


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

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Abstract

Background: Early childhood growth can affect the child's health status later in life. Maternal vitamin D status has been suggested to affect early childhood growth. However, there is a lack of studies investigating the role of maternal vitamin D status on growth trajectories during infancy. By using growth mixture modeling (GMM), maternal vitamin D status during pregnancy can be investigated in relation to different classes of infant growth trajectories.

Objectives: To examine the association between maternal 25-hydroxyvitamin D (25OHD) and classes of infant body mass index (BMI) growth trajectories.

Methods: Mother–child pairs were included from the Norwegian Mother, Father, and Child Cohort Study (MoBa, $n = 2522$) and the Swedish GraviD cohort ($n = 862$). Maternal 25OHD in pregnancy was analyzed by liquid chromatography tandem mass spectrometry. Children's weights and heights were registry-based. GMM identified classes of infant BMI growth trajectories up to 2 years. The association between maternal 25OHD and infant BMI class by cohort was estimated using a log-link generalized linear model. Mixed model analysis estimated the pooled association including both cohorts.

Results: Two infant BMI classes were identified, stable normal and stable high. In MoBa, maternal 25OHD <50 and 50 – 75 nmol/L were associated (RR 2.70, 95% CI 1.26–5.77 and RR 2.56, 95% CI 1.20–5.47) with a higher risk of the infant stable high BMI class, compared with 25OHD >75 nmol/L. In GraviD, no association was found. In pooled analysis, maternal 25OHD ≤ 75 nmol/L was non-significantly associated with a higher risk of the stable high BMI growth class.

Conclusions: Maternal 25OHD ≤ 75 nmol/L may be associated with a higher class of BMI growth trajectory during infancy.

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KEYWORDS

25-hydroxyvitamin D, body mass index, growth mixture modeling, infancy, latent classes, pregnancy, The Norwegian Mother, Father and Child Cohort Study

1 | INTRODUCTION

Growth in early childhood is critical for later weight and health status. Infants with obesity are likely to continue having obesity and to develop cardiovascular diseases in adulthood.¹ Standard growth charts, such as those developed by the World Health Organization (WHO), are widely used to track and identify unfavorable growth.^{2,3} A normal childhood body mass index (BMI) growth trajectory is characterized by an initial steep increase peaking around 6–12 months of age. Both weight and length are increasing rapidly at different rates. The peak is followed by a decreasing BMI trajectory that continues throughout early childhood and reaches a nadir around 4–6 years, the adiposity rebound, before increasing once again at puberty.^{2,3} Thus, childhood growth rate differs throughout childhood, with each previous growth phase influencing the next.^{4,5} When childhood growth is studied, differences in growth patterns might be of higher relevance than weight or height at a single time point.

To identify possible sub-groups or “classes” of growth trajectories within a population, growth mixture modeling (GMM) can be used.⁶ GMM is suitable when the population is thought to be composed of several unobserved classes. A systematic review of longitudinal studies investigating BMI growth trajectories in early childhood, based on GMM, found that in most populations studied, three to four classes were identified.⁷ In studies of growth during the first 2 years, a majority of studies found BMI classes corresponding to growth trajectories labeled stable normal, stable high, stable low or decreasing, and a rapid growth class.⁷ Rapid growth can occur to compensate for intrauterine growth restrictions and is seen when the postnatal growth rate exceeds the expected from standard growth charts.⁸ Several exposure variables have been associated with different classes of growth trajectories. For example, Aris et al.⁹ showed that higher maternal pre-pregnancy BMI, gestational weight gain and multiparity were factors associated with the stable high BMI class in infancy.⁹ In addition, higher maternal pre-pregnancy BMI and gestational weight gain were also associated with the rapid growth class. In contrast, preterm birth was associated with the stable low growth class.⁹ Different growth classes have also been associated with various childhood outcomes. In some studies, the stable high growth class has been associated with obesity at 5–6 years of age.^{9,10} Also, the stable high growth class, and the rapid growth class have been associated with higher fat mass index in 8-year-old girls and boys, and in 19-year-old girls.¹¹

