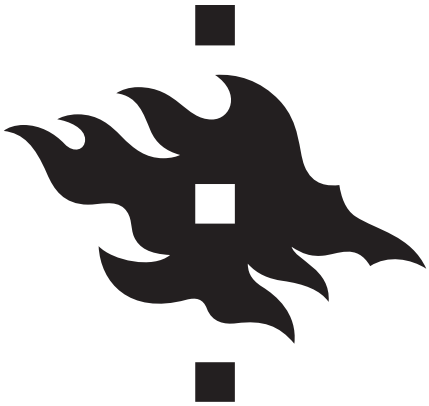

UNIVERSITY OF HELSINKI
FACULTY OF MEDICINE

VITAMIN D IN PREGNANCY AND INFANCY

DIETARY SOURCES AND ASSOCIATIONS WITH PREGNANCY OUTCOMES AND INFANT GROWTH

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Helena Hauta-alus

DOCTORAL DISSERTATION

To be presented, for public discussion with the permission of the Faculty of Medicine of the University of Helsinki, in Lecture Hall 2, Biomedicum, on the 20th of December, 2019 at 12 noon.

Helsinki 2019

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ISBN 978-951-51-5666-2 (pbk.)
ISBN 978-951-51-5667-9 (PDF)
Painosalama Oy
Turku 2019

The Faculty of Medicine uses the Urkund system (plagiarism recognition) to examine all doctoral dissertations.

"Education is the premise of progress, in every society, in every family."
-Kofi Annan

ABSTRACT

Vitamin D is vital for normal growth and development. Vitamin D is produced endogenously in the skin after sunlight exposure or obtained from dietary sources. In Finland, solar radiation is inadequate for cutaneous vitamin D synthesis in winter, leading to a high risk for vitamin D insufficiency, defined by circulating 25-hydroxyvitamin D concentration [25(OH)D] below 50 nmol/l. Poor maternal 25(OH)D has been associated with adverse pregnancy and neonatal outcomes, such as pre-eclampsia, gestational diabetes mellitus (GDM), and low birth weight. Only a few studies have explored the relationship between vitamin D and infant postnatal growth, and these studies show inconsistent results. Further, data on current maternal vitamin D status and infant vitamin D intake in Finland are lacking.

The objectives of this thesis were to 1) define maternal and newborn 25(OH)D concentrations and characterize maternal determinants of vitamin D status during pregnancy; 2) examine whether vitamin D status differs between mothers with and without GDM; 3) describe vitamin D intake from food and identify food sources of vitamin D in 1-year-old infants, and finally, 4) investigate whether maternal or infant vitamin D status associate with pre- and postnatal infant growth.

This thesis is part of the Vitamin D Intervention in Infants (VIDI) study. At Helsinki Maternity Hospital, 987 families were recruited to the study from January 2013 to June 2014. Infants were randomized to daily supplemental vitamin D dosages of 10 μg or 30 μg from 2 weeks until 2 years of age. Mothers were of Northern European ethnicity without regular medication. Infants were born at term with birth weights appropriate for gestational age. Maternal serum samples were collected at prenatal clinics between 2012 and 2013 in early pregnancy. At birth, umbilical cord blood (UCB) was obtained. Circulating 25(OH)D was analyzed with IDS-iSYS from pregnancy, UCB and infant serum samples at 1 year of age. Maternal dietary patterns were derived from a 22-item food frequency questionnaire and infant vitamin D intake was assessed with a 3-day food record. GDM diagnosis and data on infant birth size were obtained from medical records. Infant growth was measured at study visits at the ages of 6 months and 1 year.

Overall, the pregnant women and their newborns were vitamin D sufficient as the concentration of 25(OH)D in 96% of all subjects was ≥50 nmol/l. Of pregnant women, 95% used vitamin D supplements with a mean daily intake of 16 μg. Maternal positive predictors of 25(OH)D during pregnancy, based on 25(OH)D from early pregnancy to UCB, were supplemental vitamin D intake, a dietary pattern characterized by regular use of vitamin D–fortified foods and prepregnancy physical activity. In contrast, factors associating with declining 25(OH)D during pregnancy were smoking and multiparity.

GDM was observed in 11% of the pregnant women. Maternal 25(OH)D concentrations did not differ between GDM and non-GDM women. Furthermore, 25(OH)D had no relation to oral glucose tolerance test results. Mean daily intake of vitamin D from food was 7.5 μg in non-breastfed and 3.8 μg in breastfed 1-year-old infants. The main food sources of vitamin D were infant formula, dairy milk, porridge, and fish foods.

Higher maternal and infant 25(OH)D were associated with slower infant growth. At 6 months of age, infants to mothers with high pregnancy 25(OH)D (>125 nmol/l) were the shortest (in length), lightest (in weight), and thinnest (in length-adjusted weight). Higher UCB 25(OH)D had an inverse association with head circumference at birth and infant length at 6 months. In infants, higher UCB 25(OH)D associated with slower linear growth from birth to 6 months, but an accelerated growth from 6 months to 1 year of age. Infants with 25(OH)D >125 nmol/l were the lightest and thinnest at 1 year of age, whereas mothers with UCB 25(OH)D <50 nmol/l had the thinnest infants at 6 months.

In conclusion, vitamin D status was sufficient among pregnant women in Finland. Likewise, infants who participated in a vitamin D supplementation trial had sufficient vitamin D status at 1 year of age. High maternal and infant 25(OH)D associated with slower infant growth. These results may indicate a possible inverse U-shaped relationship between vitamin D status and growth. The clinical relevance of this finding remains unknown. Until more data emerge, there is no need to aim for higher maternal or infant 25(OH)D concentrations beyond vitamin D sufficiency with excessive supplementation as this may have disadvantageous effects on infant growth.

TIIVISTELMÄ

D-vitamiini on välttämätöntä normaalille kasvulle ja kehitykselle. D-vitamiinia muodostuu iholla auringonvalon vaikutuksesta ja sitä saadaan myös ruuasta tai ravintovalmisteista. Suomessa auringonvalo on riittämätöntä talviaikaan ihon D-vitamiinisynteesille lisäten D-vitamiinin puutoksen riskiä. Elimistön D-vitamiinitaso määritetään veren 25-hydroksi-D-vitamiinipitoisuutena [25(OH)D]. D-vitamiinitaso on riittämätön 25(OH)D-pitoisuuden ollessa alle 50 nmol/l. Raskausajan alhainen 25(OH)D-pitoisuus on yhdistetty raskauskomplikaatioihin, kuten raskausmyrkytykseen ja raskausdiabetekseen, sekä vastasyntyneen pienipainoisuuteen. Vain harvat tutkimukset ovat selvittäneet D-vitamiinin ja syntymän jälkeisen kasvun välisiä yhteyksiä, ja nämäkin tutkimustulokset ovat olleet keskenään ristiriitaisia. Suomalaisten raskaana olevien naisten D-vitamiinitasosta ja pikkulasten nykyisestä D-vitamiinin saannista ei ole ajantasaista tietoa.

Tämän väitöskirjan tavoitteet olivat 1) selvittää raskaana olevien naisten ja vastasyntyneiden D-vitamiinitaso sekä kuvata tekijät, jotka vaikuttavat 25(OH)D-pitoisuuteen raskausaikana; 2) tutkia eroaako raskausajan 25(OH)D-pitoisuus raskausdiabetesta sairastavien ja ei-sairastavien välillä; 3) kuvata 1-vuotiaiden lasten D-vitamiinin saanti ruuasta ja ravinnon tärkeimmät D-vitamiinin lähteet ja lopuksi 4) tutkia onko raskausajan tai varhaislapsuuden 25(OH)D-pitoisuus yhteydessä sikiöaikaiseen ja varhaislapsuuden kasvuun.

Väitöskirja on osa Lasten D-vitamiini -tutkimusta (VIDI). VIDI-tutkimukseen on rekrytoitu Helsingin Kätilöopiston sairaalassa vuosien 2013–14 aikana 987 lasta perheineen lapsen syntymän jälkeen. Lapset satunnaistettiin saamaan päivittäin D-vitamiinivalmistetta joko 10 µg tai 30 µg alkaen kahden viikon iästä kahden vuoden ikään saakka. Äidit olivat pohjoiseurooppalaista syntyperää ilman säännöllistä lääkitystä. Lapset olivat syntyneet täysiaikaisina ja syntymäpaino oli normaali raskauden kestoon nähden. Äitien alkuraskauden verinäytteet olivat kerätty normaalin neuvolaseurannan yhteydessä vuosina 2012-13 ja säilytetty Äitiysneuvolaseerumipankissa. Syntymän yhteydessä otettiin napaverinäyte. Veren 25(OH)D-pitoisuudet mitattiin raskausajan verinäytteestä, napaverestä sekä lapsen verinäytteestä hänen ollessaan 1 vuoden ikäinen. Raskausajan ruuankäyttötieto kerättiin 22-kohtaisella frekvenssikyselylomakkeella, ja lapsen D-vitamiinin saanti laskettiin kolmen päivän ruokapäiväkirjan avulla lapsen ollessa 1 vuoden ikäinen. Tiedot raskausdiabeteksesta ja syntymäkoosta kerättiin terveydenhuollon rekistereistä. Lapsen koko mitattiin tutkimuskäynneillä 6 kuukauden ja 1 vuoden iässä.

Raskaana olevien naisten ja vastasyntyneiden D-vitamiinitilanne oli riittävä, sillä suurimmalla osalla veren 25(OH)D-pitoisuus oli vähintään 50 nmol/l. Raskaana olevista naisista 95% käytti D-vitamiinivalmistetta ja

keskimääräinen D-vitamiinin saanti ravintovalmisteista oli 16 µg. Raskausajan 25(OH)D-pitoisuutta lisäsivät suurempi D-vitamiinin saanti valmisteista, ruokavaliotyyli, johon liittyi säännöllinen D-vitaminoitujen ruokien käyttö sekä liikunnallinen aktiivisuus ennen raskautta. Tupakointi ja monisynnyttäneisyys vähensivät 25(OH)D-pitoisuutta raskauden aikana.

Raskausdiabetes oli todettu 11% raskaana olevista naisista. Raskausajan 25(OH)D-pitoisuus ei eronnut raskausdiabetesta sairastavien ja ei-sairastavien välillä. Lisäksi 25(OH)D-pitoisuus ei ollut yhteydessä gluukosirasituskokeen tuloksiin. Pikkulasten keskimääräinen päivittäinen D-vitamiinin saanti ruuasta oli 7.5 µg ei-imetetyillä ja 3.8 µg imetetyillä 1 vuoden iässä. Pääasialliset D-vitamiinin saantilähteet olivat äidinmaidonkorvike, maito, puuro ja kalaruuat 1-vuotiailla lapsilla.

Korkeampi raskausajan ja pikkulapsen 25(OH)D-pitoisuus oli yhteydessä lapsen hitaampaan kasvuun. Kuuden kuukauden iässä lyhyimmät, kevyimmät ja laihimmat lapset olivat ne, joiden äideillä oli alkuraskauden 25(OH)D-pitoisuus yli 125 nmol/l. Korkeampi napaveren 25(OH)D-pitoisuus oli yhteydessä vastasyntyneen pienempään päänympärykseen sekä hitaampaan pituuskasvuun 6 kuukauden iässä. Korkeampi napaveren 25(OH)D-pitoisuus oli yhteydessä hitaampaan kasvuvauhtiin syntymästä 6 kuukauden ikään saakka, mutta kiihtyneeseen kasvuvauhtiin 6 kuukauden jälkeen 1 vuoden ikään saakka. Lapset, joilla oli korkea 25(OH)D-pitoisuus 1 vuoden iässä (25(OH)D >125 nmol/l) olivat myös kevyimmät ja laihimmat 1 vuoden iässä. Toisaalta, lapset, joilla napaveren 25(OH)D oli alle 50 nmol/l, olivat laihimmat 6 kuukauden iässä.

Yhteenvetona voidaan todeta, että raskaana olevien naisten D-vitamiinitaso oli riittävä. Samoin myös D-vitamiini-interventiotutkimukseen osallistuneiden pikkulasten D-vitamiinitaso oli riittävä. Korkea raskausajan ja varhaislapsuuden 25(OH)D-pitoisuus oli yhteydessä lapsen hitaampaan kasvuun. Nämä tulokset voivat viitata käänteiseen U-käyrän muotoiseen yhteyteen D-vitamiinin ja kasvun välillä. Löydöksen kliinistä merkitystä ei tiedetä. Tämän hetkisen tiedon valossa ei ole syytä tavoitella riittävän 25(OH)D-pitoisuuden ylittäviä pitoisuuksia syömällä suurempia D-vitamiiniannoksia raskauden tai varhaislapsuuden aikana, koska sillä voi olla epäedullisia vaikutuksia lapsen kasvuun.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Hauta-alus HH, Holmlund-Suila EM, Rita HJ, Enlund-Cerullo M, Rosendahl J, Valkama SM, Helve OM, Hytinantti TK, Surcel H-M, Mäkitie OM, Andersson S, Viljakainen HT. Season, dietary factors, and physical activity modify 25-hydroxyvitamin D concentration during pregnancy. European Journal of Nutrition 2018, Jun;57(4):1369-1379. doi: 10.1007/s00394-017-1417-z.

II Hauta-alus HH, Viljakainen HT, Holmlund-Suila EM, Enlund-Cerullo M, Rosendahl J, Valkama SM, Helve OM, Hytinantti TK, Mäkitie OM, Andersson S. Maternal Vitamin D Status, Gestational Diabetes and Infant Birth Size. BMC Pregnancy and Childbirth 2017, Dec 15;17(1):420. doi: 10.1186/s12884-017-1600-5

III Hauta-alus HH, Korkalo L, Holmlund-Suila EM, Rosendahl J, Valkama SM, Enlund-Cerullo M, Helve OM, Hytinantti TK, Mäkitie OM, Andersson S, Viljakainen HT. Food and Nutrient Intake and Nutrient Sources in 1-Year-Old Infants in Finland: A Cross-Sectional Analysis. Nutrients 2017, Dec 1;9(12):1309. doi: 10.3390/nu9121309

IV Hauta-alus HH, Kajantie E, Holmlund-Suila EM, Rosendahl J, Valkama SM, Enlund-Cerullo M, Helve OM, Hytinantti TK, Viljakainen HT, Andersson S, Mäkitie OM. High Pregnancy, Cord Blood, and Infant Vitamin D Concentrations May Predict Slower Infant Growth. The Journal of Clinical Endocrinology & Metabolism (JCEM) 2019, 104: 397-407. doi: 10.1210/jc.2018-00602.

The publications are referred to in the text by their Roman numerals. The publications reprinted with the permission of their copyright holders. In addition, some unpublished material is presented.

ABBREVIATIONS

$1,25(OH)_2D$	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
ANCOVA	analysis of covariance
BMI	body mass index
DBP	vitamin D-binding protein
DEQAS	Vitamin D Quality Assessment Scheme
DIPP	Type 1 Diabetes Prediction and Prevention study
DNA	Deoxyribonucleic acid
DP	dietary pattern
ECTS	European Calcified Tissue Society
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organization of the United Nations
FFQ	food frequency questionnaire
FGF23	fibroblast growth factor 23
GDM	gestational diabetes mellitus
GWG	gestational weight gain
HIV	human immunodeficiency virus
IGF-1	insulin-like growth factor 1
IOM	Institute of Medicine, presently NAM
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LI	lower intake level
MUAC	mid-upper-arm circumference
NAM	National Academy of Medicine
NI	not investigated
NIST	National Institute of Standards and Technology
NNR	Nordic Nutrition Recommendations
NS	non-significant
OGTT	oral glucose tolerance test
PCA	principal component analysis
PTH	parathyroid hormone
RADIEL	The Finnish Gestational Diabetes Prevention study
RCT	randomized controlled trial
SD	standard deviation
SDS	standard deviation score
SGA	small-for-gestational age
TB	tuberculosis
UCB	umbilical cord blood
UL	upper intake level
UVB	ultraviolet light B
VDR	vitamin D receptor
VDSP	Vitamin D Standardization Programme

VIDI	Vitamin D Intervention in Infants study
WHO	World Health Organization

1 INTRODUCTION

Vitamin D is vital for child development and growth and for maintaining mineral homeostasis required for normal body functions. Vitamin D is produced endogenously in the skin induced by solar ultraviolet light B (UVB). Other sources of vitamin D are food—mainly fish and fortified foods—and supplements. Vitamin D status is determined by blood 25-hydroxyvitamin D concentration [25(OH)D], but the definition for sufficient vitamin D status is under debate [1]. Severe vitamin D deficiency increases the risk of the disabling bone disease rickets in children and osteomalacia in adults. Indeed, traditionally, the main function of vitamin D has been regarded to be the maintenance of bone health and calcium-phosphate homeostasis. Recently, it has been observed that vitamin D influences processes beyond bone and mineral metabolism, and a vast amount of research has associated vitamin D deficiency with several extraskeletal diseases and conditions [2]. In addition, vitamin D status has also been recognized as a general health status indicator, associating, for example, with obesity, smoking, and physical activity [3, 4]. Therefore, it is unclear whether the relationships between vitamin D and health outcomes are causal [5].

Early-life nutrition has long-lasting consequences on offspring health. Maternal and infant undernutrition causes growth retardation and low birth weight. According to Barker's theory (or the Developmental Origins of Health and Disease hypothesis), this early-life growth restriction further leads to metabolic programming and an increased risk of several chronic diseases later in life [6-8]. Growth patterns during infancy may have long-lasting consequences for health later in life [9]. Associations between pre- and postnatal growth patterns and disease risk have also been found within the normal birth weight range, and studies suggest that this relationship is U- or J-shaped [10-13]. Vitamin D may be one contributing factor in the developmental origins of disease [14-16]. Furthermore, low maternal vitamin D status has been associated with adverse pregnancy outcomes, such as gestational diabetes mellitus (GDM), low birth weight, and small-for-gestational-age (SGA) [17], but the evidence is inconclusive [18]. GDM, moreover, increases the risk for type 2 diabetes, metabolic syndrome, obesity, and cardiovascular diseases later in life, both in the mother and in the child [19, 20].

Active discussion about optimal vitamin D status is ongoing [21-23]. Due to revised national vitamin D food fortification and supplementation policies, vitamin D intake has increased and vitamin D deficiency decreased in Finnish adults [24-26]. However, updated data on vitamin D intake and the status of pregnant women and infants are lacking. The objective of this thesis was to study the current vitamin D status among Finnish pregnant women and whether it associates with GDM, infant birth size, and postnatal growth in

term infants with normal birth weight, and whether infant vitamin D status relates to infant growth at 1 year of age. This thesis is part of the Vitamin D Intervention in Infants (VIDI) study.

2 REVIEW OF THE LITERATURE

2.1 VITAMIN D

The concept of a vitamin was first introduced by Casimir Funk in the early 1900s [27, 28]. A vitamin is defined as an essential dietary compound for normal growth, development, and health and cannot be synthesized by the organism itself. However, fat-soluble vitamin D can be regarded as a steroid hormone, which can be synthesized in the skin in the presence of sufficient sunlight. If sufficient ultraviolet light B (UVB) radiation is lacking, the only sources of vitamin D are food and supplements.

The history of vitamin D begins with the identification of a severe bone disease, rickets, which is characterized by leg deformity, osteopenia, swelling of the wrists and ankles, and growth retardation in children. The term was first mentioned as a cause of death in 1634 in London (Annual Bill of Mortality of the City of London) [29]. During the phase of industrialization and urbanization, in many European and American cities with limited sunlight exposure, rickets was highly common among children [30]. According to Arvo Ylppö in 1925, among Finnish children of pediatric population aged 1 to 2 years 50-70% suffered from rickets during that time [31]. In the late 1800s, it was recognized that rickets was prevented or cured with cod liver oil or sunlight exposure. In the early 1900s, Mellanby et al. conducted the first systematic intervention with cod liver oil to cure rickets in dogs [32]. After success, the researchers suggested that the curative factor in cod liver oil was vitamin A. However, McCollum et al. then showed that if vitamin A was destroyed in cod liver oil, the oil could still cure rickets [33]. They therefore concluded that there must be another factor, which they named vitamin D. Consequently, common rickets was recognized as a result of vitamin D deficiency. Soon, Steenbock found that, in rats, irradiation of both the rat and its food could prevent or cure rickets [34].

Evolutionarily, the role of vitamin D in human physiology is not fully understood. It has been suggested that originally the purpose of vitamin D was to protect organisms from DNA-damaging UVB rays [35]. Furthermore, it has been hypothesized that the evolution of skin depigmentation is a result of an adaptation to environments with low UVB to ensure adequate vitamin D status (The Vitamin D-Folate Hypothesis) [36].

2.1.1 VITAMIN D METABOLISM

Vitamin D refers to several similar molecules, but the main two forms are vitamin D_3 and vitamin D_2. The chemical structure of vitamin D resembles classic steroid hormones [37]. Vitamin D_3 is produced in the skin from 7-dehydrocholesterol by solar or artificial UVB. The 7-dehydrocholesterol is first

transformed into previtamin D, and through a temperature-dependent process, it is further converted to vitamin D_3. This endogenous production of vitamin D is strictly regulated, and in the presence of prolonged sunlight exposure, vitamin D metabolites in the skin are converted to inactive isomers. These "inactive" isomers may have other non-vitamin D–related active functions in the body [35]. Excessive vitamin D production in the skin is prevented by these regulatory mechanisms. In addition to cutaneous synthesis, the main natural dietary sources of vitamin D_3 are fish and eggs. Vitamin D_2, originated from ergosterol, is obtained from plant foods such as certain types of mushrooms. Other major dietary sources of vitamin D are fortified foods. All vitamin D produced in plants or animals is a result of photochemical synthesis [38].

Though not implicitly shown, the absorption of fat-soluble dietary vitamin D is assumed to occur in a similar manner as the absorption of dietary lipids or cholesterol [39-41]. Vitamin D is probably more effectively absorbed from oil than from a non-oil food matrix, but not all studies agree [39]. Moreover, the fatty acid composition possibly has an influence on the efficiency of vitamin D absorption [42].

Vitamin D is absorbed in the duodenum, jejunum, and ileum, mainly via passive diffusion, and possibly also with the help of protein transporters [42]. It has been suggested that the mechanism of vitamin D absorption in the small intestine may differ according to the supplement vehicles or food matrix in which it is incorporated [41] or according to the vitamin D content in the ingested food [39]. After absorption, vitamin D is transferred from enterocytes in the chylomicrons into the circulation, and it is transported further to the liver through chylomicron remnants.

The biologically active form of vitamin D is metabolized in the liver and kidney in reactions catalyzed by vitamin D–activating enzymes. Endogenous vitamin D is transported to the liver while bound to the vitamin D binding protein (DBP). In the liver, both dietary and endogenous vitamin D are hydroxylated into 25-hydroxyvitamin D [25(OH)D], which reflects the vitamin D intake from cutaneous synthesis and dietary sources and is the best indicator of vitamin D status [43]. Although other metabolites of vitamin D may also contribute to vitamin D status [44]. There is a non-linear dose-response relationship between vitamin D intake and circulating 25(OH)D concentration, with the response decreasing at higher vitamin D intake [45]. Vitamins D_2 and D_3 are equally bioavailable in rising circulating 25(OH)D concentration, but vitamin D_3 possibly sustains the 25(OH)D level for a longer period than vitamin D_2 [39]. Further, specific biological mechanisms may have some differences between vitamin D_2 and D_3 metabolites, but for example, both prevent and cure vitamin D deficiency rickets with similar efficacy [39].

