and its determinants, and vitamin D intake. Overall, 48% of women had vitamin D insufficiency and 61% had a vitamin D intake below the recommended 10 µg/day. Higher vitamin D status was associated with higher vitamin D intake, blood sampling between spring to autumn, use of solarium, higher education and age, origin from high income country, lower pre-pregnancy body mass index (BMI), and not smoking during pregnancy. In **Paper II**, we investigated the associations between maternal vitamin D intake and childhood growth and risk of overweight from birth up to 8 years. Among mothers with normal pre-pregnancy BMI, a vitamin D intake ≥10µg/day was associated with lower weight growth trajectories during infancy and with child overweight in preschool years. The results indicated associations in opposing directions in children of mothers with pre-pregnancy overweight or obesity. In **Paper III**, we investigated the association between maternal vitamin D status and classes of infant BMI growth trajectories up to 2 years of age. Lower maternal vitamin D status was associated with a higher BMI growth trajectory class during the first 2 years of life in MoBa, but not in GraviD. In **Paper IV**, we investigated the association between maternal vitamin D status and the child´s BMI and risk for overweight at 5 years of age. Low maternal vitamin D status was associated with lower childhood BMI, but not with overweight.

Compilation of the scientific literature indicate that maternal vitamin D intake and status during pregnancy may play a role in childhood growth and risk of overweight or obesity. However, there is not sufficient evidence to conclude if the associations are causal. If there is a causal effect of maternal vitamin D status on childhood growth or risk of overweight and obesity, it is likely small and with no clinically important effect.

**Keywords:** Vitamin D, 25OHD, pregnancy, child, growth, overweight

# Sammanfattning på svenska

Syftet med den här avhandlingen är att undersöka sambandet mellan mammans D-vitaminintag och status under graviditeten och barnets tillväxt och risken för övervikt och fetma under barndomen. Data från Den norske mor, far og barn-undersøkelsen (MoBa) och den svenska GraviD-studien användes i **delarbete I-IV** respektive **delarbete III-IV**.

I **delarbete I** undersöktes D-vitamintstatus och dess determinanter, samt D-vitaminintag. Totalt hade 48% av kvinnorna en otillräcklig D-vitaminstatus och 61% hade ett D-vitaminintag under det rekommenderade intaget på 10 µg/dag. Högre D-vitaminstatus var associerat med bland annat ett högre D-vitaminintag, vår- till höstsäsong, solarieanvändning, högre utbildning och ålder, ursprung från ett höginkomstland, lägre body mass index (BMI) före graviditeten samt att inte röka under graviditeten. I **delarbete II** undersöktes sambandet mellan mammans D-vitaminintag och barnets tillväxt och risken för övervikt från födseln upp till 8 års ålder. Bland kvinnor med ett normalt BMI före graviditeten var ett D-vitaminintag ≥10µg/dag associerat med en lägre vikttillväxtkurva under spädbarnsåren och lägre risk för övervikt under förskoleåldern. Hos barn till kvinnor med övervikt eller fetma innan graviditeten verkade sambanden gå i motsatt riktning. I **delarbete III** undersöktes sambandet mellan mammans D-vitaminstatus och barnets BMI-tillväxtkurva under spädbarnsåren. En lägre D-vitaminstatus var associerat med en högre BMI-tillväxtkurva upp till 2 års ålder i MoBa men inte i GraviD. I **delarbete IV** undersöktes sambandet mellan mammans D-vitaminstatus och barnets BMI och risk för övervikt vid 5 års ålder. En lägre D-vitaminstatus hos mamman var associerat med ett lägre BMI hos barnet, men inte med övervikt.

Sammanställning av den vetenskapliga litteraturen indikerar att det kan finnas ett samband mellan mammans D-vitaminintag eller status under graviditeten och barnets tillväxt och risken för övervikt eller fetma i barndomen. Det finns emellertid inte tillräcklig evidens för att säkerställa att sambanden är kausala. Om det finns ett kausalt samband mellan mammans D-vitaminstatus och barnets tillväxt eller risken för övervikt och fetma är det sannolikt svagt och utan klinisk relevans.

# List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Amberntsson A, Bärebring L, Winkvist A, Lissner L, Meltzer HM, Brantsæter AL, Papadopoulou E, Augustin H.

*Vitamin D intake and determinants of vitamin D status during pregnancy in the Norwegian Mother, Father and Child Cohort Study*

Under review

II. Amberntsson A, Papadopoulou E, Winkvist A, Lissner L, Meltzer HM, Brantsaeter AL, Augustin H.

*Maternal vitamin D intake and BMI during pregnancy in relation to child's growth and weight status from birth to 8 years: a large national cohort study.*

BMJ Open. 2021 Oct 1;11(10):e048980.

III. Amberntsson A, Bärebring L, Winkvist A, Lissner L, Meltzer HM, Brantsæter AL, Papadopoulou E, Augustin H.

*Maternal vitamin D status in relation to infant BMI growth trajectories up to 2 years of age in two prospective pregnancy cohorts.*

Obes Sci Pract. 2022 Apr 8;8(5):670-681.

IV. Amberntsson A, Bärebring L, Winkvist A, Lissner L, Meltzer HM, Brantsæter AL, Papadopoulou E, Augustin H.

*Maternal vitamin D status and risk of childhood overweight at 5 years of age in two Nordic cohort studies*

Under review

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# Abbreviations

| | |
|---|---|
| **1,25OH2D** | 1,25-dihydroxyvitamin D |
| **25OHD** | 25-hydroxyvitamin D |
| **AR** | Average requirement |
| **BMI** | Body Mass Index |
| **CI** | Confidence interval |
| **CRP** | C-reactive protein |
| **DEQAS** | Vitamin D External Quality Assessment Scheme |
| **DNA** | Deoxyribonucleic acid |
| **DXA** | Dual-energy x-ray absorptiometry |
| **EFSA** | The European Food Safety Authority |
| **FFQ** | Food frequency questionnaire |
| **IOM** | The Institute of Medicine |
| **IOTF** | The International Obesity Task Force |
| **LC-MS/MS** | Liquid chromatography-tandem mass spectrometry |
| **LI** | Lower intake level |
| **MD** | Mean difference |
| **MoBa** | The Norwegian Mother, Father and Child Cohort study |
| **n-3 PUFA** | Omega-3 poly unsaturated fatty acids |
| **NNR** | The Nordic Nutrition Recommendations |
| **PTH** | Parathyroid hormone |
| **RI** | Recommended intake |
| **SD** | Standard deviation |
| **UL** | Upper intake level |
| **UV-B** | Ultra-violet B |
| **VDBP** | Vitamin D binding protein |
| **VDR** | Vitamin D receptor |
| **VDSP** | Vitamin D Standardization Program |
| **WHO** | The World Health Organization |

# Introduction

Vitamin D is a nutrient found in very few foods naturally. Although vitamin D also is dermally produced after ultra-violet B-radiation of the skin, insufficiency is common worldwide. Vitamin D regulates the calcium homeostasis in the human body and prolonged deficiency can cause the bone disorders osteomalacia and rickets. However, after discovery of the vitamin D receptor in tissues and organs without connection to calcium regulation, the role of vitamin D for other health outcomes has been extensively studied.

Pregnancy is a vulnerable period of rapid growth and development for both mother and fetus. Nutrient deficiencies during this time period may cause life-long consequences for the child. It has been suggested that maternal vitamin D deficiency during pregnancy may affect the health of the fetus; effects that may continue even later in life.

# Aim

The overall aim was to investigate the association between maternal vitamin D intake and status in pregnancy and the child´s growth and risk of overweight and obesity in childhood. The specific aims of Paper I-IV were:

I. To evaluate total vitamin D intake from both diet and supplements, to investigate determinants of vitamin D status and the predicted response in vitamin D status by total vitamin D intake.

II. To examine the associations between maternal vitamin D intake and childhood weight and height growth trajectories and velocities, rapid growth, and risk of overweight up to 8 years of age. Further, to examine possible effect modification by maternal pre-pregnancy body mass index (BMI).

III. To examine the association between maternal vitamin D status and class of infant BMI growth trajectory during the first 2 years of life.

IV. To examine the association between maternal vitamin D status and the child´s BMI and risk of overweight at 5 years of age.

# Vitamin D

In the 17th century, rickets was a common disease among children living in industrialized cities in Northern Europe [1, 2]. The disease was characterized by deformations of the bone, restricted growth, and muscle weakness, caused by a defect bone mineralization. In 1822, sun exposure was found to prevent and cure rickets, but it was not until 100 years later that the aetiology of rickets was concluded. By then, it was also discovered that cod liver oil could treat the disease. This led to the 1930's discovery of a new nutritional factor, called vitamin D [1, 2].

One important role of vitamin D in the body is to regulate calcium and phosphorus homeostasis, a process that is essential for normal mineralisation of the bone [3]. Vitamin D acts in target tissues by binding to a vitamin D receptor. This receptor has been found in most tissues and organs in the human body, suggesting a role of vitamin D beyond bone health [4, 5]. Vitamin D deficiency causes poor mineralization of the bone, eventually leading to rickets or osteomalacia [6]. Deficiency has also been associated with increased risks of several diseases e.g. cardiovascular diseases and some cancers [7], and with gestational complications, e.g. pre-eclampsia, gestational diabetes, and impaired fetal growth [8, 9].

## Metabolism

Vitamin D is a micronutrient and pro-hormone with steroid-like molecule structure [10]. The term vitamin D is generic and refers to the two isomers: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). The chemical structures of these metabolites is presented in **Figure 1A-B** [3]. Vitamin D2 is mostly present in plant foods, while vitamin D3 is mostly present in animal foods. In addition, vitamin D3 can be synthesised by the human skin, a biological process induced by skin exposure to ultra-violet B (UV-B) radiation [3]. During exposure to UV-B rays of wavelength 290-315 nm, 7-dehydrocholesterol that is present in the plasma membrane in the human skin is photo-conversed into pre-vitamin D3, and rapidly further transformed into vitamin D [3, 7]. It is released from the membrane into the extracellular space, further drawn into the circulation. UV-B rays are provided from both the sun and artificially in some solariums.

When skin is exposed to UV-B rays for some time, vitamin D3 converts into less active metabolites, preventing toxic levels of vitamin D through dermal production [6].

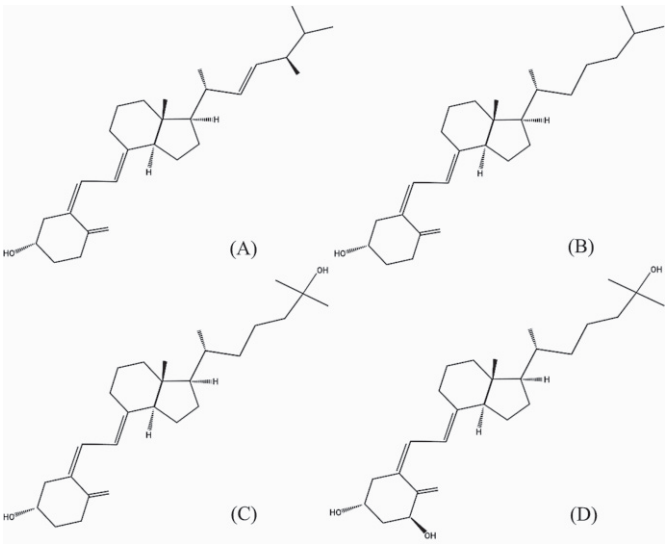


**Figure 1.** Chemical structures of the vitamin D metabolites: (A) vitamin D2, (B) vitamin D3, (C) 25-hydroxyvitamin D, and (D) 1,25-dihydroxyvitamin D. Created with BioRender.com.

After ingestion from foods or supplements, vitamin D is integrated into chylomicrons and absorbed through diffusion in the small intestine into the lymphatic system [11]. Vitamin D metabolites are fat-soluble, thereby lipophilic and is predominantly bound to a binding protein in the circulation. When entered the blood stream, either from the gut or after dermal synthesis, vitamin D binds to the vitamin D binding protein (VDBP), the main carrier of all vitamin D metabolites. Vitamin D is then transported to either the liver or to storage tissues, including the adipose tissue. In the liver, vitamin D is hydroxylated by the enzyme 25-hydroxylase into the biologically inactive metabolite 25-hydroxyvitamin D (25OHD, **Figure 1C**). Depending on the source of vitamin D, either 25OHD2 (from dietary vitamin D2) or 25OHD3 (from dietary vitamin D3 or UV-B radiation) is formed. 25OHD then binds to VDBP or albumin for transportation. The hydroxylation of vitamin D to 25OHD is unregulated. To be biologically active, a second hydroxylation is required. 25OHD is transported to the kidneys, where it is hydroxylated by the enzyme 1-α hydroxylase into the hormone 1,25-dihydroxyvitamin D (1,25OH2D, **Figure 1D**).

The conversion of vitamin D into 1,25OH2D occur within a few hours after ingestion or synthesis in the skin. Some other organs, such as bone cells, parathyroid cells, and the placenta can also hydroxylate 25OHD into 1,25OH2D. 1,25OH2D is also transported in the circulation by VDBP or albumin. To exert its biological functions, 1,25OH2D must bind to vitamin D receptors (VDR), which are located mostly in the intestinal enterocytes, renal distal tubules, osteoblasts, and pancreatic islets [3]. VDRs have also been found in the cardiovascular system, immune system, central nervous system, reproductive system, pancreas, skeletal muscle, and lung cells [7], suggesting wide metabolic functions of 1,25OH2D. The storage tissues of vitamin D and its metabolites include adipose tissue, muscles, and liver [7, 12]. An overview of the synthesis and metabolism of vitamin D is presented in **Figure 2**.

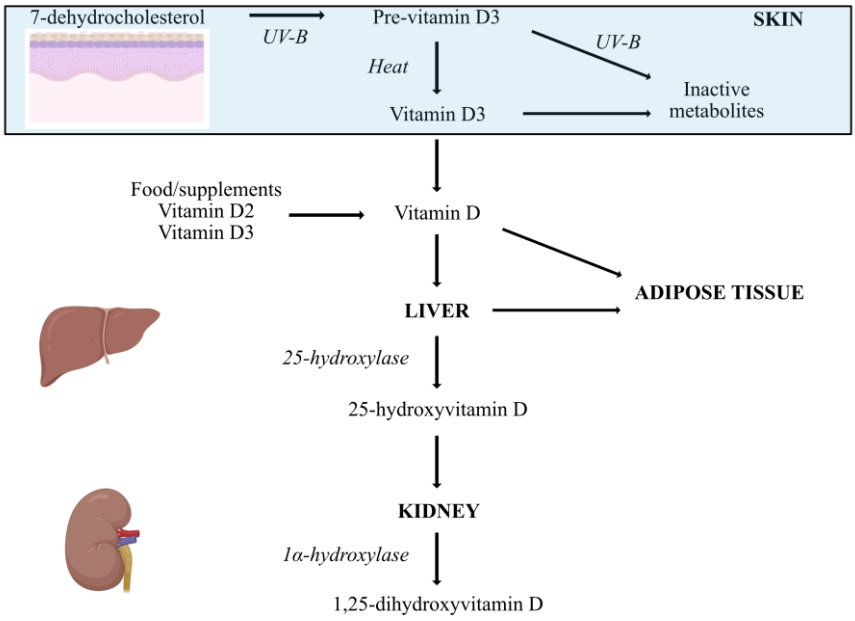


**Figure 2.** Synthesis and metabolism of vitamin D. Abbreviations: UV-B; ultraviolet B rays

The half-lives of vitamin D metabolites are a few weeks for 25OHD; 12-24 hours for vitamin D; and only a few hours for 1,25OH2D [11, 13]. The half-life depends on each metabolites' affinity for VDBP [11]. All metabolites of vitamin D are finally eliminated through the bile into feces, and only a minor part through urine [11].

## Vitamin D and bone mineral homeostasis

The main role of 1,25OH2D, is to regulate homeostasis of the bone minerals calcium and phosphate, together with parathyroid hormone (PTH), fibroblast growth factor, and calcitonin [14]. When circulating calcium concentrations falls below normal concentrations, a series of events occur to restore and maintain it within the normal range. Firstly, PTH is released from the parathyroid glands. This stimulates the hydroxylation of 1,25OH2D from 25OHD in the kidney, which in turn stimulates the renal calcium reabsorption [3]. Further, 1,25OH2D binds to VDRs in the small intestine, which stimulates the absorption of calcium and phosphorus through the intestinal wall by increasing the production of calcium channels and calcium binding protein. In the bone, PTH and 1,25OH2D interact and stimulate the osteoclasts to release stored calcium and phosphate in the bone into the circulation. There is a negative feedback loop in the calcium homeostasis where high concentrations of 1,25OH2D increase production of inactive vitamin D metabolites and lower concentrations of PTH [3].

While 1,25OH2D and PTH act by increasing concentrations of calcium, the hormone calcitonin decreases calcium concentrations [3]. Calcitonin is released in response to elevated calcium concentrations. It acts by stimulating the osteoblasts to deposit calcium in bone, inhibiting calcium reabsorption in the kidneys and absorption in the intestine, and increasing urinary calcium excretion.

By its involvement in calcium homeostasis, 1,25OH2D is essential for normal mineralisation of the bone. Low concentrations of 25OHD is associated with an impaired bone mineral density and can lead to rickets in children and osteomalacia in adults [2]. The precise threshold when rickets start developing is uncertain, but 25OHD concentrations <27.5 nmol/L [15] and <37.5 nmol/L [2] have been suggested. Rickets is characterised by skeletal deformities and growth retardation, while osteomalacia is characterized by diffuse pain in muscles and bone and muscle weakness. Vitamin D deficiency can occur if both sun exposure and dietary vitamin D intake is low. Furthermore, vitamin D supplementation combined with calcium is also associated with lower risk of total fracture, hip fracture, and falls in elderly [16].

## Vitamin D beyond bone health

Except for bone, intestine, and kidney, the main locations of vitamin D action include the immune system and pancreas.

Vitamin D seems to be an immunomodulator [17] and the importance of vitamin D in the innate immune response has been highlighted [18]. Also, vitamin D helps maintain normal levels of blood glucose, by activating the VDR in the pancreatic beta cells, thereby regulating insulin response to blood glucose [19, 20]. Insufficient concentrations of vitamin D has a potential role in development of several diseases, such as cardiovascular diseases, autoimmune diseases, and certain cancers [7].

Vitamin D may also have a role in preventing adverse maternal and pregnancy outcomes such as preeclampsia and gestational diabetes [9] and help regulate placental development and function [5, 21]. The VDR is expressed in both placenta and decidua [5, 22]. In the fetus, 1,25OH2D regulates calcium homeostasis, but may also affect development of the immune system by its immunomodulatory properties [23], and take part in regulation of the fetal organ development [24, 25]. The role of vitamin D during pregnancy for postnatal growth, overweight and obesity is further elaborated in the chapter *Maternal vitamin D and postnatal growth*.

## Vitamin D metabolism during pregnancy

During pregnancy, there are considerable changes to the maternal calcium metabolism [26, 27]. Maternal intestinal calcium absorption increases, as does osteoclastic activity, allowing for enhanced calcium mobilisation from maternal bone. Simultaneously, maternal calcium concentrations in serum remain stable. These alterations allow for accumulation of calcium within the fetal skeleton, particularly during the third trimester. The fetal calcium requirement increases from around 2 mg/day in early pregnancy to 100 mg/day in late pregnancy and during lactation.

Maternal concentrations of 1,25OH2D increase 2–3 fold in the first weeks of pregnancy and continues to increase throughout pregnancy. The increase is mainly driven by enhanced activity of the enzyme 1-α-hydroxylase in maternal kidneys and placenta, stimulating the synthesis of 1,25OH2D [26]. There is also a rise in VDBP, although not to the same degree as 1,25OH2D. PTH remains within the non-pregnant range throughout pregnancy. The increase in 1,25OH2D during pregnancy is dependent on the availability of 25OHD. However, the rise in 1,25OH2D in pregnancy seems not entirely related to the calcium regulation [9, 28]. Instead, it is suggested that 1,25OH2D play a role as an immunomodulator in early pregnancy, to prevent fetal rejection [22, 26, 29]. After delivery, maternal concentrations of 1,25OH2D return to pre-pregnancy levels.

How maternal 25OHD concentrations change during pregnancy is not entirely known as studies have yielded conflicting results [26, 27]. In the Swedish GraviD study, season-corrected 25OHD increased by 11 nmol/L from early to late pregnancy [30]. In contrast, another longitudinal study conducted in Spain found a consistent decrease in 25OHD concentration between first and third trimester, independent of season [31]. During pregnancy, the fetus is dependent on the mother for 25OHD, which can cross the placenta. 1,25OH2D is synthesized from 25OHD by the fetus already in gestational week 6–10 and circulates in fetal blood at around 50% of maternal concentration [24]. Maternal and umbilical cord 25OHD concentrations correlate, and cord blood concentrations are around 70–100 % of maternal concentrations [24].

## Vitamin D status

There is consensus that serum concentrations of the metabolite 25OHD is the best available indicator of vitamin D status [15, 32, 33]. It is considered suitable due to its relatively long half-life, that its levels are not much regulated by other factors, and that it reflects both vitamin D intake from foods and supplements and dermal synthesis. Total 25OHD is used, including both $25OHD_2$ and $25OHD_3$, assuming equal biological value [34]. Concentrations of 25OHD depend on both internal and external factors, and it is the major circulating form of vitamin D. 25OHD is stable in serum, even after long periods in room temperature [35].