Vitamin D deficiency, measured as the biomarker 25-hydroxyvitamin D (25OHD) <30 nmol/L, in utero and infancy is a risk factor for rickets and stunted growth, and there is a strong biological rationale for the importance of vitamin D status for fetal and infant growth.^{12–14} Rapid postnatal growth increases the risk of later

obesity, higher fat mass and chronic diseases in adulthood, across the whole range of birth weight.^{15,16} Several biological mechanisms have been suggested on how infant growth can affect the risk of obesity later in life. These suggestions include an enhanced insulin resistance in the infant,¹⁷ or a modified adipocyte development.¹⁸ Maternal nutrition status during pregnancy, through fetal programming, can have implications in the child's body structure, metabolism, and physiology even after birth.¹⁹ In a recent systematic review and meta-analysis, maternal vitamin D deficiency was associated with low birth weight, a higher infant body weight at 9 months of age but not with infant length.²⁰ Therefore, poor maternal vitamin D in pregnancy has been suggested to be linked to higher BMI and adiposity in infancy.²⁰

One previous study has investigated the association between maternal vitamin D status and classes of BMI z-score trajectories from birth to 3 years.²¹ Two different classes were identified. Children in the first class (17%) was born with a low BMI z-score but experienced an increased BMI z-score trajectory during the first year of life. Children in the second class (83%) had a stable moderate BMI z-score trajectory. The mean maternal vitamin D level was significantly lower in the first class, but maternal vitamin D deficiency (categorized as 25OHD <30 nmol/L) was not associated with any class.²¹

In this study involving mother–child pairs from two prospective pregnancy cohort studies, the objective was to examine if maternal 25OHD during pregnancy is associated with class of infant BMI growth trajectory during the first 2 years of life. This study hypothesized that maternal vitamin D status during pregnancy is associated with postnatal growth.

2 | METHODS

2.1 | Study population

This article is based on data from the Norwegian Mother, Father, and Child Cohort Study (MoBa) and the Swedish study GraviD. Both studies are pregnancy cohorts with available data on maternal 25OHD during pregnancy and longitudinal growth data in the children.

MoBa was conducted by the Norwegian Institute of Public Health.²² Pregnant women were recruited from all over Norway in the years 1999–2008 and 41% of pregnant women consented to participate. The target population of the study was all women who give birth during these years, with no exclusion criteria but required knowledge in the Norwegian language. The cohort includes 114,500 children, 95,200 mothers, and 75,200 fathers. Questionnaires were

sent out three times during pregnancy and six times after delivery to the participants. Maternal 25OHD is available for a selection of MoBa participants included in the Norwegian Environmental Biobank.²³ All women who had available biological samples donated during pregnancy, genetic data, questionnaire one to six, and the questionnaire answered by the father were included in the biobank. In total, 2982 women were included and had biomarkers, including vitamin D, analyzed in blood. The current study is based on version 12 of the quality-assured data files released for research on January 2019. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is now based on regulations related to the Norwegian Health Registry Act. The current study was approved by The Regional Committees for Medical and Health Research Ethics (REC 2019/770).

The GraviD study is a multi-ethnic pregnancy cohort, initiated in the southwest Sweden.²⁴ In total, 43 antenatal care clinics participated in the study where midwives invited all pregnant women whose pregnancy had not exceeded gestational week 16 to participate. The final study sample consisted of 2125 women who were recruited during autumn (September–November) 2013 and spring (February–June) 2014. After delivery, all families with a healthy singleton child ($n = 1952$) were invited to participate in a follow up study. In total, 984 (50%) of the invited families consented to participate in the follow-up, which included a questionnaire and retrieval of the children's medical records. The GraviD cohort was conducted according to the Declaration of Helsinki and approved by the Regional Ethics Committee in Gothenburg and the Swedish Ethical Review Authority (897-11, T439-13, T085-14, 2019-05219). Written informed consent was provided by all participating women and from both parents.

All women in the Norwegian Environmental Biobank, and all women in GraviD who consented to participate the follow up study, were eligible for inclusion in the current study. Exclusion criteria for this current study were multiple gestations, fetal malformations, and chromosomal abnormalities. Further, mothers and children with missing information on maternal 25OHD, maternal age, education, origin, pre-pregnancy BMI, smoking during pregnancy, parity, gestational age, sex, birth weight, and length were excluded. Inclusion criteria were at least one postnatal measurement of weight and height in addition to weight and length at birth. The final study population included 2522 (85%) mother–child pairs from MoBa and 862 (88%) mother–child pairs from GraviD.