A second hydroxylation occurs in the kidney, resulting in 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], the most active form of vitamin D. These conversion efficacies differ between the phases of vitamin D metabolism, and are dependent on other factors such as baseline vitamin D status [46-48], and

dosage [39, 49]. DBP is also a transport protein for 25(OH)D and $1,25(OH)_2D$. The latter can also be produced locally in target organs, for example, in the placenta, brain, intestine, mammary gland, prostate [37], and adipocytes [50].

Vitamin D is stored mainly in fat deposits in the body and, to some extent, in the muscle. Obesity decreases circulating 25(OH)D levels, possibly due to volumetric dilution [51] and increased vitamin D storage in adipose tissue [52]. In some studies, but not in all, weight loss has been associated with increased vitamin D status [53]. Besides storage, vitamin D in fat tissue can have also active functions, for example, anti-inflammatory effects. Vitamin D may be mobilized slowly from fat tissue into circulation when needed [53, 54], but the mechanisms are unclear.

Vitamin D is not easily excreted due to its lipophilic nature. To excrete vitamin D metabolites, they must first be transformed into more water-soluble compounds, e.g., calcitroic acid, by additional hydroxylations. Vitamin D is mainly excreted in the bile [55]. Enterohepatic circulation of vitamin D does occur, but its importance for vitamin D (re)activation and excretion is still unknown [56].

2.1.2 VITAMIN D FUNCTIONS AND REGULATION

Vitamin D is best known for maintaining bone and calcium-phosphate homeostasis. Through vitamin D receptor (VDR), $1,25(OH)_2D$ regulates gene transcription in several organs and also acts directly upon target tissues, without gene transcription, by rapid signal transduction pathways. Major target organs for $1,25(OH)_2D$ are the small intestine, kidney, and bone, which collectively regulate plasma calcium-phosphate concentrations for normal neuromuscular function and bone remodeling. $1,25(OH)_2D$ increases calcium and phosphate absorption in small intestine, resorption from bone, and reabsorption in the kidney to maintain normal plasma calcium and phosphate level. This is also how $1,25(OH)_2D$ provides calcium for bone mineralization and formation. Renal production of $1,25(OH)_2D$ is mainly targeted for calcium metabolism, but other local and tissue-specific production of $1,25(OH)_2D$ may have other functions, depending on the organ [37].

Other functions of vitamin D, apart from its major role in bone and calcium metabolism, are less well characterized. VDR has been shown to exist in various tissues, e.g., brain, lung, muscle, placenta, and many immune cells [37, 57], indicating that vitamin D has relevant functions outside the bone, although its specific actions are not yet fully understood. One established extraskeletal function of vitamin D is in the immune system [57, 58]. Already in the early 1900s, tuberculosis (TB) was treated with vitamin D–containing cod liver oil or sun exposure, and nowadays, few possible mechanisms have been reported between vitamin D and TB, although interventions have been inconclusive [5, 59]. Many different immunological cell types express vitamin D–activating enzymes or only VDR, showing that vitamin D has a specific role in their function [5]. Furthermore, vitamin D regulates immunological

functions, for example, by increasing production of the antimicrobial peptides cathelicidins against pathogens [60, 61].

Regulation of $1,25(OH)_2D$ occurs via the parathyroid hormone (PTH), whose concentration increases in the presence of low-plasma calcium (or high-plasma phosphate), leading to increased production of $1,25(OH)_2D$ in the kidney. Further regulation takes place through the feedback system, i.e., $1,25(OH)_2D$ down-regulates its own synthesis. Also, fibroblast growth factor 23 (FGF23), secreted from bone, has a role in controlling the concentration of $1,25(OH)_2D$, including suppressing its production [62]. This is also why $1,25(OH)_2D$ is not used to determine vitamin D status, as the production is highly regulated, and the half-life of $1,25(OH)_2D$ is very short (4–6 hours) [63] compared to 25(OH)D (2–3 weeks) [64].

2.1.3 EFFECTS OF VITAMIN D DEFICIENCY

In the absence of endogenous or dietary vitamin D, bone mineralization is impaired, and if prolonged, it can lead to nutritional rickets in children and osteomalacia in adults. Infants are at increased risk for vitamin D deficiency because of limited sunlight exposure and low vitamin D content in breast milk [65]. Furthermore, they are at risk of rickets due to intense skeletal growth.

In severe vitamin D deficiency, serum calcium decreases (hypocalcemia) and PTH increases, which leads to decreased renal phosphate reabsorption and hypophosphatemia. This eventually results in reduced apoptosis of hypertrophic chondrocytes, leading to deformed growth plates and rickets. Altogether, in rickets, mineralization of newly-formed bone and growth plates is impaired [66-68]. Typically, rickets evolves 6–18 months after birth, when calcium homeostasis becomes more dependent on vitamin D intake [69]. Clinical manifestations of rickets are long bone deformities, enlargement of wrists and costochondral junctions and stunted linear growth, and infants also present with craniotabes and delayed fontanelle closure. In radiological examination, widened growth plates and impaired bone mineralization can be determined [66]. Severe vitamin D deficiency causes hypocalcemia and may lead to severe complications such as seizures, cardiomyopathy, and even death [70]. In severe vitamin D deficiency, hypocalcemia usually occurs first [69], but it is then regulated to normal by increased PTH at the expense of bone. However, rickets finally evolves and hypocalcemia can re-emerge. Vitamin D–deficiency rickets can be treated with vitamin D supplementation accompanied by adequate calcium intake, and a full recovery is possible [71].

Rickets can manifest also because of rare genetic defects involving the enzymes required for vitamin D hydroxylation or bone mineralization itself, such as hereditary hypophosphatasia [66, 67]. In addition, nutritional rickets can result from calcium or phosphorus deprivation or, in many cases, simultaneous deprivation of vitamin D and calcium [67, 71, 72]. However, the most common cause of rickets is vitamin D deficiency [67], although low intake of calcium may be the predominant cause in some areas [73]. In

Finland, severe nutritional rickets has disappeared, although some ethnic groups can be at increased risk of mild forms of rickets [74].

2.1.4 VITAMIN D TOXICITY

As for all chemical compounds, excessive amounts of vitamin D are toxic; intoxication is characterized by hypercalcemic manifestations. It can be identified if serum 25(OH)D exceeds 250 nmol/l and the person is suffering from hypercalcemia, hypercalciuria, and low serum PTH [71]. Acute vitamin D intoxication can follow ingestion of very high vitamin D supplementation, such as 4000 µg, [71] and has been reported to occur due to, e.g., manufacturing errors in dietary supplements [75]. Symptoms of vitamin D intoxication include nausea, poor appetite, vomiting, constipation, thirst, muscle weakness, polyuria, and nephrocalcinosis, which can result in renal failure and death if not treated. The risk of vitamin D intoxication in children is low, but it is a matter of concern [76, 77].

2.1.5 VITAMIN D IN PREGNANCY

Adequate vitamin D status is important in pregnancy for both the mother and the fetus, as fetal and postnatal bone formation and growth require adequate calcium and mineral supplies. This increased demand for calcium may be ensured by the fact that maternal $1,25(OH)_2D$ increases considerably during pregnancy [78]. Also, the efficacy of intestinal calcium absorption doubles during pregnancy [78]. Fetal vitamin D status correlates with maternal serum 25(OH)D concentration, which reflects 50–108% of 25(OH)D in umbilical cord blood (UCB) [79, 80]. Maternal vitamin D and $1,25(OH)_2D$ do not readily cross the placenta, but 25(OH)D does, and it can then be further hydroxylated into $1,25(OH)_2D$ [78, 81]. According to Christopher Kovacs, however, it seems that the placenta and fetus can maintain calcium-phosphate homeostasis and normal bone mineralization quite independently, even in the presence of maternal vitamin D deficiency [69, 82]. The fetus obtains calcium and other necessary minerals from the mother via placenta despite mildly low maternal circulating calcium (Figure 1) [69]. Contrary to Kovacs, some consider that severe and chronic maternal vitamin D deficiency can increase the risk of hypocalcemia and congenital and infantile rickets in newborns [71, 83]. Nevertheless, maternal vitamin D deficiency is not healthy for the pregnant woman herself, and poor maternal vitamin D status may have extraskeletal effects for the offspring. In normal circumstances, after birth, when the maternal supply of calcium and phosphate is discontinued, the newborn's calcium level declines for a short period but is then increased again by the newborn's own production of PTH and $1,25(OH)_2D$ [81]. Breast milk, which utilizes calcium from the maternal skeleton, offers adequate calcium intake for the infant [84] but not vitamin D (see chapter 2.5.2).

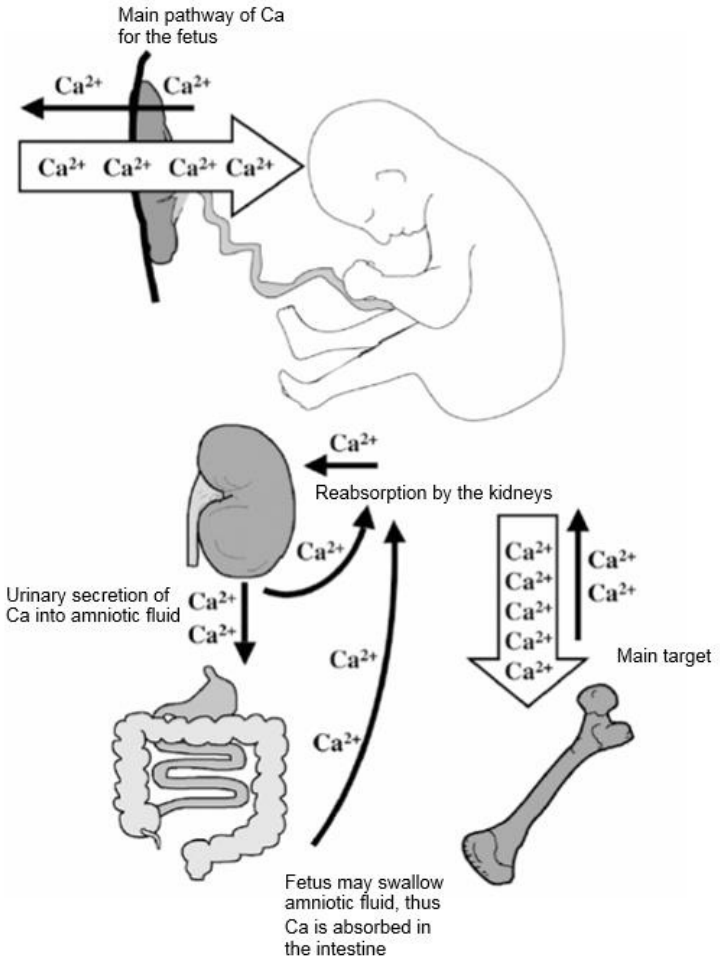

Figure 1 Calcium sources of the fetus. The main pathway of calcium is through the placenta into fetal bone. Some calcium returns to the maternal circulation, some is reabsorbed by the kidneys, and some is excreted by the kidneys into the urine and amniotic fluid, where it may be swallowed and absorbed by the intestine. Calcium is also resorbed from bone to maintain the circulating calcium concentration. Vitamin D supposedly has no regulatory role in this system. Reprinted and modified with permission from Elsevier: Fetal mineral homeostasis in Pediatric Bone, Academic Press, Kovacs 2003 [69, 85].

2.1.6 ASSESSMENT OF 25(OH)D CONCENTRATION

It is widely agreed that vitamin D status is determined by serum or plasma 25(OH)D concentration. However, the methods to assess this metabolite vary considerably [86]. Values of 25(OH)D, at least to some extent, depend on the applied method, individual laboratory, and within-laboratory variability [87]. Thus, the reliability and possibilities for comparisons between studies of 25(OH)D values are restricted. The most commonly used methods include different immunoassays and liquid chromatography methods. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) [88] is considered the golden standard; however, immunoassays are more commonly used [87]. To overcome these methodological challenges, the Vitamin D External Quality Assurance Scheme (DEQAS) has been organized to monitor the accuracy and reliability of different 25(OH)D assays and laboratories (www.deqas.org). This is achieved by providing standard reference material with assigned 25(OH)D content by the National Institute of Standards and Technology (NIST) to laboratories analyzing circulating 25(OH)D. In addition, the Vitamin D Standardization Program (VDSP) aims to standardize 25(OH)D measurements globally to make them comparable and accurate among laboratories and studies [89]. Standardization is especially important when reporting prevalence figures of vitamin D deficiency.

2.2 SOURCES OF VITAMIN D

As described above, vitamin D is endogenously produced in the skin by UVB. This is the primary source of vitamin D for the majority of people worldwide. Consequently, the amount of sunshine and exposure to sunlight largely determines a person's vitamin D status. Geographical location in terms of latitude, weather conditions, season, air pollution, and time of day have a profound impact on UVB exposure. In addition, skin pigmentation, clothing, outdoor activity, and age affect UVB-mediated vitamin D synthesis in the skin. Darker skin pigmentation reduces the production of vitamin D in the skin because of its higher content of melanin ("natural sunscreen"), which efficiently absorbs solar radiation [35].

Specker et al. have estimated that sun exposure of 30 min per week in an infant wearing only a diaper will ensure adequate 25(OH)D (>27.5 nmol/l) based on a small study (n=61) with the majority (n=51) being white-skinned infants [90]. In adults, it has been estimated that with skin type 2 (pale) in the Boston area (USA), exposing the face, neck, and hands to UVB for 15 min is equivalent to 10 μg of dietary vitamin D [91]. To produce vitamin D, UVB has to radiate in the wavelengths of 290–315 nm [35]. This sufficient solar radiation is not available in the northern latitude during winter, e.g., in Finland from October to March. Thus, during this period, the only sources of vitamin D are food and supplements.

The main dietary sources of vitamin D are fish, egg, mushrooms, vitamin D–fortified foods, and supplements. Breast milk is a poor source of vitamin D (see section 2.5.2) [65]. Based on the latest national FinDiet survey conducted in 2017, which comprises a representative sample of the Finnish adult population, the most relevant food sources of vitamin D were fortified fat spreads, fortified milk products, and fish [92]. Table 1 shows some nationally relevant foods in regards to vitamin D content. Several different fish species have relatively high vitamin D content, but less than half (44%) of Finnish women consumed fish foods measured by repeated 24-hour recall in the FinDiet survey [92]. Animal-based foods also contain 25(OH)D, which contributes to vitamin D status; however, the amounts of 25(OH)D in foods have rarely been measured [93].

2.2.1 VITAMIN D FOOD FORTIFICATION

Food fortification is applied for public health reasons and for consumer appeal. Vitamin D fortification strategies were already being applied in the 1930s to prevent rickets [64]. However, an outbreak of infantile hypercalcemia in the UK led to a decrease of vitamin D content in foods [94] and to general precaution against vitamin D food fortification [35]. Today, attitudes against food fortification and applied practices differ among countries [64]. The basis for fortification is either voluntary or by legislation. Currently, countries such as the USA, Canada, the UK, Ireland, Sweden, and Finland fortify their foods with vitamin D [95, 96]. Staple foods are usually fortified, including fluid milk products, fat spreads, cheese, juices, breads, and breakfast cereal [96].

In Finland, the national vitamin D fortification policy has been a unique approach aiming to decrease vitamin D deficiency in the general population [24, 25, 64, 96]. Vitamin D fortification was initiated in 2003 and revised in 2010 on a voluntary basis, but almost all manufacturers follow the recommended policy [95]. Currently, fluid dairy products and dietary fat spreads contain vitamin D_3 1 µg/100 ml and 20 µg/100 g, respectively. At the time of this study, common infant formulas or follow-on infant formulas (hereafter referred to as infant formula) most commonly contain 1.3 µg/100 ml vitamin D_3. However, in the near future, vitamin D content will likely increase to 1.1–1.8 (maximum of 2.1) µg/100 ml in some products because of updated EU legislation [97]. In fortified foods and supplements, vitamin D_2 is usually derived from irradiated fungi or yeast, and vitamin D_3 from fish oil or lanolin from lamb wool. Lichen can contain both vitamins D_2 and D_3 [98]. In Finland, foods are fortified with vitamin D_3.

Table 1 *Common vitamin D content in some fresh Finnish foods*[1]

Food	Vitamin D, µg/100g
Fishes	
Baltic herring	15.6
Perch	15.8
Powan, whitefish, lavaret	14.9
Roach	10
Salmon	8.0
Tuna	7.2
Zander, pike-perch	6.9
Saithe, frozen	1.5
Egg	2.2
Cheese, Edam type	0.2
Pork, minced	0.5
Chicken breast with skin	0.5
Mushrooms	
Funnel chantarelle	15.4
Chantarelle	5.8
Porcini	2.6
Champignon	0.2
Fortified foods	
Fat spread	20
Fluid milk products	1
Infant formula	1.3[2]
Oat drink	0.5–1.5

[1] Source: Fineli, the National Food Composition Database, obtained in January 2019
[2] This amount was common at the time of this study

2.2.2 ASSESSMENT OF DIETARY VITAMIN D INTAKE

To evaluate dietary intake of vitamin D, different dietary assessment methods are applied. Acknowledging that few foods contain vitamin D and that these foods are consumed rarely, it may be challenging to measure dietary intake of vitamin D. Day-to-day variation in diet should be taken into consideration when choosing a suitable dietary assessment method and interpreting results [99].

A food record, often considered the golden method in dietary assessment, is a valid method to evaluate a person's absolute vitamin D intake from food. In this prospective method, the study participant records all consumed foods, drinks, and supplements and the amounts eaten over a specific period of time, generally from three to seven days. The amounts are often estimated with household measures, or foods are weighed on a scale. The food record requires good instructions for the participant, preferably face-to-face discussion and in

written. In addition, food records should be checked retrospectively to avoid missing data or false interpretations. A longer study period usually produces more valid results. However, long recording period is laborious for the participant, which can also compromise accuracy and is often not possible due to a lack of research resources. In a group level and with young children, shorter study periods also deliver reliable results.

Other commonly used methods include single and repeated 24-hour recall and the food frequency questionnaire (FFQ). The 24-hour recall involves having a trained interviewer that inquires about all the foods and drinks consumed by the study participant the previous day. As with a food record, this gives an absolute value of vitamin D intake, and if repeated, the reliability increases from a single-day 24-hour recall. The FFQ is comprised of a list of different foods with ready-made options for frequency of consumption. It is completed retrospectively and aims to measure the usual intake of certain nutrients/foods over a longer time period than a food record (e.g., a year). The FFQ often overestimates nutrient intakes. However, it generally ranks individuals correctly according to their actual dietary intake. To compare vitamin D intake against the recommendations, a food record may be superior to the FFQ as it gives the absolute value of intake. On the other hand, vitamin D intake from fish foods might be better derived from FFQ, as fish is infrequently consumed.

To assess vitamin D intake in infants and children, their caregiver must record all food and drink. Vitamin D intake from breast milk is not always calculated as it is challenging to estimate the consumption of breast milk, and vitamin D content in breast milk may vary among individuals [100]. These methods require a reliable food composition database and computation systems to calculate dietary intake of vitamin D as accurately as possible.

The true dietary intake of vitamin D or any nutrient is almost impossible to achieve due to methodological limitations in dietary assessment. Over- or under-reporting may be emphasized in pregnant women who may answer in a more socially desirable way. This can also be a relevant issue in an infant's dietary intake. Indeed, it has been reported that parents under-report "unhealthy" food intake and over-report "healthy" food intake for their infants [101]. However, vitamin D intake and blood 25(OH)D concentration, which objectively measure vitamin D intake, consistently correlate with each other. To apply 25(OH)D as an indicator of dietary vitamin D intake, it is most suitable to do so in populations with minimal sun exposure [102].

2.3 VITAMIN D RECOMMENDATIONS

To prevent rickets and maintain sufficient vitamin D status among the population, different countries, their health authorities, and health organizations have implemented dietary reference values and guidelines for vitamin D intake [103]. These actions have nearly eradicated rickets in the vast

majority of societies. Some, however, still consider rickets a significant global health problem; for example, immigration can increase the incidence of rickets [71]. Dietary reference values include recommended intake (and recommended dietary allowance), which provides adequate intake of a nutrient for 97.5% of the population, and lower and upper intake levels.

To reach the recommended intakes, in addition to food fortification, vitamin D supplementation has been recommended. Many authorities have special recommendations for vulnerable groups of people such as pregnant and breastfeeding women and children. In Finland, vitamin D recommendations have been updated a few times as new evidence has emerged. Since the early 1900s, the recommended vitamin D supplementation for children has progressively decreased from 100 µg daily to 10 µg [104, 105]. Table 2 presents the health authorities' current recommendations for total vitamin D intake and supplemental vitamin D intake for pregnant and breastfeeding women and infants. Finnish Nutrition Recommendations [106, 107] are based on Nordic Nutrition Recommendations (NNR) [108]. Still, some additional guidelines vary in Nordic countries, such as for vitamin D supplementation.

In Finland, the current recommended daily total vitamin D intake is 10 µg for children and adults, including pregnant and breastfeeding women (Table 2) but excluding the elderly (≥75 years), for whom 20 µg is recommended [106]. The recommendation for vitamin D supplementation for pregnant and breastfeeding women is 10 µg/day, as well as for children 1–2 years old. For children 2–17 years old, the recommended supplemental vitamin D intake is 7.5 µg/day.

Finnish vitamin D supplementation guidelines for infants from 2 weeks to 1 year of age were revised in fall 2018 due to an updated EU legislation on infant formulas [109]. This was done to avoid exceeding the upper intake level (UL) of vitamin D in formula-fed infants. Presently, the amount of vitamin D supplementation decreases as the consumption of fortified infant formula increases until the infant is 1 year old (Table 2, footnote 1). However, during this study, a valid recommendation for supplemental vitamin D intake was 10 µg/day for children 2 weeks of age to 2 years of age, regardless of infant formula consumption [110].

A lower intake level (LI) of vitamin D is 2.5 µg/day for adults, but no threshold for infants has been identified [108]. Currently, ULs are 25, 35, 50, and 100 µg/day for infants 0–6 months, 6–12 months, 1–11 years, and youth and adults, respectively, as defined by the European Food Safety Authority (EFSA) [111]. These values vary to some extent by different authorities.

Table 2 *A few vitamin D recommendations for pregnant and breastfeeding women and infants by different authorities*

	Pregnant and breastfeeding women		Infants (until 1 year of age)	
	Total vitamin D intake	Supplemental vitamin D intake	Total vitamin D intake	Supplemental vitamin D intake
Health authority	μg/day			
National Nutrition Council/ National Institute for Health and Welfare (Finland) [106]	10	10	10	10[1]
National Food Agency (Sweden) [108, 112]	10	-	10	10
EFSA[2] [113]	15	-	10	-
IOM (presently NAM)[3] [114]	15	-	10	-
WHO/FAO[4] [115, 116]	5	-	5	-
Global consensus on prevention of rickets [71]	15	15	10	10

EFSA, European Food Safety Authority; IOM, Institute of Medicine; NAM, National Academy of Medicine; WHO, World Health Organization; FAO, Food and Agriculture Organization of the United Nations

[1] If infant is given 500–800 ml infant formula daily, vitamin D supplementation decreases from 10 to 6 μg/day. If the daily amount of infant formula is >800 ml, vitamin D supplementation further decreases to 2 μg/day until infant is 1 year of age. Infant formula includes infant follow-on formulas and vitamin D–fortified gruels and porridges [109].