### Recommendations of vitamin D status

The American Institute of Medicine (IOM) define a serum 25OHD concentration >50 nmol/L as vitamin D sufficiency, a concentration of 30–50 nmol/L as vitamin D insufficiency, and <30 nmol/L as vitamin D deficiency [33] (**Table 1**). The cut-offs apply to all stages of the life cycle, including pregnancy. The limits were selected based on evidence of vitamin D for prevention of rickets, osteomalacia and risk of fractures. The IOM cut-offs were supported by several organisations, such as the Global Consensus Recommendations on Prevention and Management of Nutritional Rickets [34] and the Nordic Nutrition Recommendations 2012 (NNR) [15]. NNR is the reference document providing scientific evidence of dietary guidelines for the Nordic countries. The Endocrine Society define vitamin D sufficiency as 25OHD >75 nmol/L, vitamin D insufficiency as 50-75 nmol/L and deficiency as <50 nmol/L [32].

These cut-offs were based on the associations between 25OHD and PTH, lower risk of fractures, and increased calcium absorption [32]. The European Food Safety Authority (EFSA) does not define cut-offs for deficiency but has identified a target value of 25OHD at 50 nmol/L to be used when deriving dietary reference values in both adults, infants, children, and pregnant women [36]. This target value was based on evidence for increased risk of adverse musculoskeletal health outcomes and adverse pregnancy-related health outcomes below this concentration.

**Table 1.** Overview of definitions of vitamin D deficiency, insufficiency, and sufficiency.

| | Deficiency | Insufficiency | Sufficiency |
|---|---|---|---|
| **Institute of Medicine [33]** | <30 nmol/L | 30-50 nmol/L | >50 nmol/L |
| **Nordic Nutrition Recommendations [15]** | <30 nmol/L | 30-50 nmol/L | >50 nmol/L |
| **The Endocrine Society [32]** | <50 nmol/L | 50-75 nmol/L | >75 nmol/L |

The absence of a global consensus regarding the definition of sufficient vitamin D status might partly be explained by the variability in 25OHD assay methods and laboratories [37]. Sempos et al. concluded that even within the golden standard method liquid chromatography-tandem mass spectrometry (LC-MS/MS), analysis results are not necessarily neither accurate nor precise [37]. Variability in 25OHD concentrations makes it hard to draw conclusions, even from meta-analyses, and reach consensus regarding optimal 25OHD concentrations.

## Recommendations of vitamin D status during pregnancy

Although there is variation between recommendations from the IOM, the NNR, and the Endocrine Society, the recommendations are all formulated based on evidence from clinical trials of vitamin D status and skeletal outcomes. Due to lack of further evidence, the recommendations for vitamin D are all the same for pregnant and lactating women as for non-pregnant adults. It is possible that a vitamin D status higher than the current recommendations would favour the pregnant woman and her child. In a review from 2022, 25OHD concentrations >100 nmol/L in pregnant women were found to be preventive of respiratory and autoimmune diseases in the child [38]. However, the World Health Organization (WHO) only recommends vitamin D supplementation in pregnant women with vitamin D deficiency, and not as part of routine antenatal care [39, 40]. Thus, further studies are needed to conclude the optimal vitamin D concentration during pregnancy for both prenatal and postnatal outcomes.

## Effect of vitamin D intake on 25OHD concentration

Intervention studies have reported different dose-response relationships between vitamin D intake from supplements and vitamin D status. Most studies have found a positive linear relationship between vitamin D intake and response in 25OHD, but some studies have also found a negative response or no change in 25OHD concentration [41]. Studies indicating a positive association between vitamin D intake and 25OHD concentration also show an eventual plateau in the dose-response relationship in different populations [42, 43] (**Paper I**). The concentration where this plateau occurs varies between 20-50 µg/day.

## Vitamin D status globally

Globally, concentrations of 25OHD <50 nmol/L are common [44]. In 2011, Shoor and Lips mapped current global 25OHD data and found suboptimal concentrations of 25OHD worldwide [45]. The authors identified the Middle East and Asia as regions where risk of vitamin D deficiency was especially high. In 2014, Palacios and Gonzales confirmed that vitamin D deficiency was a public health issue in all regions and age groups globally [46]. However, data on vitamin D status were lacking in South America and Africa. In 2016, a study was conducted in 14 European study populations, including 55,844 children and adults. After standardization of the data, 13.0% had 25OHD concentrations <30 nmol/L and 40.4% had concentrations <50 nmol/L [47]. Stratified by season, 17.7% had 25OHD concentrations <30 nmol/L during October to March and 8.3% during April to November.

## Vitamin D status in pregnancy

Pregnancy has been identified as a period of high risk of vitamin D deficiency [45, 48]. Globally, 25OHD concentrations <30nmol/L during pregnancy has been found in 4-23% in Europe, 15% in Australia, 38-50% in Middle East, and 45-60% in South Asia, including studies conducted between 2003-2013 [46]. Another systematic review and meta-analysis of studies reporting vitamin D status in pregnant populations between 1959–2014 found 25OHD concentrations <25 nmol/L in 2–20% in America, 20–40% in Europe, 40–96% in the Eastern Mediterranean, and 5–61% in the Western Pacific region [48] (**Figure 3)**. Within Europe, 25OHD concentrations are higher in Northern compared with Southern Europe and higher in Western compared with Eastern Europe [45]. Suggestively, this might be due to higher intake of fatty fish and fish liver oil in Northern Europe, and more skin pigmentation and sun avoiding behaviour in Southern Europe.


**Figure 3.** Prevalence (%) of 25OHD concentration <50 nmol/L (grey numbers) and <25 nmol/L (black numbers) in pregnant women between 1959-2014 from Saraf [48].

In the Nordic countries, concentrations of 25OHD varied from 47-75 nmol/L in Denmark [49-51], 41-89 nmol/L in Finland [52, 53], 51-66 nmol/L in Norway [54, 55] (**Paper III**), and 47-65 nmol/L in Sweden [30, 56, 57]. Prevalence of vitamin D insufficiency (25OHD <50 nmol/L) varied from 14-50% in Denmark [49, 51], to 1-77% in Finland [52, 53], 36-50% in Norway [54] (**Paper III**), and 25-65% in Sweden [30, 56] (**Paper III**). The studies with the highest prevalence of vitamin D insufficiency were conducted with small study populations. When only studies with >200 participants are included, the prevalence of 25OHD <50 nmol/L does not exceed 48% in any Nordic country. Differences in prevalence of vitamin D insufficiency between studies can partly be explained by methodological differences in assessment methods and variation in individual factors such as country of origin. Since it is unknown how concentrations of 25OHD change during pregnancy, the time point of measurement of 25OHD might contribute to differences in 25OHD concentrations between studies. In addition, as vitamin D status in the Nordic countries follow a seasonal variation [30, 58], season at blood sampling will also affect the 25OHD concentrations.

## Determinants of vitamin D status

The major determinants of vitamin D status are sun exposure and vitamin D intake from foods and supplements [59]. Dermal sun exposure is the most important determinant of 25OHD concentration for most individuals [60]. The basic requirement of vitamin D can be met solely by sun exposure. As little as 7–36 minutes (depending on skin pigmentation) of sunshine exposure will produce the daily need of vitamin D during summer months in the Nordic countries (62,5° N) [61]. Thereby, factors affecting sun exposure i.e., season, latitude, recent travels to sunny climates [60], sun-seeking behaviour and clothing style [30] will also affect vitamin D status.

The amount of synthesized vitamin D in the skin will be influenced by anything that either affect UV-B irradiation or the amount of 7-dehydrocholesterol in the skin [7]. Vitamin D cannot be synthesized all year round in countries above latitude 35° North (N) [10], such as the Nordic countries (55°–72° N). Mean monthly UV-B doses over a typical year were modelled and applied to a selection of European countries in a study from O´Neil et al. [62]. In Finland (60–67° N) and Denmark (56° N), vitamin D could be synthesized from April to September, while from April to August in Iceland (64° N). Within Norway, vitamin D could be synthesized from April to September in Oslo (60° N), but only from May to August in Tromsø (69° N) [62].

Except for latitude and season, other individual factors affecting dermal capacity to synthesize 25OHD is age [63] and skin pigmentation [64]. More melanin in the skin requires longer exposure to UV-B rays to produce the same amount of vitamin D as skin with less melanin [64]. In a Swedish study, the overall prevalence of vitamin D deficiency among pregnant women was 10%, but 51% among women born in Africa and 46% among women born in Asia [30]. Similar findings were obtained in a Norwegian study, where the prevalence of 25OHD <25 nmol/L was 1.3% in women from Western Europe and 2.5% in women from East Asia, but as high as 45% among women from South Asia, 40% among women from the Middle East, and 26% among women from Sub-Saharan Africa [55]. Thus, ethnicity can be a risk factor for 25OHD <30 nmol/L. In addition, time spent indoors, and covered clothing will restrict the dermal production of vitamin D. The amount of 7-dehydrocholesterol in the skin declines by age, leading to a lower capacity to synthesize vitamin D later in life [63].

BMI is also a determinant of 25OHD concentration [65]. An inverse association has been reported between adiposity and 25OHD concentration [66]. Available evidence suggests that increased fat mass is a cause of low 25OHD concentration, rather than a consequence [66, 67]. A smaller response in 25OHD after supplementation with vitamin D has been found in individuals with obesity compared with normal weight [68]. There are several suggested mechanism for this relationship, including sequestration of vitamin D in the body fat [69], volumetric dilution of vitamin D in larger body mass [70], and behaviour-related alterations in sun exposure, in individuals with obesity [71]. The mechanism is currently not fully understood and whether individuals with obesity could benefit from a higher recommended intake of vitamin D is unclear.

### *Determinants of vitamin D status during pregnancy*

Determinants of 25OHD concentration in pregnancy might not differ from those in non-pregnant individuals [72]. However, gaining less weight, having a higher baseline 25OHD, delivering in summer, higher maternal age, and supplementation have been independently related to a higher 25OHD concentration in late pregnancy in a study from the United Kingdom [72]. Among pregnant women in the Nordic countries, 25OHD concentration has been associated with vitamin D intake from foods and supplements, sun exposure, outdoor physical activity, solarium use, smoking during pregnancy, season, gestational week, education, age, country of origin, parity, and pre-pregnancy BMI [30, 49, 50, 56, 57, 73] (**Paper I**).

## Vitamin D intake

### Recommendations of vitamin D intake

Equal to the lack of consensus of the definition of sufficient vitamin D status, different authorities have different recommended intakes (RI), as shown in **Table 2**. The IOM set the average requirement (AR) to 10 µg/day and the RI to 15 µg/day for adults, including during pregnancy [33]. EFSA sets the average intake for vitamin D at 15 µg/day, as the available evidence did not allow for determining an AR [36]. This average intake assumes minimal contribution of vitamin D from dermal production. Under conditions when dermal vitamin D can be produced, requirement of vitamin D intake is lower, maybe even zero [36]. The Endocrine Society has set the RI of vitamin D to 15 µg/day, including in pregnancy [32].

**Table 2.** Recommended intake of vitamin D from different authorities.

| | Recommended intake for adults (including in pregnancy) |
|---|---|
| **Institute of Medicine [33]** | 15 µg/day |
| **Nordic Nutrition Recommendations [15]** | 10 µg/day |
| **Endocrine Society [32]** | 15 µg/day |

In NNR 2012, the RI of vitamin D for adults, including during pregnancy, was 10 µg/day [15]. This RI considers contribution of dermally produced vitamin D from late spring to early autumn. For people with little or no sun exposure, and people >75 years of age, an intake of 20 µg/d is recommended. The AR was based on supplemental studies, showing that a dose of 7.2 µg/day would maintain a mean 25OHD concentration during winter at about 50 nmol/L. The AR was thereby set at 7.5 µg/day [15]. The cut-off for the lower intake level (LI) was set to 2.5 µg/day, based on intervention studies indicating that this dose would maintain 25OHD concentrations around 30 nmol/L also during winter. The upper intake level (UL) was based on the current cut-offs recommended by EFSA [74]. For individuals >11 years of age, the UL is set at 100 µg/day, which is the same cut-off set also by the IOM [33].

## Sources and intake of vitamin D

The absorption of vitamin D from a normal diet is on average 80%, but varies between 55-99% [36]. Data on factors that affect absorption of vitamin D metabolites are scarce, but the absorption is likely more efficient in the presence of lipids, while the food matrix has limited effect on vitamin D bioavailability [75, 76]. The absorption of vitamin D likely decrease with increasing dose [75].

Few foods naturally contain significant amounts of vitamin D (**Table 3**). Most vitamin D rich foods are of animal origin [6]. Oily fish such as herring, mackerel, and salmon have a high content of vitamin D. Some lean fishes, such as tuna and cod, but also egg yolk and certain mushrooms also contain some vitamin D [6]. Meat and meat products, especially liver, contain a smaller amount of vitamin D. Such foods of animal origin also contain different concentrations of the metabolite 25OHD, which also contribute to the total vitamin D intake [77].

**Table 3.** Vitamin D content in some non-fortified foods from The Swedish Food Agency's food database [a]

| Foods | Vitamin D (µg/100g) |
|---|---|
| **Herring, mackerel** | 5.4-5.8 |
| **Salmon, farmed** | 7.4 |
| **Tuna** | 4.2 |
| **Cod** | 1.8 |
| **Egg, whole** | 3.7 |
| **Champignon** | 0.2 |
| **Chanterelle** | 15.4 |
| **Chicken** | 1.5 |
| **Pork** | 0.6 |
| **Beef** | 0.2 |
| **Liver (beef, pork, chicken)** | 0.1-0.4 |

a Database version 2022-05-24

Because of the few natural vitamin D rich foods, some countries have policies regarding food fortification with vitamin D. For example, in Canada, there is mandatory vitamin D fortification of milk and margarine [78, 79]. In the United States, cow´s milk, plant-based milk, some breakfast cereals, orange juice, yogurt, and margarine are voluntarily fortified with vitamin D [78, 79]. Milk, sour milk, yoghurt, and different types of fat spreads are commonly fortified with vitamin D in the Nordic countries [80]. In Sweden, fortification with vitamin D is mandatory, while in the other Nordic countries, fortification is voluntary or recommended [80] (**Table 4)**.

**Table 4.** Vitamin D fortification policies in the Nordic countries

| Country | Type of foods | Amount of vitamin D |
|---|---|---|
| Sweden | Milk <3% fat, including lactose-free and plant-based alternatives<br>Sour milk <3% fat, including lactose-free and plant-based alternatives<br>Margarine, fat spreads and fluid margarine | 0.95–1.10 µg/100 g<br>0.75–1.10 µg/100 g<br>19.5–21.0 µg/100 g |
| Norway | Low-fat milk, including lactose-free milk<br>Margarine and butter | 0.4 µg/100 g<br>10 µg/100 g |
| Finland | Milk, yoghurt, and sour milk<br>Margarine and fat spreads (not butter) | 1 µg/100 g<br>20 µg/100 g |
| Denmark | - | - |
| Iceland | - | - |

From each country's latest national dietary survey, the median vitamin D intake from foods (not including supplements) in men and women were 11.2 µg/day in Finland [81], 5.7 µg/day in Sweden [82], 4.9 µg/day in Iceland [83], 4.6 µg/day in Norway [84], and 3.3 µg/day in Denmark [85]. The major food sources of vitamin D in the Nordic countries from the latest national dietary surveys among adults are presented in **Figure 4**.

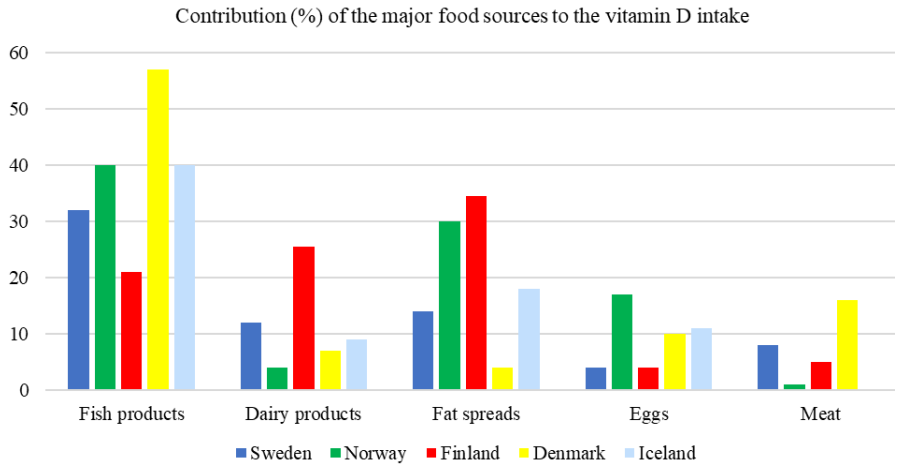


**Figure 4.** Contribution of the major food sources to total vitamin D intake among adults in the Nordic countries [81, 82, 84, 85].

Supplements are also a common source of vitamin D [6]. Both vitamin D2 and vitamin D3 are used in supplements. How much supplements contribute to the total vitamin D intake varies between countries. In Finland, 57% of women and 40% of men used vitamin D supplements in 2017 [81]. In Norway, 40% of men and women reported use of vitamin D supplements in 2010–2011 [84]. In Sweden, 27 % of women and 15% of men reported supplement use, of which 25-30% contained vitamin D, in 2010-2011 [82]. In Denmark, 83% of all women and 54% of all men used a vitamin D containing supplement in 2011-2013 [86]. In Iceland, 55% of all women and men reported use vitamin D supplements in 2010–2011 [83].

## Vitamin D intake in pregnancy

Vitamin D intake during pregnancy differ between countries. In a study of 2,251 pregnant women living in Camden, United States, between 1996-2006, mean vitamin D intake was 4.8 µg/day from diet and 5.5 µg/day from supplements, adding up to a total of 10.3 µg/day [87]. In another study from 1999 to 2002 conducted in Massachusetts, United States, mean vitamin D intake from foods was 5.6 µg/day and 8.0 µg/day from supplements, adding up to a total of 13.7 µg/day [88]. In a study on 439 pregnant women living in New Zealand, mean vitamin D intake from both foods and supplements was 2.1 µg/day in both mid and late pregnancy [89]. The use of supplements in this study was overall very low. A systematic review and meta-analysis of studies on dietary intake in pregnant women living in developed countries found that vitamin D intake differed by geographical region, but not by socioeconomic status or dietary assessment method [90]. Median vitamin D intakes from food were 5.7 µg/day in Canada and the United States, 2.2 µg/day in the United Kingdom, 3.6 µg/day in European countries, 1.3 µg/day in Australia and New Zealand, and 5.7 µg/day in Japan. Another study conducted in 239 pregnant women in Cape Town, South Africa, found a median vitamin D intake of 4.0 µg/day from foods, not assessing vitamin D supplement use [91].

The vitamin D intake during pregnancy differ also between the Nordic countries. In Sweden, mean vitamin D intake from foods was 6.1 µg/day and total vitamin D intake was 9.3 µg/day in a study on pregnant women in 2008-2011 [56]. Of the 95 participants, 56% were taking vitamin D supplements. Similar intakes were found in a study from 2006-2009 [92]. In a more recent Swedish study, median intake of vitamin D from foods were around 5 µg/day assessed by food record and a food frequency questionnaire (FFQ) in 2013-2014 [93]. In total, 44% of all women used a vitamin D supplement. New fortification policies were adapted in Sweden in 2018, where more food items were mandated to be fortified and with higher amounts of vitamin D. Therefore, the current vitamin D intake might be higher than previously estimated. However, no new studies have investigated the current vitamin D status or intake in either pregnant women or other populations in Sweden. In Norway, the median vitamin D intake in pregnancy from supplements was 5.2 µg/day, and the total vitamin D intake was 8.3 µg/day, investigated during 2003-2008 (**Paper I**). While 80% of the participants reported vitamin D supplement use, 61% had a total vitamin D intake below the RI. Another study conducted during 2007-2009 in Norway found a mean vitamin D intake from supplements of 5.5 µg/day, and total vitamin D intake at 10.4 µg/day [54]. In Finland, a voluntary fortification policy of all fluid milk products and fat spreads was adapted in 2002 and fortification was further doubled in 2010 [80, 94].

Studies in pregnant women conducted after this has found vitamin D intakes from foods between 6.0-7.8 µg/day and supplemental intake between 2-15 µg/day [95]. The studies have reported a high use of vitamin D supplements, between 72-95%. In Denmark, mean total intake of vitamin D was 9.2 µg/day in the Danish National Birth Cohort, conducted 1996-2002 [96]. However, in the more recent Danish COPSAC2010, mean total vitamin D intake during pregnancy in 2009-2010 was 4.8 µg/day [49]. Thus, when supplements are reported, the vitamin D intake in pregnancy generally meet the recommended 10 µg/day [80]. An overview of the current recommendations of vitamin D supplements in pregnancy in the Nordic countries is provided in **Table 5**.