2.2 | Data collection

In MoBa, the participating women were asked to answer three questionnaires during pregnancy at gestational weeks 15, 22, and 30. The first and third questionnaires assessed sociodemographic and other relevant background information (e.g., education), while the second assessed dietary information (including supplement use). Venous blood samples were obtained once during pregnancy (mean

gestational week 18) from both parents and from mothers and children (umbilical cord) at birth.²⁵ Samples were shipped by ordinary mail (unrefrigerated shipment) in a vacutainer for long-term freezing at a central biorepository. Storage temperature for plasma was -80°C . Birth weight and length were retrieved from the Medical Birth Registry, a national health registry containing information about all births in Norway.²⁶ The children were followed up by questionnaires, where the parents were asked to report the child's weights and lengths/heights at 11 ages; 6 weeks, 3, 6, 8, 12, and 18 months, 2, 3, 5, 7, and 8 years. The six first measurements were requested to be the measurement conducted at the child health services. In total, 24,358 and 23,845 measurements of weight and height were available in MoBa. On average, there were nine measurements of weight and height per child.

In GraviD, women were requested to complete a questionnaire and to leave non-fasting venous blood samples, in the first (gestational week <17) and third (gestational week >31) trimester of pregnancy. The questionnaires were requesting background information (e.g., education and origin) and lifestyle factors (e.g., supplement use). Serum was stored in -70°C until analysis. After delivery, medical records from the obstetrics care were obtained. When the children had turned 5 years old, an additional questionnaire was sent to the families, regarding for example, infant feeding and vitamin D supplement use as part of the follow up. Measurements of weight and height throughout childhood were extracted from medical records, obtained from the child health services at around 5 years of age. In total, 13,281 and 13,275 postnatal measurements of weight and height respectively were available for the children followed up in GraviD. On average, there were 16 measurements of weight and height per child.

2.3 | Blood sample analysis

For all women, 25OHD concentrations were measured by liquid chromatography–tandem-mass spectrometry (LC-MS/MS). The LC-MS/MS measures both 25OHD₂ and 25OHD₃ and the sum of these two is regarded as the exposure 25OHD. In MoBa, 25OHD was analyzed in plasma at the National Institute for Health and Welfare, Helsinki, Finland. In GraviD, 25OHD was analyzed in serum at the clinical chemistry laboratory in Skåne, Sweden.²⁷ Both laboratories were certified by the Vitamin D External Quality Assessment Scheme.

The Vitamin D Standardization Program protocol for standardization of 25OHD data as previously described²⁸ and validated,²⁹ was applied in the GraviD study. A sample of 175²⁹ previously analyzed serum samples were reanalyzed using the LC-MS/MS method at the Cork Center for Vitamin D and Nutrition Research, which is traceable to the Centers for Disease Control and Prevention reference measurement procedure.³⁰ Previously analyzed 25OHD data were split into quartiles and a uniform sampling procedure was used to identify samples to be reanalyzed based on the within-quartile range of values. In this way, samples were selected across the entire range of

25OHD values, with oversampling at the lower and upper ends of the distribution. The previous serum 25OHD dataset was then converted to a standardized 25OHD dataset.

2.4 | Statistical analysis

Differences in study population characteristics by cohort were investigated using Chi-2 test of categorical variables, independent samples *t*-test of normally distributed variables and Wilcoxon-Mann-Whitney test of not normally distributed variables.

The main analysis was a three-stage process. A visual representation of the statistical processes is presented in Figure 1.

2.4.1 | Child anthropometric data

Individual growth trajectories were predicted by applying the parametric non-linear Jenss-Bayley growth curve model,^{31,32} using the SAEMIX algorithm. All measurements of weight and height from the questionnaires and medical charts were used, regardless of the available number per child. The growth models were executed in MoBa and GraviD separately, due to differences in standard deviations (SD) in weight and height between the cohorts. The reported measures were compared with the predicted value derived from the growth model and excluded if the difference exceeded three SD. In total, 1.2% of the weights and 0.7% of the heights in MoBa, and 0.5% of the weights and 0.3% of the heights from GraviD, were consequently excluded as misreported values. Remaining reported and predicted weights and heights correlated at 0.99 in both MoBa and GraviD. The reported values were then used to predict weights and heights at the following predetermined ages; 1, 3, 6, 9, 12, 18 months, and 2 years. As the Jenss-Bayley model assumes that weight growth is constantly increasing, birth weight was not included in the model.³³ The children's BMI were calculated from the predicted values at each time point.