[2] Values are adequate intakes (AI), and only valid in the presence of minimal cutaneous vitamin D synthesis

[3] In the presence of minimal sun exposure

[4] If insufficient vitamin D synthesis

2.4 DEFINITIONS FOR VITAMIN D DEFICIENCY AND SUFFICIENCY

A clear consensus of thresholds of vitamin D deficiency and sufficiency is lacking [88], not to mention a threshold of optimal vitamin D status. However, a widely accepted value for vitamin D sufficiency is 25(OH)D ≥50 nmol/l (Table 3). This is applied in adults, children, and pregnant and breastfeeding women. In addition, the Institute of Medicine (IOM) (presently the National Academy of Medicine [NAM]) has set a threshold for excessive 25(OH)D concentration at >125 nmol/l, which may pose possible health risks [114], although it is not yet considered toxic. The Endocrine Society favors higher 25(OH)D values of >75 nmol/l [117] (Table 3).

Table 3 *Circulating 25-hydroxyvitamin D concentration [25(OH)D] thresholds for vitamin D deficiency and sufficiency by different health authorities*

	Vitamin D deficiency, 25(OH)D (nmol/l)	Vitamin D sufficiency, 25(OH)D (nmol/l)
EFSA [113]	<50	≥50
NNR [108]	<25	≥50
IOM (presently NAM) [114]	<30	≥50
ECTS [88]	<50	≥50
Endocrine Society [117]	<50	≥75
Global consensus on prevention of rickets [71]	<30	≥50

EFSA, European Food Safety Authority; NNR, Nordic Nutrition Recommendations; IOM, Institute of Medicine; NAM, National Academy of Medicine; ECTS, European Calcified Tissue Society

2.5 DIETARY INTAKE OF VITAMIN D AND VITAMIN D STATUS

Globally, dietary intake of vitamin D is often estimated to be low, as only a few foods naturally contain vitamin D. This is not a problem unless UVB exposure is also low. Poor vitamin D status is a concern in many parts of the world, especially in northern latitudes with limited sunlight or in regions where the population covers most of their skin with clothing [88, 118]. Vitamin D status is measured by circulating 25(OH)D concentrations, which is also the biochemical indicator for dietary vitamin D intake.

Dietary intake of vitamin D varies considerably even within Europe, from a mean daily intake of 2 μg in Spanish women to 10 μg in Norwegian women [119]; in Northern Europe, it varies from 4 to 14 μg [88]. These dissimilarities are due to different dietary patterns (DP), recommendations about vitamin D intake and supplementation, food fortification strategies, dietary assessment methods, and different approaches in accounting in supplemental vitamin D intake [119].

Vitamin D status also varies among the European population. Lips et al., employing unstandardized prevalence figures, reported that 7–62% of the European population had 25(OH)D below 50 nmol/l [88]. Some of the large variation in prevalence figures are due to methodological differences in 25(OH)D assessment (see section 2.1.6). Utilizing standardized 25(OH)D values, including Finnish data, Cashman et al. have estimated that 13% of Europeans suffer from vitamin D deficiency as determined by 25(OH)D <30 nmol/l [74]. Furthermore, the risk of vitamin D deficiency was multifold in dark-skinned ethnic subgroups [74]. In Finland, 56–90% of dark-skinned women had 25(OH)D <50 nmol/l [120-122].

2.5.1 MATERNAL VITAMIN D INTAKE AND STATUS

Many experts recommend maternal vitamin D supplementation to achieve adequate vitamin D intake, although consensus is lacking [123, 124]. Maternal vitamin D deficiency has been associated with adverse pregnancy outcomes [17, 125]. In Europe, the unstandardized prevalence of 25(OH)D <50 nmol/l ranged from 18% to 90% in pregnant women [126]. In the literature and in this thesis, maternal vitamin D status indicates both serum 25(OH)D during pregnancy and UCB 25(OH)D at birth.

In Canada, pregnant women's (n=537) total vitamin D intake was 20 μg/day on average, with the majority coming from supplements [127]. Also, their 25(OH)D concentration was relatively high, and only 2% had 25(OH)D <50 nmol/l [127]. In a study conducted in the USA (n=321), 25(OH)D was below 50 nmol/l in 8–17% of pregnant women [128]. In a cohort of 1050 Irish mother-newborn pairs, however, 80% had 25(OH)D <50 nmol/l measured from UCB [129]. Of these mothers, 42% used vitamin D supplements during pregnancy, and 82% of the supplements contained 5 μg vitamin D [129]. Among Norwegian pregnant women (n=855), 27–34% had 25(OH)D <50 nmol/l in 2007–2009 [130]. Their mean daily vitamin D intake was 10.4 μg, but the majority of them (59%) still did not reach the recommended intake of 10 μg [130]. In a large Swedish cohort (n=1985), only 42–43% used vitamin D supplements during pregnancy [131]. Altogether, 25% had 25(OH)D <50 nmol/l. In their study, the corresponding prevalences were 13% in women of North European origin and 69–82% in women of Asian and African origin [131].

Previously, among Finnish pregnant women, vitamin D intake has been reported to be below the recommended level, and poor vitamin D status has been common. Table 4 shows vitamin D intake and status in Finnish pregnant women during the last two decades. In a birth cohort of Type 1 Diabetes Prediction and Prevention Study (DIPP), in 1998-1999, the mean intake of vitamin D from food was approximately 5 μg/day, and from supplements almost 4 μg/day [132]. However, only 40% were supplement users [132]. The mean total vitamin D intake of pregnant and breastfeeding women was 6.9 and 7.3 μg/day in 1998-2004 [133]. In the same cohort, vitamin D intake among pregnant women increased from 6.2 μg/day in 1997–2000 to 8.9 μg/day in 2003–2004 [134]. Within the DIPP study in 1993–2004, 69% of pregnant women had 25(OH)D <50 nmol/l [135]. Furthermore, in 1994–2004, 88% of mother-newborn pairs had 25(OH)D <50 nmol/l [136].

In 2007 (n=125), 77% of Finnish pregnant women had 25(OH)D <50 nmol/l in the first trimester, although the total mean vitamin D intake was 14.3 μg/day in the third trimester [137] (Table 4). Approximately half of vitamin D intake came from supplements, and 80% of women used vitamin D supplements [137]. In another sample of 113 mothers, dietary intake of vitamin D was 11.1 μg/day in 2010–2011 [138]. A Finnish gestational diabetes prevention study (RADIEL) found that the median vitamin D intake from food in pregnant women at an increased risk of GDM was 6 μg/day in 2008–2011

[139]. Together with supplements, the total median vitamin D intake rose to 12 µg/day, with 72% of supplement users [139]. In that study, only 30% (65/219) of pregnant women had 25(OH)D <50 nmol/l [140]. However, it should be mentioned that 56% of these women were obese (body mass index [BMI] >30 kg/m²) due to study recruitment criteria, which probably affected 25(OH)D by decreasing its concentration [140]. Based on the national Infant feeding report in 2010 (n=3406), 62% of mothers used some supplements during pregnancy, 18% used only vitamin D supplements, and 45% multivitamin supplements (which most likely contained vitamin D) [141].

Some of the discrepancy between studies may be a result of different methodologies in assessing and reporting vitamin D intake. In addition, the solar contribution in vitamin D status is difficult to measure and is not evaluated in all studies. Vitamin D recommendations have been updated a few times during the last two decades to improve vitamin D status in the Finnish population. Regarding pregnant and breastfeeding women, the guideline for supplementation (10 µg/day) was changed from winter-only to year-round supplementation in 2011. Total maternal vitamin D intake has increased, but the current vitamin D status of Finnish pregnant women is unknown.

Table 4 *Vitamin D intake and status among Finnish pregnant women during the last two decades*

Study	Year of study	N	Mean intake of dietary vitamin D, µg/day	Prevalence of 25(OH)D <50 nmol/l, %	Dietary assessment method	25(OH)D assay
DIPP [132]	1998–99	797	4.8-6.7		181-item FFQ	
DIPP [134]	1997–2000	4880	6.2		181-item FFQ	
	2003–04		8.9			
DIPP [135]	1993–04	686		69		IDS OCTEIA[2]
Viljakainen et al. 2010 [137]	2007	125	14.3	77	70-item FFQ	IDS OCTEIA[2]
RADIEL [139]	2008–11	234	12[1]		3-day food record	
RADIEL [140]	2008–14	219		30		IDS-iSYS[2]

25(OH)D, 25-hydroxyvitamin D; DIPP, Type 1 Diabetes Prediction and Prevention Study; FFQ, food frequency questionnaire; RADIEL, The Finnish Gestational Diabetes Prevention Study

[1] Median

[2] Immunoassay provided by Immunodiagnostic Systems (IDS)

2.5.2 INFANT VITAMIN D INTAKE AND STATUS

Infants require vitamin D for normal development and growth. Vitamin status of the newborn depends on the maternal vitamin D status. It is presumed that the maternal supply for the infant lasts for weeks after birth [142]. However, maternal vitamin D status and the infant's own capacity to utilize possible stores of vitamin D metabolites may affect the time period when the supply of vitamin D is exhausted. After birth, the infant's only sources of vitamin D are breast milk, infant formula, supplements, and sunlight-induced skin synthesis until complementary feeding is started. Globally, vitamin D deficiency is common in newborns [126], but in older infants, the situation is less clear.

Breast milk is the ideal food for the newborn and infant. In Finland, breastfeeding is recommended exclusively until 4–6 months, and partially until 1 year, or longer if the family prefers. Vitamin D and 25(OH)D pass into the breast milk, and the vitamin D content in breast milk relies on the maternal vitamin D intake and status [81, 84]. However, only small amounts of vitamin D metabolites are secreted into breast milk [143]. Authors of a Danish study estimated that infants' daily median intake of vitamin D and 25(OH)D from breast milk was 0.1 and 0.3 µg, respectively, among mothers with sufficient vitamin D status [65]. To gain noteworthy vitamin D content in the breast milk, a multifold maternal vitamin D supplementation may be required [144, 145]. Thus, infant vitamin D supplementation is the preferred, safest and most effective method to reach sufficient vitamin D status in the infant.

The role of sunlight exposure in the infant's vitamin D status is small because infants are not generally exposed to sunlight, and it is not even recommended due to increased risk of sunburn and skin cancer. This is often demonstrated by the lack of seasonal variation in vitamin D status in infants compared with older children [146]. Infants are at high risk of vitamin D deficiency because of low vitamin D content in breast milk, minimal sun exposure, and critical demand for vitamin D for normal growth and bone development. Therefore, vitamin D supplementation is required and recommended for infants in many parts of the world.

Infant formulas are fortified with vitamin D, and thus, infants who are exclusively breastfed compared with formula-fed infants commonly have lower circulating 25(OH)D concentrations. As vitamin D supplementation is usually recommended to all infants, infants who consume high amounts of infant formula may exceed the UL [147]. In Finland, the current recommendation of vitamin D supplementation for infants is adjusted according to the consumption of infant formula (see section 2.3).

Among US primary care patients aged 8–24 months, 12% had 25(OH)D below 50 nmol/l in 2005–2007 (n=380) [148]. Of Norwegian infants 9–16 months old with immigrant backgrounds, 47% had 25(OH)D <50 nmol/l in (n=102) [149]. Besides the possibly darker skin pigmentation of immigrants, which increases the odds for low 25(OH)D, this high prevalence may also indicate socioeconomic factors known to associate with vitamin D status.

Among Finnish infants, vitamin D intake was below the recommended intake of 10 µg/day two decades ago (Table 5). On the other hand, supplementation has been widely accepted in young children. In the DIPP study in 1999–2000, 1-year-old infants' (including partly-breastfed) total daily intake of vitamin D was 9.8 µg, of which 4.0 µg was from food [150]. However, in 2004, total vitamin D intake had risen to 12.2 µg/day, and of supplement users, the supplemental vitamin D intake was 6.8 µg/day (only non-breastfed) [151]. In Finnish 1-year-old infants, the main food sources of vitamin D intake have been infant formula, dairy products, mass-produced baby foods, cereal foods, and fish [150, 152].

In young children, vitamin D intake has been shown to decrease with increasing age, which has been mainly due to a decline in the proportion of supplement usage [150, 151]. The proportion of children who received vitamin D supplements was 91%, 81%, and 26% in 3-month-olds, 1-year-olds, and 3-year-old children, correspondingly [150], and more recently, within the same cohort, it was 86% in 1-year-olds [151]. Furthermore, in the DIPP study (n=387), 25(OH)D concentration rose 16 nmol/l on average between 1998–2002 and 2003–2006 among children aged 3 months to 12 years [153]. Mean 25(OH)D concentrations in that study were 89–91 nmol/l in children under the age of 2 years [153].

According to the Infant feeding report in 2010, 90% of 1-year-old infants received vitamin D supplements [141]. In another study of 86 infants, infants' mean total vitamin D intake was 12 µg/day [154]. Of those infants, 2% had 25(OH)D <37.5 nmol/l [154]. In a pediatric population of infants under the age of 2 years with chronic illness studied between 2007 and 2010, 7% suffered from vitamin D deficiency (<37.5 nmol/l) [146]. In a vitamin D supplementation trial (VIDI pilot study) conducted in 2010–2011, newborns' mean 25(OH)D was 52 nmol/l, and after 10 µg/day supplementation until 3 months of age, the mean value increased to 93 nmol/l [138].

To conclude, a larger proportion of 1-year-old infants are consuming vitamin D supplements, and it seems that vitamin D deficiency is not common in infants in Finland. However, considering the fact that vitamin D food fortification doubled in 2010, updated data on infant vitamin D intake is needed.

Table 5 *Vitamin D intake in Finnish 1-year-old infants during the last two decades*

Study	Year of study	N	Mean total intake of dietary vitamin D[1]	Mean intake of vitamin D from food	Dietary assessment method
DIPP [150]	1999–2000	267	9.8	4	3-day food record
DIPP/ The Diet of Finnish Preschoolers 2008 [151]	2004	567	10.2–12.2	5.4	3-day food record
Viljakainen et al. 2011 [154]	2009	86[2]	12.3	4[3]	3-day food record

[1] Including supplements
[2] Infants were 14 months old
[3] [155]

2.6 MATERNAL DETERMINANTS OF VITAMIN D STATUS

Factors associating with vitamin D status have been vastly studied. Along with skin pigmentation, several genetic determinants, also within similar ethnic groups, influence vitamin D status [156, 157] and the response of vitamin D intake on 25(OH)D concentration [158-160]. Furthermore, besides the apparent determinants of vitamin D status, such as UVB exposure, season, and total dietary vitamin D intake, certain lifestyle-related factors have been identified to associate with 25(OH)D. In short, these lifestyle factors are commonly DPs, age, education, BMI, physical activity, and smoking [161-164]. Usually, a diet rich in vitamin D but also healthy otherwise correlates with 25(OH)D [162]. It is often observed that unhealthy lifestyle factors, as well as healthy ones, are cumulative, making it difficult to identify the independent role of a specific determinant for vitamin D status or for other health outcomes.

In pregnant women, factors similar to non-pregnant adults determine 25(OH)D levels. Moon et al. studied the tracking of 25(OH)D during pregnancy in the UK (n=1753), i.e., the change between early and late pregnancy 25(OH)D [165]. In that study, vitamin D supplement use and physical activity in late pregnancy enhanced maternal 25(OH)D, while gestational weight gain reduced maternal 25(OH)D. Surprisingly, prepregnancy BMI or smoking during pregnancy did not associate with tracking of 25(OH)D [165]. However, in another study (n=829), Moon et al. observed that age had a positive association with 25(OH)D, but BMI, smoking, and weight gain had an inverse association[166].

According to Perreault et al. in Canadian pregnant women (n=523), the strongest factors related to maternal 25(OH)D were ethnicity, season, and prepregnancy BMI, but dietary intake of vitamin D played an oddly lesser role in vitamin D status [167]. As Perreault et al. in Canada, Sauder et al. (n=605) in the USA identified collateral factors, except vitamin D intake also significantly modified maternal 25(OH)D [168].

In some studies, parity has been observed to associate with maternal vitamin D status [169, 170]. In a Danish cohort (n=2082), vitamin D supplementation was a significant determinant of maternal 25(OH)D, and multiparity was detected as a risk factor for not taking vitamin D supplements [171]. Maternal age has also been identified as a negative determinant for UCB 25(OH)D in Greece (n=60), which was recognized to be a result of increased UVB exposure in younger pregnant women compared to older ones [172].

2.7 MATERNAL VITAMIN D AND GDM

To ensure adequate glucose and energy supply for the fetus in normal pregnancy, insulin resistance is developed, and gluconeogenesis is increased in the liver. Further, fasting glucose levels are decreased, but postprandial glucose levels are elevated [173]. To compensate for insulin resistance, insulin secretion is increased in pregnancy. In GDM, a type of diabetes that is diagnosed during pregnancy and disappears after pregnancy, this system is impaired, and hyperglycemia evolves [174]. Definition and glucose thresholds of diagnosis vary, but they are usually based on an oral glucose tolerance test (OGTT), with one or more values exceeding the thresholds [175, 176]. Globally, GDM prevalences vary around 1–14% [177] and in Europe around 1.5–10% [178]. GDM prevalence has been rising globally, alongside obesity [179]. Also, the older age of parturients is one reason for increased GDM incidence [180, 181]. In Europe [175] and in Finland, GDM is the most common pregnancy complication. In Finland in 2014, 11% of pregnant women were diagnosed with GDM [182]. In 2017, the corresponding figure was 16% [183].

GDM has detrimental consequences for the offspring, such as macrosomia [184], increased odds for obesity and diabetes later in life [19, 185, 186], in addition to possible consequences for the mother herself, such as diabetes and hypertension [19, 187]. Adverse associations between maternal glucose levels and pregnancy outcomes have also been observed without the diagnosis of GDM [188, 189]. Hence, potential underlying factors for hyperglycemia during pregnancy have been investigated along with vitamin D.

Low maternal 25(OH)D has been associated with adverse pregnancy outcomes, including pre-eclampsia, bacterial vaginosis, and GDM [190, 191]. Lower maternal 25(OH)D has also been associated with increased risk of GDM in numerous meta-analyses (Table 6) [17, 124, 192-195]. Observational studies and meta-analyses utilizing those studies have been criticized for not taking

into account the relevant confounders such as maternal BMI [196]. In the most recent meta-analysis studying the association between maternal 25(OH)D and GDM by Amraei et al., the authors concluded that lower 25(OH)D increased the risk of GDM [195]. This result remained after stratifying studies by regions [195].

A meta-analysis employing 5 randomized clinical trials (RCT) of vitamin D supplementation during pregnancy by Roth et al. concluded that vitamin D supplementation could reduce the risk of GDM [125], contrary to an older meta-analysis [197], although the researchers considered the RCTs to be of low quality [125]. A new Cochrane review estimated with moderate evidence that maternal vitamin D supplementation decreased the risk of GDM based on 4 RCTs [198].

Many meta-analyses face a problem of heterogeneity [193]. Different study locations have varying prevalences of vitamin D deficiency as well as GDM and obesity. In light of these issues, high variability in adjusting for covariates [17, 195] and varying thresholds applied in GDM diagnosis [178] and for vitamin D deficiency [195] further produces limitations for the interpretation of the results. On the other hand, meta-analyses, if conducted appropriately, produce higher levels of evidence compared with a single study.

In women already diagnosed with GDM, vitamin D supplementation has not improved glucose metabolism based on a meta-analysis by Rodrigues et al. [199], but not all agree [200]. The possible mechanisms for how vitamin D could affect glucose metabolism are by improving insulin sensitivity [201] or stabilizing beta cell function [202, 203]. To summarize, vitamin D deficiency could probably increase the possibility of GDM, but this is uncertain since results are often confounded [192, 196].

Table 6. *Results of latest systematic reviews and meta-analyses based on observational studies about maternal vitamin D status and GDM*

Publication	Maternal determinant	N of studies	Risk of GDM	Heterogeneity
Amraei et al. 2018 [195]	vitamin D deficiency with no defined 25(OH)D cut-off, mean difference of 25(OH)D between GDM and non-GDM	26	+	no, yes
Lu et al. 2016 [192]	vitamin D insufficiency with 25(OH)D cut-offs of 50 or 75 nmol/l	20	+	yes
Zhang et al. 2015 [193]	vitamin D deficiency with 25(OH)D cut-off of 50 nmol/l, mean difference of 25(OH)D between GDM and non-GDM	20	+	no, yes
Harvey et al. 2014[1] [124]	25(OH)D	8	NS	-
Aghajafari et al. 2013 [17]	vitamin D insufficiency with 25(OH)D cut-offs of 50 or 75 nmol/l	10	+	no
Poel et al. 2012 [194]	vitamin D deficiency with 25(OH)D cut-off of 50 nmol/l, mean difference of 25(OH)D between GDM and non-GDM	7	+	no, yes

GDM, gestational diabetes mellitus; 25(OH)D, 25-hydroxyvitamin D; + indicates an association between low vitamin D status and increased risk of GDM; NS, non-significant

[1] systematic review without meta-analysis

2.8 VITAMIN D AND INFANT GROWTH

Fetal and infant growth is intense and, therefore, especially sensitive for environmental adverse effects such as nutritional inadequacies. An infant gains an average of 25 cm in length during the first year of life, as compared with the yearly growth of 6 cm later in childhood [204]. Fetal and infant growth are regulated by several hormonal factors in the systemic endocrine network and locally in the growth plate, but the specific mechanisms are still not completely understood. The main growth-regulating hormones during the fetal period are insulin and insulin-like growth factors (IGF), and in infancy, they are growth hormone, IGF-1, fibroblast growth factors, thyroxine, and sex steroids. Linear growth (i.e., length/height) is dependent on skeletal growth. Thus, one could assume that vitamin D has a role in linear growth while acknowledging the significant role in normal bone development.

Already in early 1900, it was suggested that more rapid weight gain in children was related to sunshine or vitamin D [205]. Stearns and colleagues examined an optimal dose of vitamin D in relation to infant length (n=36), and they observed that increased linear growth was seen in infants who were fed 1 teaspoon of cod liver oil daily (containing roughly 10 μg of vitamin D) compared with infants given approximately a fourth of that amount [205]. They continued with their research and found that a much larger dose of vitamin D (45–115 μg) decreased infants' (n=9) linear growth [206]. Despite the small number of infants in these early studies, which has raised well-deserved criticisms, the findings have left a mark in vitamin D history by prompting a general cautiousness against vitamin D fortification and supplementation [207]. An exception for this has been Finland, where high doses have been recommended in the past [104].

Studies examining the relationship between vitamin D and infant growth are scarce and their results conflicting. In rickets, stunted growth or slow linear growth is perceived as one of the symptoms. However, in many cases of rickets, the patient may suffer from other nutrient deficiencies or illnesses as well, possibly in addition to other poor living conditions. Indeed, it has been suggested that the effect of severe vitamin D deficiency on growth is secondary, as deficient status probably increases the risk of infectious diseases, which are known to restrict growth. Consequently, it is difficult to recognize the independent role of vitamin D in the regulation of growth. In a case report from the USA, an inherited 25-hydroxylase deficiency lead to rickets and stunted growth in a Caucasian child [208]. This condition was successfully treated with $1,25(OH)_2D$ [208]. Generally, it is assumed that vitamin D supplementation or higher vitamin D status in either the mother or infant promotes infant growth also without the presence of rickets.