**Table 5.** Current vitamin D supplementation recommendations during pregnancy in the Nordic countries

| Country | Recommendation |
|---|---|
| Nordic Nutrition Recommendations | - |
| Sweden | Those who do not include fortified products or fish in their diet, or are using concealed clothing should consult with their midwife |
| Norway | 10 µg/day if sun exposure and consumption of vitamin D–rich foods is low |
| Finland | 10 µg/day |
| Denmark | 10 µg/day |
| Iceland | Total intake from diet and supplements should be 15 µg/day |

The main sources of vitamin D during pregnancy differ between countries due to different policies and recommendations regarding both vitamin D supplements in pregnancy and type and amount of vitamin D fortified foods. Few studies have investigated the major contributors to vitamin D intake in pregnancy. In Norway, vitamin D supplements (66%), fish (14%), and fortified margarine (10%) were the main contributors to vitamin D intake in pregnancy (**Paper I**). In Denmark, supplements were the main contributor to the vitamin D intake (61%), followed by fish and seafood, low fat dairy, and egg [96]. In Sweden, the largest food groups contributing with most vitamin D during pregnancy were fish (36%) and fortified products; margarine (16%), milk (10%), and yoghurt/sour-milk (2%) [93].

# The first 1000 days and beyond

The first 1000 days is the period from conception to 2 years of age. It represents a vulnerable period of rapid growth and development. Certain stimuli or exposures that occur during this time can have impact on the individual beyond the perinatal period. Such exposures can produce permanent structural, metabolic, and physiological adaptations, thereby predisposing the individual to cardiovascular, metabolic and endocrine disease in the adult life [97]. This concept was formalized by the epidemiologist David Barker, stating that many non-communicable diseases may originate from the fetal period, referred to as 'the Barker Hypothesis' [98, 99] or 'the Developmental origins of health and disease hypothesis'. Exposures occurring during embryonic and fetal development which leads to adaptations are often referred to as fetal programming [97]. Today, emerging evidence demonstrate that early life environment influences risk of developing non-communicable diseases in later life, also supported by biological evidence from animal experiments [100]. In addition, all growth phases in life are dependent on the previous and growth is strongly genetic [101]. Thus, the first 1000 days represents a critical window of early childhood growth and development with great importance that may also impact health beyond this time.

## Pregnancy

Pregnancy is a unique event with large metabolic adaptions, lasting around 40 weeks. The maternal immune system must balance between allowing the fetus to grow, and still maintain the barricade for pathogens [102, 103]. The uterine environment shifts from proinflammatory in early pregnancy; after the attachment to the uterine wall by the embryonic cytotrophoblast cells, to anti-inflammatory throughout the pregnancy; allowing the fetus to grow, and finally back to proinflammatory to allow the onset of labour. After fertilization, cell division of the egg occurs to form germ layers, creating different types of cells [102, 103]. The placenta regulates nutritional supply from mother to fetus [104]. The placenta is fully functional in gestational week 4, and during gestational week 4-10, the organs of the fetus are formed. By the end of the third month, the fetus is fully formed. Fetal fat cells are developed at around gestational week 14-16 [105].

In the second half of pregnancy, maternal insulin resistance is developed, leading to increased circulating concentrations of glucose and free fatty acids, allowing for greater substrate availability, and increased fetal growth velocity [106]. Macro and micronutrient requirements increase throughout pregnancy to meet the demands of the developing fetus [15].

The WHO provides guidelines on routine antenatal care for pregnant women, in order to prevent pregnancy-related complications [39]. In the guidelines, a healthy diet is recommended to prevent poor pregnancy outcomes such as excessive gestational weight gain and neonatal macrosomia. A nutrient and energy appropriate intrauterine environment is crucial for optimal development and growth of the fetus [107]. Iron and folic acid are the only recommended supplements during pregnancy in well-nourished populations by the WHO [39]. These micronutrients prevent low birth weight and preterm birth in the infant [39]. Vitamin D supplementation in pregnancy is currently not recommended from the WHO [40].

## Fetal programming

Fetal programming is proposed to ensure adaptation to postnatal life and later health [108]. The fetus will develop in accordance with the nutrient supply in utero, with the expectation of being born into a similar environment. If there is a mismatch between fetal and postnatal environments, these adaptations may instead cause an increased risk of diseases later in life [108]. This mismatch is referred to as the 'thrifty phenotype hypothesis' [101, 109].

Epigenetic mechanisms are suggested to be the mechanism behind fetal programming, thereby the link between environmental exposures in utero and health outcomes postnatally. Epigenetics are characterized as changes on the genome without changes to the underlying deoxyribonucleic acid (DNA) sequence [110]. Modifications include methylation, demethylation, histone deacetylation, and increased histone acetylation. The epigenetic changes in the development of obesity may lead to the attachment of methyl groups to the chromosomes [111]. This modification may alter gene expression, resulting in an increased or decreased expression of some genes [111]. During fertilization and the early embryonic time, DNA synthesis is high and therefore prone to modifications in DNA methylation. Modifications can be caused by several exposures such as maternal undernutrition [108] or maternal obesity [112], and may lead to metabolic adaptations in the fetus. This emphasises the importance of embryonic and fetal environment, as programming towards future disease may be founded already during this period [110].

## Childhood growth

Although human growth can be defined most simply as a progressive development and increase in the amount, size, and complexity of cells of an individual, growth is much more than just an increase in body mass over time. The weight and height growth of a child is the result of a complex system of genetics, epigenetics, hormones, and environment and is a function of time [113]. Growth is a marker of a child's physical and emotional well-being and has long-term consequences for health [114]. Childhood growth is mainly regulated by insulin-like growth factor-I and growth hormone, but also insulin, thyroid hormones, leptin, and sex hormones [115, 116].

### *Evaluation of growth*

Both fetal and postnatal growth is routinely assessed by clinicians and compared towards growth standards [113]. The purpose is to identify whether a child is growing "normally" or has a deviated growth trajectory. The WHO has developed both fetal growth charts [117] and postnatal growth charts, called the WHO Child Growth Standards [113]. The growth charts were developed to provide a reference of how children should grow.

The fetal growth charts provide growth references for biparietal diameter, head circumference, abdominal circumference, femur length, humerus length, estimated fetal weight, femur length/head circumference ratio, and femur length/biparietal diameter ratio from gestational week 14-40 [117]. The reference charts were based on a sample of pregnant women from ten different countries with low-risk singleton pregnancies. The women had high or middle socioeconomic status and no known environmental disadvantages on fetal growth. The ten countries included were Argentina, Brazil, Democratic Republic of the Congo, Denmark, Egypt, France, Germany, India, Norway, and Thailand, and 1,362 women participated in the study. Participants had on average six ultrasound examinations performed during pregnancy [117].

The postnatal growth charts from birth to 5 years of age were based on a sample of 8,440 children from six countries: Brazil, Ghana, India, Norway, Oman, and the United States [113]. Children included in the study were selected based on the criteria of optimal growth i.e., the children were breastfed, provided standard paediatric care, and were children of non-smoking mothers. The growth standards are provided both for weight, length/height, BMI, head circumference, and skinfolds.

The charts are constructed from 0-2 years of age and 2-5 years of age, to correct for the difference in length and height. Reference growth charts between 5-19 years of age are also available [118]. The charts were based on a sample of 22,917 children from the United States. The data were additionally merged with data from the children from the 0-5 years reference charts, to create an overlap between the reference curves. The study also showed that regardless of country of origin, children grow in similar patterns, given that their needs are met of nutrition, care, and health.

In addition, many countries have developed national growth reference curves, providing a country-specific, customized growth reference. In Norway, it is recommended to use the WHO growth charts from 0-5 years of age [119]. After 5 years of age, growth references from The Bergen growth study are recommended. The Bergen growth study collected data on more than 8,000 children between 0-19 years of age in Bergen between 2003-2006 [120, 121]. In Sweden, there are three recommended growth charts to use within the child health care [122]: 'Göteborg 1974', 'Sverige 1981', and the WHO growth charts from 0-5 years. The reference 'Göteborg 1974' is based on longitudinal data from 3,650 children from Gothenburg, Sweden, born between 1973-1975. Children with chronic diseases or who were born premature were excluded. 'Sverige 1981' is based on data from a longitudinal study including 3,158 children. Children with chronic diseases or who were born outside of Sweden, or with a birthweight <2,500g were excluded [122].

## Infant growth

Infant growth, meaning growth from birth to 2 years, is characterized by an initial decrease in body weight during the first days after birth (**Figure 5**) [113]. The decrease is followed by a rapid increase in both weight and length, and there is a significant accumulation of fat mass during this period. Around 6-8 months of age, there is a peak in BMI, which is followed by a slight decrease [113]. Infant growth is mainly influenced by factors such as genetic growth potential, infant nutrition, and the growth trajectory obtained from the fetal stage [101, 123]. Growth during early infancy is mostly controlled by insulin-like growth factor-I, and the regulation of this hormone is mainly dependent on the infant's nutrition [115].

Infant nutrition is a strong influencer of growth and adequate nutrition during infancy decrease morbidity and mortality, lower risk of chronic diseases, and promotes overall health and development. Breastfeeding is considered the optimal nutrition for the infant [124].

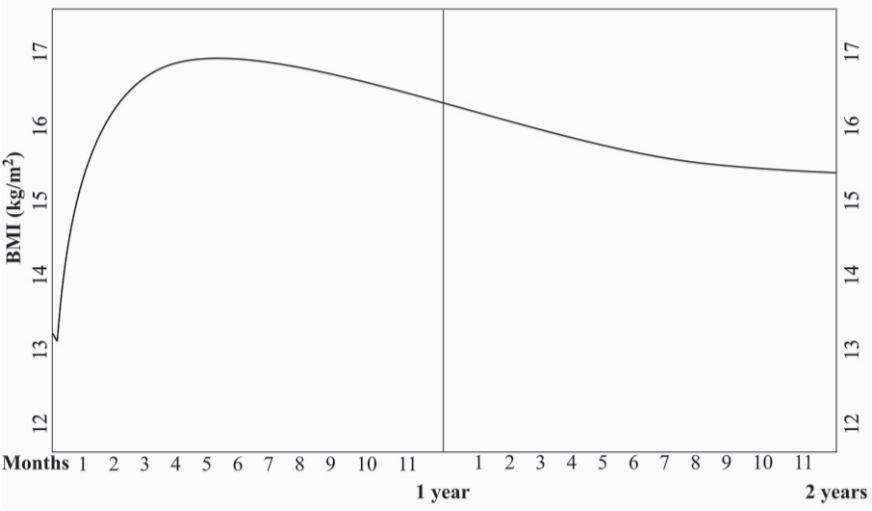


**Figure 5.** Characteristics of a hypothetical body mass index (BMI) trajectory from birth to 2 years of age.

Breastmilk contains all essential nutrients except for vitamin D, which is why vitamin D supplements are recommended to breastfed children [125]. WHO recommend exclusive breastfeeding during the first six months of life and complementary breastfeeding until at least 2 years of age [124]. Breastfed infants experience slower growth rates and weight gain, and are less likely to have overweight or obesity and diabetes, compared with infants who receive infant formula [126]. Formula fed infants have higher concentrations of insulin-like growth factor-I [127]. Commercial infant formula is typically higher in energy, protein, and fat compared with breastmilk, which taken together likely affects the increased metabolic risks [128].

## *Fetal and infant growth restriction*

Under adequate circumstances, a fetus will grow according to its genetic potential and follow its appropriate growth trajectory in utero. In case of fetal exposure to maternal undernutrition, placental dysfunction, or other adverse intrauterine exposures, the initial adaptation of the fetus is to alter its metabolism, including both glucose and insulin metabolism, in order to continue to grow [109]. Thus, unfavourable programming of fetal metabolism can occur even with no alteration in birth size [109]. However, if these adaptations fail, the fetus will change the trajectory of its development and reduce its growth velocity [101, 109].

This may lead to fetal growth restriction. Maternal risk factors for restricted fetal growth include low pre-pregnancy BMI, low gestational weight gain, some disorders, and tobacco or alcohol use [39]. Metabolic and physiologic adaptations that can occur following fetal growth restrictions are insulin resistance, predisposition to accumulate fat, reduced skeletal mass and bone mineralization [97, 101, 107]. These adaptations during the fetal period can be risk factors for rapid growth in infancy, and obesity, diabetes, hypertension, and cardiovascular disease later in life [101, 129].

In circumstances of inadequate nutritional access postnatally, the child may not ever reach its genetic growth potential. If a child's height-for-age is >2 standard deviations (SD) below the WHO Child Growth Standards median, the child suffers from stunting [130]. Stunting has adverse consequences, including poor educational achievement, and an enhanced risk of nutrition-related chronic disorders later in life [113]. Stunting can occur also in children without fetal growth restriction. The majority of all stunted children are born in Asia and Africa, while the prevalence in high-income countries is low [131]. Wasting is also a growth restriction, defined as weight-for-length/height >2 SD below the WHO Child Growth Standards median [132]. Children with wasting and stunting are at higher risk of mortality, compared with children with no growth restriction [132]. Underweight is considered when weight-for-age is low [133].

### *Rapid infant growth*

Fetal growth restriction followed by adequate or excess energy availability postnatally can cause rapid infant growth [123, 134]. The rapid growth aims to compensate the restricted fetal growth to achieve the genetic growth potential. Rapid growth also lowers the risk of postnatal infections and infant mortality for the growth restricted infant [134]. However, it also has some drawbacks. Rapid growth seems to negatively affect glucose and fat metabolism and increase risk of chronic adult diseases [134, 135]. Risk factors for rapid infant growth are maternal smoking during pregnancy, primiparity, and low birth weight [136]. Catch-up growth is one type of rapid growth. It has no uniform definition, but has been referred to as "height velocity above the statistical limits of normal for age or maturity during a defined period of time following a period of growth inhibition" [137]. However, catch-up growth can also refer to an infant growth pattern where both height and weight growth are moving up across centiles of standard growth charts [101].

Some children who grow with too little space in utero without any other adverse exposure in the womb will also experience rapid growth in infancy to catch up to their genetic growth potential [123]. Studies have found that some infants born with appropriate weight for gestational age may also follow a rapid growth trajectory [136]. Thus, all forms of rapid growth in infancy are not necessarily caused by recovery from previously impaired growth or malnutrition.

Although most women with obesity give birth to normal sized infants [138], maternal obesity is associated with a higher risk of excessive fetal growth, increased birth weight, and preterm birth [128, 139]. The mechanisms underlying the association between maternal obesity and impaired child growth are not fully understood, but may involve a combination of genetic, metabolic, and environmental factors. Obesity increases insulin resistance through adipose tissue inflammation, improper lipolysis, and impaired insulin function in muscle and liver [140]. In pregnant women with obesity, insulin resistance occurs earlier in pregnancy and is exaggerated, and circulating triglyceride concentrations are higher, compared with women without obesity [112]. Both maternal obesity and diabetes can cause higher placental transfer of nutrients [141]. Such adaptations can lead to fetal hyperinsulinism and increased fetal growth, but also to restricted fetal growth [107]. In addition to the immediate effects on birth outcomes, maternal obesity has also been linked to long-term effects on child growth and development. Maternal obesity is well known to affect the infant's weight growth trajectory and increase the risk for the child to develop obesity, diabetes, and cardiovascular disease later in life [138, 142, 143].

### *Childhood growth*

Childhood is here considered as the period from 2 years of age until around 8 years of age. The growth during these years is initially characterized by a modestly decreasing BMI trajectory after the infancy BMI peak. Around 4–6 years of age, the BMI growth trajectory reaches a nadir, followed by a modest increase in BMI until the start of puberty. The BMI nadir at 4-6 years of age is referred to as the adiposity rebound (**Figure 6**) [144]. At 6-8 years of age, the adrenal glands mature and start to produce increasing amounts of adrenal androgens [116]. This is called the adrenarche and begins before the start of puberty. During childhood, the child will most often follow the growth trajectory that was set during infancy. Except for infant growth, growth during childhood is influenced by hormonal regulators, certain diseases, stress, and nutrition [116].

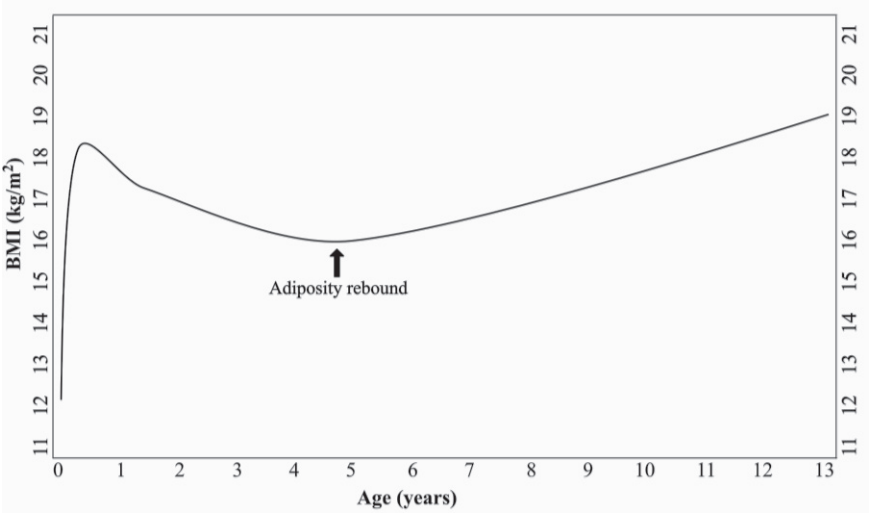


**Figure 6.** Characteristics of a hypothetical body mass index (BMI) trajectory from birth to 13 years of age.

## Childhood overweight and obesity

According to the WHO, overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health [145]. Both conditions are caused by an imbalance between energy intake and expenditure [145]. The ideal definition of overweight and obesity would be based on percentage body fat. However, techniques that measure body fat e.g., dual-energy x-ray absorptiometry (DXA) and Bod Pod are less available, costly, and challenging in young children. BMI provides a fair estimation of adiposity in children on a group level and is an accepted clinical standard measure of risk of overweight and obesity for children from 2 years of age [113].

Several approaches of classifying overweight and obesity exist. BMI with applied cut-offs at 25 kg/m² and 30 kg/m² is commonly used to classify overweight and obesity in adults [145]. However, BMI in childhood changes largely with age due to the growth and there is not a single BMI cut-off that can define overweight or obesity during this entire time. To classify overweight and obesity, WHO uses the weight-for-height index for children under the age of 5, with cut-offs >2 SD and >3 SD above the age and sex specific WHO Child Growth Standards median, respectively [113].

For children between 5–19 years, BMI-for-age >1 SD and >2 SD above the WHO Child Growth Standards median classifies overweight and obesity. BMI centiles are also used to categorize overweight and obesity, with cut-offs at the 85$^{th}$ and 95$^{th}$ centile [113]. The International Obesity Task Force (IOTF) has constructed age- and sex specific BMI cut-offs for overweight and obesity from 2–18 years of age, based on and linked to the corresponding adult BMI cut-offs [146, 147]. These cut-offs were used in **Paper II** and **IV** and are further discussed under *Methodological considerations*.

The prevalence of overweight and obesity in children is increasing. In 1975, the global prevalence of overweight and obesity in children between 5-9 years of age was 4% and 1%, respectively [148]. In 2016, the global prevalence had risen to 21% and 9%, while in Europe, the prevalence of overweight and obesity was 29% and 11%. In the Nordic countries during the same year, the prevalence of overweight and obesity spanned between 25-30% and 8-12%. Childhood obesity increases the risk of developing early puberty, hormonal issues, sleep disorders, and cardiovascular risk factors [111, 146]. Additionally, children with obesity have an increased risk of psychological issues, poor self-esteem, and eating disorders [111]. The excess adiposity will likely also follow the child into adulthood [149].

There are several causes for childhood obesity, including biological, developmental, behavioural, genetic, and environmental factors [111]. Parental education, ethnicity, and BMI influence the child's risk of gaining excessive weight [150]. Gestational weight gain exceeding the IOM maternal weight gain recommendations has been associated with higher childhood BMI z-score and risk of overweight and obesity [151]. Growth and nutrition in early life are, as mentioned in a previous section, large risk factors for later metabolic disease. Maternal vitamin D status has also been suggested to be involved in fetal programming of metabolic diseases, which is further elaborated in the chapter *Maternal vitamin D and postnatal growth*.

# Maternal vitamin D and postnatal growth

Maternal vitamin D insufficiency during pregnancy is suggested to qualify for the Barker hypothesis [26]. It is hypothesised that low maternal vitamin D status, through fetal programming, may increase the risk of both pregnancy complications and adverse postnatal outcomes. Vitamin D deficiency during pregnancy may increase the risk of pre-eclampsia, gestational diabetes, and low birth weight [9]. Low maternal vitamin D status has also been associated with postnatal length/height growth [152] but also with weight growth, BMI, and body composition [8].

## Evidence from intervention studies

Intervention studies investigating the role of maternal vitamin D on fetal and postnatal growth differ in dose, type, time point and duration of vitamin D supplementation, as well as geographical differences, sample size, and baseline maternal 25OHD. Despite heterogeneity, intervention trials suggests that vitamin D supplements increase fetal growth in both weight and length, as well as postnatal weight and height. Vitamin D supplementation during pregnancy might also decrease childhood BMI but has not been found to influence childhood body composition.

A systematic review and meta-analysis from 2015 included 13 randomized controlled trials (n=2,299) [153]. Included studies were conducted in both low- middle-, and high-income countries. Interventions were vitamin D alone or in combination with multivitamins, calcium, or iron, and the controls were active, placebo, or no intervention. Mean 25OHD concentrations were significantly higher at term following vitamin D intervention, compared with the control groups. Birth weight and birth length were significantly greater for infants in the intervention groups (mean difference: (108 g, 95% confidence interval (CI): 60, 155) and 0.3 cm (95% CI: 0.10, 0.41)), respectively. However, there were no differences between intervention and control groups in incidence of small for gestational age, low birth weight, or preterm birth.