2.4.2 | Classification of BMI growth trajectories

Classes of BMI growth trajectories from 1 month to age 2 years were analyzed using GMM³⁴ in the two cohorts jointly. A longitudinal change model was assumed where each class was allowed random intercepts and slopes, linear and quadratic terms by age, and sex included as a covariate. Inclusion of sex allowed for sex-specific modeling of trajectories. Variance-covariance matrix of random effects were allowed to vary across classes. For each class, 100 random start values and maximum 30 iterations were allowed. The estimation procedure was finalized only for the departure that provided the best log-likelihood after the given iterations. Based on previous literature,⁷ up to five classes were explored. To identify the number of classes that best fitted the data, Bayesian information criterion (BIC), sample-size adjusted BIC (saBIC), entropy,

posterior probabilities, and the shape of the trajectories were inspected.^{6,35,36} A lower BIC and saBIC generally corresponds to a better model fit. Entropy is an indicator of the conditional probabilities of class membership that ranges from zero to one, with high values (>0.8) indicating that subjects overall are classified with confidence.⁶ Posterior probabilities represent the average class probability of all individuals in their most probable class, ranges from zero to one and should be >0.7 for all individual classes.³⁵ Individuals were assigned to the class for which they had the highest probability of membership. The chosen number of classes were coded as an ordinal variable and labeled. The median BMI derived from the Jenss-Bayley growth curve models for each class were compared against the WHO BMI-for-age growth standards.² To be able to statistically proceed with the following step, classes with <5% of the population were discarded. The Guidelines for Reporting on Latent Trajectory Studies Checklist guided the planning of the analyses and reporting in the manuscript.³⁷

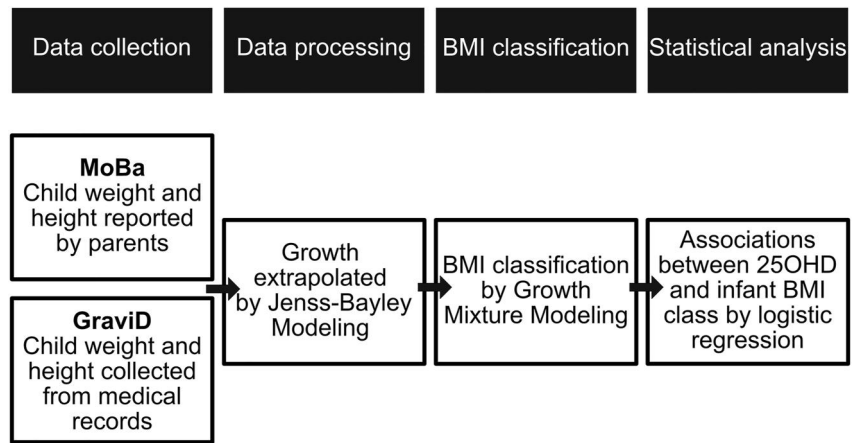
3 | MATERNAL 25OHD AND CLASSES OF INFANT BMI GROWTH TRAJECTORY

Risk ratios (RRs) were estimated using a log-link generalized linear model to investigate if maternal 25OHD was associated with infant BMI growth trajectory class, in each cohort separately. The most commonly occurring class was chosen as the reference. The dependent variable maternal 25OHD concentration was modeled as a categorical variable (>75 nmol/L (reference), 50-75 nmol/L, and <50 nmol/L) and as a continuous variable. To account for possible non-linearity, the association was also explored using restricted cubic splines, with five knots positioned at percentiles 5%, 27.5%, 50%, 72.5%, and 95% as recommended by Harrell.³⁸ *p*-values are reported for overall associations between 25OHD as a continuous exposure and the outcome by testing the coefficients of all spline transformations equal to zero.

The potential confounders were maternal age, education, origin, pre-pregnancy BMI, smoking during pregnancy, parity, excessive gestational weight gain, gestational age, lactation, and paternal BMI, identified by a directed acyclic graph³⁹ (Supplementary Figure S1). Excessive gestational weight gain (below or above a normal weight gain according to pre-pregnancy BMI⁴⁰) was removed due to collinearity with maternal pre-pregnancy BMI. Gestational age was removed due to collinearity with birth weight. The models are presented as (1) crude; (2) minimally adjusted, including maternal education, origin, and pre-pregnancy BMI; and (3) fully adjusted model, including maternal education, origin, pre-pregnancy BMI, maternal age, smoking during pregnancy, and parity. Child's birth weight and season of blood sampling were investigated as interaction variables. Season was dichotomously categorized into the month of blood sampling (May-October or November-April). Interaction was considered when *p* < 0.200.

Finally, the overall association between maternal 25OHD and infant BMI growth trajectory class (including both MoBa and GraviD)

FIGURE 1 Flowchart of statistical processes. BMI, body mass index; 25OHD, 25-hydroxyvitamin D



was examined by multilevel mixed effects logistic regression model, with a random intercept by cohort. The pooled models are presented as crude, minimally adjusted, and fully adjusted, including the covariates listed above as fixed.