2.8.1 MATERNAL VITAMIN D AND INFANT PRENATAL GROWTH

There have been quite a lot of reviews and meta-analyses about the effect of vitamin D supplementation during pregnancy on birth size [124, 197, 198, 209-212]. The results are presented in Table 7. The meta-analysis by Bi et al. concluded that maternal vitamin D supplementation decreased the risk of SGA and increased birth weight, but no association was observed with birth length or head circumference [209]. Roth et al. came to similar conclusions but emphasized the low quality of RCTs (Table 7) [125]. An updated Cochrane review concluded with moderate evidence that maternal vitamin D supplementation decreased the risk of low birth weight (<2500 g) based on 5 RCTs [198].

To study 25(OH)D rather than vitamin D supplementation against a health outcome has a strength: it overcomes challenges in estimating dietary intakes and cutaneous synthesis, although the causality remains unanswered. According to a meta-analysis by Aghajafari et al., maternal 25(OH)D <37.5 nmol/l increased the risk of SGA compared with maternal 25(OH)D >37.5 nmol/l (Table 7) [17]. According to a more recent meta-analysis by Tous et al., mothers with 25(OH)D <30 nmol/l had newborns with lower weight and head circumference but not length compared with mothers with >30 nmol/l [213]. Furthermore, no relation was detected with a cut-off of 50 nmol/l or 75 nmol/l [213]. Nonetheless, based on a Mendelian randomization study with known genetic variants associating with 25(OH)D, no evidence for an effect of maternal 25(OH)D on birth weight was observed [18].

A problem again in the meta-analyses can be the high heterogeneity between included studies [213, 214]. The single studies are carried out in different geographical areas, leading to inconsistencies related to, for example, sunlight exposure, ethnicity, DPs, supplementation policy, baseline vitamin D status, and overall nutritional status. In addition, different study protocols, for example, a wide variation in the supplementation procedure (20–125 μg/day, 875–1250 μg/week, 1250 μg/4 days, 1500 μg/month/2 months, or single bolus dose of 1500–5000 μg versus placebo or a standard treatment/10 μg/day) and different 25(OH)D cut-offs applied can create challenges in data analysis [209, 213].

Exploring this topic from a Scandinavian perspective, the results appear to be equally inconsistent as from a global point of view. In a Norwegian study (n=719, mean 25(OH)D 50 nmol/l, included in the Tous et al. meta-analysis), after adjusting for ethnicity, there was no relation between maternal vitamin D status and birth size [215]. In a Danish study, applying two cohorts with Caucasian women (n=1038, mean 18–22 nmol/l, included in Tous et al.), UCB 25(OH)D was not associated with weight or head circumference but was associated positively with infant length at age 2 weeks [216]. In another Danish cohort (n=2082, mean 65–79 nmol/l), Lykkedegn et al. observed no association between 25(OH)D measured at three time points during pregnancy and birth weight [171]. But in that study, UCB 25(OH)D (mean 47 nmol/l) correlated positively with birth weight, surprisingly indicating a U-

shaped association, i.e., both low and high UCB 25(OH)D values associated with higher birth weight [171]. In a recent cohort of Swedish women (n=2052, mean 25(OH)D 64–75 nmol/l, included in Tous et al.), mothers with 25(OH)D ≥100 nmol/l and 30–49.9 nmol/l were at decreased risk for having a low birth weight infant compared with mothers with 25(OH)D <30 nmol/l [217]. These associations existed when 25(OH)D measurements were conducted in the third trimester but not in the first trimester. In this cohort, ethnicity may have been a confounder as in the <30 nmol/l category only 14% of the women were born in Sweden compared with 94% in the ≥100 nmol/l category [217]. In Finland, there have been very few studies on maternal 25(OH)D and infant growth, but in one study by Viljakainen et al. (n=124, median 43 nmol/l), no association between maternal 25(OH)D and birth size was observed [154].

To summarize, there are inconsistencies in studies examining the relationship between maternal vitamin D status and birth size. However, severe maternal vitamin D deficiency probably increases the risk of lower birth weight, and correction of the deficient status, i.e., with vitamin D supplementation, decreases the risk of low birth weight, but for birth length and other birth size measures, the relationship is inconclusive.

Table 7. *Results of the latest meta-analyses of RCTs and observational studies examining the association between maternal vitamin D supplementation and vitamin D status and birth size*

		Length/Height		Weight		Head circumference	
Publication	Maternal determinant	Effect/ association	N of studies, heterogeneity	Effect/ association	N of studies, heterogeneity	Effect/ association	N of studies, heterogeneity
Maugeri et al. 2019 [210]	vitamin D supplementation	+	7, yes	+	12, no	+	6, no
Bi et al. 2018 [209]	vitamin D supplementation	NS	12, yes	+	17, yes	NS	11, yes
Roth et al. 2017 [125]	vitamin D supplementation	NS	19, yes	+	30, yes	NS	17, yes
Perez-Lopez et al. 2015 [212]	vitamin D supplementation	+	2, yes	+	5, yes	NI	-
Thorne-Lyman et al. 2012 [211]	vitamin D supplementation	NS	2, yes	NS	5, yes	NI	-
Tous et al. 2019 [213]	25(OH)D cut-offs of 30, 50 and 75 nmol/l	NS	4, yes	+ [1]	15, yes	+ [1]	7, yes
Santamaria et al. 2018 [214]	25(OH)D cut-offs of 25, 27.5, 28, 30 and 50 nmol/l	NS	10, yes	+	16, yes	NS	7, yes
Aghajafari et al. 2013 [17]	25(OH)D <37.5 vs >37.5	NS	2, not reported	+	4, not reported	NS	2, not reported

RCT, randomized controlled trial; 25(OH)D, 25-hydroxyvitamin D; + indicates a positive effect of vitamin D supplementation or an association of higher 25(OH)D toward newborn growth; NS, non-significant; NI, not investigated

[1] with cut-off of 30 nmol

2.8.2 MATERNAL VITAMIN D AND INFANT POSTNATAL GROWTH

Research related to maternal vitamin D and pregnancy and birth outcomes is mounting, but fewer studies have investigated vitamin D and postnatal outcomes. Naturally, it is of interest as to whether the possible effect of maternal vitamin D on birth size persists into later infancy and childhood. Table 8 presents original studies that have investigated the association between maternal 25(OH)D and infant postnatal growth.

The meta-analysis by Bi et al. examined maternal vitamin D supplementation in regard to postnatal growth parameters and found three studies, involving only subjects of Asian origin [209]. In that study, maternal vitamin D supplementation increased weight at 3, 6, 9, and 12 months, height at 3, 9, and 12 but not at 6 months, and head circumference at 3 months but not at 6, 9, and 12 months [209]. However, a large vitamin D supplementation trial conducted in Bangladesh (n=1300, 5 groups of supplementations from placebo to 700 μg/week pre- and postnatally), not included in the meta-analysis of Bi et al., found no effect of maternal vitamin D supplementation on infant growth until 1 year of age [218]. In this RCT, a dose-dependent effect on 25(OH)D (mean between 24 and 110 nmol/l) was achieved in a study population with an originally high prevalence of vitamin D deficiency [218].

In a study conducted in the USA, pregnant women with 25(OH)D above 30 nmol/l had heavier and taller 4-month-old infants compared with women with <30 nmol/l, although the relationships attenuated to some extent at 1 year of age [219] (Table 8). Few studies have not found an association between maternal vitamin D status and child growth or body composition at infancy [168, 220-224], and some have observed both positive and negative associations [225] (Table 8). A meta-analysis by Santamaria et al. employed 4 observational studies with maternal 25(OH)D as a determinant for infant postnatal growth, ([219, 220, 225, 226], included in Table 8 below) [214]. They concluded that low vitamin D status was associated with higher weight at 9 months (2 studies) but smaller head circumference at 1 year of age (2 studies) and no association for length (4 studies) [214].

Overall, studies on maternal vitamin D and postnatal growth are conflicting. Also, adjustment procedures vary between studies from zero adjustments [227] to adjustments for up to 11 variables [225], which further complicates comparisons between the studies.

Table 8 *Summary of the negative (-) and positive (+) relationships between higher maternal 25(OH)D concentration and infant postnatal growth in original studies*

Publication, country, year of the study	Design, N	Mean 25(OH)D, nmol/l	Applied cut-offs for 25(OH)D, nmol/l	Anthropometric outcomes			
				Length/Height	Weight	Head circumference	Other
Eckhardt et al. 2015, USA, 1959–1965 [219]	cohort, 2438 mothers, 2473 infants	59	<30 vs. ≥30	+ 4, 12 mo	+ 4 mo NS 12 mo	+ 4, 12 mo	NS BMIZ
Neelon et al. 2018, USA, 2009–2012 [228]	cohort, 211	41	quartiles	NI	- 12 mo	NI	- BMIZ 3 years
Sauder et al. 2017, USA, 2009–2014 [168]	cohort, 348	56	continuous UCB 25(OH)D	NI	NS 5 mo	NI	NS fat and fat-free mass
Leffelaar et al. 2010, Netherlands, 2003–2004 [225]	cohort, 2739	54[1]	≤29.9 vs. ≥50	+ 1 mo - 12 mo NS 3, 6, 9 mo	- 6, 9 mo NS 1, 3, 12 mo	NI	
Javaid et al. 2006 and Gale et al. 2008, UK, 1991–1992 [220, 229]	cohort, 440	50[1]	<30 vs. 30–50 vs. 50–75 vs. >75	NS 9 mo	NS 9 mo	NS 9 mo	NS MUAC, BMI, fat and lean mass + bone measures at 9 years NS for other at 9 years
Egge et al. 2017, Denmark, 2010–2012 [221]	cohort, 1780	47-66	continuous and quartiles of pregnancy and UCB 25(OH)D	NI	NI	NS 3, 6 mo	NS cranial measures
Vieth Streym et al. 2013, Denmark, 2008–2011 [222]	cohort, 107	43-73	continuous pregnancy and UCB 25(OH)D	NS 4, 9 mo	NS 4, 9 mo	NI	

Table 8 continues.

Gould et al. 2017, Australia, 2006–2010 [226]	secondary analysis of DHA supplementation trial, 323	56	continuous and UCB 25(OH)D <25 vs. 25–50 vs. >50	NS 18 mo	NS 18 mo	+ 18 mo	+ head circumference at 4 years NS for other at 4 years
Hanieh et al. 2014, Vietnam, 2010–2012 [230]	cohort, 960	71	continuous	- 6 mo	NS 6 mo	NS 6 mo	
Prentice et al. 2009, Gambia, 1995–2000, [223]	secondary analysis of calcium supplementation trial, 125	103-111	continuous and <80 vs. >80	NS 3, 12 mo	NS 3, 12 mo	NS 3, 12 mo	
Ong et al. 2016, Singapore, 2009–2011 [224]	cohort, 807	81	<50 vs. 50–74.9 vs. >75	NS 3, 6, 9, 12 mo	NS 3, 6, 9, 12 mo	NS 3, 6, 9, 12 mo	NS MUAC, abdominal circumference, BMI, skinfolds NS 15, 18, 24 mo
Chi et al. 2018, China, 2014–2015 [227]	cohort, 160	31-65	continuous and <50 vs ≥50 pregnancy and UCB 25(OH)D	+ 6 mo	+ 6 mo	+ 6 mo	

Roth et al. 2013 excluded due to insufficient data [231].

25(OH)D, 25-hydroxyvitamin D; mo, months; NS, non-significant; NI, not investigated; BMI, body mass index; BMIZ, BMI-for-age score; UCB, umbilical cord blood; MUAC, mid-upper-arm circumference; DHA, docosahexaenoic acid

[1] median

2.8.3 INFANT VITAMIN D AND GROWTH

Surprisingly few studies have examined infants' own vitamin D status in relation to growth. Table 9 summarizes the original studies on infant vitamin D and growth. In a small RCT among Canadian infants by Gallo et al., subjects were randomized to receive a daily vitamin D supplementation dose of 10, 20, 30, and 40 μg from 1 month until 1 year [232]. They found no differences in growth parameters between groups despite a dose-response effect on infants' vitamin D status (Table 9). In this study, the intervention was discontinued in the 40 μg group due to 25(OH)D values exceeding 250 nmol/l [232]. A follow-up study of these infants at the age of 3 years (n=87/132) confirmed no difference in growth patterns [233]. Similarly, in Finland, Holmlund-Suila et al. conducted an RCT in 113 newborns until they were 3 months old [138]. Infant 25(OH)D values rose from median 53 nmol/l to mean 88, 124 and 153 nmol/l according to supplementation groups of 10, 30, and 40 μg, respectively. There were no differences between groups in length, weight, head circumference, or leg length at 3 months of age [138].

In another RCT among Indian low–birth weight infants with a high prevalence of vitamin D deficiency, vitamin D supplementation of 35 μg/week (n=1039) from the age of 1 week until 6 months improved infant length, weight, and MUAC at 6 months compared with placebo (n=1040) [234] (Table 9). The mean 25(OH)D in the supplemented infants was 55 nmol/l (n=216), and in infants receiving placebo, it was 36 nmol/l (n=237). In this study, 38% were lost to follow-up at 6 months and even more from 25(OH)D analyses [234]. In a follow-up at 3–6 years of age, no effect was observed in length and weight (when mean 25(OH)D were 32–34 nmol/l) [235]. However, the supplemented children were thinner at 3–6 years old [235]. An Ecuadorian vitamin A and zinc trial reported that stunting was more common among children 6–36 months old with 25(OH)D <42.5 nmol/l compared to those with ≥42.5 nmol/l [236]. These children had an overall high prevalence of stunting (62%) and low socioeconomic status [236].

Among Danish 9-month-old infants, 25(OH)D correlated inversely with BMI, waist circumference, and length [237] (Table 9). Within a large Finnish prospective birth cohort (n=10 060), Hyppönen et al. investigated whether infant vitamin D supplementation had long-term consequences on height at 1 and 14 years of age and on adult height [207]. They concluded that either vitamin D supplementation of <50, 50 (the recommendation at the time) or >50 μg/day, or supplementation categorized as none, irregular, or regular use were associated with heights at any age. However, a small number of participants in the "none vitamin D supplementation" (n=20–31) group may have constrained the analysis [207].

To conclude, the data concerning vitamin D and infant growth are scarce, and no definite deduction can be made.

Table 9 *Summary of the negative (-) and positive (+) relationships between infant vitamin D and infant growth in original studies*

Publication, country, year of the study	Design, N	Mean baseline 25(OH)D, nmol/l	Exposure	Length/ Height	Weight	Head circumference	Other
Gallo et al. 2013 and 2016, Canada, 2007–2011 [232, 233]	RCT, 132	51-62	10, 20, 30 and 40 µg/day	NS 1, 2, 3, 6, 9, 12 mo	NS 1, 2, 3, 6, 9, 12 mo	NS 1, 2, 3, 6, 9, 12 mo	NS at 3 years
Kumar et al. 2011 and 2015, India, 2007–2010 [234, 235]	RCT, 2079	NI	placebo and 35 µg/week	+ 6 mo	+ 6 mo[1]	NS 6 mo	+ MUAC 6 mo; - BMIZ, MUAC at 3–6 years; NS for other at 3–6 years
Mokhtar et al. 2018, Ecuador, 2000–2003[2] [236]	secondary cross-sectional analysis of vitamin A and zinc trial, 516	58	25(OH)D <42.5 vs. ≥42.5 nmol/l	+ 6-36 mo	+ 6-36 mo	NI	
Arnberg et al. 2011, Denmark, 2007–2008 [237]	cross-sectional, 255	77	continuous 25(OH)D	- 9 mo	NI	NI	- BMI, waist circumference
Holmlund-Suila et al. 2012, Finland, 2010–2011 [138]	RCT, 113	53[3]	10, 30, and 40 µg/day	NS 3 mo	NS 3 mo	NS 3 mo	NS bone measures
Hyppönen et al. 2011, Finland, 1967–1998 [207]	cohort, 10 060	NI	<50 vs. 50 vs. >50 µg/day, and none vs. irregular vs. regular use of vitamin D supplementation at 1 year of age	NS 12 mo	NI	NI	NS height at 14 years and in adulthood

Greer et al., Chan et al. and Ala-houhala et al. [238-240] excluded due to small numbers of subjects and data availability.
25(OH)D, 25-hydroxyvitamin D; RCT, randomized controlled trial; mo, months; NI, not investigated; NS, non-significant; BMI, body mass index; BMIZ, BMI-for-age score; MUAC, mid-upper-arm circumference
[1] NS in weight-z-score [2] 70% of subjects were >12 months old [3] Median.

3 AIMS OF THE STUDY

The main objective of this study was to investigate whether maternal or infant vitamin D status associate with fetal and infant growth. The specific aims of the thesis were:

I	To define maternal and newborn 25(OH)D concentration and to characterize maternal determinants of vitamin D status during pregnancy.
II	To examine if vitamin D status differs between mothers with and without GDM.
III	To describe vitamin D intake from food and identify food sources of vitamin D in 1-year-old infants.
II–IV	To investigate whether maternal or infant vitamin D status associate with pre- and postnatal infant growth.

4 SUBJECTS AND METHODS

4.1 STUDY DESIGN

This thesis is part of the VIDI study. The VIDI study was a double-blinded intervention study in infants comparing the health effects of a recommended (10 μg) and a higher daily dose (30 μg) of supplemental vitamin D_3 in infants from 2 weeks until 2 years of age [241, 242]. VIDI included three study visits of the infant at ages 6, 12, and 24 months. The study recruitment started in January 2013, and the last study visit was in June 2016. This thesis employs data from pregnancy until the infant is 1 year old, without information on the infant's dose of vitamin D supplementation.

4.2 RECRUITMENT AND SUBJECTS

At Kätilöopisto Maternity Hospital in Helsinki, Finland, 987 families were recruited into the VIDI study between January 2013 and June 2014 after delivery during the mother's hospital stay. Mothers were of Northern European origin without regular medication and with a singleton pregnancy. The infants, 492 girls and 495 boys, were born at term (37.0–42.0 weeks) with birth weights appropriate for gestational age (birth weight SD score between -2.0 and +2.0). Exclusion criteria for the newborns were nasal continuous positive airway pressure treatment, a need for a nasogastric tube for more than one day, intravenous glucose infusion, seizures, and duration of phototherapy for more than three days.

Of the informed eligible families, 29% (987/3408) agreed to participate in the VIDI study (Figure 2). In Figure 2 and Table 10, the data- and study-specific number of subjects and the inclusion and exclusion criteria are shown. The number of subjects varies between Studies I–IV due to different data applied and different study-specific inclusion criteria. In Study I, the number of subjects was 584 as they had complete data on baseline background information including maternal food frequencies. In Study II, the number of subjects was 723 as they had data on the prenatal clinic record or baseline background information. Some missing background information was imputed in Study II. In both Studies I and II, subjects had full data on pregnancy and UCB 25(OH)D concentrations but without 25(OH)D outliers. In Studies II and IV, subjects with congenital disease were excluded. In Study III, the number of subjects was 739 as they had complete data on food consumption. In Study IV, the number of subjects was 798 as they had data on infant 25(OH)D concentration at 1 year of age and body size measurements at 6 months and 1 year of age. Missing background information was multiple imputed, and

subjects not meeting the VIDI study inclusion criteria were excluded in Study IV.

Written informed consent was collected from the parents at recruitment. This study was conducted according to the guidelines laid down in the Declaration of Helsinki. Ethical approval was obtained from the Research Ethics Committee of the Hospital District of Helsinki and Uusimaa (107/13/03/03/2012). The project protocol is registered in ClinicalTrials.gov (NCT01723852).

Table 10 *Number of subjects in Studies I–IV and the basis for subject inclusion and exclusion*

Study	N	Inclusion criteria	Exclusion
I	584 mother-infant pairs	Available data on the complete baseline background questionnaire including FFQ, and early pregnancy and UCB 25(OH)D concentrations.	25(OH)D outliers (n=9)
II	723 mother-infant pairs	Available data on the prenatal clinic record or baseline background questionnaire, and pregnancy and UCB 25(OH)D concentrations.	25(OH)D outliers (n=18), pregnancy samples in the third trimester (n=2), infants with congenital disease (n=2)
III	739 infants	Available data on the complete infant food record at 1 year of age.	-
IV	798 infants	Available data on infant 25(OH)D concentrations at 1 year of age, and body size measurements at 6 months and 1 year of age.	Not meeting the VIDI study inclusion criteria (n=12), infant with congenital disease (n=1)

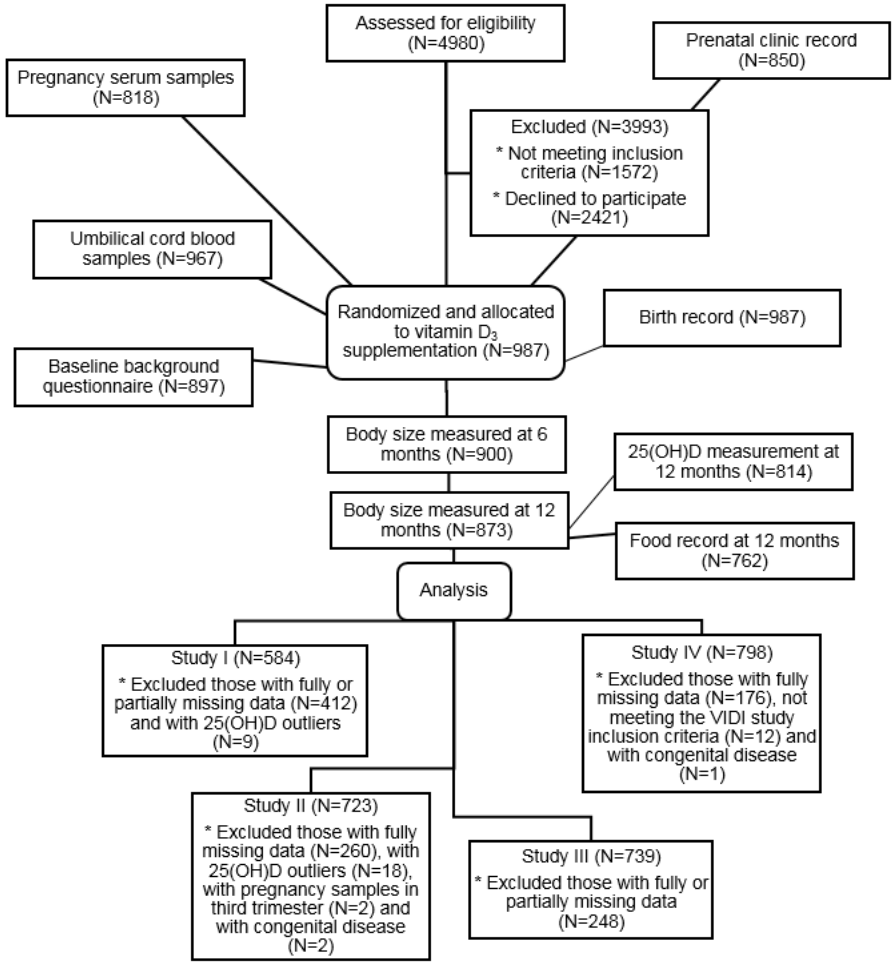

Figure 2 Flow chart on VIDI study recruitment, and available data and number of participants in Studies I–IV.

4.3 METHODS

4.3.1 MATERNAL AND FAMILY BACKGROUND FACTORS (I–IV)

Maternal and family data were obtained using self-administered questionnaires, filled in after delivery and when the child was 2 years old, and from medical records. Maternal height (cm) and weight (kg) before pregnancy and parity were collected primarily from the prenatal record or, if missing, from our baseline questionnaire in Studies II and IV. For Study I, the data originated solely from the baseline questionnaire. Paternal height, weight, and BMI were attained from the baseline questionnaire. The prepregnancy body mass index (BMI) (kg/m^2) was categorized as underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), and obese (>30.0). The duration of gestation was determined from a first-trimester ultrasound examination and recorded retrospectively from prenatal records.