The latest Cochrane review from 2019 included 30 trials involving 7,033 pregnant women [9]. Interventions studied were: 1) vitamin D alone vs. placebo or no intervention (no vitamins or minerals), 2) vitamin D + calcium vs. placebo or no intervention, or 3) vitamin D + calcium vs. calcium supplementation alone. Authors suggested that supplementing pregnant women with vitamin D alone probably reduces the risk of pre-eclampsia (risk ratio (RR) 0.48, 95% CI: 0.30, 0.79, 4 trials, n=499), gestational diabetes (RR 0.51, 95% CI: 0.27, 0.97, 4 trials, n=446), and low birth weight (RR 0.55, 95% CI: 0.35, 0.87, 5 trials, n=697). The evidence was assessed as having moderate certainty, due to limitations in study design, imprecision, and indirectness. Vitamin D in combination with calcium had no further effects on any if the pregnancy outcomes. In addition, the effect of the dose of vitamin D (15 µg/day versus 100 µg/day) on these pregnancy outcomes were investigated [154]. The authors found that vitamin D supplements in higher doses made little or no difference on the risk of pre-eclampsia, low birth weight, and preterm birth, but might decrease the risk of gestational diabetes.

A systematic review and meta-analysis from 2018 investigated the effect of vitamin D supplementation during pregnancy on fetal and infant growth [155]. Results showed that vitamin D supplementation during pregnancy was associated with 75 g higher weight at birth (95% CI: 22.9, 127.9, n=4,087, 17 trials), and with higher weight at 3 months (0.21 kg, 95% CI: 0.13, 0.28, n=216), 6 months (0.46 kg, 95% CI: 0.33, 0.58, n=199), 9 months (0.50 kg, 95% CI: 0.01, 0.99, n=179), and 12 months (0.32 kg, 95% CI: 0.12, 0.52, n=252). Vitamin D supplementation during pregnancy was also associated with 1.1 cm greater height at 3 months (95% CI: 0.64, 1.54, n=216), 1.5 cm greater hight at 9 months (95% CI: 0.13, 2.82, n=179), and 1.4 cm greater hight at 12 months (95% CI: 0.81, 1.92, n=252). However, only three trials contributed to the results on postnatal growth [156-158].

A meta-analysis from 2022 including 25 intervention trials and 20 observational studies with a total population of 44,992 investigated the effect of maternal vitamin D supplementation on the height growth of children [152]. Results from intervention trials showed that mothers who received vitamin D supplements during pregnancy had a 0.25 cm longer child at birth (95% CI: 0.06, 0.43, 23 trials). When observational studies were also included in the meta-analysis, the effect estimates were enhanced (0.4 cm, 95% CI: 0.15, 0.65, 40 studies), but with large heterogeneity between studies. Maternal vitamin D supplementation during pregnancy was also associated with 1.48 cm longer child length at 9 months (95% CI: 0.13, 2.82, 2 trials) but no association at 1, 3, 6, or 12 months of age. When including both interventional and observational studies,

maternal vitamin D supplementation/higher maternal vitamin D status during pregnancy was associated with 0.50 cm longer child length at 3 months (95% CI:0.03, 0.97, 5 studies) but no association at any other age. Observational studies showed significance between higher maternal vitamin D status and child's length at 1 month (0.62 cm, 95% CI:0.1, 0.63, 1 study), 3 months (0.41 cm, 95% CI:0.40, 0.42, 1 study), 6 months (0.2 cm, 95% CI: 0.19, 0.21, 2 studies), 9 months (0.1 cm, 95% CI:0.09, 0.11, 2 studies), and 12 months (−0.05 cm, 95% CI:−0.06, −0.04, 2 studies).

A systematic review and meta-analysis from 2021 compiled evidence from randomized controlled trials to investigate the effect of vitamin D supplementation (20–125 µg/day vs. control group; placebo or usual care) during pregnancy, lactation and infancy on childhood growth and body composition [159]. Vitamin D supplementation during pregnancy was associated with 0.33 mm greater triceps skinfold thickness (95% CI: 0.12, 0.54) at birth. Vitamin D supplementation during pregnancy or infancy was associated with 0.12 lower BMI z-score at 3-6 years of age (95% CI: −0.21, −0.04, 4 trials, n=1,674), and 0.29 higher length-for-age z-score in 1 year old infants (95% CI: 0.03, 0.54, 4 trials, n=1,196), but not at 3-6 years of age. The meta-analysis found no association between vitamin D supplementation and fat mass, lean mass, and weight-for-age z-score until 3 years of age.

Two later clinical trials have been published. The first one was a paper from the randomized, double-blind trial MAVIDOS [160]. The MAVIDOS trial was conducted in the United Kingdom in 2008-2014. Participants received either 25 µg/day of vitamin D3 or placebo from gestational week 14 to delivery. All women were allowed to supplement with up to 10 µg/day of vitamin D and children were followed-up by DXA. At 4 years of age, lean mass was greater among the children in the intervention group (mean 9.2 kg, 95% CI: 9.1, 9.4 compared with mean 9.0 kg, 95% CI: 8.8, 9.2, p=0.05, n=452). However, the difference became non-significant when adjusting for age and sex. There was no difference in fat mass or BMI between intervention and control groups.

The second newly published paper was a randomized, double-blind trial conducted between 2014-2016 [161]. Pregnant women in Bangladesh received vitamin D supplements containing either 105 µg/week, 420 µg/week, 700 µg/week, or placebo. Supplementation was initiated in gestational week 17–24 and children were followed up by DXA. There was no difference in fat mass or lean mass between intervention groups, or between the highest supplementation group compared with placebo, at 4 years of age (n=608). There was also no interaction between maternal baseline 25OHD concentration and intervention group for child body composition.

## Evidence from observational studies

Evidence from observational studies is mixed, due to different study settings; different gestational age at blood sampling, 25OHD assay method, and different definitions and ages of the outcomes. However, results suggests that postnatal growth and body composition, in particular adiposity, are associated with maternal vitamin D and most studies find a beneficial effect of higher maternal vitamin D status.

A meta-analysis of observational studies conducted by Santamaria et al. in 2017 investigated the association between maternal vitamin D deficiency (by any definition) and childhood growth and adiposity [8] (**Table 5**). The meta-analysis included 30 studies (n=35,032) of which most investigated associations with birth weight. Infants of mothers with vitamin D deficiency had lower birth weight, but with significant heterogeneity between studies. No association was found between maternal vitamin D deficiency and birth length. Maternal vitamin D deficiency was also associated with heavier infant weight at 9 months of age, based on two studies (no significant heterogeneity), but not infant length at 9 months [162, 163]. Evidence was not found for an association between maternal vitamin D status and weight-for-age z-score or length-for-age z-score at 1 year of age, based on two studies [164, 165]. Neither was there evidence of an association between maternal vitamin D status and child's adiposity at birth or 4–6 years of age [166, 167]. However, only two studies contributed with data that could not be pooled, of which one study did find an association between lower maternal vitamin D status and higher fat mass at 6 years of age [166]. No overall association was found between maternal vitamin D status and height, BMI, or fat mass at 9 years of age [162, 167]. Authors concluded that low maternal vitamin D status may be associated with an increased postnatal growth and infant adiposity.

Several studies have been published after the meta-analysis by Santamaria et al. [8], summarized in **Table 5.** Despite conflicting results, many observational studies have found an association between maternal vitamin D status and postnatal growth and adiposity. These studies mainly present an inverse association between maternal vitamin D intake or status and childhood BMI or risk of overweight [168-170] (**Paper II** and **III**). Also, the studies mainly show evidence for associations in younger ages, up until around 3 years of age. However, there seems to be no strong evidence for an association with rapid growth in infancy. Some studies also indicate an association between maternal 25OHD and childhood body composition around 5-6 years of age [170-174]. The association between maternal vitamin D status and markers of cardiovascular risk show diverge results, with both positive and negative associations, and null findings [170, 173-177].

**Table 5.** Summary of observational studies of maternal vitamin D during pregnancy in relation to child's growth, overweight, obesity, and markers of cardiovascular risk.

| Study ID | Country, year | N | Exposure | Results |
|---|---|---|---|---|
| Benjamin Neelon, 2018 [169] | USA, 2009-11 | 476 | Maternal 25OHD in gestational week 13 Mean 25OHD was 41 nmol/L | Maternal 25OHD in quartile 1 compared with quartile 4 was associated with higher 1-year weight for-length z-scores (0.78 units; 95% CI: 0.08, 1.54) and higher 3-year BMI z-scores (0.83 units; 95% CI: 0.11, 0.93). |
| Boyle, 2017 [172] | New Zealand, 2005-08 | 1,208 | Maternal 25OHD in gestational week 15 Mean 25OHD was 73 nmol/L | Each 10 nmol/L higher maternal 25OHD was associated with 0.2% lower fat mass (95% CI: −0.36, −0.04), but no association with lean mass or BMI z-score at 5-6 years of age. |
| Carreras-Badosa, 2018 [174] | Spain | 66 | Maternal 25OHD in gestational week 24-28 Mean 25OHD was 47 nmol/L | Maternal 25OHD was associated with 0.288 lower carotid intima-media thickness (p=0.04), 0.304 lower intra-abdominal fat (p=0.01), and 0.281 lower visceral fat (p=0.01) in the child at 5-6 years of age. |
| Daraki, 2018 [170] | Greece, 2007-08 | 532 | Maternal 25OHD in gestational week 14 Mean 25OHD was 46 nmol/L | 1) Every 10 nmol/L decrease in maternal 25OHD was associated with 0.06 higher BMI z-score (95% CI: 0.01, 0.11) and 0.24 cm greater waist circumference (95% CI: 0.02, 0.46) at 4 years age<br>2) Maternal 25OHD <37.7 nmol/L was associated with 0.2 higher BMI z-score (95% CI: 0.03, 0.37) at both 4 and 6 years of age, and 0.87 cm greater waist circumference (95% CI: 0.12, 1.63) at 4 years of age, and 1.6% higher body fat percentage (95% CI: 0.13, 3.05) at 6 years of age, compared with children of mothers with 25OHD ≥37.7 nmol/L<br>3) No association between maternal 25OHD and rapid growth during the first two years of life, or child's blood pressure or serum lipids at 4 or 6 years of age. |

**Table 5 (continued).**

| Study ID | Country, year | N | Exposure | Results |
|---|---|---|---|---|
| Hrudey, 2015 [171] | Netherlands, 2003-04 | 1,882 | Maternal 25OHD in gestational week 16<br>Mean 25OHD was 60 nmol/L | 1) Every 10 nmol/L increase in 25OHD associated with 0.13% decrease in body fat percentage (99% CI: −0.3, −0.003) at 5-6 years<br>2) In children of overweight mothers, but not normal weight mothers, every 10 nmol/L increase in 25OHD was associated with a 0.007 nmol/L decrease in child C-peptide (99% CI: −0.01, −0.001) and a 0.02 decrease in child HOMA-IR (99% CI: −0.03, −0.004) at 5-6 years<br>3) No association between maternal 25OHD and child blood pressure, BMI, waist-to-height ratio, total cholesterol, LDL or HDL cholesterol, triglycerides, or glucose at 5-6 years. |
| Hyde, 2018 [178] | Australia, 2002-04 | 209 | Maternal 25OHD in gestational weeks 16 and 30<br>Mean 25OHD was 56 nmol/L at both time points | 1) Overall, no associations were found between maternal 25OHD in early or late pregnancy and child body composition<br>2) In mothers who smoked during pregnancy, higher 25OHD in early pregnancy was associated with 0.2 higher child lean mass percentage (95% CI: 0.08, 0.31) and 0.21 lower fat percentage (95% CI: −0.32, −0.07)<br>3) In non-smoking mothers, no association between vitamin D status and child body composition |
| Jensen, 2017 [179] | Denmark, 1930-91 | Cases 871, controls 1,311 | Neonatal 25OHD3 from dried blood samples at birth | No association between neonatal 25OHD3 and risk of over-weight at age 7 years |
| Jiang, 2021 [180] | China, 2016-17 | 329 | Maternal 25OHD in gestational week 11-29<br>Mean 25OHD was 35 nmol/L | 1) No association between maternal 25OHD and child weight, length, or BMI up to 3 years of age<br>2) No association between maternal 25OHD and child BMI z-score trajectory class |

**Table 5 (continued).**

| Study ID | Country, year | N | Exposure | Results |
|---|---|---|---|---|
| Miliku, 2019 [173] | Netherlands, 2002-06 | 4,903 | Maternal 25OHD in gestational week 20<br>Median 25OHD was 50 nmol/L | 1) Children of mothers with 25OHD <25 nmol/L had a 0.12 SD higher fat mass percentage (95% CI: 0.03, 0.21) and a 0.13 SD lower lean mass percentage (95% CI: −0.22, −0.04) at 6 years of age, compared with 25OHD ≥75 nmol/L.<br>2) Maternal 25OHD was not associated with child blood pressure, total cholesterol, triglycerides, or insulin at 6 years age |
| Morales, 2015 [168] | Spain, 2003-08 | 1,468 | Season-adjusted maternal 25OHD3 in gestational week 14<br>Median 25OHD3 was 74 nmol/L | 1) Every 25 nmol/L reduction in 25OHD were associated with 0.07 higher BMI at 1 year (95% CI: −0.001, 0.14) but not at 4 years of age.<br>2) 25OHD <50 nmol/L was associated with 1.42 higher odds of overweight at 1 year of age (95% CI: 1.02, 1.97), but not at 4 years of age, compared with 25OHD ≥75 nmol/L<br>3) No association to rapid growth from birth to 1 year of age |
| Rytter, 2016 [177] | Denmark, 1988–89 | 410 | Maternal 25OHD in gestational week 30 | 1) An inverse association between maternal 25OHD with HDL cholesterol in women at 20 years of age<br>2) No association between maternal 25OHD and height, weight, waist circumference, blood pressure, glucose, insulin, HbA1c, insulin-like growth factor 1, leptin, adiponectin, cholesterol, triglycerides, and CRP |
| Santamaria, 2017 [8] | Meta-analysis of 30 studies | 35,032 | Maternal vitamin D deficiency (different cut-offs used, from <25 nmol/L to <50 nmol/L) | 1) Maternal vitamin D deficiency was associated with 120g heavier infant weight at 9 months of age (95% CI: 33, 207) but not length (MD −0.09, 95% CI: −0.30, 0.13)<br>2) No association between maternal vitamin D status and weight-for-age (MD −0.09, 95% CI: −0.18, 0.01, n=2,789) or length-for-age z-score (MD −0.05, 95% CI: −0.38, 0.27, n=2791) at 1 year of age, adiposity at birth or 4–6 years of age, or to height (−0.11 ,cm, 95% CI: −1.07, 0.84), BMI (−0.34 kg/m$^2$, 95% CI: −0.78, 0.10), or fat mass (−0.40, 95% CI: −1.36, 0.57) at 9 years of age (n=647) |

**Table 5 (continued).**

| Study ID | Country, year | N | Exposure | Results |
|---|---|---|---|---|
| Tint, 2018 [181] | Singapore, 2009-10 | 292 | Maternal 25OHD in gestational weeks 26-28<br>Mean 25OHD was 78 nmol/L | 1) Higher maternal 25OHD was associated with 0.14 ml lower superficial subcutaneous adipose tissue volume (95% CI: −0.24, −0.04) and 0.04 ml lower deep subcutaneous adipose tissue volume (95% CI: −0.06, −0.01) at 2-weeks post-partum<br>2) Maternal 25OHD ≤75 nmol/L was associated with 7 ml higher superficial subcutaneous adipose tissue volume (95% CI: 2.1, 12.4), and 2 ml higher deep subcutaneous adipose tissue volume (95% CI: 0.6, 3.4) within 2-weeks post-partum, compared with 25OHD >75 nmol/L |
| Tornhammar, 2014 [176] | Sweden, 1975 | 275 | Neonatal 25OHD3 from dried blood samples taken at birth | 1) Every 50 nmol/L higher 25OHD was associated with 25.8% (95% CI: 1.0, 58.4) higher fasting insulin at 35 years of age<br>2) In women, 30% (95% CI: 5.1, 58.4) higher triglycerides, and 4.6 (95% CI: 1.93, 7.36) mmol/L higher serum cholesterol was found for each 50 nmol/L increase in 25OHD. Also, every 1 nmol/L increase in neonatal 25OHD3 was associated with 3% higher risk of overweight (95% CI: 1.01, 1.05) and 9% higher risk of obesity (95% CI: 1.02, 1.17)<br>3) No association was found with aortic pulse wave velocity, blood pressure, fasting glucose, HDL cholesterol, LDL cholesterol, or CRP |
| Williams, 2013 [175] | England, 1991-92 | 4,109 | Maternal 25OHD sampled at any time during pregnancy<br>Mean 25OHD was 68 nmol/L | 1) Every 50 nmol/L increase in maternal 25OHD was associated with 0.48 mm Hg lower systolic blood pressure (95% CI: −0.95, −0.01), 0.01 mg/dL lower Apo-B (95% CI: −0.02, −0.001), and 6.1% lower CRP (95% CI: −11.5, −0.3) at 10 years of age, but not at 15 years of age<br>2) No associations with triglycerides, glucose, or insulin |

**Table 5 (continued).**

| Study ID | Country, year | N | Exposure | Results |
|---|---|---|---|---|
| **Paper II** | Norway, 2002-09 | 66,840 | Maternal vitamin D intake in gestational week 22 | 1) In children of mothers with normal pre-pregnancy BMI, higher maternal vitamin D intake was associated with lower weight during the first 3 months, lower odds of having a rapid weight gain during the first year of life, and lower odds of overweight at 3 and 5 years of age, compared with <5µg/day<br>2) In children of mothers with pre-pregnancy overweight, higher maternal vitamin D intake was associated with higher weight from 12 months onwards, and higher risk of overweight at 5 and 8 years of age, but not with rapid growth, compared with intakes <5µg/day. |
| **Paper III** | Norway (MoBa) 2002-09, Sweden (GraviD) 2013-14 | 2,513 (MoBa), 802 (GraviD) | Maternal 25OHD in gestational week 18 (MoBa) and 10 (GraviD).<br>Mean 25OHD was 51 nmol/L (MoBa) and 60 nmol/L (GraviD) | 1) In MoBa, lower maternal 25OHD (<75 nmol/L) was associated with a higher risk of a higher infant BMI trajectory, compared with 25OHD >75 nmol/L<br>2) In GraviD, no association was found between maternal 25OHD and infant BMI trajectory |
| **Paper IV** | Norway (MoBa) 2002-09, Sweden (GraviD) 2013-14 | 3,635 | Maternal 25OHD in gestational week 18 (MoBa) and 10 (GraviD)<br>Mean 25OHD was 51 nmol/L (MoBa) and 60 nmol/L (GraviD) | 1) Maternal 25OHD <30 nmol/L was associated with 0.2 $kg/m^2$ lower child' s BMI (95% CI: -0.39, -0.01), but not overweight, at 5 years of age in the pooled dataset.<br>2) Maternal pre-pregnancy BMI modified the association and maternal 25OHD <30 nmol/L was associated with 0.48 $kg/m^2$ lower child´s BMI (95% CI: −0.91 to −0.05) at 5 years of age in children of mothers with pre-pregnancy overweight |

Abbreviations: 25OHD; 25-hydroxyvitamin D, Apo-B; Apolipoprotein B, BMI; Body mass index, CI; confidence interval, CRP; C-reactive protein, HDL; high-density lipoprotein, HOMA-IR; Homeostatic model assessment for insulin resistance, I2; proportion of variation across studies due to heterogeneity rather than chance, LDL; low-density lipoprotein, MD; Mean difference, MoBa; The Norwegian Mother, Father and Child Cohort study, N; Number of mother-child pairs, SD; standard deviation

In the study by Morales et al. lower maternal vitamin D status in pregnancy was associated with higher BMI and risk of overweight at 1 year of age but not at 4 years of age [168]. Similar results were obtained from both Benjamin Neelon et al., who found that lower maternal vitamin D status was associated with higher 1-year weight-for-length and 3-year BMI z-scores [169], and Daraki et al., who found an association between low maternal vitamin D status and higher BMI z-score and waist circumference at 4 and 6 years of age [170]. We found that, in children of women with normal pre-pregnancy BMI, higher maternal vitamin D intake was associated with lower child weight growth trajectory and lower risk of overweight (**Paper II**). In contrast, in children of mothers with pre-pregnancy overweight, higher maternal vitamin D intake was associated with higher weight growth trajectory, and with higher risk of overweight. We also found an association between lower maternal vitamin D status and increased risk of a higher infant BMI growth trajectory until 2 years of age (**Paper III**) in The Norwegian Mother, Father and Child Cohort study (MoBa) but not in the GraviD study. In addition, maternal 25OHD <30 nmol/L was associated with lower childhood BMI, but not with risk of overweight, at 5 years of age (**Paper IV**). We found evidence for effect modification by pre-pregnancy BMI, and interaction analysis showed that the association was predominant among children of mothers with pre-pregnancy BMI overweight (**Paper IV**). In the study by Jiang et al., maternal vitamin D status was not related to child weight, length, BMI, or BMI z-score trajectory class up to 3 years of age [180]. However, only 9% had a 25OHD ≥50 nmol/L. Another study that presented null findings was the Danish D-tect case-cohort study, where Jensen et al. found no association between neonatal 25OHD3 concentration and risk of overweight at age 7 years [179]. Neither Hrudey et al. [171] nor Boyle et al. [172] found an association between maternal vitamin D status and child's BMI at 5-6 years.