RStudio version 3.4.2 was used for the Jenss–Bayley growth curve model (Saemix package) and the GMM (lcmm package). Stata version 16 was used for all other statistical analyses (Stata Corporation, College Station, Texas).

4 | RESULTS

4.1 | Study population characteristics

Mean (SD) gestational week for blood sampling and analysis of maternal 25OHD was 18.3 (1.3) in MoBa and 10.7 (1.8) in GraviD. Compared with MoBa, the women in the GraviD cohort had a higher maternal age, fewer smokers, a larger variation in country of origin, a higher vitamin D status, and more women were multiparous (Table 1). The children in GraviD also had a shorter duration of breastfeeding and a lower birth weight, compared with the children in MoBa. There were no differences in maternal education or pre-pregnancy BMI between the study populations.

4.2 | Classes of BMI growth trajectories up to 2 years

A three-class model was selected as the most appropriate to describe the different BMI growth patterns (Table 2). This model had the lowest BIC and saBIC. The model entropy was fairly high for the overall model (0.71) and the average posterior probabilities in the three classes were 0.89, 0.74, and 0.82, respectively. The final model included 14 iterations.

The majority of the children (89.4%, $n = 3026$) were classified into class 1 which was labeled “stable normal class” and used as reference. Class 2, the second largest class (8.5%, $n = 289$), was labeled “stable high class.” The children in this class were experiencing more rapid growth between 1 and 6 months, but since the trajectory

subsequently remain stable between 6 and 24 months the class was finally labeled stable high. Class 3 was excluded from further analyses due to small class size (<5%). A visual representation of predicted classes of infant BMI growth trajectories by sex is presented in Figure 2A,B. Table 3 presents median BMI and corresponding WHO BMI-for age z-score and percentiles² as derived from the Jenss–Bayley growth curve model³¹ by class and sex in MoBa and GraviD.

4.3 | Maternal 25OHD and classes of infant BMI growth trajectories

4.3.1 MoBa

In the crude model, maternal 25OHD of 50–75 nmol/L and <50 nmol/L were significantly associated with a higher risk of belonging to the stable high BMI growth class (RR 3.04, 95% confidence interval (CI) 1.42–6.51 and RR 3.10, 95% CI 1.46–6.60), compared with maternal 25OHD >75 nmol/L (Table 4). After adjustment of the models, the association remained significant. There was an interaction (considered when $p < 0.200$) between maternal 25OHD and birth weight ($p = 0.059$) but not season ($p = 0.883$) in associations with BMI growth class. A higher birth weight was significantly associated with a higher prevalence of the stable high BMI growth class for maternal 25OHD ≤ 75 nmol/L (Supplementary Figure S2).

Continuous maternal 25OHD was significantly associated with the stable high BMI growth class in the linear crude model (RR 0.99, 95% CI 0.98–0.99). After adjustment, the association remained, however non-significant (RR 0.99, 95% CI 0.99–1.00). Maternal 25OHD was not associated with the stable high BMI growth class in the non-linear model (overall $p = 0.231$, Figure 3A), derived from restricted cubic splines.

4.3.2 GraviD

In GraviD, maternal 25OHD as a categorical variable was not associated with the stable high BMI growth class in either crude or adjusted models (Table 4). Maternal 25OHD as a continuous variable

TABLE 1 Study population characteristics in the MoBa and GraviD cohorts

	MoBa (n = 2522) N (%)	GraviD (n = 862) N (%)	p-Value ^a
Maternal education (years)			0.164
<13	664 (26.3)	186 (21.6)	
13–16	1211 (48.0)	459 (53.2)	
>16	647 (25.7)	217 (25.2)	
Born in Norway or Sweden			<0.001
Yes	2373 (94.1)	734 (85.2)	
Pre-pregnancy BMI (kg/m ²)			0.600
<18.5	73 (2.9)	18 (2.0)	
18.5–24.9	1628 (64.6)	553 (64.2)	
25–29.9	626 (24.8)	222 (25.8)	
≥30	195 (7.7)	69 (8.0)	
Maternal smoking in pregnancy			0.007
Never	2369 (94.4)	832 (96.5)	
Ever	140 (5.6)	28 (3.5)	
Parity			<0.001
Multiparous	1210 (48.0)	476 (55.2)	
Maternal 25OHD (nmol/L)			<0.001
<30	272 (10.8)	45 (5.2)	
30–49.9	975 (38.7)	193 (22.4)	
50–75	1003 (39.8)	477 (55.3)	
>75	272 (10.8)	147 (17.1)	
Season of blood sampling			<0.001
Jan–Mar	698 (27.7)	145 (16.8)	
Apr–Jun	628 (24.9)	239 (27.7)	
Jul–Sep	560 (22.1)	177 (20.6)	
Oct–Dec	637 (25.3)	301 (34.9)	
Vitamin D supplement use in pregnancy			<0.001
Yes	2031 (80.5)	408 (47.3)	
	Median (p25–p75)	Median (p25–p75)	
Maternal 25OHD (nmol/L)	51.0 (39.0–64.0)	60.1 (49.0–70.4)	<0.001
Maternal age (years)	30 (27–33)	32 (29–35)	<0.001
Gestational age (days)	281 (275–287)	281 (275–287)	0.887
Birth weight (g)	3650 (3340–3970)	3560 (3250–3885)	<0.001
Lactation (months)	10 (7–13)	8 (6–12)	<0.001