Prepregnancy weight and weight recorded in prenatal clinics were utilised to calculate gestational weight gain (GWG) (kg) (II). GWG was recorded at five time points during pregnancy from first measurement until last measurement. Total GWG was categorised into inadequate, adequate and excessive based on national recommendations by prepregnancy BMI: recommended GWG for underweight mothers was 12.5-18.0 kg, for normal weight 11.5-16.0 kg, for overweight 7.0–11.5 kg, and for obese 5.0–9.0 kg [243]. Parity was determined by the number of biological children from the baseline questionnaire or the prenatal record and then categorized (primipara/nullipara, secundipara, and multipara).

Maternal use of vitamin D supplements, specific brand names, dosing, and date of commencement were recorded (Studies I and II). We calculated the average daily intake of vitamin D from supplementation during the last two months of pregnancy.

Maternal history of physical activity before pregnancy was obtained as guided and unsupervised exercise and active commuting to work, but only guided exercise (minutes per day) was chosen for analysis due to collinearity issues (hereafter referred to as physical activity). Parental smoking was assessed from questionnaires as the number of daily cigarettes before pregnancy (prepregnancy), after delivery, and when the child was 2 years old (current), and it was then categorized as a dichotomous variable. Alcohol consumption before pregnancy was assessed by the number of dosages per week. The family's income level was gathered via questionnaire, which was completed when the child was 2 years old.

Education level was graded from 1 (=comprehensive school/lower secondary education) to 6 (university degree/first or second stage of tertiary education). It was then re-categorized into "lower" and "higher" education

(lower = lower or upper secondary or post-secondary non-tertiary education/less than a bachelor's degree, higher = first or second stage of tertiary education/at least a bachelor's degree). Parental education was defined according to the parents' highest degree received.

4.3.2 25(OH)D CONCENTRATION (I, II, IV)

Maternal pregnancy serum samples were collected at prenatal clinics on average at gestational week 11, between June 2012 and February 2014, as part of the mothers' normal follow-ups. Samples were stored in the Finnish Maternity Cohort serum bank, which is organized by the National Institute for Health and Welfare. UCB samples were obtained at birth between January 2013 and June 2014. At the 1-year follow-up visit, infant serum samples were obtained between December 2013 and June 2015. Study covered all seasons and seasonal variation of 25(OH)D were considered in statistical analyses.

The UCB plasma and pregnancy serum 25(OH)D were analyzed simultaneously, and infant serum 25(OH)D in a separate series using the IDS-iSYS fully automated immunoassay system with chemiluminescence detection (Immunodiagnostic Systems Ltd., Bolton, UK). The 25(OH)D value derived with this method represents combined $25(OH)D_2$ and $25(OH)D_3$. The intra-assay variations were <13% for UCB samples and <5% for pregnancy and infant samples. The quality and accuracy of the serum 25(OH)D analysis are validated on an ongoing basis by participation in the vitamin D External Quality Assessment Scheme (DEQAS, Charing Cross Hospital, London UK). The method showed a constant ≤10% positive bias against the NIST Reference Measurement Procedure.

Plasma UCB 25(OH)D concentrations were corrected with formula 19.13 + 0.897 * UCB 25(OH)D to be comparable with pregnancy serum 25(OH)D concentrations. The equation is based on the comparison of paired 25(OH)D measurements in plasma and serum UCB samples in 84 subjects at birth. In Studies II and IV, UCB and pregnancy 25(OH)D concentrations were further corrected by applying a linear regression equation (correct value (nmol/l)=[(initial value)–8.2]/0.99) provided by the manufacturer due to methodological changes in the IDS-iSYS system between 2014 and 2016.

We employed UCB 25(OH)D to reflect both the mother's vitamin D status at the end of pregnancy and the newborn's vitamin D status at birth. Maternal 25(OH)D refers to both 25(OH)D measured during pregnancy and UCB 25(OH)D measured at birth. In Study I, pregnancy 25(OH)D values were restricted to subjects sampled at early pregnancy (until 13 weeks of gestation). We defined vitamin D sufficiency as 25(OH)D ≥50 nmol/l [71, 114]. Other 25(OH)D cut-offs used in this thesis were 75 nmol/l based on possible optimal bone health [117] and 125 nmol/l based on possible health risks [114]. In the original publication of Study II, a threshold of 80 nmol/l was used based on calcium absorption studies [244].

4.3.3 GDM (II)

According to national recommendations, the diagnosis of GDM was based on a two-hour 75 g oral glucose tolerance test (OGTT) [243]. GDM was diagnosed if the OGTT results exceeded cut-offs for one or more values: fasting plasma glucose ≥ 5.3 mmol/l, 1-h ≥ 10.0 mmol/l and 2-h ≥ 8.6 mmol/l. OGTT was performed on 490/723 (54.5%) of the participating mothers at gestational weeks 10–40 between October 2012 and March 2014. These data were collected from prenatal and medical records.

4.3.4 DIETARY DATA (I AND III)

Data on maternal diet during the last month of pregnancy were collected retrospectively using a 22-item semi-quantitative FFQ. Mothers filled in the frequency of food group usage with a given standard portion size. The frequency of food groups consumed was recorded from 0 = not used to 8 = four to six times a day or more.

Infant food consumption and vitamin D intake at 1 year of age were collected between January 2014 and June 2015 with a 3-day food record administered to parents or daycare personnel who had received written instructions on how to accurately fill it out (III). At the 1-year follow-up, families were instructed to record all of the infant's foods, drinks and supplements with their amounts, as well as breastfeeding frequencies during the food record period. The volume of breast milk ingested was not recorded. Only 2% (16/739) were at daycare at the time of the food record.

Food records and nutrient intakes were processed with AivoDiet software (version 2.0.2.3, Aivo Oy, Turku, Finland), which utilizes Fineli (version Fine68, 2016), the National Food Composition Database maintained by the National Institute for Health and Welfare. Five infants had a 2-day, and the rest (n=734) had a 3-day food record. Categorizing the food items into more general food groups was based on the FinDiet survey [245] with some modifications. Composite food items from the food record were unable to be further broken down into individual food items. Thus, for example, the "meat dishes" food group includes all ingredients used in the dish, such as meat, cream, potatoes, and carrots.

The infant's breastfeeding status at 1 year of age was based on the food records in Study III. In Study IV, breastfeeding duration was obtained from repeated questionnaires within study diaries.

4.3.5 INFANT ANTHROPOMETRICS (II–IV)

Birth size, including birth weight (kg), length (cm), and head circumference (cm), was measured by midwives according to standard procedure. These data and the duration of the pregnancy were retrospectively collected from birth records. Birth size and postnatal growth parameters were transformed into

standard deviation scores (SDSs) using Finnish sex- and age-specific normative data for fetal [246] and postnatal growth [247]. The Ponderal index was calculated (birth weight (kg) / birth length (m)^3) and standardized into a sex-specific z-score within the study subjects.

Infant postnatal growth was measured at 6-month and 1-year follow-up visits by a pediatrician or research nurse. Head circumference was measured with an inelastic tape and recorded to the nearest 0.5 cm (Seca®, Hamburg, Germany). Length (cm) was measured with a tabletop meter in a supine position, and weight (kg) was measured with a scale (Seca®, Hamburg, Germany). Normal weight, length, length-adjusted weight, and head circumference were determined between -2.0 and +2.0 SDS.

4.3.6 STATISTICS

The normality of the variables was visually inspected. Descriptive subject characteristics were reported as means, medians, standard deviations, or percentages and were tested with independent sample t-tests, Mann-Whitney U-tests, ANOVA, Pearson's chi-squared and Fisher's exact tests. Outliers of UCB and pregnancy 25(OH)D were omitted in Studies I and II to obtain reliable results. Outliers were identified with a Normal probability plot of residuals, Leverage and Cook's Distance diagnostic tests. ANOVA and ANCOVA with Bonferroni post hoc tests were used when applicable. Univariate and multivariate linear regression models were employed. A change of 25(OH)D during pregnancy [Δ25(OH)D] was calculated as UCB 25(OH)D – early pregnancy 25(OH)D (I).

Covariates were chosen based on their significant associations with the outcome or independent variable and literature. Some missing information of covariates was imputed in Study II using median or mean values in subgroups by GDM status. In Study IV, missing values of covariates were multiple imputed (5 imputations). In Study IV, infant 25(OH)D concentration was used as a proxy for the infant's total vitamin D intake.

Seasons were defined as follows: winter from December to February; spring from March to May; summer from June to August; and fall from September to November. Seasons as a covariate were coded using dummy variables (with fall as a reference) in linear regression models.

Maternal DPs were created based on food group frequencies in the FFQ using principal component analysis (PCA) (I). Standardized PCA scores were calculated for each mother. These scores ranked pregnant women according to their adherence to the specific DP.

An elaboration model [248] was applied to study the tracking of 25(OH)D from early pregnancy to UCB by conducting a series of regression models in Study I. We examined changes in the beta coefficient of pregnancy 25(OH)D in regression models; a decline in beta coefficients meant that the added factor promoted the tracking of 25(OH)D from pregnancy to UCB, and an increase prevented it. A multivariate linear regression model was used to determine the

most important predictors for declining and increasing 25(OH)D during pregnancy in subgroups of Declined (Δ25(OH)D < 0 nmol/l) and Increased (Δ25(OH)D > 0 nmol/l) 25(OH)D during pregnancy.

The difference in 25(OH)D between GDM and non-GDM mothers was investigated with ANCOVA adjusted for season, maternal age, education, and prepregnancy BMI (II). Birth size was examined by 25(OH)D categories of <50 nmol/l, 50–74.9 nmol/l, 75–125 nmol/l and >125 nmol/l with ANCOVA adjusted for maternal education, prepregnancy BMI, maternal prepregnancy smoking, gestational diabetes mellitus, parity, maternal height, maternal GWG, and UCB/pregnancy 25(OH)D as changing covariates.

Infant postnatal size was investigated in linear regression models and in 25(OH)D categories of <50 nmol/l, 50–74.9 nmol/l (reference group), 75–125 nmol/l and >125 nmol/l with ANCOVA adjusted for corresponding birth size SDS, maternal and paternal height z-scores, and infant 25(OH)D at 1 year when applicable (II and IV). Statistical significance between only the reference group of 50–74.9 nmol/l and other groups were tested with linear regression. In linear regression models, three models were used: Model 1, unadjusted; Model 2, adjusted for corresponding birth size SDS, maternal and paternal height z-scores, and infant 25(OH)D (except in analyses of infant 25(OH)D); and Model 3, adjusted for Model 2 covariates and for maternal and paternal prepregnancy BMI, parental smoking status, parental education level, family income level, and duration of breastfeeding.

A change in infant growth (length, weight, length-adjusted weight, and head circumference) between birth, 6 months, and 1 year of age was calculated by saving the residuals from linear regression models of body size SDS at each successive age versus the corresponding body size SDS at all earlier ages. These residuals were referred to as "conditional growth." Conditional growth reflects growth rates between growth periods. Univariate and multivariate linear regression analyses were used to explore associations between 25(OH)D and infant conditional growth with similar adjustments as described above.

Associations were considered significant at $P < 0.05$. All statistical analyses were conducted using the IBM SPSS program for Windows version 22 (IBM, Chicago, IL, USA).

5 RESULTS

5.1 SUBJECT CHARACTERISTICS (I–IV)

The characteristics of the parents and infants are reported in Tables 12 and 13. Mothers and fathers averaged 32 and 34 years old, respectively (Table 12). Of the participating mothers, 76% were highly educated (I). The majority of the mothers (72%, I) and almost half of the fathers (47%, IV) had a normal BMI. Of the mothers, 95% took vitamin D supplements during pregnancy, with a mean intake of 16 µg/day (I). In pregnant women, daily supplemental intake of vitamin D ranged from zero to 197.5 µg, with the majority consuming 10 µg (Table 11). Of the mothers, 15% smoked before pregnancy (II) (Table 12). For 63% of the mothers, the infant was their firstborn.

Infants were born with birth weights appropriate for gestational age according to the VIDI study protocol. Infant size parameters were measured at three time points; at birth, 6 months, and 1 year of age (Table 13). Almost all infants had a normal body size at all time points. Half the infants were girls, and 79% and 40% were breastfed at the age of 6 months and 1 year, respectively (IV) (Table 12).

Table 11 *Maternal supplemental intake of vitamin D in Study I (n=584)*

Supplemental vitamin D intake, µg/day	Proportion of women, %
<10	15
10	54
10.1–19.9	6
20	9
>20	16

Table 12 *Subject characteristics in Studies I–IV*

	Study I	Study II	Study III	Study IV
N	584	723	739	798
Maternal				
Age, years	31.6 (4.2)	32.1 (4.4)	31.6 (4.2)	31.7 (4.3)
Prepregnancy BMI, kg/m[2]	23.3 (3.8)	24.6 (4.2)	-	23.2 (3.6)
Missing, n		*3*		*4*
Supplemental vitamin D intake, µg/day	15.7 (16.9)	14.5 (13.7)	-	-
Missing, n		*26*		
Education, higher[2], %	76	75	76	75
Missing, n		*12*	*1*	*10*
Nullipara, %	63	63	-	63
Missing, n				*2*
Smoking, yes[1], %	14	15	15	16
Missing, n		*22*		*5*
Paternal				
Age, year[3]	-	-	34.1 (5.3)	33.6 (5.3)
Missing, n			*7*	*39*
Prepregnancy BMI, kg/m[2]	-	-	-	25.7 (3.4)
Missing, n				*27*
Education, higher[3], %	-	-	61	62
Missing, n			*10*	*20*
Smoking, yes[1], %	-	-	24	26
Missing, n			*7*	*14*
Family income level				
<40,000 €/year, %	-	-	17	19
40,000–89,000 €/year, %	-	-	62	60
>90,000 €/year, %	-	-	21	21
Missing, n			*73*	*109*
Infant				
Sex, girls, %	52	51	49	51
Breastfed at 1 year[4], %			36	40
Duration of breastfeeding, months	-	-	-	10.7 (5.6)
Missing, n				*13*

Values are mean (SD) unless stated otherwise. A dash indicates no data available or not applied in the study. All values are unimputed.
BMI, body mass index.
[1] In Studies I–II, smoking status refers to prepregnancy smoking, and in Studies III–IV, smoking refers to combined smoking status at prepregnancy and at infant age of 2 years.
[2] At least a bachelor level education.
[3] Refers to age when infant was 1 year old.
[4] In Study III, breastfeeding status was obtained from food records, and in Study IV from study diaries.

Table 13 *Infant size at three time points*

	At birth n=723	At 6 months n=798	At 1 year n=798
Gestational age, week	40.2 (1.1)	-	-
Age, months	-	6.0 (0.2)	12.0 (0.4)
Length, cm	50.4 (1.7)	67.5 (2.2)	75.3 (2.5)
Length, SDS	-0.19 (0.88)	-0.47 (0.97)	-0.54 (1.01)
Weight, kg	3.5 (0.4)	8.0 (0.9)	9.8 (1.1)
Weight, SDS	-0.25 (0.80)	0.21 (1.07)	-0.24 (1.01)
Length-adjusted weight, SDS	-	0.15 (1.11)	0.02 (1.02)
Head circumference[1], cm	35.3 (1.4)	43.6 (1.2)	46.5 (1.2)
Head circumference[1], SDS	-0.10 (0.96)	-0.30 (0.94)	-0.42 (0.94)
Mid-upper-arm circumference[2], cm	-	-	15.3 (1.2)
Normal length SDS (-2.0–2.0), %	98	94	93
Normal weight SDS (-2.0–2.0), %	100	94	96
Normal length-adjusted weight SDS (-2.0–2.0), %	-	94	96
Normal head circumference SDS (-2.0–2.0), %[1]	96	96	96

Values are means (SD) unless stated otherwise; a dash indicates no data available.
SDS, standard deviation score, which is based on Finnish sex- and age-specific normative data for fetal and infant growth.
[1] At birth, 2 values are missing; at 6 months, 21 values are missing; and at 1 year, 5 values are missing.
[2] 39 values are missing.

5.2 25(OH)D CONCENTRATION (I, II, IV)

Table 14 demonstrates the mean 25(OH)D concentrations at three time points: in early pregnancy, at birth, and in infancy at 1 year of age. Pregnancy samples were collected on average at gestational week 11. Almost all pregnant women, newborns, and infants were vitamin D sufficient (25(OH)D ≥50 nmol/l) (96–99%). In Study I, pregnancy and UCB 25(OH)D values applied were uncorrected (see section 4.3.2). Thus, the prevalence figure of maternal vitamin D sufficiency in Study I differs from Studies II and IV (99% in Study I vs. 96% in Studies II and IV). Figure 3 presents prevalence values of vitamin D status in categories of <50 nmol/l, 50–74.9 nmol/l, 75–125 nmol/l and >125 nmol/l (IV). The majority of subjects had 25(OH)D concentration between 75 and 125 nmol/l (Figure 3).

Pregnancy and UCB 25(OH)D correlated positively, although the correlation was modest ($r=0.27$; $P<0.001$). Further, pregnancy and infant 25(OH)D had no correlation ($r=0.07$; $P=0.081$), but UCB and infant 25(OH)D at 1 year of age had a weak positive correlation ($r=0.15$; $P<0.001$).

Table 14 *Mean 25-hydroxyvitamin D concentration [25(OH)D] in pregnancy, in umbilical cord blood (UCB) and in infancy at the age of 1 year*

	Study I	Study II	Study IV
N	584	723	798 [1]
		Mean (SD)	
Pregnancy 25(OH)D, nmol/l [uncorrected, reported in Study I][2]	81.5 (19.1) [88.8 (19.0)]	81.7 (19.7)	82.4 (20.3)
Gestational age at sampling, week	11.0 (1.0)	11.3 (1.9)	11.3 (2.2)
UCB 25(OH)D, nmol/l [uncorrected, reported in Study I][2]	80.9 (22.3) [88.3 (22.0)]	79.9 (19.9)	82.5 (25.8)
Infant 25(OH)D at 1 year, nmol/l	-	-	98.9 (29.0)

A dash indicates no data available for the study.
[1] Number of participants for pregnancy values was 671, for UCB values 780.
[2] The uncorrected 25(OH)D value was reported in Study I, as these were not yet corrected for the methodological changes in the IDS-iSYS system (see section 4.3.2).

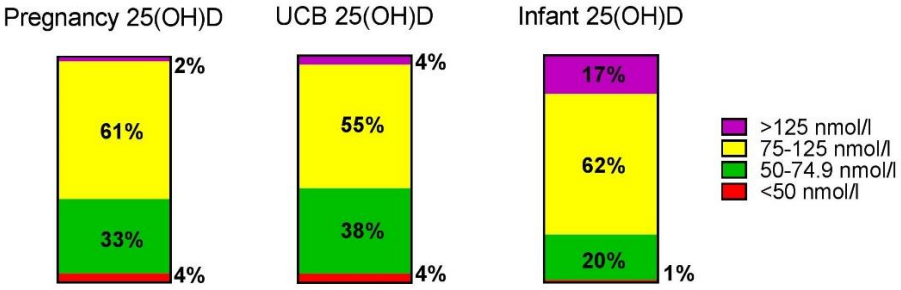

Figure 3 25-hydroxyvitamin D concentration [25(OH)D] in categories of <50, 50–74.9, 75–125, and >125 nmol/l in pregnancy (n=671), umbilical cord blood (UCB) (n=780), and in infancy at the age of 1 year (n=798) (IV).

5.3 DETERMINANTS OF MATERNAL AND NEWBORN 25(OH)D CONCENTRATIONS (I)

5.3.1 SEASON

Seasonal differences in 25(OH)D occurred but were relatively modest (Figure 4). In pregnancy and at birth, the 25(OH)D concentration was highest in summer, but in infancy, it was highest in winter.

5.3.2 MATERNAL DIET

The role of maternal diet was investigated as dietary patterns (DP) derived from FFQ data with PCA. Five DPs were chosen as the most interpretable, explaining 46% of the variation in maternal diet. The first was named "goodies and snacks," and it was characterized by frequent consumption of sweets/candy/lollipops, pudding/chocolate/ice cream, sweet and salty pastries, snacks and squash/soft drink. The second DP was named "health-conscious" and was characterized by foods such as fresh and cooked vegetables (including potato), fruits/berries (including fruit or berry juice), fish, and seeds/beans. The third DP, "meat," included meat, chicken, or egg foods, cold cuts from sausages, sausages, and ready-made marinated meat or fish products. The fourth DP, named "sandwich and dairy," was characterized by frequent consumption of rye bread/other whole-grain bread/muesli, cheese, margarine, and fluid dairy/vegetable milk products. The fifth DP included mild and strong alcoholic drinks and was named "alcohol." Standardized DP scores were calculated for each of the mothers and for each DP. This means that all the mothers had a score for goodies and snacks DP, health-conscious DP and meat DP, sandwich and dairy DP and alcohol DP.

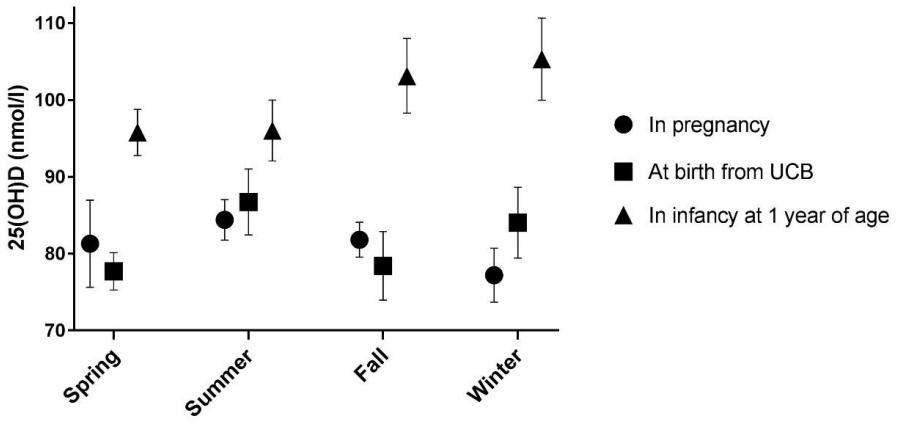

Figure 4 Mean (SEM) values of 25-hydroxyvitamin D at different seasons in pregnancy (n=584, ANOVA P=0.036), in umbilical cord blood (UCB) (n=584, ANOVA P=0.001) (I) and in infancy at 1 year of age (n=798, ANOVA P=0.001; IV).

5.3.3 TRACKING OF 25(OH)D DURING PREGNANCY

To establish the most important modifiers for maternal and newborn 25(OH)D concentrations, we investigated which maternal and other underlying factors influenced the relationship between early pregnancy 25(OH)D and UCB 25(OH)D, i.e., the tracking of 25(OH)D during pregnancy (Figure 5, Table 15). This was achieved by multiple linear regressions, in which we examined how the standardized beta coefficient of pregnancy 25(OH)D changed (as UCB 25(OH)D was the dependent) when adding other factors into the regression model (Figure 5), besides identifying significant associations between the factors and UCB 25(OH)D (Table 15). A decline in beta coefficient indicated that the factor promoted the tracking of 25(OH)D from pregnancy to UCB, and an increase in beta coefficient indicated that the factor prevented it. Factors are grouped by their similar characteristics (Figure 5).