Several studies have found associations between maternal 25OHD and body composition. In the Growing Up in Singapore Towards healthy Outcomes cohort study, Tint et al. showed that maternal vitamin D status in pregnancy was associated with neonatal adiposity within 2-weeks after delivery [181]. However, most studies have investigated body composition later in childhood. In the Vitamin D in Pregnancy Study, Hyde et al. found no overall association between maternal 25OHD in either early or late pregnancy and child body composition [178]. However, they found that higher maternal vitamin D status was associated with higher lean mass percentage and lower fat mass percentage (measured by DXA) at 11 years of age in children of mothers who were smokers. The sub-sample of women who were smokers during pregnancy was however very small (n=35).

Hrudey et al. found that maternal 25OHD was associated with lower fat mass percentage at 5-6 years of age [171]. These results were confirmed in the Screening for Pregnancy Endpoints study, where Boyle et al. found that higher maternal vitamin D status was associated with lower fat mass, but not lean mass (measured by impedance) at 5-6 years of age [172]. Another study supporting these results is the Generation R Study, where Miliku et al. also found that lower maternal vitamin D status was associated with higher fat mass and lower lean mass (measured by DXA) at 6 years of age [173]. Similarly, Daraki et al. found an association between lower maternal 25OHD and greater waist circumference at 4 and 6 years of age, and higher fat mass percentage at 6 years of age [170].

Carreras-Badosa et al. found that lower maternal vitamin D status was related to increased cardiovascular risk in childhood, measured as carotid intima-media thickness and fat mass (measured by ultrasonography) [174]. Similar results were presented by Williams et al. that also found associations between higher maternal vitamin D status and lower systolic blood pressure, Apolipoprotein-B, and C-reactive protein (CRP) at 10 years, but not at 15 years of age in the Avon Longitudinal Study of Parents and Children cohort [175]. The study found no association between maternal 25OHD and triglycerides, glucose, or insulin at 10 or 15 years of age. Contradictory, Tornhammar et al. found evidence for an association between higher neonatal vitamin D status and increased risk of overweight and obesity, and higher fasting insulin, triglycerides, and total cholesterol at 35 years of age [176]. However, they did not find an association with blood pressure, fasting glucose, HDL or LDL cholesterol, or CRP. In addition, Rytter et al. found no association between maternal vitamin D status and anthropometry or cardiometabolic health (blood pressure and analysis of blood glucose, insulin, HbA1c, insulin-like growth factor, leptin, adiponectin, cholesterol, triglycerides, and CRP) at 20 years of age [177]. Neither Daraki et al. [170] nor Miliku et al. [173] found associations between maternal 25OHD and child's cardiometabolic risk factors at 4 or 6 years of age.

## Potential biological mechanisms

Low maternal vitamin D status may expose the fetus to a suboptimal nutritional environment in utero, which may have long-term effects on child health. The biological mechanisms by which low vitamin D concentrations during pregnancy could increase the risk of postnatal metabolic unhealth are largely unknown, but there are several potential mechanisms.

It has been known for many years that 1,25OH2D can block pre-adipocyte differentiation [182]. In vitro studies give support for vitamin D insufficiency leading to epigenetic changes of the fetus, which might play a role in the development of childhood obesity. Sufficient vitamin D concentration in early life support the conversion of pre-adipocyte maturation to form myocytes rather than mature adipocytes [159]. Another in vitro study suggests that 1,25OH2D treatment of adipocytes might decrease the adipocyte lipid storage through a decrease in intracellular fat accumulation and an increase of the lipolysis [183]. 1,25OH2D was shown to inhibit lipid accumulation, and increase concentration of both hormone-sensitive lipase and lipoprotein lipase [183]. There is also some supportive evidence from animal studies. A mouse study showed that offspring exposed to a vitamin D deficient environment in utero have lower weight at birth, experienced a rapid postnatal weight gain, and obtained more visceral body fat compared with mice of vitamin D sufficient mothers [159, 184].

Another suggested pathway relating poor maternal vitamin D status to child obesity include changes in glucose homeostasis. Vitamin D has important roles in glucose and insulin metabolism, which regulates the availability of energy to the fetus [185]. Vitamin D deficiency and insufficiency during pregnancy is associated with altered markers of glucose homeostasis [186] and increased risk of gestational diabetes [26]. Vitamin D deficiency may lead to an accelerated insulin resistance [187], while sufficient vitamin D status may improve insulin sensitivity. Thus, low maternal vitamin D status might lead to an enhanced insulin resistance, and/or earlier onset of insulin resistance in pregnancy. This might lead to higher circulating glucose and triglyceride levels in the mother. Fetal exposure to hyperglycaemic in utero, may increase the fetal insulin production and elevate the risk of later type 2 diabetes [188]. Maternal glucose and triglyceride concentrations are both associated with infant adiposity, and children born after a pregnancy affected by gestational diabetes mellitus have a higher risk of overweight [189]. Thus, low maternal vitamin D status may lead to an increased fetal exposure to hyperglycaemia, increasing the risk of adiposity in childhood.

Further, vitamin D deficiency might induce inflammation. Vitamin D is suggested to regulate inflammation in the placenta [190] and fetal exposure to elevated inflammation in utero is associated with detrimental health outcomes including fetal growth restriction [191]. Placental inflammation also relates to greater expression of fatty acid transport proteins and vitamin D sufficiency could contribute to prevent excess lipid distribution to the fetus [192]. It is also hypothesized that vitamin D could affect glucose homeostasis through inflammation [193]. Activation of inflammatory pathways disrupts normal insulin metabolism. Inflammation causes oxidative stress and triggers insulin resistance. Hence, vitamin D deficiency could influence both glucose homeostasis and placental fatty acid transportation, thereby programming the fetus towards increased adiposity, as well as development of metabolic diseases.

# Discussion

## Methodological considerations

### Study populations

The papers included in this thesis were based on data from two cohorts: The Norwegian Mother, Father and Child Cohort Study (MoBa) [194, 195] and the Swedish GraviD study [30]. A flow chart of the data collection in each study cohort relevant to this thesis is presented in **Figure 7**.

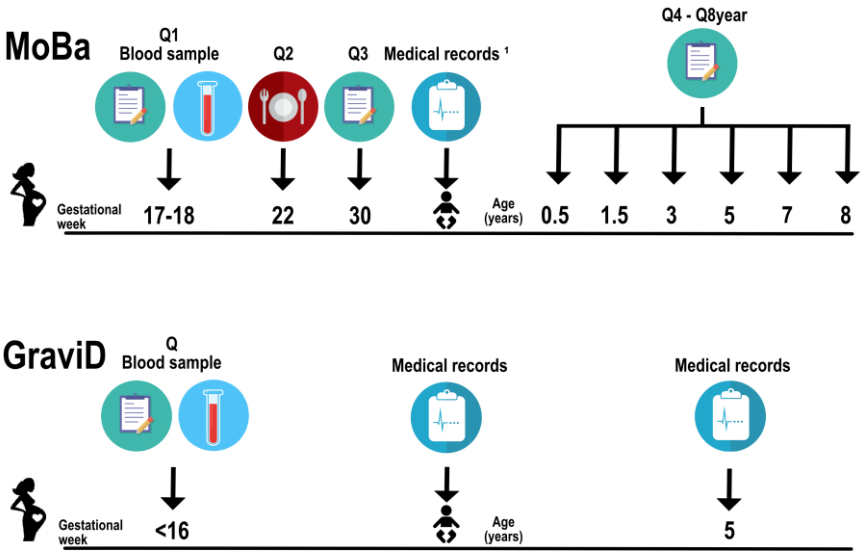


**Figure 7.** An overview of the relevant data collection in MoBa and the GraviD study. Abbreviations: MoBa; The Norwegian Mother, Father and Child Cohort Study, Q; Questionnaire

[1] Variables retrieved from the child's birth records in the Medical Birth Registry of Norway

The recruitment in both cohorts were population-based, but there was a selection of women included in the papers in this thesis. In **Paper I** and **II**, only MoBa women with a completed FFQ and other relevant covariates were included. Women in the Norwegian Environmental Biobank (**Paper I, III** and **IV**) were selected based on high compliance of responding the study questionnaires. Further, the participants included in **Paper III** and **IV** from the GraviD study also required available data collected 5 years after birth. Thus, the study populations included in this thesis are no longer considered to be population-based. The selection bias may weaken the generalizability of the results, but likely not the results per se [196]. However, selection bias might have led to less variation of e.g., vitamin D status within the study populations. In the GraviD study, where the number of study participants already was fewer compared with MoBa, the selection bias negatively affected the power to detect true differences.

## Assessment of exposures and outcomes

### *Assessment of vitamin D intake*

Dietary intake can be assessed by several methods, and the appropriateness of a method depend on the purpose or research question to be addressed [197]. Food records, 24-h recalls, and FFQs are some commonly used dietary assessment methods. Different methods might capture different dietary intakes, with different measurement errors. Dietary intake varies from day to day, over periods of time, and seasons. This leads to a variation in the intake of nutrients between days. Total energy and macronutrient intake has quite small day to day variation, while most micronutrients have a much larger variation. The assessment methods need to be sufficiently precise to measure differences that truly exist between individuals, to be useful when studying associations between diet and outcomes. Vitamin D is a nutrient which is concentrated to few foods, and the day-to-day variation can be large. To capture the vitamin D intake by food records or 24-h recall would be very costly and may not even be feasible in larger studies.

Regardless of dietary assessment method, there is always a risk that people report other dietary habits than their "true" intake, either to make them appear more socially acceptable (social desirability bias), or that they simply cannot recall their intakes (recall bias). Intake of healthy foods, such as fish and dietary supplements, is commonly overreported, while foods considered unhealthy is more often underreported [198].

The estimated intake from the FFQ in MoBa might suffer from both social desirability bias and recall bias which might have led to misclassification bias of the vitamin D intake and impacted our results in **Paper I** and **II.**

When using an FFQ for dietary assessment, the individual will answer a questionnaire regarding their habitual food intake. One drawback of the FFQ method is that it suffers from recall bias due to retrospective recording and reflect the perception of the individual´s dietary intake. Although FFQs are not appropriate for estimating true dietary intake, they are often used in epidemiological studies as they are more practical and cost-effective, compared with food records or 24-h recalls [197]. FFQs has the ability to rank individuals along the distribution of intake, which is often sufficient to provide accurate estimates of associations between an intake and the outcome of interest [199].

In MoBa, a semi-quantitative FFQ including 225 questions was used as dietary assessment method mid-pregnancy [194]. A validation study in MoBa showed only marginally lower correlation between the biomarker 25OHD and the vitamin D intake estimated by the FFQ ($r = 0.45$, $p<0.01$), compared with a 4-day weighed food record during wintertime ($r=0.51$, $p<0.01$) [200]. Another validation study of the MoBa FFQ found a significant increase in 25OHD concentrations across increasing quintiles of vitamin D intakes, and significantly different intakes between the upper and lower quintiles [201]. However, the dose-response relation between maternal 25OHD and vitamin D intake investigated in **Paper I** might lack some precision due to the use of FFQ to estimate the vitamin D intake.

### *Competing dietary exposures*

In **Paper II**, we included milk intake as a covariate in the model as it previously has been shown to be positively associated with birth weight [202]. It is likely the milk protein that drives this enhanced fetal growth, and not the calcium content in dairy products. Milk intake was not included in the other papers where vitamin D status was the exposure. However, there is no reason to believe that the dairy intake and the vitamin D status would co-vary, and it is not likely that the association is confounded by the milk intake in **Paper II-IV**.

Fish was found to be the main food source of vitamin D in MoBa (**Paper I**). Another nutrient which also is found in fish, which might co-vary with the vitamin D intake and status, is omega-3 poly unsaturated fatty acids (n-3 PUFAs).

Supplementation with n-3 PUFAs during pregnancy have been associated with higher birth weight [203], but no association have been found between supplementation with n-3 PUFAs during pregnancy and metabolic risk or adiposity in children [192]. However, like vitamin D, n-3 PUFA might also affect the insulin sensitivity and has been reported to reduce placental inflammation in pregnant women with obesity [192]. The latest Cochrane review concluded that there was possibly a reduced risk of the child being born with low birth weight, and possibly a small increased risk of being born large for gestational age in women supplementing with n-3 PUFA compared with placebo [204]. Thus, n-3 PUFA might affect the children's birth weight. Adjusting for birth weight only marginally affected the effect estimates and significance levels in the models in **Paper II-VI**.

### *Assessment of vitamin D status*

Several assay methods exist for assessment of vitamin D status, of which two are most frequently used: chromatography-based assays and automated immunoassays [37]. LC-MS/MS is considered to be the best available method for measuring concentrations of 25OHD [205]. It has high specificity, sensitivity, and reproducibility [205]. Automated immunoassays have been considered convenient due to high sample throughput. However, it has been reported to suffer from cross-reactivity between different vitamin D metabolites [34], and provide lower 25OHD concentrations compared with LC-MS/MS [206]. Regardless of assay method, there is variation in the analysis performance. Except for the challenge of methodological variability in analytical methods, results from 25OHD analysis are also known to vary between laboratories, despite similar analytic method [207].

As an attempt to handle laboratory variability, the Vitamin D External Quality Assessment Scheme (DEQAS) was initiated in 1989 to provide laboratories with external accuracy control [208]. DEQAS provide laboratories with samples with known concentrations of 25OHD to analyse and the results are thereafter reported back to DEQAS. This way, laboratories can ensure their assay method's analytical reliability.

The Vitamin D Standardization Program (VDSP) is another project aiming to standardize measurements of 25OHD. It is an international initiative, where laboratories can send serum aliquots for re-analysis by LC–MS/MS, calibrating the results using a validated statistical approach [209]. Samples can be both prospectively and retrospectively standardised, using a standardised assay, or using methods developed by the VDSP.

The idea is that by standardizing 25OHD, analytical differences can be equalized and 25OHD values and prevalence can be compared between studies. A study by Cashman et al. applied the VDSP protocol to serum 25OHD data from 14 European populations [47], including Norway, Denmark, and Finland. While one Finnish population obtained the same vitamin D deficiency prevalence estimate, all other studies obtained different prevalence after standardization. Two Norwegian studies and one Danish study originally provided prevalence of vitamin D deficiency at 4.9%, 28.9%, and 5.0%, but after calibration 0.9%, 39.6%, and 6.2% respectively [47]. Due to these methodological differences, the median 25OHD between studies with unstandardized 25OHD measurements should be compared and interpreted with caution.

### *Definition of outcomes*

In **Paper II** and **IV**, cut-offs from the IOTF [147] were used to assess if the children had overweight or obesity. The IOTF cut-offs for overweight and obesity are based on and linked to the centiles corresponding to BMI 25 and 30 kg/m², respectively, at 18 years of age [146]. These cut-offs were based on a pooled reference population of children from six nationally representative datasets on growth from Brazil, United Kingdom, Hong Kong, the Netherlands, Singapore, and the United States. Each study had over 10,000 children between 0-25 years of age and was collected between 1963-1993. In total, 97,876 boys and 94,851 girls were included [146]. Growth curves of BMI with centiles was constructed by dataset and sex using the LMS-method [210]. This method estimates the centiles in terms of three cubic spline curves: the M-curve (median), S-curve (coefficient of variation), and L-curve (Box-Cox power transformation removing skewness) at each age and for each dataset. Finally, the centile curves from each dataset were averaged to provide a single smooth curve representative of all the datasets involved. In 2012, the cut-offs were revised to allow BMI to be expressed as both centiles and SD scores [147]. Instead of averaging each datasets centile curves, the LMS-curves were averaged, and the pooled curves were then used to produce the cut-off values.

The IOTF cut-offs are considered international, as they are based on a heterogeneous mix of datasets from different countries. However, there is a predominance in Western populations. In addition, although the cut-offs correspond to adult cut-off points, the health consequences might not reflect those in adults [146]. Also, the cut-off for obesity is high, (>98$^{th}$ centile), meaning that fewer will be classified as having obesity according to this definition compared to other definitions, such as the WHO.

The WHO cut-offs for overweight and obesity are based on the reference population used to construct the WHO Child Growth Standards [113]. The growth curves were constructed using cubic splines with Box-Cox-power-exponential distribution applied, containing four parameters: the median, coefficient of variation, Box-Cox transformation power, and a parameter of kurtosis. Centiles and z-scores were then constructed using the LMS-method. The WHO define overweight as weight-for-height >2 SD above the WHO Child Growth Standards median before 5 years of age and >1 SD between 5-19 years of age. Obesity is defined as weight-for-height >3 SD above the WHO Child Growth Standards median between 0-5 years and >2 SD between 5-19 years of age. One drawback with the WHO Child Growth Standards is that between 5-19 years, the charts are constructed merely based on an American population.

The IOTF cut-offs are suggested to be less arbitrary and more internationally based than the definitions suggested by the WHO, due to the populations which the references are based on [146]. The WHO define overweight at a consistently lower BMI compared with the IOFT until around 6 years of age, and consistently higher after. This is likely also a reflection of the American reference population in the WHO. These are the major reasons for using the IOTF in our papers. The prevalence of overweight and obesity in our papers would suggestively have been higher at 3 and 5 years of age but lower at 8 years of age if the WHO cut-offs would have been used instead, and the choice of definition may have impacted our results.

A common definition of catch-up growth or rapid growth is >0.67 change in weight SD score during the first one or two years of life [211]. A gain in weight of 0.67 SD scores represent the width of each percentile band on the WHO Child Growth Standards [212]. However, this definition does not consider that weight gain is a result of both height and weight growth at earlier time points. Another approach is conditional growth modelling, which was used in **Paper II**. This approach creates growth measures independent of prior growth measures and statistically separate the effects of height growth and weight growth, as they are strongly correlated [114]. Standardised residuals are obtained by a regression of the weight or height measure of interest, adjusting for all prior measurements of both weight and height. The model estimates represent the child's deviation from the expected size based on their own previous measures and the growth of the other children. Rapid weight or height growth can then be defined by selecting a cut-off for the deviation of the residuals, such as >1 SD from the expected value [114]. However, there is yet no uniform definition of rapid growth using this approach, which makes it harder to compare results between studies.

## Statistical analysis

All regression models were adjusted for covariates, to decrease the risk of confounding bias. Different approaches for covariate selection were used in the different papers. In **Paper I**, backwards selection was used due to the nature of the prediction model. In **Paper II**, covariates were included if the changed the beta coefficient >10%. In **Paper III** and **IV**, covariates were selected a priori, and models presented with two different sets of covariates. The latter approach was selected since different variables was considered as confounders in MoBa and GraviD when tested according to the 10% rule. Although the most important variables for the studies associations were included in the models, there is still risk of residual confounding, which may have impacted our results.

All results presented in our papers are based on the same data from MoBa and GraviD. In **Paper II**, multiple testing might be a concern as numerous tests were conducted on similar outcomes. Thus, the p-values should be interpreted with caution. The analyses performed throughout the four papers of this thesis have been conducted with multiple exposures (vitamin D intake and status, continuous and categorical), from two cohorts, and with several different outcomes. Although the results from **Paper II-IV** are not comparable to each other since they have both different exposures and outcomes, it is an attempt to broaden and complement the methodology, as they are different ways to investigate the same association [213]. Using this approach, we look at the possible association in a more explorative way, and the diversity in methods can be considered a strength of this research project. Further, we do not know if there is a specific cut-off in maternal vitamin D status where the associations to postnatal growth or overweight will appear. Also, sensitivity analyses are an important step in understanding the data and the investigated association and revealing possible drivers of the association.

Simple pooling was used to combined data from MoBa and GraviD. In simple pooling, data are merged without being weighted [214]. The drawback in using simple pooling is that potentially important subgroup characteristics are being ignored, and that association is being created that does not actually exist. However, we believed that no cohort specific subgroups would be present in our sample. In **Paper III** and **IV**, the pooled dataset was analysed using mixed models, including cohort origin as random effect to statistically consider the two individual studies. This allows for the data being analyzed as two units within the dataset, and not fully combine the data.

Another aspect to consider of the statistical analyses is the prevalence of the exposure and the outcome. To be able to find associations statistically, there needs to be a variation in both exposure and outcome. Selection bias contribute to less variation in data. In addition, overweight and obesity are conditions which have more than one cause and is highly prevalent in many countries. As the specificity to the outcome is low, it also becomes harder to detect potential associations.

## Growth modelling

Growth curve modelling typically refers to statistical methods that allow for the estimation of variability within and between individuals in longitudinal patterns of change [215]. Growth modelling is a powerful statistical tool for studying child growth curves.

### *The Jenss-Bayley growth curve model*

The Jenss-Bayley growth curve model [216] that were used in **Paper II-IV** is one of the most common structural models used to model child growth trajectories. The Jenss-Bayley model was first developed in 1937 on solely one boy and one girl [216]. The children had fair skin, were lean, and had a typical history of childhood infections. Weight and height had been measured several times from birth to 6 years of age at irregular intervals. Using their growth measurements, an equation was constructed describing non-linear growth in both weight and height. The equation of the Jenss-Bayley model is presented in **Equation (1)**.

$$y_{ij} = a_i + b_i * t_{ij} - e^{ci+di*tij} \qquad (1)$$

It is expressed as the *j*th growth measure of the *i*th subject with y being the weight or height and *t* age in days [216]. The model assumes a steep growth increase in the first months of life, followed by a decelerating growth velocity, and a linear growth pattern after infancy (**Figure 8**). This linear term allows for describing growth until around the age of 8 years, before growth rates increase again due to puberty. The model parameters are biologically meaningful and can be interpreted, where *a* describes the birth weight or length, *b* describes the growth velocity beyond two years, *c* is the infant growth spurt and *d* is the curvature of the trajectories during the first two years. The model has later been extended to fit growth data until the age of 12 years, with addition of a fifth parameter which is a quadratic term modelling increase in growth velocity at the onset of puberty [217].

The Jenss-Bayley model cannot directly model BMI growth trajectories, as the shape of this growth curve in early childhood is non-monotonic, and the Jenss-Bayley assumes constant growth. BMI growth trajectories can however be calculated using the model derived weight and height growth trajectories [218], as in **Paper IV**.

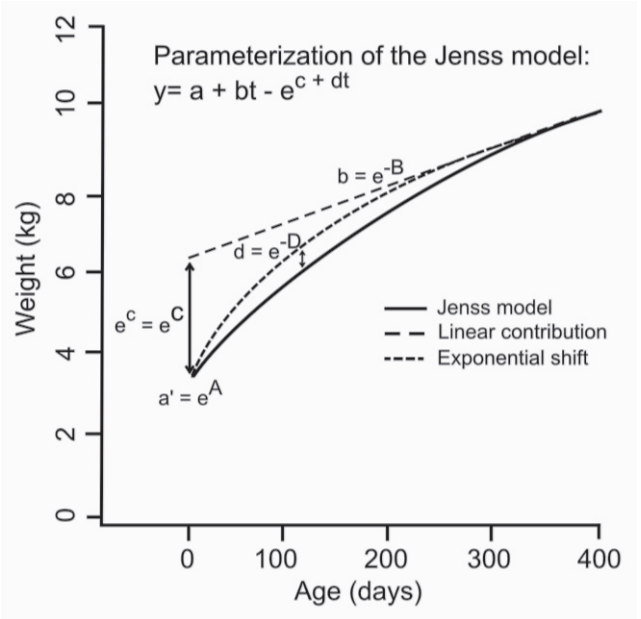


**Figure 8.** Characteristics of the Jenss-Bayley growth curve model in terms of interpretation of the coefficients.

Using a mixed-effect approach, the Jenss-Bayley model allows for modelling both the population mean growth curve (fixed effect) and individual growth trajectories (random effect). It also accounts for the dependence of measurements within individuals and heterogeneity in age at measurement, handle missing data and irregularly spaced growth measurements, and smooths measurement error [219]. The strength in using a structural model is that the parameters in the model have meaningful interpretations.

Except for the Jenss-Bayley model, there are several other growth curve models. Non-structural models, such as spline model and polynomials, are easy to fit, but tend to be more unstable at the extremities. These models do not define a particular shape of the growth curve and their parameters do not have any biological meaning.

Compared with the WHO Child Growth standards, which tries to fit the child's growth data into a reference, the Jenss-Bayley model provides a more flexible way of estimating growth data. The Jenss-Bayley showed the best model fit in both weight and height from birth to 6 years of age in an American population, compared with the Count model [220]. Later was both Jenss-Bayley models compared with the Reed 1st and 2nd order models, also in an American population from birth until the age of 9 years, where the extended Jenss-Bayley model provided the best fit in both weight and height [219]. In a study on children in South-Africa from birth to 10 years of age, the fit of the Reed, the Count, the Jenss-Bayley, and the adapted Jenss-Bayley models, as well as second and third order polynomial models was compared [221]. While the Reed 1st order model showed a consistent well fit from infancy into childhood, both Jenss-Bayley models did not fit well to growth data in the early years. In another study, the fit of the Jenss-Bayley, the Reed, and an adapted version of the Gompertz growth curve model was compared in children from sub-Saharan Africa up to 6 years of age [222]. While all models presented a good fit of both weight and height curves, the Jenss-Bayley model provided the best fit both in boys and girls. The most suitable model to model growth may depend on the anthropometric measure, the number and frequency of the measurements, the growth period, and the study population [219, 221].

There is a risk of misclassification of childhood overweight (including obesity) in **Paper II** and **IV**. This outcome was modelled using the Jenss-Bayley growth curve model to compensate for the missing anthropometrics due to loss to follow-up and decrease risk of selection bias. There are some points of discussion with regards to misclassification and use of the Jenss-Bayley growth curve model.

In **Paper IV**, the prevalence of overweight (including obesity) at 5 years of age was 19.8% in MoBa and 8.6% in GraviD using model-derived anthropometric values. Using reported anthropometrics, the prevalence was 11.0% in MoBa and 8.7% in GraviD. In the paragraphs below, the prevalence of overweight includes both overweight and obesity.

The first point of discussion is whether the prevalence of overweight using reported anthropometrics and the IOTF cut-offs found in MoBa (11%) and GraviD (8.7%) is comparable to other studies of Norwegian and Swedish children. In the Bergen Growth Study, the prevalence of overweight was 11.3% at 5 years of age in 2003-2006 [223]. A study conducted in Oppland County, Norway, in 2007, found a prevalence of overweight at 5-6 years of age was 14.1% using measured anthropometrics and IOTF cut-offs [224].

In a national survey in Sweden, the prevalence of overweight was 16.3% at 6 years of age in 2018, using the IOTF cut-offs [225]. Thus, the prevalence of overweight using reported anthropometrics was lower in GraviD compared with the national survey. However, the prevalence of overweight in MoBa was similar or marginally lower compared with previous studies. There is, as discussed previously, selection bias in both study cohorts than can cause this lower prevalence. Thus, the prevalence of overweight in both cohorts are likely not nationally representative.

The second point of discussion is with regards to the difference in prevalence of overweight using the model-derived anthropometrics compared with the reported at 5 years of age. This difference is prevalent in both the larger MoBa cohort (**Paper II**) and in the even more selected population (**Paper IV**). In the larger study population in **Paper II**, only around 46% and 35% of the MoBa children had reported anthropometrics at 5 and 8 years of age, respectively. The prevalence of overweight in MoBa using model-derived anthropometrics at 3, 5, and 8 years of age was 10%, 19-21%, and 6-8%, respectively. The observed prevalence was around 12%, 11%, and 10% correspondingly. It is hard to explain why there is a large difference in prevalence of overweigh at 5 years of age within MoBa but not in GraviD. There were much more reported anthropometrics available in GraviD than in MoBa. However, at 5 years of age, retention rates were similar with 71% of the children having reported anthropometrics in MoBa and 70% in GraviD in **Paper IV**. Another difference between the anthropometrics in MoBa and GraviD is that the measurements were reported by the parents in MoBa and collected from childcare records in GraviD. Thus, there might be larger variation in reported anthropometrics within each child in MoBa, leading to a poorer model fit. In addition, we included all children with at least one postnatal measurement of weight and length/height in the Jenss-Bayley model. The growth curve of a child with few measures is then very similar to the population mean growth trajectory but may be inaccurate and increase the risk of misclassification bias. However, there were more children with only one postnatal measurement reported in GraviD (5%) than in MoBa (<1%). To remove children with few measurements, especially those with no measurements around the time points of interest, in a sensitivity analysis would have provided an opportunity to evaluate the influence of such measurements. With this large discrepancy between predicted and reported prevalence in MoBa, misclassification bias is likely with an overestimation of children with overweight.

### *Growth Mixture Modelling*

Another parametric approach to model longitudinal data is the Growth Mixture Modelling (GMM) [226, 227], which was used in **Paper III**. GMM is a latent trajectory modelling technique which aims to identify trajectories of unobserved classes/clusters among longitudinal data. This type of model can be used when the study population is believed to contain different clusters of patterns. Latent trajectory models identify classes of individuals with similar patterns so that there is less variance within a group than between groups. Each individual has a probability of belonging to each identified class and is classified according to the highest probability. In contrast, single-class approaches assume that the study population can be described by a single set of parameters and does not contain specific clusters or patterns of interest [226]. Thus, latent trajectory models and single-class models has different assumptions of the underlying data and addresses different research hypotheses [228]. GMM allows for both fixed and random effects. Fixed effect is given by each identified trajectory that represents the mean growth curve over time within the specific class [226, 227]. GMM also allows for random intercepts and slopes within each class, to capture the inter-individual variation. GMM combines two types of models: latent growth models and mixture models. The GMM framework of a simple univariate latent growth curve with latent growth factors is presented in **Figure 9**, where *C* is a categorical variable for class, *I* is the class-specific intercept, and *S* the class-specific slope, formed by the observed variables $T_1$, $T_2$, and $T_3$ that represent repeated measures across three time points, and ε represents class-specific errors (intra-individual variation).

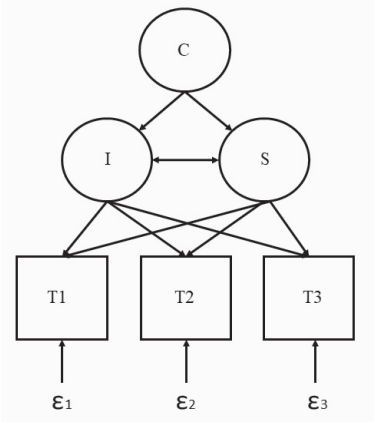


**Figure 9.** Framework of a Growth Mixture Model with a simple univariate latent growth curve with latent growth factors. Abbreviations; *C*: categorical variable for class, *I:* class-specific intercept, *S:* class-specific slope, *T*: observed variables of repeated measures, and *ε*: class-specific errors

Model estimation is conditional on a pre-determined finite number of classes. However, if the number of classes is unknown, a combination of approaches must be used to decide which number of classes are the most appropriate. These include assessing interpretability, characteristics, and plausibility of classes (if classes show biologically plausibility), information criteria, entropy (class separation statistics), and meaningful sub-groups with regards to the number of individuals assigned (e.g., ≥5% class size). There is not one fit statistic index that consistently emerges as superior in class selection. Thus, it is recommended to use multiple approaches to enhance the statistical objectivity to the model selection process [226, 227, 229].

The GMM is a flexible and powerful model which allows for partially missing data [230]. It has previously been used to model BMI growth trajectories in several different settings [231, 232]. Compared with the mixed effects linear regression model used in **Paper II**, the GMM provide a more person-centred methodology by focusing on the relation between individuals instead of between variables [233]. By investigating the same association by different approaches with different sources of bias, it potentially adds to more reliable answers to research questions [213], as discussed previously. By using the Growth Mixture Modelling in **Paper III**, we are characterizing growth as categorical parameter estimates, instead of as continuous. However, latent trajectory modelling has some drawbacks. Although multiple indices are used for model selection, it remains to determine the theoretical biological relevance of the classes obtained [226, 227]. The GMM will model the number of classes requested by the user, regardless of if they have conceptual meaningfulness or not. In addition, the number and nature of the identified trajectories tend not to replicate in other cohorts, which makes it harder to extrapolate results.

One could argue that the growth of the children in MoBa and GraviD in fact does not consist of any unobserved clusters of growth patterns and that all children in fact have a similar growth pattern. However, the model did identify children with rapid growth in infancy and children with a higher BMI trajectory throughout infancy. A systematic review of group-based modelling approaches investigating BMI trajectories in infancy found that three or four trajectories were most commonly identified: one stable normal, one stable high, one stable low/decreasing, and one rapid gain [232]. The trajectories identified in our study were biologically relevant and interesting growth patterns to study in this context. Unfortunately, the study sample was not sufficiently large to use the rapid growth class as an outcome in the association to maternal vitamin D status in **Paper III** as planned.

The Jenss-Bayley growth curve model was used in **Paper III** before the use of the GMM to handle missing data. Although the GMM does allow for missing data, the model did not converge with the unevenly distributed reported anthropometric measurements in MoBa and GraviD. To handle this, we used Jenss-Bayley to predict weight and height growth at 7 time points from birth to 2 years of age for all children at the same ages. This might have introduced misclassification bias in the sample. However, the obtained trajectories were relevant, both in terms of nature and the children's reported BMI. An alternative approach would have been to choose certain time points and include only children with complete data on these time points and include a coding scheme for time. However, this would most likely have introduced an even stronger selection bias and less variation in the study population.

## Results and implications

In summary, intervention trials investigating the role of maternal vitamin D on fetal growth show that vitamin D supplements seems to increase both birth weight [9, 153, 155] and birth length [152, 153]. These results are supported by evidence from observational studies, suggesting a lower birth weight in vitamin D deficient mothers [8]. Maternal vitamin D supplementation also seems to increase the postnatal weight [155] and height [152, 155, 159] growth during the first year of life. Observational studies have found a higher weight during the first two years of life in children of mothers with lower vitamin D intake (**Paper II**) or status [162, 163]. There is also suggestive evidence from intervention trials that vitamin D supplements during pregnancy decreases child's BMI at 3-6 years of age [159], supported by observational studies indicating an inverse relation between maternal vitamin D intake (**Paper II**) or status [168-170] (**Paper III**) and childhood BMI and risk of overweight. In addition, we also found that maternal pre-pregnancy BMI was an effect modifier in the associations between maternal vitamin D intake (**Paper II**) or status (**Paper IV**) and childhood growth or risk of overweight and obesity. Intervention trials have found no effect of vitamin D supplements during pregnancy on childhood body composition until 4 years of age [159-161]. However, several observational studies give support for an inverse association between maternal vitamin D status and childhood adiposity at 5-6 years of age [166, 170-174]. Methodological differences such as 25OHD assay methods, gestational week of intervention or analysis of 25OHD, different seasons or latitudes when and where the study were conducted, age of the children at follow-up, and different definitions and measures of outcomes might explain disparate results between studies.

Both intervention trials and observational studies give support for an inverse association between maternal vitamin D intake (**Paper II**) or status [159, 168-170] (**Paper III** and **IV**) and childhood BMI. There is epidemiological evidence suggesting that pre-pregnancy BMI is an important predisposing factor of childhood overweight and obesity [143]. In addition, as there is an inverse relation between vitamin D status and adiposity [68], maternal pre-pregnancy BMI might be an important effect modifier in the association between maternal vitamin D status and childhood growth. Thus, children of women with high pre-pregnancy BMI may be at higher risk for higher BMI or overweight when maternal vitamin D status is low, compared with higher maternal vitamin D concentrations. The role of pre-pregnancy BMI as an effect modifier in these associations is still unclear.

Another hypothesis is that maternal BMI drives the inverse association between maternal vitamin D status and childhood BMI. As mothers with high BMI in general may experience lower vitamin D status, insufficient adjustment or residual confounding of maternal pre-pregnancy BMI might explain the inverse association seen in observational studies [168-170] (**Paper III**). Although maternal pre-pregnancy BMI has been adjusted for in our analyses, there might still be residual confounding causing the association. On the other hand, some studies have found associations between higher maternal vitamin D status in pregnancy and longer infant length [152, 155, 159]. However, this might be an effect lingering from the fetal period, as vitamin D supplementation also seems to increase birth length and no association to child's length have been found beyond infancy [159].

Although several studies suggests that there are associations between maternal vitamin D status and childhood growth and risk of overweight and obesity, there is not sufficient evidence to conclude if the associations are causal. In addition, the effect estimates are overall very small. Many studies, both intervention trials [160] and observations studies [162, 164, 165, 167, 234] (**Paper IV**), have also failed to find an association between vitamin D supplements or higher vitamin D status in pregnancy and childhood growth or risk of overweight and obesity. Possibly, the associations found between maternal vitamin D status and childhood BMI might be explained by maternal BMI, as these variables are closely correlated. If there is a causal effect of maternal vitamin D status on childhood growth and risk of overweight and obesity, it is likely small and with no clinically important effect.

## Ethical considerations

Both MoBa and GraviD were conducted in accordance with the declaration of Helsinki and have received ethical approval from Ethical Review Boards. Informed written consent was provided from all study participants, and they received oral and written information about the study procedures. However, children were not asked to leave consent due to the young ages. In MoBa, children born within the study receives information when they turn 18 years old regarding continuous participation in the study.

Study information, consent forms, and questionnaires were only available in Norwegian in the MoBa study. In the GraviD study, study information and consent forms were available in eight different languages. However, in the follow up of the children in the GraviD study, information was only available in Swedish. This is a limitation in both cohort studies, which may have contributed with exclusion of women of other ethnic origin.

In MoBa, study participants were not informed at enrolment about the specific research questions that was to be investigated. However, there is a website where on-going research projects are presented and participants in MoBa receive regular newsletters with information of obtained research results.

In both cohorts, 25OHD was analyzed after the child was born. In the GraviD study, the women received the analysis results of 25OHD 8 weeks post-partum at the maternity health centres. In case of clinically low vitamin D status within the GraviD study, the pregnant women were referred to their primary health care centre for a second blood sample and follow-up. In MoBa, the analysis of 25OHD was conducted in 2015, several years after blood sampling and thus, the women with vitamin D deficiency were not given any treatment during the pregnancy.

# Conclusions

Several studies have investigated the relationship between maternal vitamin D intake and status during pregnancy and various outcomes related to child growth and overweight or obesity. The findings from these studies are mixed, and the strength and direction of the association often depend on the timing and method of assessing maternal vitamin D status, as well as the age of the child at the time of outcome measurement. While there is some evidence to suggest that maternal vitamin D status may play a role in childhood growth and risk of overweight or obesity, it is not sufficient to conclude if the association is causal. If there is a causal effect of maternal vitamin D status on childhood growth or risk of overweight and obesity, it is likely small and with no clinically important effect.

Conclusion from the studies conducted within this doctoral project are:

1) Vitamin D intake from both foods and supplements according to the recommended intake (10 µg/day) might be sufficient to reach adequate vitamin D concentrations in pregnant women during months when dermal synthesis of vitamin D is absent. Except for the vitamin D intake, the most important determinants of vitamin D status were season, country of origin, age, and pre-pregnancy BMI.

2) There is an association between vitamin D intake during pregnancy and postnatal growth, but it is modified by pre-pregnancy BMI. In children of mothers with normal pre-pregnancy weight, vitamin D intake during pregnancy according to the recommended intake is associated with lower risk of childhood overweight.

3) Maternal vitamin D status <75 nmol/L during pregnancy may be associated with a higher BMI growth trajectory during the first 2 years of life.

4) Low maternal vitamin D status was associated with lower BMI, but not overweight, at the age of 5. However, pre-pregnancy BMI may modify the association.

# Future perspective

Traditionally, vitamin D has been linked to bone health and the importance and biological mechanism of vitamin D is well known. Nowadays, the role of vitamin D for human health has expanded and vitamin D is considered a modifying factor for a range of diseases. Since vitamin D still receives great scientific attention, and as we and others keep finding associations between maternal vitamin D and with fetal and postnatal outcomes, we can rest assured that further functions will be revealed.

The role of vitamin D for the pregnant woman and her child is still largely unknown. Knowing that deficiency of vitamin D in pregnant women is common globally, the potential health benefits of improving vitamin D status during pregnancy for the child are immense. Observational studies have consistently pointed towards an increased risk of high childhood BMI and overweight related to low vitamin D status during pregnancy. However, results from observational studies cannot establish causality and associations can be caused by residual confounding. Nevertheless, observational studies are valuable in pointing intervention research in certain directions. To determine whether interventions to improve maternal vitamin D status can lead to improved health outcomes in childhood would require sufficiently powered, long-term intervention studies. At this point, it is unclear if the current scientific literature justifies such a trial.

In addition, there is also a need to further explore the optimal vitamin D intake and status during pregnancy. To date, we do not know if higher intakes of vitamin D are required in pregnancy and which vitamin D status that is sufficient to cover the need of both the mother and fetus, in both high- and lower-income countries, throughout all trimesters, and regardless of maternal BMI.

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# References


1. Rajakumar, K., *Vitamin D, cod-liver oil, sunlight, and rickets: a historical perspective.* Pediatrics, 2003. **112**(2): p. e132-5.
2. Holick, M.F., *Resurrection of vitamin D deficiency and rickets.* J Clin Invest, 2006. **116**(8): p. 2062-72.
3. Lips, P., *Vitamin D physiology.* Prog Biophys Mol Biol, 2006. **92**(1): p. 4-8.
4. Holick, M.F. and T.C. Chen, *Vitamin D deficiency: a worldwide problem with health consequences.* Am J Clin Nutr, 2008. **87**(4): p. 1080s-6s.
5. Shin, J.S., et al., *Vitamin D effects on pregnancy and the placenta.* Placenta, 2010. **31**(12): p. 1027-34.
6. Holick, M.F., *Vitamin D deficiency.* N Engl J Med, 2007. **357**(3): p. 266-81.
7. Holick, M.F., *Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease.* Am J Clin Nutr, 2004. **80**(6 Suppl): p. 1678s-88s.
8. Santamaria, C., et al., *Prenatal vitamin D status and offspring's growth, adiposity and metabolic health: a systematic review and meta-analysis.* Br J Nutr, 2018. **119**(3): p. 310-319.
9. Palacios, C., L.K. Kostiuk, and J.P. Peña‐Rosas, *Vitamin D supplementation for women during pregnancy.* Cochrane Database Syst Rev, 2019(7).
10. Tsiaras, W.G. and M.A. Weinstock, *Factors influencing vitamin D status.* Acta Derm Venereol, 2011. **91**(2): p. 115-24.
11. Hollis, B.W. and C.L. Wagner, *Clinical review: The role of the parent compound vitamin D with respect to metabolism and function: Why clinical dose intervals can affect clinical outcomes.* J Clin Endocrinol Metab, 2013. **98**(12): p. 4619-28.
12. Heaney, R.P., et al., *Vitamin D3 distribution and status in the body.* J Am Coll Nutr, 2009. **28**(3): p. 252-6.
13. Smith, J.E. and D.S. Goodman, *The turnover and transport of vitamin D and of a polar metabolite with the properties of 25-hydroxycholecalciferol in human plasma.* J Clin Invest, 1971. **50**(10): p. 2159-67.
14. Hossein-nezhad, A. and M.F. Holick, *Vitamin D for health: a global perspective.* Mayo Clin Proc, 2013. **88**(7): p. 720-55.
15. *Nordic Council of Ministers. Nordic Nutrition Recommendations 2012: Integrating nutrition and physical activity* 2014.