High maternal physical activity, education level, supplemental vitamin D intake, and number of daily supplements promoted the tracking of 25(OH)D during pregnancy (Figure 5), but multiparity prevented it. Maternal 25(OH)D was also dependent on the season, of which the strongest modifier was summer season at delivery promoting 25(OH)D during pregnancy. Other relevant factors that had no effect on the tracking of 25(OH)D but associated with UCB 25(OH)D were maternal smoking and the “sandwich and dairy” DP during pregnancy (Table 15). All these factors were chosen for further analysis.

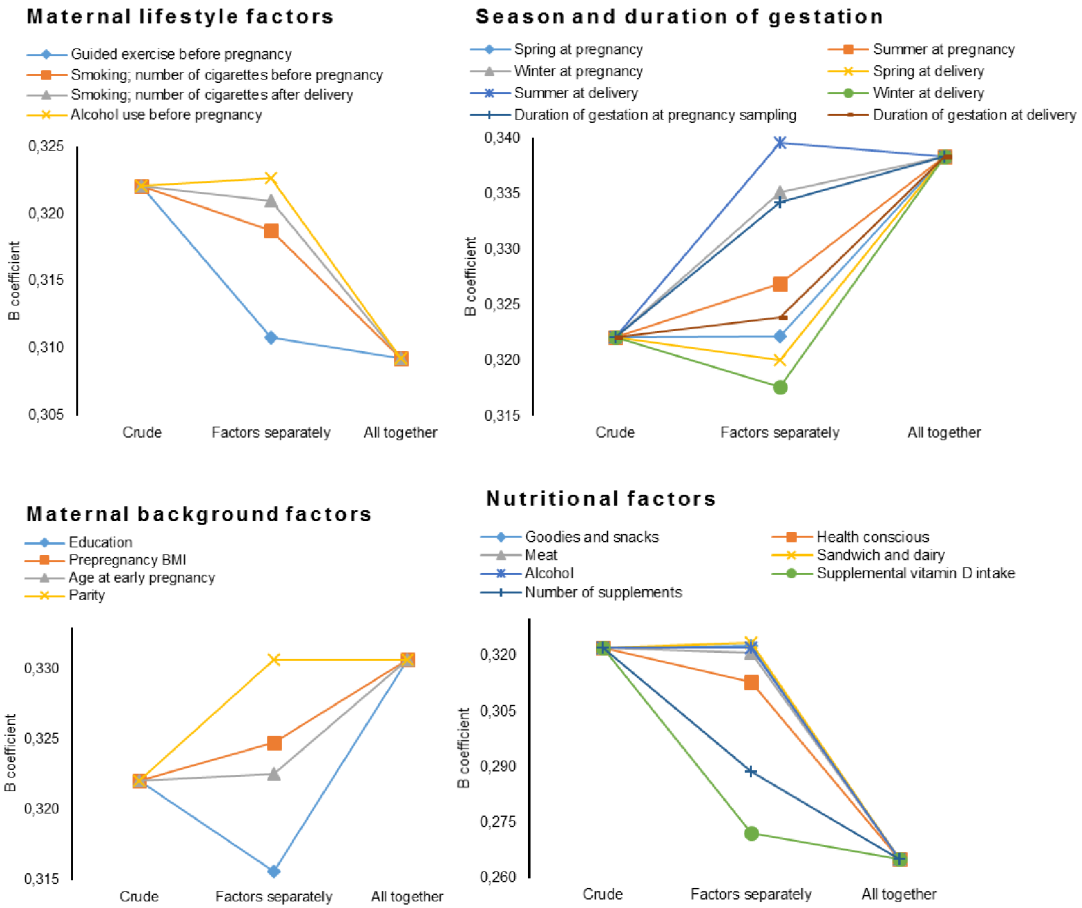

Figure 5. Modifiers affecting the tracking of 25-hydroxyvitamin D [25(OH)D] from early pregnancy to umbilical cord blood in a crude model after adding factors separately and together. A decline in B coefficient reflects a promoting effect of the factor, and an increase reflects the prevention of tracking the 25(OH)D during pregnancy. Reprinted and modified with permission from Springer Nature: European Journal of Nutrition, Hauta-alus et al. 2018 (Study I).

Table 15 *Factors associating with UCB 25(OH)D*

	β	B	95% CI	P
Pregnancy 25(OH)D, nmol/l	0.28	0.32	0.23, 0.41	**<0.001**
Maternal lifestyle factors				
Prepregnancy physical activity, min/day	0.11	0.13	0.04, 0.22	**0.005**
Prepregnancy smoking, number of cigarettes/day	-0.10	-0.57	-1.02, -0.12	**0.014**
Postpregnancy smoking, number of cigarettes/day	-0.08	-1.26	-2.51, -0.01	**0.049**
Prepregnancy alcohol use, portion/week	0.03	0.36	-0.49, 1.21	0.411
Maternal background factors				
Education, higher vs. lower	0.08	4.17	0.15, 8.19	**0.042**
Prepregnancy BMI, kg/m^2	0.03	0.15	-0.30, 0.61	0.510
Age, year	0.04	0.20	-0.21, 0.60	0.346
Parity	-0.15	-6.62	-10.16, -3.08	**<0.001**
Nutritional factors				
Goodies and snacks DP score	0.02	0.49	-1.24, 2.21	0.579
Health conscious DP score	0.07	1.63	-0.09, 3.36	0.064
Meat DP score	-0.05	-1.02	-2.75, 0.70	0.244
Sandwich and dairy DP score	0.09	1.97	0.25, 3.69	**0.025**
Alcohol DP score	0.02	0.52	-1.20, 2.25	0.551
Supplemental vitamin D intake, µg/day	0.17	0.23	0.12, 0.33	**<0.001**
Number of supplements	0.18	2.99	1.72, 4.25	**<0.001**
Season and duration of gestation				
Spring at pregnancy sampling	0.03	1.96	-3.02, 6.95	0.439
Summer at pregnancy sampling	-0.05	-2.20	-6.10, 1.69	0.266
Winter at pregnancy sampling	0.10	5.18	0.97, 9.39	**0.016**
Spring at delivery	-0.12	-5.45	-8.89, -2.01	**0.002**
Summer at delivery	0.16	8.77	4.59, 12.96	**<0.001**
Winter at delivery	0.02	1.35	-3.14, 5.85	0.555
Pregnancy sampling, gestational week	-0.13	-0.40	-0.64, -0.16	**0.001**
Duration of gestation, days	0.07	0.19	-0.03, 0.41	0.096

Values are standardized β, and unstandardized B coefficients with 95% confidence intervals (95% CI) conducted with standard linear regression; the modifier and pregnancy 25(OH)D are independent variables and UCB 25(OH)D is dependent. P values <0.05 are in bold.
25(OH)D, 25-hydroxyvitamin D concentration; BMI, body mass index; DP, dietary pattern

5.3.4 PREDICTORS FOR DECLINING AND INCREASING 25(OH)D CONCENTRATION DURING PREGNANCY

After identifying the factors modifying the tracking of 25(OH)D (Figure 5 and Table 15), the most relevant factors were investigated further in two groups: Declined (Δ25(OH)D < 0 nmol/l) and Increased (Δ25(OH)D > 0 nmol/l) 25(OH)D during pregnancy (Table 15). This enabled us to identify the key predictors for 25(OH)D in pregnancy. These relevant factors were selected based on results in the tracking analyses besides issues of collinearity and simplicity.

Maternal supplemental vitamin D intake was a positive predictor of UCB 25(OH)D in both groups (Table 16). Furthermore, in the Declined 25(OH)D group, physical activity and higher education were positive predictors. In the Increased group, sandwich and dairy DP characterized by frequent consumption of vitamin D–fortified foods and summer season were positive predictors, but multiparity was a negative predictor of UCB 25(OH)D (Table 16). A subanalysis was further conducted among pregnant women with a clinically relevant decline in 25(OH)D concentration during pregnancy (Δ25(OH)D ≤ -10.0; n=209). Factors associating with an extensive decline in 25(OH)D were prepregnancy smoking (B= -0.45; 95% CI: -0.83, -0.07; P= 0.021) and multiparity (B= -2.79; 95% CI: -5.39, -0.18; P= 0.036).

Table 16 *Predictors of UCB 25(OH)D in groups with Declined and Increased 25(OH)D during pregnancy*

	Declined (n=321)			Increased (n=263)		
	B	95% CI	P	B	95% CI	P
Prepregnancy smoking, number of cigarettes/day	-0.24	-0.57, 0.09	0.152	-0.54	-1.13, 0.06	0.075
Prepregnancy physical activity, min/day	0.07	0.00, 0.13	**0.041**	0.05	-0.06, 0.16	0.397
Pregnancy 25(OH)D, nmol/l	0.49	0.42, 0.55	**<0.001**	0.86	0.73, 1.00	**<0.001**
Supplemental vitamin D intake, µg/day	0.07	0.00, 0.14	**0.037**	0.17	0.02, 0.32	**0.031**
Sandwich and dairy DP, score	0.27	-0.85, 1.39	0.633	3.07	0.77, 5.38	**0.009**
Summer season at delivery, yes vs. no	2.58	-0.53, 5.69	0.104	8.81	3.81, 13.81	**0.001**
Parity, multi- vs. nulliparous	-1.51	-3.85, 0.83	0.204	-6.11	-10.93, -1.29	**0.013**
Education, higher vs. lower	4.32	1.42, 7.22	**0.004**	-4.96	-10.35, 0.43	0.071

Values are unstandardized B coefficients with 95% confidence intervals (95% CI) conducted with standard multivariate linear regression; all determinants are used simultaneously as independent variables and UCB 25(OH)D as dependent. P values <0.05 are in bold.
25(OH)D, 25-hydroxyvitamin D; UCB, umbilical cord blood; Declined group, Δ25(OH)D <0.00 nmol/l; Increased group, Δ25(OH)D >0.00 nmol/l; DP, dietary pattern.

5.4 ASSOCIATION BETWEEN MATERNAL 25(OH)D AND GDM (II)

Of the mothers, 11% (81/723) were diagnosed with GDM. Mean pregnancy and UCB 25(OH)D concentrations were similar in GDM and non-GDM mothers, adjusted for season, age, education, and prepregnancy BMI (Table 17, Figure 6). OGTT was performed on 55% (490/723) of the mothers. Results remained unchanged after including only those mothers with performed OGTT (data not shown). Further, there was no association between pregnancy 25(OH)D and fasting plasma glucose, 1-h glucose, or 2-h glucose (P for all >0.53) or between UCB 25(OH)D and glucose values (P for all >0.25) (data not shown).

The prevalence of vitamin D deficiency [25(OH)D <50 nmol/l] in pregnancy was 4.9% (4/81) in GDM and 3.3% (21/642) in non-GDM mothers (P = 0.51). However, at delivery in UCB, more GDM mothers were vitamin D deficient compared with non-GDM mothers [7.4% (6/81) vs. 2.8% (18/642) (P = 0.042)]. Of the 6 deficient GDM mothers, 5 (83%) were smokers, whereas in non-GDM mothers, 4 out of 18 were smokers (24%) (P = 0.018).

Table 17 *Mean pregnancy and UCB 25(OH)D in 81 GDM and 639 non-GDM mothers*

	Unadjusted model			Adjusted model		
	Mean	95% CI	P	Mean	95% CI	P
	Pregnancy 25(OH)D, nmol/l					
GDM	80.0	75.7, 84.3	0.403	81.7	77.3, 86.2	0.998
Non-GDM	82.0	80.4, 83.5		81.7	80.2, 83.3	
	UCB 25(OH)D, nmol/l					
GDM	78.4	74.0, 82.7	0.444	79.1	74.7, 83.5	0.692
Non-GDM	80.2	78.6, 81.7		80.1	78.5, 81.6	

Values are mean and 95% confidence interval (95% CI) conducted with ANCOVA.
Adjustments are for season, maternal age, education, and prepregnancy BMI.
GDM, gestational diabetes mellitus; 25(OH)D, 25-hydroxyvitamin D; UCB, umbilical cord blood.

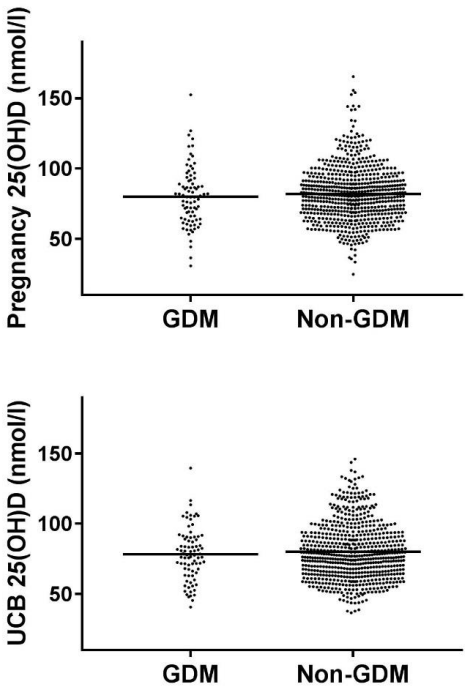

Figure 6 Scatter plot of GDM (n=81) and non-GDM (n=639) mothers' pregnancy and UCB 25(OH)D concentrations. The line represents an unadjusted mean value. GDM, gestational diabetes mellitus; 25(OH)D, 25-hydroxyvitamin D; UCB, umbilical cord blood.

5.5 INFANT VITAMIN D INTAKE AND FOOD SOURCES (III)

Mean (SD) daily vitamin D intake from food (excluding breast milk) was 7.5 µg (3.2) in non-breastfed (n=476), and 3.8 µg (3.0) in partially breastfed infants (n=263) at the age of 1 year. The range of vitamin D intake from food was 0–30.7 µg/day. The main food sources of vitamin D were infant formula, dairy milk, porridge, and fish dishes (Table 18). The vitamin D in porridges originated from vitamin D–fortified mass-produced porridges and porridges containing vitamin D–fortified milk. For non-breastfed infants, over half the vitamin D came from dairy, especially infant formula, and for breastfed

infants, the food sources of vitamin D were more varied, including dairy milk and fish foods (Table 18).

Table 18 *Food sources of vitamin D in non-breastfed (n=476) and breastfed (n=263) 1-year-old infants*

Foods	Non-breastfed		Breastfed	
	Mean daily intake, µg	Proportion of daily intake, %	Mean daily intake, µg	Proportion of daily intake, %
Dairy and plant-based milk products	4.8	64	1.3	35
Infant formula	2.3	31	0.4	11
Skim milk	1.3	17	0.3	7
Low-fat milk (1.5%)	0.9	12	0.3	7
Plant-based milk products	0.1	2	0.1	3
Porridges	1.5	19	1.0	25
Mass-produced baby food porridge	1.0	13	0.6	17
Milk-based porridge	0.5	6	0.3	8
Fish dishes	0.6	8	0.9	24
Dietary fats	0.3	3	0.3	7
Meat dishes	0.2	3	0.2	5
Other	0.1	2	0.1	5
Total[1]	7.5	99	3.8	101

[1] Percentages do not add up to 100% due to rounding.

5.6 INFLUENCE OF 25(OH)D CONCENTRATION IN PREGNANCY AND INFANCY ON INFANT GROWTH (II AND IV)

5.6.1 PREGNANCY AND UCB 25(OH)D AND PRENATAL GROWTH (II)

Birth size was investigated in categories of 25(OH)D of <50 nmol/l, 50–74.9 nmol/l, 75–125 nmol/l, and >125 nmol/l (Figure 7) (Hauta-alus et al. unpublished results). Pregnancy 25(OH)D had no association with fetal growth (P for all ≥0.073) (Figure 7). However, newborns with UCB 25(OH)D 75–125 nmol/l had smaller head circumference compared with newborns of 50–74.9 nmol/l (P=0.015) (Figure 7). Further examination revealed a linear negative association between UCB 25(OH)D and head circumference (B -1.74; 95% CI -3.25, −0.23; P = 0.024). This association remained after adjusting for maternal education, prepregnancy BMI, maternal prepregnancy smoking,

GDM, parity, maternal height, maternal GWG and pregnancy 25(OH)D, and mode of delivery (vaginal, vacuum-assisted, or cesarean section).

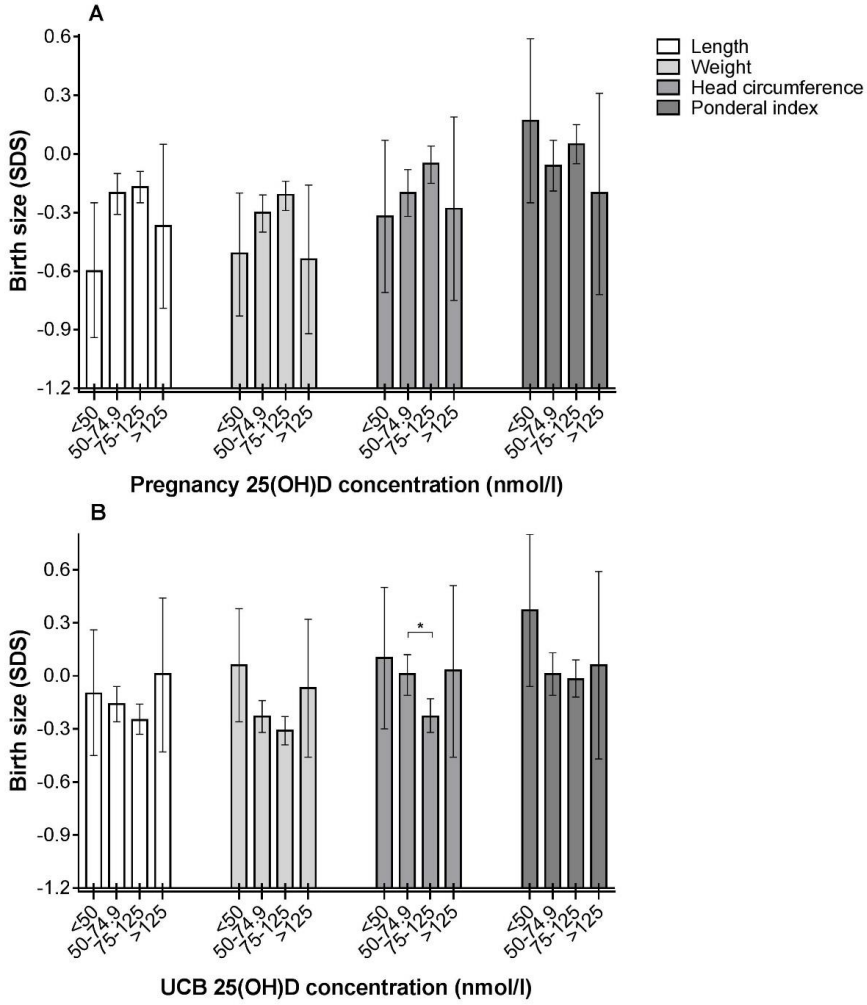

Figure 7 Association of pregnancy (A) and umbilical cord blood (UCB) (B) 25-hydroxyvitamin D concentration [25(OH)D] with birth size adjusted for maternal education, prepregnancy body mass index, maternal prepregnancy smoking, gestational diabetes, parity, maternal height, maternal gestational weight gain, and UCB/pregnancy 25(OH)D as changing covariates. 25(OH)D concentration is expressed in categories of <50 nmol/l, 50–74.9 nmol/l, 75–125 nmol/l and >125 nmol/l. Values are adjusted means with 95% confidence intervals. * indicates a statistically significant association by ANCOVA (P <0.05). Number of subjects in pregnancy 25(OH)D categories: <50, n=22; 50–74.9, n=237; 75–125, n=400 (398 in head circumference analysis); >125, n=15. Number of subjects in UCB 25(OH)D categories: <50, n=22; 50–74.9, n=269 (267 in head circumference analysis); 75–125, n=369; >125, n=14. SDS, standard deviation score, based on Finnish sex- and gestational age-specific data for fetal growth. The ponderal index is in z-scores.

5.6.2 PREGNANCY AND UCB 25(OH)D AND POSTNATAL GROWTH (IV)

Pregnancy 25(OH)D had no linear association with infant growth at 6 months or 1 year of age (Table 19). However, when dividing pregnancy 25(OH)D into categories, it was discovered that mothers whose pregnancy 25(OH)D was above 125 nmol/l had the shortest (in length) (P=0.048), lightest (in weight) (P=0.016), and thinnest (in length-adjusted weight) (P=0.013) infants at 6 months of age compared with the 50–74.9 nmol/l reference group (Figure 8). Further, at 1 year of age, infants of mothers of above 125 nmol/l during pregnancy were the thinnest compared with the reference group (P=0.021) (Figure 9).

UCB 25(OH)D had a negative linear association with length at 6 months (Table 19). Infants with UCB 25(OH)D above 125 nmol/l were the shortest (P=0.011), and infants with UCB 25(OH)D below 50 nmol/l were the thinnest at 6 months compared with the reference group (P=0.034) (Figure 8). The negative linear association between UCB 25(OH)D and head circumference in birth remained until 6 months and 1 year of age but attenuated after adjustments (Tables 19 and 20). The growth rate of infants with higher UCB 25(OH)D was slower between birth and 6 months but was accelerated between 6 months and 1 year (Table 21 and 22).

Table 19 *Associations between 25(OH)D concentrations and infant postnatal growth at 6 months of age*

	SDS			
Pregnancy 25(OH)D, 10 nmol/L, n=671	Length	Weight	Length-adjusted weight	Head circumference[3]
Model 1, unadjusted	-0.02 (-0.06, 0.01)	-0.03 (-0.07, 0.01)	-0.03 (-0.07, 0.01)	-0.02 (-0.05, 0.02)
Model 2, adjusted[1]	-0.02 (-0.05, 0.01)	-0.03 (-0.07, 0.00)	-0.03 (-0.07, 0.01)	-0.02 (-0.05, 0.01)
Model 3, adjusted[2]	-0.02 (-0.05, 0.01)	-0.03 (-0.06, 0.01)	-0.03 (-0.07, 0.02)	-0.02 (-0.05, 0.01)
UCB 25(OH)D, 10 nmol/L, n=780				
Model 1, unadjusted	-0.04 (-0.06, -0.01)*	-0.01 (-0.04, 0.02)	0.00 (-0.03, 0.03)	-0.03 (-0.06, -0.01)*
Model 2, adjusted[1]	-0.03 (-0.05, -0.01)*	0.00 (-0.01, 0.02)	0.01 (-0.02, 0.04)	-0.02 (-0.03, 0.00)
Model 3, adjusted[2]	-0.03 (-0.05, -0.01)*	0.00 (-0.02, 0.03)	0.01 (-0.02, 0.04)	-0.02 (-0.04, 0.01)

Values are B coefficients (95% CI) per 10 nmol/L higher in 25(OH)D concentration based on linear regression.
* Statistically significant linear association, P <0.05.
SDS, standard deviation score, based on Finnish sex- and age-specific normative data for infant growth; 25(OH)D, blood 25-hydroxyvitamin D concentration; UCB, umbilical cord blood.
[1] Model 2 is adjusted for corresponding birth size SDS, maternal and paternal height z-scores, and Infant 25(OH)D which served as a marker of infant supplemental vitamin D intake.
[2] Model 3 is adjusted for model 2 covariates and in addition to maternal and paternal prepregnancy BMI, smoking status of the parents, parental education, family income level, and duration of breastfeeding.
[3] The number of subjects varies in analyses due to missing values of head circumferences; for pregnancy 25(OH)D in Model 1: n=650, in Models 2 and 3: n=649; for UCB 25(OH)D in Model 1: n=759, in Models 2 and 3: n=757.

Table 20 *Associations between pregnancy and UCB 25(OH)D concentrations and infant growth at 1 year of age*

	SDS			
Pregnancy 25(OH)D, 10 nmol/L, n=671	Length	Weight	Length-adjusted weight	Head circumference[3]
Model 1, unadjusted	-0.01 (-0.05, 0.03)	-0.02 (-0.06, 0.01)	-0.03 (-0.07, 0.01)	-0.02 (-0.05, 0.02)
Model 2, adjusted[1]	-0.01 (-0.05, 0.02)	-0.03 (-0.06, 0.01)	-0.03 (-0.07, 0.01)	-0.02 (-0.05, 0.02)
Model 3, adjusted[2]	-0.01 (-0.04, 0.02)	-0.02 (-0.06, 0.01)	-0.02 (-0.06, 0.02)	-0.02 (-0.05, 0.02)
UCB 25(OH)D, 10 nmol/L, n=780				
Model 1, unadjusted	-0.01 (-0.03, 0.02)	-0.01 (-0.04, 0.01)	-0.02 (-0.04, 0.01)	-0.03 (-0.05, 0.00)*
Model 2, adjusted[1]	0.00 (-0.03, 0.02)	0.00 (-0.02, 0.01)	-0.01 (-0.04, 0.02)	-0.01 (-0.02, 0.00)
Model 3, adjusted[2]	0.00 (-0.03, 0.02)	-0.01 (-0.03, 0.02)	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.01)

Values are B coefficients (95% CI) per 10 nmol/L higher in 25(OH)D concentration based on linear regression.
* Statistically significant linear association, P <0.05.
SDS, standard deviation score, based on Finnish sex- and age-specific normative data for infant growth; 25(OH)D, blood 25-hydroxyvitamin D concentration; UCB, umbilical cord blood.
[1] Model 2 is adjusted for corresponding birth size SDS, maternal and paternal height z-scores, and Infant 25(OH)D, which served as a marker of infant supplemental vitamin D intake.
[2] Model 3 is adjusted for model 2 covariates and in addition to maternal and paternal prepregnancy BMI, smoking status of the parents, parental education, family income level, and duration of breastfeeding.
[3] Number of subjects varies in analyses due to missing values of head circumferences; for Pregnancy 25(OH)D in Model 1: n=666, in Models 2 and 3: n=665; for UCB 25(OH)D in Model 1: n=775, in Models 2 and 3: n=773.

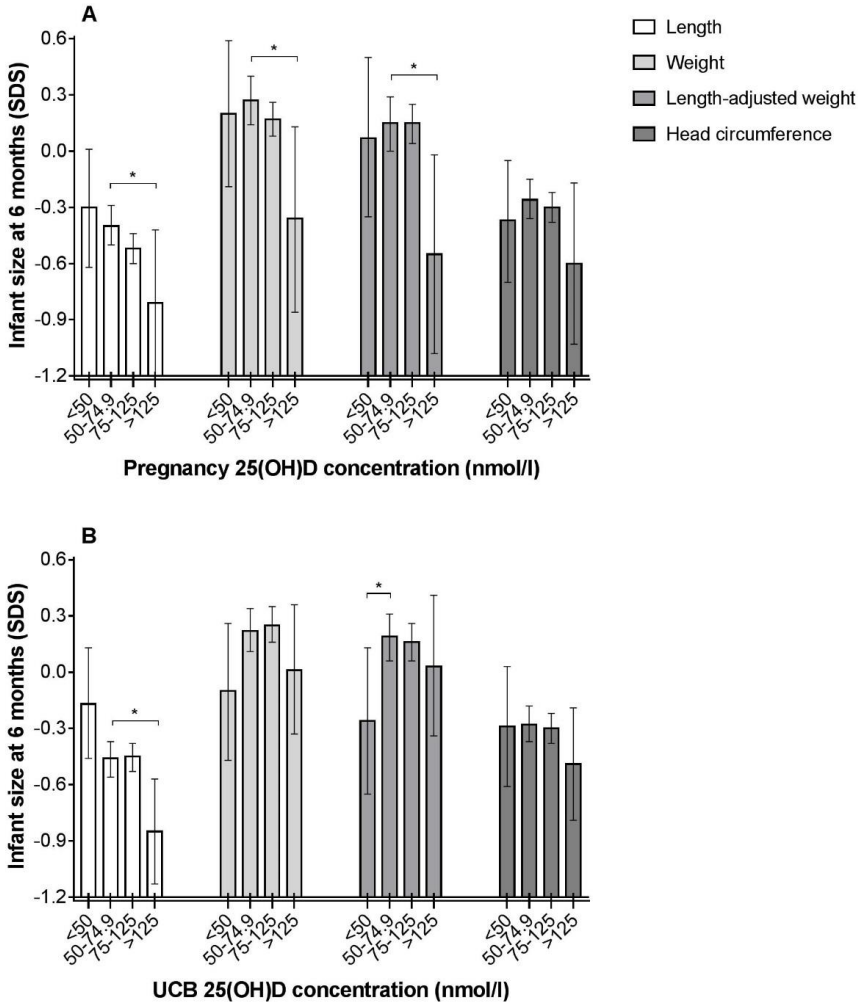

Figure 8 Association of (A) pregnancy and (B) umbilical cord blood (UCB) 25-hydroxyvitamin D concentration [25(OH)D] with infant growth parameters at 6 months of age. 25(OH)D concentration is expressed in categories of <50 nmol/l, 50–74.9 nmol/l (reference group), 75–125 nmol/l and >125 nmol/l. Values are adjusted means with 95% confidence intervals. Analyses are adjusted for corresponding birth size standard deviation score (SDS), maternal and paternal height z-scores, and infant 25(OH)D, which served as a marker of infant supplemental vitamin D intake. ***** indicates a statistically significant association (P <0.05), and is only shown between the reference group and other groups. Number of subjects in pregnancy 25(OH)D categories: <50, n=25; 50–74.9, n=218; 75–125, n=412; >125, n=16, and in UCB 25(OH)D categories: <50, n=29; 50–74.9, n=294; 75–125, n=425; >125, n=32.

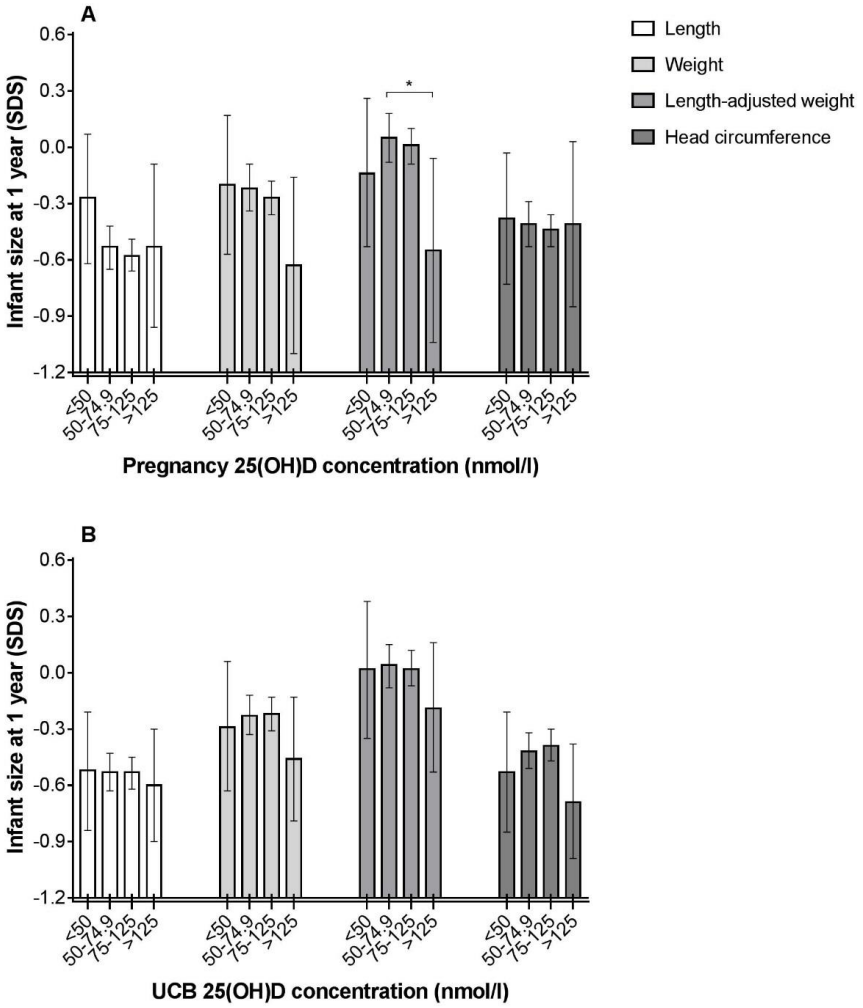

Figure 9 Association of (A) pregnancy and (B) cord blood (UCB) 25-hydroxyvitamin D concentration [25(OH)D] with infant growth parameters at 1 year of age. 25(OH)D concentration is expressed in categories of <50 nmol/l, 50–74.9 nmol/l (reference group), 75–125 nmol/l and >125 nmol/l. Values are adjusted means with 95% confidence intervals. Analyses are adjusted for corresponding birth size standard deviation score (SDS), maternal and paternal height z-scores, and infant 25(OH)D, which served as a marker of infant supplemental vitamin D intake. * indicates a statistically significant association (P <0.05) and is only shown between the reference group and other groups. Number of subjects in pregnancy 25(OH)D categories: <50, n=25; 50–74.9, n=218; 75–125, n=412; >125, n=16, and in UCB 25(OH)D categories: <50, n=29; 50–74.9, n=294; 75–125, n=425; >125, n=32.

Table 21 *Associations between 25(OH)D and infant conditional growth at 6 months of age*

	Conditional growth at 6 months			
Pregnancy 25(OH)D, 10 nmol/L, n=671	Length	Weight	Length-adjusted weight	Head circumference[3]
Model 1, unadjusted	-0.02 (-0.06, 0.01)	-0.04 (-0.07, 0.00)	-0.03 (-0.07, 0.00)	-0.02 (-0.06, 0.02)
Model 2, adjusted[1]	-0.03 (-0.06, 0.01)	-0.03 (-0.07, 0.00)	-0.03 (-0.07, 0.01)	-0.02 (-0.06, 0.01)
Model 3, adjusted[2]	-0.02 (-0.06, 0.01)	-0.03 (-0.06, 0.01)	-0.02 (-0.06, 0.02)	-0.03 (-0.07, 0.01)
UCB 25(OH)D, 10 nmol/L, n=780				
Model 1, unadjusted	-0.03 (-0.06, -0.01)*	0.00 (-0.03, 0.03)	0.01 (-0.02, 0.03)	-0.02 (-0.04, 0.01)
Model 2, adjusted[1]	-0.03 (-0.06, -0.01)*	0.00 (-0.01, 0.02)	0.01 (-0.02, 0.04)	-0.02 (-0.03, 0.00)
Model 3, adjusted[2]	-0.03 (-0.06, -0.01)*	0.00 (-0.02, 0.03)	0.01 (-0.02, 0.04)	-0.02 (-0.05, 0.01)

Values are B coefficients (95% CI) per 10 nmol/L higher in 25(OH)D concentration based on linear regression.
* Statistically significant linear association, $P < 0.05$.
25(OH)D, 25-hydroxyvitamin D concentration; UCB, umbilical cord blood.
[1] Model 2 is adjusted for maternal and paternal height z-scores, and infant 25(OH)D, which served as a marker of infant supplemental vitamin D intake.
[2] Model 3 is adjusted for model 2 covariates and in addition to maternal and paternal prepregnancy BMI, smoking status of the parents, parental education, family income level, and duration of breastfeeding.
[3] Number of subjects varies in analyses due to missing values of head circumferences; for Pregnancy 25(OH)D in Models 1, 2, and 3: n=649; for UCB 25(OH)D in Models 1, 2, and 3: n=757.

Table 22 *Associations between 25(OH)D and infant conditional growth at 1 year of age*

	Conditional growth at 1 year			
Pregnancy 25(OH)D, 10 nmol/L, n=671	Length	Weight	Length-adjusted weight	Head circumference[3]
Model 1, unadjusted	0.02 (-0.02, 0.05)	-0.01 (-0.05, 0.03)	-0.01 (-0.05, 0.02)	0.00 (-0.04, 0.04)
Model 2, adjusted[1]	0.01 (-0.03, 0.05)	-0.01 (-0.04, 0.03)	-0.01 (-0.05, 0.03)	0.00 (-0.04, 0.04)
Model 3, adjusted[2]	0.01 (-0.02, 0.05)	0.00 (-0.04, 0.04)	0.00 (-0.04, 0.03)	0.00 (-0.04, 0.04)
UCB 25(OH)D, 10 nmol/L, n=780				
Model 1, unadjusted	0.04 (0.01, 0.07)*	-0.01 (-0.04, 0.02)	-0.03 (-0.05, 0.00)	0.00 (-0.03, 0.03)
Model 2, adjusted[1]	0.04 (0.01, 0.07)*	-0.01 (-0.02, 0.01)	-0.02 (-0.04, -0.01)	0.00 (-0.01, 0.02)
Model 3, adjusted[2]	0.04 (0.01, 0.07)*	-0.01 (-0.04, 0.02)	-0.03 (-0.05, 0.00)	0.00 (-0.03, 0.03)
Infant 25(OH)D, 10 nmol/L, n=798				
Model 1, unadjusted	0.00 (-0.03, 0.02)	-0.02 (-0.04, 0.01)	-0.02 (-0.05, 0.00)	-0.02 (-0.05, 0.00)
Model 2, adjusted[1]	0.00 (-0.03, 0.02)	-0.02 (-0.04, 0.01)	-0.02 (-0.05, 0.00)	-0.02 (-0.05, 0.00)
Model 3, adjusted[2]	0.00 (-0.03, 0.02)	-0.02 (-0.04, 0.01)	-0.02 (-0.05, 0.00)	-0.02 (-0.05, 0.00)

Values are B coefficients (95% CI) per 10 nmol/L higher in 25(OH)D concentration based on linear regression.
* Statistically significant association, P < 0.05.
25(OH)D, 25-hydroxyvitamin D concentration; UCB, umbilical cord blood.
[1] Model 2 is adjusted for maternal and paternal height z-scores and infant 25(OH)D, which served as a marker of infant supplemental vitamin D intake (except when infant 25(OH)D was used as a dependent).
[2] Model 3 is adjusted for model 2 covariates and in addition to maternal and paternal prepregnancy BMI, smoking status of the parents, parental education, family income level, and duration of breastfeeding.
[3] Number of subjects varies in analyses due to missing values of head circumference; for Pregnancy 25(OH)D in Models 1, 2, and 3: n=644; for UCB 25(OH)D in Models 1, 2, and 3: n=752; for infant 25(OH)D in Models 1, 2, and 3: n=770.

5.6.3 INFANT 25(OH)D AND GROWTH (IV)

Infant 25(OH)D at 1 year of age associated negatively with length, weight, length-adjusted weight, and head circumference at 1 year, although the association with length and head circumference attenuated after adjustments (Table 23). Further, infants above 125 nmol/l were the lightest (P=0.022) and thinnest compared with the 50–74.9 nmol/l reference group (P=0.032) (Figure 10). Table 24 summarizes the findings between maternal and infant vitamin D status and infant growth.

Table 23 *Associations between infant 25(OH)D concentration and growth at 1 year of age*

	SDS			
Infant 25(OH)D, 10 nmol/l, n=798	Length	Weight	Length-adjusted weight	Head circumference[3]
Model 1, unadjusted	-0.03 (-0.05, 0.00)*	-0.03 (-0.06, -0.01)*	-0.02 (-0.05, 0.00)*	-0.02 (-0.05, 0.00)*
Model 2, adjusted[1]	-0.02 (-0.04, 0.00)	-0.03 (-0.05, -0.01)*	-0.03 (-0.05, 0.00)*	-0.02 (-0.04, 0.01)
Model 3, adjusted[2]	-0.02 (-0.04, 0.00)	-0.03 (-0.05, -0.01)*	-0.03 (-0.05, 0.00)*	-0.02 (-0.04, 0.01)

Values are B coefficients (95% CI) per 10 nmol/l higher in 25(OH)D concentration based on linear regression.
* Statistically significant linear association, P <0.05.
SDS, standard deviation score, based on Finnish sex- and age-specific normative data for infant growth; 25(OH)D, blood 25-hydroxyvitamin D concentration; UCB, umbilical cord blood.
[1] Model 2 is adjusted for the corresponding birth size SDS, maternal and paternal height z-scores, and infant 25(OH)D, which was served as a marker of infant supplemental vitamin D intake (except when infant 25(OH)D was used as a dependent).
[2] Model 3 is adjusted for model 2 covariates and in addition to maternal and paternal prepregnancy BMI, smoking status of the parents, parental education, family income level, and duration of breastfeeding until 1 year of age.
[3] Number of subjects varies in analyses due to missing values of head circumferences in Model 1: n=793, in Models 2 and 3: n=791.

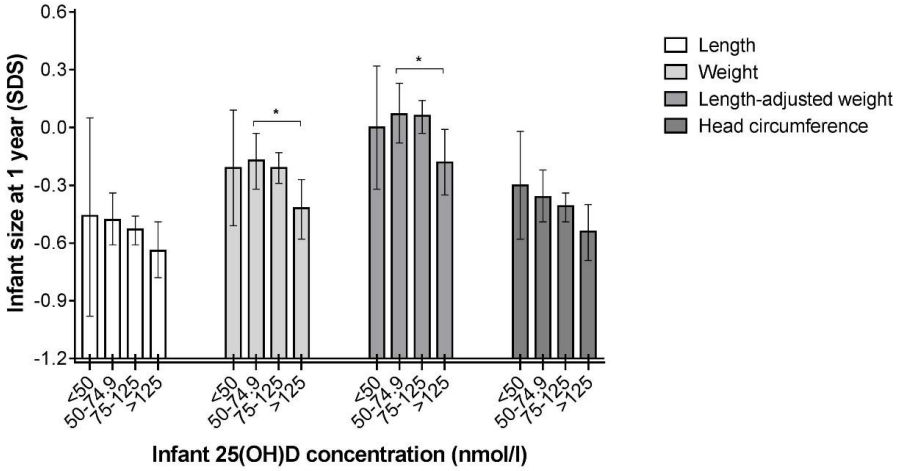

Figure 10 A cross-sectional association between infant 25-hydroxyvitamin D concentration [25(OH)D] and infant growth parameters at 1 year of age. 25(OH)D concentration is expressed in categories of <50 nmol/L, 50–74.9 nmol/L (reference group), 75–125 nmol/L and >125 nmol/L. Values are adjusted means with 95% confidence intervals and are adjusted for corresponding birth size standard deviation score (SDS), maternal and paternal height z-scores. * indicates a statistically significant association (P <0.05) and is only shown between the reference group and other groups. Number of subjects in infant 25(OH)D categories: <50, n=10; 50–74.9, n=160; 75–125, n=493; >125, n=135.

Table 24 *Summary of the negative (-) and positive (+) associations between 25(OH)D and infant growth. Details about the association are shown in parentheses as linear (L) and non-linear (N-L); Only significant associations are in unadjusted analysis; non-significant associations are shown as "NS" (II and IV)*

Infant growth	Pregnancy 25(OH)D	UCB 25(OH)D	Infant 25(OH)D at 1 year
At birth			
Length	NS	NS	
Weight	NS	NS	
Length-adjusted weight	NS	NS	
Head circumference	NS	- (L, N-L)	
At 6 months of age			
Length	- (N-L)	- (L, N-L)	
Weight	- (N-L)	NS	
Length-adjusted weight	- (N-L)	+ (N-L)	
Head circumference	NS	- (L unadjusted)	
At 1 year of age			
Length	NS	NS	- (L unadjusted)
Weight	NS	NS	- (L, N-L)
Length-adjusted weight	- (N-L)	NS	- (L, N-L)
Head circumference	NS	- (L unadjusted)	- (L unadjusted)

25(OH)D, 25-hydroxyvitamin D concentration; UCB, umbilical cord blood.

6 DISCUSSION

6.1 SUMMARY OF THE MAIN FINDINGS

This study explored current vitamin D status in pregnant women and their newborns and whether it associates with GDM, infant birth size, and postnatal growth in full-term infants with normal birth weight. In addition, we examined whether infant vitamin D status associates with growth at 1 year of age in infants participating in a vitamin D intervention trial. The main findings can be summarized as follows:

Our data indicated that, overall, the pregnant women and their newborns were vitamin D sufficient as the concentration of 25(OH)D in almost all of the participating subjects was ≥50 nmol/l. Moreover, 99% of 1-year-old infants were vitamin D sufficient.

Of pregnant women, 95% used vitamin D supplements with a mean daily intake of 16 μg. Seasonal variations of 25(OH)D were moderate, with values being highest in summer both during pregnancy and at birth. Besides vitamin D supplementation, other positive predictors of 25(OH)D during pregnancy were dietary pattern (DP) characterized by regular use of vitamin D–fortified foods and prepregnancy physical activity. In contrast, factors associating with declining 25(OH)D in pregnancy were prepregnancy smoking and multiparity.

GDM was observed in 11% of the pregnant women. Pregnancy and UCB 25(OH)D concentrations did not differ between GDM and non-GDM women. Furthermore, 25(OH)D did not associate with OGTT results.

The mean daily intake of vitamin D from food was 7.5 μg in non-breastfed and 3.8 μg in breastfed 1-year-old infants. The main food sources of vitamin D were infant formula, dairy milk, porridge, and fish foods.

Higher maternal and infant 25(OH)D were associated with slower infant growth. Mothers with high pregnancy 25(OH)D (>125 nmol/l) had the shortest (in length), lightest (in weight) and thinnest (in length-adjusted weight) infants at 6 months of age. Higher UCB 25(OH)D associated with smaller head circumference at birth and slower linear growth at 6 months of age, whereas infants with UCB 25(OH)D <50 nmol/l were thinnest at 6 months. In infants, higher UCB 25(OH)D associated with slower linear growth from birth to 6 months but with accelerated growth from 6 months to 1 year of age. Infants with 25(OH)D >125 nmol/l were lightest and thinnest at 1 year of age.

6.2 INTERPRETATION OF THE RESULTS

6.2.1 VITAMIN D STATUS (I, IV)

The majority (96%) of the pregnant women and their newborns and infants at 1 year of age (99%) were vitamin D sufficient, defined as 25(OH)D ≥50 nmol/l. Infants in this study were allocated to daily vitamin D supplementation doses of 10 μg and 30 μg. It appears that maternal and newborn 25(OH)D concentrations have increased compared with previous reports from Finland. In line with studies in adults [24, 25], elderly [26], and older children [153, 249, 250], vitamin D status has improved in Finland. The majority of pregnant women (61%), newborns (55%), and 1-year-old infants (62%) had 25(OH)D between 75 and 125 nmol/l. Values above 125 nmol/l in pregnancy, UCB, and infancy, which are considered a possible threshold for adverse effects by IOM (presently NAM) [114], were observed as 2%, 4%, and 17%, respectively. In the VIDI study, 32% of the infants receiving 30 μg vitamin D had 25(OH)D >125 nmol/l at 1 year and 39% at 2 years of age [242], without evidence for vitamin D toxicity [242, 251].