16. Lamberg-Allardt, C., et al., *Vitamin D - a systematic literature review for the 5th edition of the Nordic Nutrition Recommendations.* Food Nutr Res, 2013. **57**.
17. Villamor, E., *A potential role for vitamin D on HIV infection?* Nutr Rev, 2006. **64**(5 Pt 1): p. 226-33.
18. Liu, P.T., et al., *Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response.* Science, 2006. **311**(5768): p. 1770-3.
19. Xuan, Y., H.Y. Zhao, and J.M. Liu, *Vitamin D and type 2 diabetes mellitus (D2).* J Diabetes, 2013. **5**(3): p. 261-7.
20. Palomer, X., et al., *Role of vitamin D in the pathogenesis of type 2 diabetes mellitus.* Diabetes Obes Metab, 2008. **10**(3): p. 185-97.
21. Evans, K.N., et al., *Vitamin D and placental-decidual function.* J Soc Gynecol Investig, 2004. **11**(5): p. 263-71.
22. Ji, J.-L., et al., *Immunological function of vitamin D during human pregnancy.* 2017. **78**(2): p. e12716.
23. Reichrath, J. and K. Querings, *Vitamin D deficiency during pregnancy: a risk factor not only for fetal growth and bone metabolism but also for correct development of the fetal immune system?* Am J Clin Nutr, 2005. **81**(5): p. 1177; author reply 1177-8.
24. Kiely, M.E., C.L. Wagner, and D.E. Roth, *Vitamin D in pregnancy: Where we are and where we should go.* J Steroid Biochem Mol Biol, 2020. **201**: p. 105669.
25. Kaludjerovic, J. and R. Vieth, *Relationship between vitamin D during perinatal development and health.* J Midwifery Womens Health, 2010. **55**(6): p. 550-60.
26. Hollis, B.W. and C.L. Wagner, *New insights into the vitamin D requirements during pregnancy.* Bone Res, 2017. **5**: p. 17030.
27. Karras, S.N., C.L. Wagner, and V.D. Castracane, *Understanding vitamin D metabolism in pregnancy: From physiology to pathophysiology and clinical outcomes.* Metabolism, 2018. **86**: p. 112-123.
28. Pludowski, P., et al., *Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence.* Autoimmun Rev, 2013. **12**(10): p. 976-89.
29. Curtis, E.M., et al., *Maternal vitamin D supplementation during pregnancy.* Br Med Bull, 2018. **126**(1): p. 57-77.
30. Barebring, L., et al., *Vitamin D Status during Pregnancy in a Multi-Ethnic Population-Representative Swedish Cohort.* Nutrients, 2016. **8**(10).
31. Fernández-Alonso, A.M., et al., *First-trimester maternal serum 25-hydroxyvitamin D3 status and pregnancy outcome.* International Journal of Gynecology & Obstetrics, 2012. **116**(1): p. 6-9.
32. Holick, M.F., et al., *Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline.* J Clin Endocrinol Metab, 2011. **96**(7): p. 1911-30.

33. Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin, D. and Calcium, *The National Academies Collection: Reports funded by National Institutes of Health*, in *Dietary Reference Intakes for Calcium and Vitamin D*, A.C. Ross, et al., Editors. 2011, National Academies Press (US) Copyright © 2011, National Academy of Sciences.: Washington (DC).
34. Munns, C.F., et al., *Global Consensus Recommendations on Prevention and Management of Nutritional Rickets.* Horm Res Paediatr, 2016. **85**(2): p. 83-106.
35. Borai, A., et al., *The pre-analytical stability of 25-hydroxyvitamin D: Storage and mixing effects.* J Clin Lab Anal, 2020. **34**(2): p. e23037.
36. Efsa Panel on Dietetic Products, N. and Allergies, *Dietary reference values for vitamin D.* EFSA Journal, 2016. **14**(10): p. e04547.
37. Sempos, C.T. and N. Binkley, *25-Hydroxyvitamin D assay standardisation and vitamin D guidelines paralysis.* Public Health Nutr, 2020. **23**(7): p. 1153-1164.
38. Mansur, J.L., et al., *Vitamin D: Before, during and after Pregnancy: Effect on Neonates and Children.* Nutrients, 2022. **14**(9).
39. *WHO Guidelines Approved by the Guidelines Review Committee*, in *WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience*. 2016, World Health Organization: Geneva.
40. *WHO Guidelines Approved by the Guidelines Review Committee*, in *WHO antenatal care recommendations for a positive pregnancy experience: Nutritional interventions update: Vitamin D supplements during pregnancy*. 2020, World Health Organization: Geneva.
41. Cashman, K.D., et al., *A systematic review and meta-regression analysis of the vitamin D intake-serum 25-hydroxyvitamin D relationship to inform European recommendations.* Br J Nutr, 2011. **106**(11): p. 1638-48.
42. Cashman, K.D., et al., *Estimation of the dietary requirement for vitamin D in healthy adolescent white girls.* Am J Clin Nutr, 2011. **93**(3): p. 549-55.
43. Cranney, A., et al., *Effectiveness and safety of vitamin D in relation to bone health.* Evid Rep Technol Assess (Full Rep), 2007(158): p. 1-235.
44. Roth, D.E., et al., *Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries.* Ann N Y Acad Sci, 2018. **1430**(1): p. 44-79.
45. van Schoor, N.M. and P. Lips, *Worldwide vitamin D status.* Best Pract Res Clin Endocrinol Metab, 2011. **25**(4): p. 671-80.
46. Palacios, C. and L. Gonzalez, *Is vitamin D deficiency a major global public health problem?* J Steroid Biochem Mol Biol, 2014. **144 Pt A**: p. 138-45.
47. Cashman, K.D., et al., *Vitamin D deficiency in Europe: pandemic?* Am J Clin Nutr, 2016. **103**(4): p. 1033-44.
48. Saraf, R., et al., *Global summary of maternal and newborn vitamin D status - a systematic review.* Matern Child Nutr, 2016. **12**(4): p. 647-68.

49. Schoos, A.M., et al., *Environmental and Genetic Determinants of Serum 25(OH)-Vitamin D Levels during Pregnancy and Early Childhood.* Children (Basel), 2019. **6**(10).
50. Andersen, L.B., et al., *Parity and tanned white skin as novel predictors of vitamin D status in early pregnancy: a population-based cohort study.* Clin Endocrinol (Oxf), 2013. **79**(3): p. 333-41.
51. Grønborg, I.M., et al., *Vitamin D-fortified foods improve wintertime vitamin D status in women of Danish and Pakistani origin living in Denmark: a randomized controlled trial.* Eur J Nutr, 2020. **59**(2): p. 741-753.
52. Viljakainen, H.T., et al., *Maternal vitamin D status determines bone variables in the newborn.* J Clin Endocrinol Metab, 2010. **95**(4): p. 1749-57.
53. Hauta-Alus, H.H., et al., *Season, dietary factors, and physical activity modify 25-hydroxyvitamin D concentration during pregnancy.* Eur J Nutr, 2018. **57**(4): p. 1369-1379.
54. Gustafsson, M.K., et al., *Alterations in the vitamin D endocrine system during pregnancy: A longitudinal study of 855 healthy Norwegian women.* PLoS One, 2018. **13**(4): p. e0195041.
55. Eggemoen Å, R., et al., *Vitamin D deficiency and supplementation in pregnancy in a multiethnic population-based cohort.* BMC Pregnancy Childbirth, 2016. **16**: p. 7.
56. Brembeck, P., A. Winkvist, and H. Olausson, *Determinants of vitamin D status in pregnant fair-skinned women in Sweden.* Br J Nutr, 2013. **110**(5): p. 856-64.
57. Lundqvist, A., et al., *Vitamin D Status during Pregnancy: A Longitudinal Study in Swedish Women from Early Pregnancy to Seven Months Postpartum.* PLoS One, 2016. **11**(3): p. e0150385.
58. Godang, K., et al., *Seasonal variation in maternal and umbilical cord 25(OH) vitamin D and their associations with neonatal adiposity.* European journal of endocrinology, 2014. **170**(4): p. 609-617.
59. Lips, P., N.M. van Schoor, and R.T. de Jongh, *Diet, sun, and lifestyle as determinants of vitamin D status.* Ann N Y Acad Sci, 2014. **1317**: p. 92-8.
60. Wacker, M. and M.F. Holick, *Sunlight and Vitamin D: A global perspective for health.* Dermatoendocrinol, 2013. **5**(1): p. 51-108.
61. Webb, A.R. and O. Engelsen, *Calculated ultraviolet exposure levels for a healthy vitamin D status.* Photochem Photobiol, 2006. **82**(6): p. 1697-703.
62. O'Neill, C.M., et al., *Seasonal Changes in Vitamin D-Effective UVB Availability in Europe and Associations with Population Serum 25-Hydroxyvitamin D.* Nutrients, 2016. **8**(9).
63. MacLaughlin, J. and M.F. Holick, *Aging decreases the capacity of human skin to produce vitamin D3.* J Clin Invest, 1985. **76**(4): p. 1536-8.

64. Clemens, T.L., et al., *Increased skin pigment reduces the capacity of skin to synthesise vitamin D3.* Lancet, 1982. **1**(8263): p. 74-6.
65. Kimlin, M.G., et al., *The Contributions of Solar Ultraviolet Radiation Exposure and Other Determinants to Serum 25-Hydroxyvitamin D Concentrations in Australian Adults: The AusD Study.* Am J Epidemiol, 2014. **179**(7): p. 864-874.
66. Golzarand, M., et al., *Vitamin D supplementation and body fat mass: a systematic review and meta-analysis.* Eur J Clin Nutr, 2018. **72**(10): p. 1345-1357.
67. Vranić, L., I. Mikolašević, and S. Milić, *Vitamin D Deficiency: Consequence or Cause of Obesity?* Medicina (Kaunas), 2019. **55**(9).
68. Hyppönen, E. and B.J. Boucher, *Adiposity, vitamin D requirements, and clinical implications for obesity-related metabolic abnormalities.* Nutr Rev, 2018. **76**(9): p. 678-692.
69. Wortsman, J., et al., *Decreased bioavailability of vitamin D in obesity.* Am J Clin Nutr, 2000. **72**(3): p. 690-3.
70. Drincic, A.T., et al., *Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity.* Obesity (Silver Spring), 2012. **20**(7): p. 1444-8.
71. Vanlint, S., *Vitamin D and obesity.* Nutrients, 2013. **5**(3): p. 949-56.
72. Moon, R.J., et al., *Determinants of the Maternal 25-Hydroxyvitamin D Response to Vitamin D Supplementation During Pregnancy.* J Clin Endocrinol Metab, 2016. **101**(12): p. 5012-5020.
73. Bjorn Jensen, C., et al., *Development and validation of a vitamin D status prediction model in Danish pregnant women: a study of the Danish National Birth Cohort.* PLoS One, 2013. **8**(1): p. e53059.
74. *Scientific Opinion on the Tolerable Upper Intake Level of vitamin D. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) EFSA Journal. 2012;10(7):2813.*
75. Borel, P., D. Caillaud, and N.J. Cano, *Vitamin D bioavailability: state of the art.* Crit Rev Food Sci Nutr, 2015. **55**(9): p. 1193-205.
76. Silva, M.C. and T.W. Furlanetto, *Intestinal absorption of vitamin D: a systematic review.* Nutr Rev, 2017. **76**(1): p. 60-76.
77. Schmid, A. and B. Walther, *Natural vitamin D content in animal products.* Adv Nutr, 2013. **4**(4): p. 453-62.
78. Calvo, M.S., S.J. Whiting, and C.N. Barton, *Vitamin D fortification in the United States and Canada: current status and data needs.* Am J Clin Nutr, 2004. **80**(6 Suppl): p. 1710s-6s.
79. *National Institutes of Health (NIH) Office of Dietary Supplements. Vitamin D Fact Sheet for Health Professionals. Updated August 12, 2022. Cited in November 2022.* . Available from: https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/#en23.
80. Itkonen, S.T., et al., *Vitamin D status and current policies to achieve adequate vitamin D intake in the Nordic countries.* Scand J Public Health, 2021. **49**(6): p. 616-627.
81. Valsta, L., et al., *Ravitsemus Suomessa-FinRavinto 2017-tutkimus.* 2018.

82. Amcoff, E., *Riksmaten-vuxna 2010-11: Livsmedels-och näringsintag bland vuxna i Sverige*. 2012: Livsmedelsverket.
83. Þorgeirsdóttir, H., H. Gunnarsdóttir, and I. Gísladóttir, *Hvað borða Íslendingar? Könnun á mataræði Íslendinga 2010-2011 Helstu niðurstöður. I %J Embætti landlæknis: Rannsóknastofa í næringarfræði við Háskóla Íslands og Landspítala-háskólasjúkrahús, Reykjavík.* 2011.
84. Helsedirektoratet. *Norkost 3. A nationwide dietary survey among men and women in Norway aged 18-70 years, 2010-2011. [Available in Norwegian]. 06/2012. IS-2000* 2012.
85. Pedersen, A.N., et al., *Danskernes kostvaner 2011-2013*. 2015: Fødevareinstituttet, Danmarks Tekniske Universitet.
86. Knudsen, V.K., *E-artikel fra Danmarks Tekniske Universitet, Fødevareinstitutet. Danskernes forbrug af kosttilskud.* 2014(2): p. 1-6.
87. Scholl, T.O. and X. Chen, *Vitamin D intake during pregnancy: association with maternal characteristics and infant birth weight.* Early Hum Dev, 2009. **85**(4): p. 231-234.
88. Camargo, C.A., Jr., et al., *Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age.* Am J Clin Nutr, 2007. **85**(3): p. 788-95.
89. Watson, P.E. and B.W. McDonald, *The association of maternal diet and dietary supplement intake in pregnant New Zealand women with infant birthweight.* Eur J Clin Nutr, 2010. **64**(2): p. 184-93.
90. Blumfield, M.L., et al., *A systematic review and meta-analysis of micronutrient intakes during pregnancy in developed countries.* Nutr Rev, 2013. **71**(2): p. 118-32.
91. Krige, S.M., et al., *Dietary Intake and Beliefs of Pregnant Women with Gestational Diabetes in Cape Town, South Africa.* Nutrients, 2018. **10**(9).
92. Lundqvist, A., et al., *Reported dietary intake in early pregnant compared to non-pregnant women - a cross-sectional study.* BMC Pregnancy Childbirth, 2014. **14**: p. 373.
93. Barebring, L., et al., *Validation of Dietary Vitamin D Intake from Two Food Frequency Questionnaires, Using Food Records and the Biomarker 25-Hydroxyvitamin D among Pregnant Women.* Nutrients, 2018. **10**(6).
94. Prasad, M., et al., *Diet composition of pregnant Finnish women: changes over time and across seasons.* Public Health Nutr, 2010. **13**(6a): p. 939-46.
95. Meinilä, J., et al., *Nutrient intake of pregnant women at high risk of gestational diabetes.* Food Nutr Res, 2015. **59**: p. 26676.
96. Jensen, C.B., et al., *Sources and determinants of vitamin D intake in Danish pregnant women.* Nutrients, 2012. **4**(4): p. 259-72.
97. Kwon, E.J. and Y.J. Kim, *What is fetal programming?: a lifetime health is under the control of in utero health.* Obstet Gynecol Sci, 2017. **60**(6): p. 506-519.

98. Barker, D.J., *The origins of the developmental origins theory.* J Intern Med, 2007. **261**(5): p. 412-7.
99. Barker, D.J., *In utero programming of chronic disease.* Clin Sci (Lond), 1998. **95**(2): p. 115-28.
100. Bertram, C.E. and M.A. Hanson, *Animal models and programming of the metabolic syndrome.* Br Med Bull, 2001. **60**: p. 103-21.
101. Weaver, L.T., *Rapid growth in infancy: balancing the interests of the child.* J Pediatr Gastroenterol Nutr, 2006. **43**(4): p. 428-32.
102. Racicot, K., et al., *Understanding the complexity of the immune system during pregnancy.* Am J Reprod Immunol, 2014. **72**(2): p. 107-16.
103. Mor, G. and I. Cardenas, *The immune system in pregnancy: a unique complexity.* Am J Reprod Immunol, 2010. **63**(6): p. 425-33.
104. Lager, S. and T.L. Powell, *Regulation of nutrient transport across the placenta.* J Pregnancy, 2012. **2012**: p. 179827.
105. Poissonnet, C.M., A.R. Burdi, and F.L. Bookstein, *Growth and development of human adipose tissue during early gestation.* Early Hum Dev, 1983. **8**(1): p. 1-11.
106. Lain, K.Y. and P.M. Catalano, *Metabolic changes in pregnancy.* Clin Obstet Gynecol, 2007. **50**(4): p. 938-48.
107. Damhuis, S.E., W. Ganzevoort, and S.J. Gordijn, *Abnormal Fetal Growth: Small for Gestational Age, Fetal Growth Restriction, Large for Gestational Age: Definitions and Epidemiology.* Obstet Gynecol Clin North Am, 2021. **48**(2): p. 267-279.
108. Gicquel, C., A. El-Osta, and Y. Le Bouc, *Epigenetic regulation and fetal programming.* Best Pract Res Clin Endocrinol Metab, 2008. **22**(1): p. 1-16.
109. Hales, C.N. and D.J. Barker, *The thrifty phenotype hypothesis.* Br Med Bull, 2001. **60**: p. 5-20.
110. Galjaard, S., R. Devlieger, and F.A. Van Assche, *Fetal growth and developmental programming.* J Perinat Med, 2013. **41**(1): p. 101-5.
111. Kansra, A.R., S. Lakkunarajah, and M.S. Jay, *Childhood and Adolescent Obesity: A Review.* Front Pediatr, 2020. **8**: p. 581461.
112. Heerwagen, M.J., et al., *Maternal obesity and fetal metabolic programming: a fertile epigenetic soil.* Am J Physiol Regul Integr Comp Physiol, 2010. **299**(3): p. R711-22.
113. *World Health Organization. (2006). WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight -for-height and body mass index-for-age: methods and development. World Health Organization.*
114. Adair, L.S., et al., *Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: findings from five birth cohort studies.* Lancet, 2013. **382**(9891): p. 525-34.
115. Hill, D.J. and J. Hogg, *Growth factors and the regulation of pre- and postnatal growth.* Baillieres Clin Endocrinol Metab, 1989. **3**(3): p. 579-625.

116. Benyi, E. and L. Sävendahl, *The Physiology of Childhood Growth: Hormonal Regulation.* Horm Res Paediatr, 2017. **88**(1): p. 6-14.
117. Kiserud, T., et al., *The World Health Organization Fetal Growth Charts: A Multinational Longitudinal Study of Ultrasound Biometric Measurements and Estimated Fetal Weight.* PLoS Med, 2017. **14**(1): p. e1002220.
118. de Onis, M., et al., *Development of a WHO growth reference for school-aged children and adolescents.* Bull World Health Organ, 2007. **85**(9): p. 660-7.
119. *Helsedirektoratet. Helsestasjon, skolehelsetjeneste og helsestasjon for ungdom.* . [cited 2023 March 14]; Available from: https://www.helsedirektoratet.no/retningslinjer/helsestasjons-og-skolehelsetjenesten/helsestasjon-05-ar/veiing-og-maling#veiing-og-maling-helsestasjon-bor-male-vekt-og-lengdehoyde-pa-barn-0-5-ar-referanser.
120. *The Bergen growth study.* . [cited 2023 March 14]; Available from: http://www.vekststudien.no/en/.
121. Júlíusson, P.B., et al., *Growth references for 0-19 year-old Norwegian children for length/height, weight, body mass index and head circumference.* Ann Hum Biol, 2013. **40**(3): p. 220-7.
122. *Rikshandboken barnhälsovård för professionen. Tillväxtkurvor och tillväxtreferenser*. 2022-08-08 [cited 2023 March 14]; Available from: https://www.rikshandboken-bhv.se/tillvaxt--utveckling/tillvaxt---oversikt/metoder-for-matning-och-vagning---oversikt/tillvaxtkurvor-och-tillvaxtreferenser/.
123. Singhal, A., *Long-Term Adverse Effects of Early Growth Acceleration or Catch-Up Growth.* Ann Nutr Metab, 2017. **70**(3): p. 236-240.
124. *Infant and young child feeding. WHO. 2021*. 2022-12-16]; Available from: https://www.who.int/news-room/fact-sheets/detail/infant-and-young-child-feeding.
125. Martin, C.R., P.R. Ling, and G.L. Blackburn, *Review of Infant Feeding: Key Features of Breast Milk and Infant Formula.* Nutrients, 2016. **8**(5).
126. Victora, C.G., et al., *Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect.* The Lancet, 2016. **387**(10017): p. 475-490.
127. Ong, K.K., et al., *Insulin-like growth factor I concentrations in infancy predict differential gains in body length and adiposity: the Cambridge Baby Growth Study.* The American Journal of Clinical Nutrition, 2009. **90**(1): p. 156-161.
128. Mameli, C., S. Mazzantini, and G.V. Zuccotti, *Nutrition in the First 1000 Days: The Origin of Childhood Obesity.* Int J Environ Res Public Health, 2016. **13**(9).
129. Jebasingh, F. and N. Thomas, *Barker Hypothesis and Hypertension.* Front Public Health, 2021. **9**: p. 767545.
130. *World Health Organization. Training Course on Child Growth Assessment. Geneva, WHO, 2008*.