Some researchers consider that higher maternal vitamin D status (>100 nmol/l) than is generally considered sufficient (≥50 nmol/l) should be achieved to prevent maternal and neonatal health risks [23, 252]. Further, they highlight the need for maternal vitamin D intake of at least 100 μg/day. A similar discussion has been ongoing regarding non-pregnant adults [1, 21, 253]. Based on the findings of this thesis, such views on vitamin D appear extravagant.

The exceptionally high maternal 25(OH)D levels in Finnish pregnant women can be explained by the high adherence to vitamin D supplementation and the national vitamin D food fortification policy. Vitamin D food fortification in fluid dairy products and dietary fats was doubled in 2010. Likewise, in 2011, vitamin D supplementation guidelines were revised in pregnant women to year-round supplementation (10 μg) instead of only winter-time supplementation.

Finland is an exceptional example of successful public health policy regarding vitamin D [64, 96]. Parallel to observations in countries with similar strategies, vitamin D intake has increased, and vitamin D deficiency has declined [127, 128, 131, 167, 254]. However, still in 2011, 9% of Finnish women had a serum 25(OH)D concentration of <50 nmol/l [24], but this was a great improvement from 2000, when 57% of women had 25(OH)D <50 nmol/l [24]. Although it was not examined in this thesis, pregnant immigrant women may be at increased risk of vitamin D deficiency [254, 255]. Our results suggest that vitamin D status is generally sufficient among Finnish pregnant women, at least in women of Northern European ethnicity.

6.2.2 DETERMINANTS OF MATERNAL 25(OH)D (I)

The key determinants of maternal 25(OH)D were season, education, supplemental vitamin D intake, DP characterized by frequent consumption of vitamin D–fortified dairy products and margarine, physical activity, smoking before pregnancy, and parity. As expected, maternal 25(OH)D was highest in summer. Supplemental vitamin D intake and DP with frequent consumption of vitamin D–fortified foods were positive predictors of 25(OH)D during pregnancy. On average, a daily dose of supplemental vitamin D was 16 μg, ranging from zero to 198 μg. Our findings indicate that the proportion of pregnant women taking vitamin D supplements has increased from 40% in 1998–99 to current 95% [132], which is in accordance with other recent reports [137, 139].

In pregnant women, the mean intake of supplemental vitamin D was higher than recommended. Based on data acquired in 2008–2011, the median intake of supplemental vitamin D was 6 μg among pregnant women [139]. Our findings are parallel to the FinDiet 2012 survey, which reported that vitamin D intake from supplements was 16 μg/day in non-pregnant women (excluding the elderly). In that survey, the total intake of vitamin D was 25 μg/day, with 55% of women using vitamin D supplements [245]. Based on the most recent FinDiet survey in 2017, vitamin D intake and the proportion of supplement users has continued to rise [92]. Currently in Finland, the average daily total intake of vitamin D is 10 μg in women (13 μg in men). However, in those women who consumed vitamin D supplements, the mean vitamin D intake was 36 μg/day, while in those not taking supplements, it was 9 μg/day. Comparing FinDiet 2017 to the 2012 survey is limited due to different methodologies and statistical modeling in vitamin D intake [92].

The contribution of vitamin D food fortification to maternal vitamin D status was clearly indicated in this thesis, although we could not measure the absolute total dietary intake of vitamin D. The “sandwich and dairy” DP included frequent consumption of vitamin D–fortified dairy and margarine and correlated with maternal 25(OH)D. This is logical, as the main food sources of vitamin D in Finnish adults, besides fish, have been described as dietary fats and dairy milk [92, 245]. Moreover, consumption of these foods has been linked to 25(OH)D in previous Finnish studies [24, 161, 162].

Prepregnancy physical activity promoted the tracking of 25(OH)D during pregnancy, which is parallel to few other studies [166, 256]. The effect of physical activity may be a result of more outdoor activities, i.e., more UVB exposure, or it may be explained by BMI, as physical activity most likely reduces BMI, and lower BMI associates with higher 25(OH)D. However, contrary to many studies [166-168, 256], prepregnancy BMI was not associated with UCB 25(OH)D in this study. This may be because the majority of women had normal BMI (72%). Nevertheless, physical activity might indicate an overall healthy lifestyle, which has been linked to vitamin D status.

Determinants for a decline in 25(OH)D during pregnancy were prepregnancy smoking and multiparity. A similar trend has been observed in

other studies on pregnant women [166, 169, 170, 216]. Multiparity has been detected to correlate with lack of supplement use [171]. Hence, the effect of multiparity on maternal 25(OH)D might reflect changed family circumstances, as personal resources are limited and vitamin D supplementation neglected. In general, and based on the results of this study, health promotion in dark-skinned, smoking, and multiparous pregnant women should be emphasized in prenatal clinics to ensure sufficient vitamin D status in all pregnant women.

6.2.3 MATERNAL 25(OH)D AND GDM (II)

GDM was observed in 11% of the pregnant women, which was in accordance with national statistics. Vitamin D status in pregnancy or in UCB did not differ between GDM and non-GDM women. Furthermore, 25(OH)D concentrations had no linear association with OGTT results. The proportion of women with UCB 25(OH)D <50 nmol/l was higher in GDM (7.4%) than in non-GDM women (2.8%). However, almost all GDM women with 25(OH)D below 50 nmol/l were smokers prior to pregnancy. This may imply that vitamin D status presented as a general health indicator. In addition, it has been speculated that smoking and vitamin D deficiency may have synergistic effects on the risk of GDM [257]. Because our cohort included a very low number of subjects with 25(OH)D <50 nmol/l, we could not reliably examine this.

There is evidence that vitamin D status is inferior in pregnant women with GDM compared to non-GDM women [195] and that vitamin D supplementation decreases the risk of GDM [125], but the full picture remains uncertain due to the low quality of RCTs [125, 258]. Furthermore, the high heterogeneity of studies included in the meta-analyses limits the conclusions. The challenge in examining the relationship between vitamin D and GDM is in their common determinants, such as obesity, smoking, ethnicity, and other socioeconomic and lifestyle factors, which often confound the results. Indeed, Lu et al. estimated that low maternal vitamin D status associated with increased GDM risk only in analyses without adjustments for confounders [192]. It may be that in populations with overall sufficient vitamin D status, as in our cohort, maternal 25(OH)D has no relation to GDM.

6.2.4 INFANT VITAMIN D INTAKE FROM FOOD AND FOOD SOURCES (III)

Vitamin D intake from food averaged 7.5 and 3.8 μg/day in non-breastfed and breastfed 1-year-old infants, respectively, thus not reaching the recommended intake of 10 μg. This emphasizes the need for vitamin D supplementation to achieve the recommended intake. Nevertheless, vitamin D intake from food has increased markedly in infants from the latest estimation of 4–5 μg/day in 1999–2004, prior to the doubling of the vitamin D food fortification [150, 151]. Recently, a parallel increase in vitamin D intake in older children has been

observed. Total vitamin D intake from supplements and food has averaged 6–7 μg/day in the early 2000s among children 3–4 years old [151], but recently (2015–2016), vitamin D intake from only food was 8.8 μg/day in the same age group [259]. Since infants in this study received vitamin D supplements, the total vitamin D intake was probably adequate. Formerly, the average total vitamin D intake has been adequate among 1-year-olds [151, 154].

In the USA, a country with vitamin D food fortification, comparable daily mean intake of 7.0 μg of vitamin D from food has been calculated among infants aged 6–11 months [260]. In a comparison, in Italy, which has no vitamin D fortification guidelines, infants 6–12 months old have a mean daily vitamin D intake of 4.0 μg [261].

In line with earlier findings [150, 152], we observed that the main vitamin D food sources were infant formula, dairy milk, porridge, and fish foods. The porridges that contained vitamin D were either vitamin D–fortified mass-produced porridges or porridges cooked in vitamin D–fortified milk. The main dietary sources varied somewhat between non-breastfed and breastfed infants. In non-breastfed infants, infant formula and dairy milk were the predominant contributors of vitamin D intake, and in breastfed infants, they were dairy milk and fish foods.

6.2.5 VITAMIN D AND INFANT GROWTH (II, IV)

In contrast to our expectations, maternal vitamin D status associated inversely with pre- and postnatal growth in infants. This is a novel finding. The reason this is emerging not until now may be because only recently there have been populations with high 25(OH)D, especially in environments with minimal UVB exposure.

Previous evidence suggests a relationship between maternal vitamin D deficiency (<30 nmol/l) and low birth weight [213]. Our results were based on vitamin D–sufficient subjects. Moreover, infants in this study were healthy and full-term with normal birth weight. In this thesis, no linear relation or association with the applied 25(OH)D cut-offs 50, 75 and 125 nmol/l existed between maternal 25(OH)D and birth weight. However, in the original publication of Study II, we observed that mothers with pregnancy 25(OH)D >80 nmol/l had heavier newborns compared to those with <80 nmol/l. An additional analysis in this thesis showed a tendency that newborns of mothers with pregnancy 25(OH)D above 125 nmol/l had the lowest mean birth weight, although not statistically significant. Some experts reckons that the positive effects of maternal vitamin D on offspring growth are due to general improvement in nutritional or health status [69], but this relationship may be more complex.

In this study, at birth, higher UCB 25(OH)D associated with smaller head circumference. This association remained until 1 year of age but attenuated after adjustments with birth head circumference. Inconsistent evidence exists for the relationship between maternal vitamin D status and head

circumference at birth. A meta-analysis by Tous et al. concluded that vitamin D deficiency (<30 nmol/l) associated with smaller head circumference at birth but low 25(OH)D defined as <50 or <75 nmol/l did not [213]. Yet some studies, including ours, have observed an inverse linear association between maternal vitamin D status and head circumference at birth [230, 262]. In those studies, the mean or median maternal 25(OH)D has been relatively high (71–74 nmol/l) compared with other studies. Bi et al. concluded in their meta-analysis based on 11 RCTs that maternal vitamin D supplementation had no effect on birth head circumference [209].

In this thesis, infants born to mothers with pregnancy 25(OH)D above 125 nmol/l were the shortest (in length), lightest (in weight), and thinnest (in length-adjusted weight) at 6 months of age, and thinnest also at 1 year of age. In addition, an inverse relationship existed between UCB 25(OH)D and linear growth at 6 months, but not at 1 year of age. This may be explained by a slower growth between birth and 6 months and a catch-up growth between 6 months and 1 year. Infants with UCB 25(OH)D <50 nmol/l at birth were the thinnest at 6 months of age.

Only a few studies have examined maternal vitamin D status and postnatal growth in infancy, and they show inconsistent results. This may be partly due to low data quality, varying thresholds for vitamin D deficiency, and residual confounding. Furthermore, subjects in previous studies have had quite a low vitamin D status. In Gambian and Singaporean studies with relatively high maternal 25(OH)D, maternal vitamin D status had no relation to postnatal growth parameters [223, 224] or had an inverse association with length at 6 months [230]. Even though Bi et al. concluded that maternal vitamin D supplementation increased several growth parameters during infancy [209], Roth et al. did not detect any effect of vitamin D supplementation on postnatal growth in a large RCT [218]. Severe vitamin D deficiency (<30 nmol/l) may possibly impair fetal and infant growth, but if this cut-off is exceeded, no benefits are observed with higher 25(OH)D concentrations [213, 224, 263].

One further possible explanation for the inconsistent results between vitamin D and growth may be catch-up or accelerated growth in lower birthweight infants of vitamin D–deficient mothers. This can lead to inverse [225, 264] or nonexistent associations between maternal 25(OH)D and offspring growth in later infancy [168]. Our results may indicate a similar catch-up growth, not in infants born to vitamin D–deficient mothers, but to mothers with high vitamin D status. Rapid growth or pronounced adiposity accrual in childhood can increase the risk for later obesity [228, 265-267]. Regarding later childhood growth, maternal 25(OH)D had no effect on linear growth at 9 years [214], but lower maternal 25(OH)D associated with greater fat mass at 6 years of age [264]. The newborn's own 25(OH)D concentration had no effect on overweight in 7-year-old children [268].

As with maternal vitamin D status, the infant's own 25(OH)D concentration also associated inversely with infant growth in this study. This was seen in all growth parameters in unadjusted analyses, while only

associations for weight and length-adjusted weight were confirmed after adjustments for birth size and parental heights. Infants with 25(OH)D >125 nmol/l were the lightest and thinnest at 1 year of age. In the VIDI cohort, on average, growth parameters did not differ between the supplementation groups of 10 μg and 30 μg [242]. Thus, our results might imply an individual response to vitamin D supplementation on 25(OH)D concentrations [269]. The few previous reports on infant vitamin D and growth have been conflicting. In line with our results, vitamin D status correlated negatively with length and BMI among Danish 9-month-old infants [237].

Altogether, our findings may suggest an inverse U-shaped association between vitamin D status and infant growth, as has been suggested by a few previous studies [270-273]. Moreover, higher vitamin D status or intake have been associated with other impaired health outcomes in children [220, 274, 275] as well as in adults [72, 276-278]. Within the VIDI cohort, we have reported that higher UCB 25(OH)D associated with higher inflammation markers at birth and increased allergic sensitization at 1 year of age [279, 280]. Studies involving subjects with high 25(OH)D (>100 nmol/l) have been scarce [281], and therefore, data on the effects of high vitamin D status on health outcomes is limited.

Multiple factors influence infant growth patterns, including nutrition and hormonal regulation. Linear growth is largely long bone growth localized to the growth plate. It has been suggested that sufficient 25(OH)D would increase bone mineral density and, hence, lead to enhanced growth, but the evidence is constricted [18]. The mechanisms by which vitamin D could affect childhood growth beyond maintaining normal bone mineralization (i.e., preventing rickets) are unclear. Though not yet clearly understood, $1,25(OH)_2D$ probably has several regulatory functions in bone remodelling in the growth plate [282].

High vitamin D status and the mechanism for how it could impair growth may also be related to the normal mineral homeostasis regulated by vitamin D. The central function of vitamin D is to maintain normal circulating calcium at the expense of bone, if needed. High $1,25(OH)_2D$ levels have been linked to factors inhibiting bone mineralization and enhancing bone resorption through stimulation of osteoclasts [283], thus possibly affecting growth. However, it is not known whether elevated 25(OH)D also leads to a significant increase in $1,25(OH)_2D$.

Another possible pathway through which vitamin D can act on infant growth is the growth hormone IGF-1 axis, which is essential for normal growth. In vitamin D–deficient children, vitamin D supplementation has resulted in a significant increase in IGF-1 concentrations [284, 285]. Furthermore, IGF-1 may stimulate renal production of $1,25(OH)_2D$ [286]. It has been speculated that high 25(OH)D stunts infant growth by inhibiting the function of IGF-1 [273]. The pathways mediating the effects of vitamin D on growth and the clinical relevance of our findings remain to be explored in future studies.

6.3 STRENGTHS AND LIMITATIONS

The main strength of this large VIDI study is in the data, which were collected in a standardized manner from a single maternity hospital. All mothers were of Northern European ethnicity, which resulted in a relatively homogenous group of subjects that can be perceived both as a strength and a limitation. A multi-center study would have probably resulted in a larger variation in subject characteristics in terms of socioeconomic status. In general, mothers were highly educated, were of normal weight, and a majority of them gave birth to their first child. In addition, families were mainly from Helsinki or the surrounding capital area. Thus, the results of this thesis may not be generalized to all pregnant women and infants in Finland. The strength of this thesis is in its in-depth analysis between vitamin D and health outcomes with relevant adjustments for possible confounders. A further strength is that this study covered all seasons.

One limitation in this study was that we did not have information on the absolute vitamin D intake during pregnancy or infancy. We applied circulating 25(OH)D concentration as an indicator of total vitamin D intake from diet and skin synthesis. Several confounding variables were extracted from self-administered questionnaires, but these were checked by study nurses. Not all women underwent OGTT according to national guidelines. This may have underestimated the true prevalence of GDM. However, subgroup analyses of women with performed OGTT confirmed our results.

The volume of breast milk was unknown; however, its contribution to infant vitamin D intake is estimated to be minimal. We could not calculate the absolute contribution of specific food items on vitamin D intake because limitations in the applied software programme, i.e., composite foods, could not be dismantled. Further, we were unable to calculate an estimation of the usual dietary intake of vitamin D, taking into account the day-to-day variability of food consumption [287, 288]. Yet, we calculated the mean value of the 3-day food record rather than proportions of infants with below or above the recommended intake diminishing the possible bias.

Another restraint was maternal 25(OH)D values, which were corrected to achieve better comparability between plasma and serum samples and because of changes in the IDS-iSYS method by the manufacturer. This method had a slight tendency to overestimate the 25(OH)D values, though it did not affect the associations between 25(OH)D and health outcomes. We did not take part in the VDSP; thus, comparing the prevalence of vitamin D deficiency with other studies, populations, and decades should be done with caution. A limited number of subjects on both extreme ends of vitamin D status may have constrained our analysis. This study can be regarded as longitudinal because we had data from early pregnancy until the offspring was 1 year old, albeit cross-sectional characteristics prevail in many analyses. Thus, causal relationships cannot be determined.

7 CONCLUSIONS AND FUTURE PERSPECTIVES

Vitamin D status was sufficient among pregnant women and newborns in this study. Likewise, infants at the age of 1 year who participated in a vitamin D supplementation trial had sufficient vitamin D status. Key maternal factors that increased 25(OH)D during pregnancy were dietary intake of vitamin D by both supplementation and diet and physical activity. Determinants associating with declining maternal vitamin D status were smoking and multiparity. Maternal vitamin D status had no relation to GDM. Daily mean dietary intake of vitamin D from food was 7.5 μg in non-breastfed and 3.8 μg in breastfed 1-year-old infants, indicating that vitamin D supplementation is required to achieve the recommendation of 10 μg.

Higher maternal and infant 25(OH)D associated with slower infant growth. These results may indicate a possible inverse U-shaped relationship between vitamin D status and growth. Thus, there is no need to aim for higher maternal or infant 25(OH)D concentrations with excessive supplementation, as this may be disadvantageous for infant growth.

The clinical relevance and long-term effects of these findings are to be explored in future studies. Regarding the VIDI cohort, the first step is to repeat these analyses in 2-year-old infants. In addition, it would be of interest to examine the effect of the infant's total and supplemental intake of vitamin D on growth. The long-term effects are to be investigated in the VIDI follow-up study starting in 2019-2020 when the children are 6 to 7 years of age.

ACKNOWLEDGEMENTS

This study was carried out between 2014 and 2019 at the Children's Hospital, Pediatric Research Center, University of Helsinki and Helsinki University Hospital. I warmly thank Professor Markku Heikinheimo of the Children's Hospital, and Jari Petäjä, the Director of Children's Hospital for research facilities. I am grateful to Professor Kim Vettenranta, Docent Turkka Kirjavainen, and Docent Jussi Merenmies, the present and former programme directors of Pediatric Graduate School, and Professor Taneli Raivio, head of the Pediatric Research Center, for providing excellent research facilities, scientific education, and financial support.

This thesis was financially supported by the Juho Vainio Foundation and the Päivikki and Sakari Sohlberg Foundation. I thank everybody who has helped me during this doctoral training.

My greatest gratitude goes to all the participating children and their families. Your invaluable contribution to this study made it possible.

It was and is a privilege to work in the VIDI study group. I am deeply grateful for my thesis supervisors, Docent Heli Viljakainen, Professor Outi Mäkitie, and Professor Sture Andersson, for guiding and teaching me throughout the process of my doctoral education. Heli, thank you for the inspirational scientific discussions and beyond, hands-on guidance, and encouraging support. Outi, thank you for your determined, patient, and intellectual supervision. Sture, principal investigator of the VIDI study, thank you for the financial support, warm and perceptive discussions, and for creating a relaxed atmosphere in all the research meetings.

I am truly grateful for the whole VIDI study group. Thank you Täydelliset tutkijanaiset: PhD Jenni Rosendahl, PhD Elisa Holmlund-Suila, MD Saara Valkama, and MD Maria Enlund-Cerullo. Your kind support, friendship, and intense work in the VIDI study have been invaluable. Jenni, I warmly thank you for all the high-level scientific and non-scientific discussions and for being such a lovely friend. Elisa, my astute and efficient roommate, your help and major role in revising our manuscripts are greatly acknowledged. Also, the senior researchers of VIDI, PhD Timo Hytinantti and Docent Otto Helve, thank you for your support. I cannot thank our study nurses enough for their contributions to fieldwork, i.e., deriving the high-quality data of this thesis. Thank you Sirpa Nolvi, Rhea Paajanen, Päivi Turunen, Nea Boman, and lab technician Sari Linden for your help and friendship. Emma Kynkäänniemi and Sonja Kaijanen are acknowledged for their accurate recording of food records. The Outi Mäkitie research group is also greatly acknowledged for your pleasant research meetings.

I thank my thesis committee members, Docent Maijaliisa Erkkola and Docent Päivi Luukkainen, for support and encouragement. Maikki, you inspired me to become a researcher during my master's education. Thank you

for fruitful collaboration and for your humane and educational approach and broad understanding in science and life.

I wish to thank the excellent reviewers of this thesis. Thank you Docent Jyrki Virtanen and Docent Hanna Huopio for your great comments and suggestions, which improved this thesis significantly.

I want to express my gratitude to my other co-authors. Thank you Docent Heljä-Marja Surcel, PhD Liisa Korkalo, Professor Eero Kajantie, and the late Professor Hannu Rita for your significant contributions to our manuscripts. I thank Professor Kari Teramo and Docent Kalevi Laitinen for your expertise in Study II, and PhD Antti Saari and MD Marjo Karvonen for providing growth references. I warmly thank Docent Suvi Itkonen for your vitamin D expertise and friendship. I wish to acknowledge the midwives and laboratory staff at Kätilöopisto Maternity Hospital for obtaining umbilical cord blood samples. I would also like to thank all my co-workers at Biomedicum 2C, especially Laura Puhakka, Sonja Piippo, Maija Seppä-Moilanen, Johanna Sivunen, Marjaana Peussa, Satu Lindström, and Anne Nikkonen, for the refreshing lunch and coffee breaks and peer support.

My friends, their families, and my godchildren, words are not enough to express my gratitude. I thank Kuopion kasvatit, Ravi Girls, Reso-friends, and Arja and your families for your support, friendship, and laughter. Jelena, I am deeply grateful for the numerous scientific discussions at our frequent lunch breaks and for peer support. Taru, thank you for your support and faith in me.

I thank my beloved family with all the extensions for support and balance in life. Thank you, Henri and Heikki, my darling big brothers, for repeatedly reminding me of my place in the world order. My parents, Marjo-Riitta and Raimo, I thank you for being interested in my research work and for acknowledging my moments of success. I also thank my parents-in-law, Eija and Eero. Eija, thank you for providing me with the time to write this thesis by taking care of our son, Seve. I am deeply grateful to my family members who live with me every day. Kyllikki, thank you for your endless love and comfort. Dear Mika, thank you for loving and accepting me as I am, for being a dedicated father, and for enabling me to finalize this thesis during the intense period at the end. Seve, I am lucky to be your mother. Thank you for the constant smiles and laughter you bring.

Lastly, I feel very fortunate for having had the opportunity to educate myself to this point. Most people in the world do not have the possibility to earn a university degree.

Helsinki, November 2019
Helena Hauta-alus

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ISBN 978-951-51-5666-2 (pbk.)
ISBN 978-951-51-5667-9 (PDF)
Painosalama Oy
Turku 2019