131. *Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults.* Lancet, 2017. **390**(10113): p. 2627-2642.
132. Thurstans, S., et al., *The relationship between wasting and stunting in young children: A systematic review.* Matern Child Nutr, 2022. **18**(1): p. e13246.
133. *Malnutrition. The World Health Organization.* . [cited 2023 March 14]; Available from: https://www.who.int/health-topics/malnutrition#tab=tab_1.
134. Ma, D., et al., *Effects of rapid growth on fasting insulin and insulin resistance: a system review and meta-analysis.* Eur J Clin Nutr, 2021. **75**(8): p. 1193-1204.
135. Monteiro, P.O.A. and C.G. Victora, *Rapid growth in infancy and childhood and obesity in later life--a systematic review.* Obesity reviews : an official journal of the International Association for the Study of Obesity, 2005. **6**(2): p. 143-154.
136. Chrestani, M.A., et al., *Associated factors for accelerated growth in childhood: a systematic review.* Matern Child Health J, 2013. **17**(3): p. 512-9.
137. Wit, J.M. and B. Boersma, *Catch-up growth: definition, mechanisms, and models.* J Pediatr Endocrinol Metab, 2002. **15 Suppl 5**: p. 1229-41.
138. Kelly, A.C., T.L. Powell, and T. Jansson, *Placental function in maternal obesity.* Clin Sci (Lond), 2020. **134**(8): p. 961-984.
139. Vats, H., et al., *Impact of maternal pre-pregnancy body mass index on maternal, fetal and neonatal adverse outcomes in the worldwide populations: A systematic review and meta-analysis.* Obes Res Clin Pract, 2021. **15**(6): p. 536-545.
140. Kahn, B.B. and J.S. Flier, *Obesity and insulin resistance.* J Clin Invest, 2000. **106**(4): p. 473-81.
141. Dubé, E., et al., *Modulation of fatty acid transport and metabolism by maternal obesity in the human full-term placenta.* Biol Reprod, 2012. **87**(1): p. 14, 1-11.
142. Dabelea, D. and T. Crume, *Maternal environment and the transgenerational cycle of obesity and diabetes.* Diabetes, 2011. **60**(7): p. 1849-55.
143. Voerman, E., et al., *Maternal body mass index, gestational weight gain, and the risk of overweight and obesity across childhood: An individual participant data meta-analysis.* PLoS Med, 2019. **16**(2): p. e1002744.
144. Rolland-Cachera, M.F., et al., *Adiposity rebound in children: a simple indicator for predicting obesity.* Am J Clin Nutr, 1984. **39**(1): p. 129-35.
145. WHO. *Obesity and overweight*. 2023 [cited 2023 15-02]; Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.

146. Cole, T.J., et al., *Establishing a standard definition for child overweight and obesity worldwide: international survey.* Bmj, 2000. **320**(7244): p. 1240-3.
147. Cole, T.J. and T. Lobstein, *Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity.* Pediatr Obes, 2012. **7**(4): p. 284-94.
148. *Prevalence of overweight among children and adolescents, BMI > +1 standard deviations above the median (crude estimate) (%)*. [cited 2022-09-29; Available from: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/prevalence-of-overweight-among-children-and-adolescents-bmi-1-standard-deviations-above-the-median-(crude-estimate)-(-).
149. Kumar, S. and A.S. Kelly, *Review of Childhood Obesity: From Epidemiology, Etiology, and Comorbidities to Clinical Assessment and Treatment.* Mayo Clin Proc, 2017. **92**(2): p. 251-265.
150. Stephenson, J., et al., *Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health.* Lancet, 2018. **391**(10132): p. 1830-1841.
151. Lau, E.Y., et al., *Maternal weight gain in pregnancy and risk of obesity among offspring: a systematic review.* J Obes, 2014. **2014**: p. 524939.
152. Tareke, A.A., et al., *Maternal vitamin D and growth of under-five children: a systematic review and meta-analysis of observational and interventional studies.* Glob Health Action, 2022. **15**(1): p. 2102712.
153. Pérez-López, F.R., et al., *Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controlled trials.* Fertility and sterility, 2015. **103**(5): p. 1278-88.e4.
154. Palacios, C., et al., *Regimens of vitamin D supplementation for women during pregnancy.* Cochrane Database Syst Rev, 2019(10).
155. Bi, W.G., et al., *Association Between Vitamin D Supplementation During Pregnancy and Offspring Growth, Morbidity, and Mortality: A Systematic Review and Meta-analysis.* JAMA pediatrics, 2018. **172**(7): p. 635-645.
156. Kalra, P., et al., *Effect of vitamin D supplementation during pregnancy on neonatal mineral homeostasis and anthropometry of the newborn and infant.* The British journal of nutrition, 2012. **108**(6): p. 1052-1058.
157. Roth, D.E., et al., *Maternal vitamin D3 supplementation during the third trimester of pregnancy: effects on infant growth in a longitudinal follow-up study in Bangladesh.* The Journal of pediatrics, 2013. **163**(6): p. 1605-1611.e3.
158. Brooke, O.G., et al., *Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth.* British medical journal, 1980. **280**(6216): p. 751-754.

159. Ma, K., et al., *Effect of Vitamin D Supplementation in Early Life on Children's Growth and Body Composition: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.* Nutrients, 2021. **13**(2).
160. Curtis, E.M., et al., *Pregnancy Vitamin D Supplementation and Childhood Bone Mass at Age 4 Years: Findings From the Maternal Vitamin D Osteoporosis Study (MAVIDOS) Randomized Controlled Trial.* JBMR Plus, 2022. **6**(7): p. e10651.
161. O'Callaghan, K.M., et al., *Effect of maternal prenatal and postpartum vitamin D supplementation on offspring bone mass and muscle strength in early childhood: follow-up of a randomized controlled trial.* Am J Clin Nutr, 2022. **115**(3): p. 770-780.
162. Gale, C.R., et al., *Maternal vitamin D status during pregnancy and child outcomes.* Eur J Clin Nutr, 2008. **62**(1): p. 68-77.
163. Leffelaar, E.R., T.G.M. Vrijkotte, and M. van Eijsden, *Maternal early pregnancy vitamin D status in relation to fetal and neonatal growth: results of the multi-ethnic Amsterdam Born Children and their Development cohort.* The British journal of nutrition, 2010. **104**(1): p. 108-117.
164. Eckhardt, C.L., et al., *Maternal vitamin D status and infant anthropometry in a US multi-centre cohort study.* Ann Hum Biol, 2015. **42**(3): p. 215-222.
165. Gould, J.F., et al., *Association of cord blood vitamin D with early childhood growth and neurodevelopment.* Journal of paediatrics and child health, 2017. **53**(1): p. 75-83.
166. Crozier, S.R., et al., *Maternal vitamin D status in pregnancy is associated with adiposity in the offspring: findings from the Southampton Women's Survey.* The American journal of clinical nutrition, 2012. **96**(1): p. 57-63.
167. Krishnaveni, G.V., et al., *Maternal vitamin D status during pregnancy and body composition and cardiovascular risk markers in Indian children: the Mysore Parthenon Study.* The American journal of clinical nutrition, 2011. **93**(3): p. 628-635.
168. Morales, E., et al., *Deficit of vitamin D in pregnancy and growth and overweight in the offspring.* Int J Obes (Lond), 2015. **39**(1): p. 61-68.
169. Benjamin Neelon, S.E., et al., *Maternal vitamin D, DNA methylation at imprint regulatory regions and offspring weight at birth, 1 year and 3 years.* Int J Obes (Lond), 2018. **42**(4): p. 587-593.
170. Daraki, V., et al., *Low maternal vitamin D status in pregnancy increases the risk of childhood obesity.* Pediatr Obes, 2018. **13**(8): p. 467-475.
171. Hrudey, E.J., et al., *The Association between Maternal 25-Hydroxyvitamin D Concentration during Gestation and Early Childhood Cardio-metabolic Outcomes: Is There Interaction with Pre-Pregnancy BMI?* PloS one, 2015. **10**(8): p. e0133313-e0133313.
172. Boyle, V.T., et al., *The relationship between maternal 25-hydroxyvitamin D status in pregnancy and childhood adiposity and allergy: an observational study.* Int J Obes (Lond), 2017. **41**(12): p. 1755-1760.

173. Miliku, K., et al., *Associations of maternal and fetal vitamin D status with childhood body composition and cardiovascular risk factors.* Matern Child Nutr, 2019. **15**(2): p. e12672-e12672.
174. Carreras-Badosa, G., et al., *Serum 25-hydroxyvitamin D and cardiovascular disease risk factors in women with excessive weight gain during pregnancy and in their offspring at age 5-6 years.* Int J Obes (Lond), 2018. **42**(5): p. 1019-1028.
175. Williams, D.M., et al., *Associations of maternal 25-hydroxyvitamin D in pregnancy with offspring cardiovascular risk factors in childhood and adolescence: findings from the Avon Longitudinal Study of Parents and Children.* Heart, 2013. **99**(24): p. 1849-56.
176. Tornhammar, P., et al., *Season of birth, neonatal vitamin D status, and cardiovascular disease risk at 35 y of age: a cohort study from Sweden.* The American journal of clinical nutrition, 2014. **99**(3): p. 472-478.
177. Rytter, D., et al., *Maternal Vitamin D Status at Week 30 of Gestation and Offspring Cardio-Metabolic Health at 20 Years: A Prospective Cohort Study over Two Decades.* PLoS One, 2016. **11**(10): p. e0164758.
178. Hyde, N.K., et al., *Vitamin D during pregnancy and offspring body composition: a prospective cohort study.* Pediatr Obes, 2018. **13**(8): p. 514-521.
179. Jensen, C.B., et al., *Neonatal Vitamin D Levels in Relation to Risk of Overweight at 7 Years in the Danish D-Tect Case-Cohort Study.* Obesity facts, 2017. **10**(3): p. 273-283.
180. Jiang, X., et al., *Association between maternal vitamin D status with pregnancy outcomes and offspring growth in a population of Wuxi, China.* Asia Pac J Clin Nutr, 2021. **30**(3): p. 464-476.
181. Tint, M.T., et al., *Association between maternal mid-gestation vitamin D status and neonatal abdominal adiposity.* Int J Obes (Lond), 2018. **42**(7): p. 1296-1305.
182. Wood, R.J., *Vitamin D and adipogenesis: new molecular insights.* Nutr Rev, 2008. **66**(1): p. 40-6.
183. Chang, E. and Y. Kim, *Vitamin D decreases adipocyte lipid storage and increases NAD-SIRT1 pathway in 3T3-L1 adipocytes.* Nutrition, 2016. **32**(6): p. 702-8.
184. Belenchia, A.M., et al., *In utero vitamin D deficiency predisposes offspring to long-term adverse adipose tissue effects.* J Endocrinol, 2017. **234**(3): p. 301-313.
185. Thorne-Lyman, A. and W.W. Fawzi, *Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis.* Paediatr Perinat Epidemiol, 2012. **26 Suppl 1**(0 1): p. 75-90.
186. Senti, J., D.K. Thiele, and C.M. Anderson, *Maternal vitamin D status as a critical determinant in gestational diabetes.* J Obstet Gynecol Neonatal Nurs, 2012. **41**(3): p. 328-38.
187. Szymczak-Pajor, I. and A. Śliwińska, *Analysis of Association between Vitamin D Deficiency and Insulin Resistance.* Nutrients, 2019. **11**(4).

188. Tian, M., et al., *Low birth weight, a risk factor for diseases in later life, is a surrogate of insulin resistance at birth.* J Hypertens, 2019. **37**(11): p. 2123-2134.
189. Gillman, M.W., et al., *Maternal gestational diabetes, birth weight, and adolescent obesity.* Pediatrics, 2003. **111**(3): p. e221-6.
190. Liu, N.Q., et al., *Vitamin D and the regulation of placental inflammation.* J Immunol, 2011. **186**(10): p. 5968-74.
191. Amarilyo, G., et al., *Increased cord serum inflammatory markers in small-for-gestational-age neonates.* J Perinatol, 2011. **31**(1): p. 30-2.
192. Satokar, V.V., et al., *Omega-3 fats in pregnancy: could a targeted approach lead to better metabolic health for children?* Nutr Rev, 2020. **79**(5): p. 574-584.
193. Chagas, C.E., et al., *Focus on vitamin D, inflammation and type 2 diabetes.* Nutrients, 2012. **4**(1): p. 52-67.
194. Magnus, P., et al., *Cohort profile: the Norwegian Mother and Child Cohort Study (MoBa).* Int J Epidemiol, 2006. **35**(5): p. 1146-50.
195. Magnus, P., et al., *Cohort Profile Update: The Norwegian Mother and Child Cohort Study (MoBa).* Int J Epidemiol, 2016. **45**(2): p. 382-8.
196. Nilsen, R.M., et al., *Self-selection and bias in a large prospective pregnancy cohort in Norway.* Paediatr Perinat Epidemiol, 2009. **23**(6): p. 597-608.
197. Willett, W., *Nutritional epidemiology*. Biochemical indicators od dietary intake, ed. D.H. Rob M. Van Dam. 2012, Oxford Scholarship Online.
198. Olafsdottir, A.S., et al., *Comparison of women's diet assessed by FFQs and 24-hour recalls with and without underreporters: associations with biomarkers.* Ann Nutr Metab, 2006. **50**(5): p. 450-60.
199. Masson, L.F., et al., *Statistical approaches for assessing the relative validity of a food-frequency questionnaire: use of correlation coefficients and the kappa statistic.* Public Health Nutr, 2003. **6**(3): p. 313-321.
200. Brantsaeter, A.L., et al., *Self-reported dietary supplement use is confirmed by biological markers in the Norwegian Mother and Child Cohort Study (MoBa).* Ann Nutr Metab, 2007. **51**(2): p. 146-54.
201. Brantsaeter, A.L., et al., *Validity of a new food frequency questionnaire for pregnant women in the Norwegian Mother and Child Cohort Study (MoBa).* Matern Child Nutr, 2008. **4**(1): p. 28-43.
202. Achón, M., et al., *Effects of Milk and Dairy Product Consumption on Pregnancy and Lactation Outcomes: A Systematic Review.* Adv Nutr, 2019. **10**(suppl_2): p. S74-s87.
203. Imhoff-Kunsch, B., et al., *Effect of n-3 long-chain polyunsaturated fatty acid intake during pregnancy on maternal, infant, and child health outcomes: a systematic review.* Paediatr Perinat Epidemiol, 2012. **26** p. 91-107.
204. Middleton, P., et al., *Omega‐3 fatty acid addition during pregnancy.* Cochrane Database Syst Rev, 2018(11).

205. Ross, A.C., *The 2011 report on dietary reference intakes for calcium and vitamin D.* Public Health Nutr, 2011. **14**(5): p. 938-9.
206. Snellman, G., et al., *Determining vitamin D status: a comparison between commercially available assays.* PLoS One, 2010. **5**(7): p. e11555.
207. Binkley, N., et al., *Assay variation confounds the diagnosis of hypovitaminosis D: a call for standardization.* J Clin Endocrinol Metab, 2004. **89**(7): p. 3152-7.
208. Walker, E. *DEQAS. Vitamin D External Quality Assessment Scheme*. [cited 2022 2 March]; Available from: http://www.deqas.org/.
209. Durazo-Arvizu, R.A., et al., *The Vitamin D Standardization Program (VDSP) Manual for Retrospective Laboratory Standardization of Serum 25-Hydroxyvitamin D Data.* J AOAC Int, 2017. **100**(5): p. 1234-1243.
210. Cole, T.J., J.V. Freeman, and M.A. Preece, *British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood.* Stat Med, 1998. **17**(4): p. 407-29.
211. Ong, K.K. and R.J. Loos, *Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful suggestions.* Acta Paediatr, 2006. **95**(8): p. 904-8.
212. Ong, K.K., et al., *Association between postnatal catch-up growth and obesity in childhood: prospective cohort study.* Bmj, 2000. **320**(7240): p. 967-71.
213. Lawlor, D.A., K. Tilling, and G. Davey Smith, *Triangulation in aetiological epidemiology.* Int J Epidemiol, 2016. **45**(6): p. 1866-1886.
214. Bravata, D.M. and I. Olkin, *Simple pooling versus combining in meta-analysis.* Eval Health Prof, 2001. **24**(2): p. 218-30.
215. Curran, P.J., K. Obeidat, and D. Losardo, *Twelve Frequently Asked Questions About Growth Curve Modeling.* Journal of cognition and development : official journal of the Cognitive Development Society, 2010. **11**(2): p. 121-136.
216. Jenss and Bayley, *A mathematical method for studying the growth of a child.* . Human Biology, 1937. **9**: p. 556-563.
217. Botton, J., et al., *Postnatal weight and height growth velocities at different ages between birth and 5 y and body composition in adolescent boys and girls.* Am J Clin Nutr, 2008. **87**(6): p. 1760-8.
218. Botton, J., et al., *Postnatal weight and height growth modeling and prediction of body mass index as a function of time for the study of growth determinants.* Ann Nutr Metab, 2014. **65**(2-3): p. 156-66.
219. Regnault, N., et al., *Comparative study of four growth models applied to weight and height growth data in a cohort of US children from birth to 9 years.* Annals of nutrition & metabolism, 2014. **65**(2-3): p. 167-174.
220. Berkey, C.S., *Comparison of two longitudinal growth models for preschool children.* Biometrics, 1982. **38**(1): p. 221-34.

221. Chirwa, E.D., et al., *Multi-level modelling of longitudinal child growth data from the Birth-to-Twenty Cohort: a comparison of growth models.* Ann Hum Biol, 2014. **41**(2): p. 168-179.
222. Ahmadi, S., et al., *Comparison of growth models to describe growth from birth to 6 years in a Beninese cohort of children with repeated measurements.* BMJ Open, 2020. **10**(9): p. e035785.
223. Júlíusson, P.B., et al., *Overweight and obesity in Norwegian children: prevalence and socio-demographic risk factors.* 2010. **99**(6): p. 900-905.
224. Donkor, H.M., et al., *Social and somatic determinants of underweight, overweight and obesity at 5 years of age: a Norwegian regional cohort study.* BMJ Open, 2017. **7**(8): p. e014548.
225. *FolkhälsoStudio. Web-based tool for public health statistics in Sweden. Available at: https://www.folkhalsomyndigheten.se/datavisualisering/ Folkhälsomyndigheten. 2022. [Access Date 2022-01-05]. .*
226. Ram, N. and K.J. Grimm, *Growth Mixture Modeling: A Method for Identifying Differences in Longitudinal Change Among Unobserved Groups.* Int J Behav Dev, 2009. **33**(6): p. 565-576.
227. van der Nest, G., et al., *An overview of mixture modelling for latent evolutions in longitudinal data: Modelling approaches, fit statistics and software.* Advances in Life Course Research, 2020. **43**: p. 100323.
228. Elhakeem, A., et al., *Using linear and natural cubic splines, SITAR, and latent trajectory models to characterise nonlinear longitudinal growth trajectories in cohort studies.* BMC Med Res Methodol, 2022. **22**(1): p. 68.
229. van de Schoot, R., et al., *The GRoLTS-Checklist: Guidelines for Reporting on Latent Trajectory Studies.* Structural Equation Modeling: A Multidisciplinary Journal, 2017. **24**(3): p. 451-467.
230. Nguena Nguefack, H.L., et al., *Trajectory Modelling Techniques Useful to Epidemiological Research: A Comparative Narrative Review of Approaches.* Clin Epidemiol, 2020. **12**: p. 1205-1222.
231. Buscot, M.J., et al., *Distinct child-to-adult body mass index trajectories are associated with different levels of adult cardiometabolic risk.* Eur Heart J, 2018. **39**(24): p. 2263-2270.
232. Mattsson, M., et al., *Group-based trajectory modelling for BMI trajectories in childhood: A systematic review.* Obes Rev, 2019. **20**(7): p. 998-1015.
233. Muthén, B. and L.K. Muthén, *Integrating person-centered and variable-centered analyses: growth mixture modeling with latent trajectory classes.* Alcohol Clin Exp Res, 2000. **24**(6): p. 882-91.
234. Ong, Y.L., et al., *The association of maternal vitamin D status with infant birth outcomes, postnatal growth and adiposity in the first 2 years of life in a multi-ethnic Asian population: the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort study.* The British journal of nutrition, 2016. **116**(4): p. 621-631.