Abbreviations: BMI, body mass index; 25-hydroxyvitamin D; 25OHD, p25, 25th percentile; p75, 75th percentile.

^aDifference between GraviD and MoBa, using Chi2 test of categorical variables, independent samples t-test of normally distributed variables and Wilcoxon–Mann–Whitney test of not normally distributed variables.

was not associated with the stable high BMI growth class in either crude or adjusted linear models (RR 1.00, 95% CI 0.99–1.01) or modeled by restricted cubic splines (overall $p = 0.845$, Figure 3B). In

GraviD, no interaction between maternal 25OHD and birth weight ($p = 0.641$) or season ($p = 0.812$) in associations with BMI growth class was found.

TABLE 2 Model selection process for infant BMI growth classes in MoBa and GraviD ($n = 3384$)

Classes in model	Log likelihood	BIC	saBIC	Entropy	% class 1	% class 2	% class 3	% class 4	% class 5
1 class	-32,664	65,417	65,382	1.00	100.0				
2 classes	-32,385	64,900	64,850	0.97	98.2	1.8			
3 classes ^a	-32,336	64,843	64,776	0.71	89.4	8.5	2.1		
4 classes	-32,341	64,894	64,812	0.56	54.7	30.7	12.5	2.1	
5 classes	-32,326	64,904	64,806	0.62	40.8	28.7	18.1	10.1	2.3

Abbreviations: BIC, Bayesian information criteria; BMI, body mass index; saBIC, sample-size adjusted BIC.

^aThe selected model.

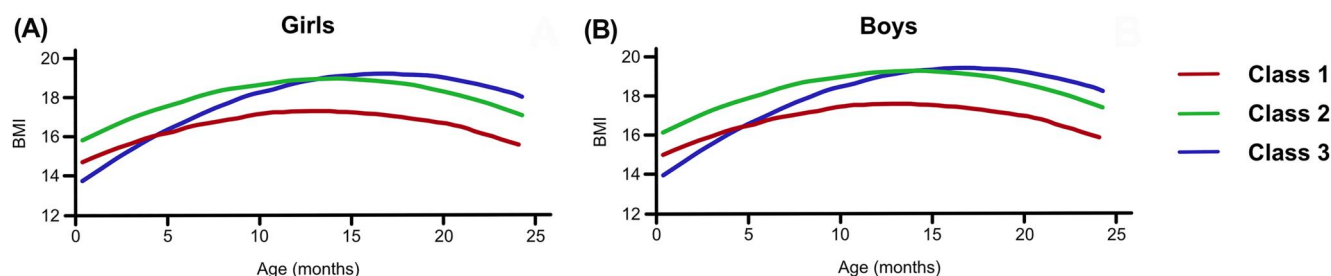


FIGURE 2 Classes of infant BMI growth trajectories in (A) girls ($n = 1636$) and (B) boys ($n = 1748$) during the first 2 years of life in MoBa and GraviD derived from the growth mixture model. N (%); Class 1: 1467 (43%) girls, 1559 (46%) boys, Class 2: 135 (4%) girls, 154 (5%) boys, Class 3: 34 girls (1%), 35 boys (1%). Labels; Class 1: stable normal, Class 2: stable high

4.4 | MoBa and GraviD

In the pooled analyses including both MoBa and GraviD, there were non-significant associations ($p = 0.052$ - 0.098) between maternal $25\text{OHD} \leq 75$ nmol/L and risk of the infant belonging to the stable high BMI growth class in the crude and adjusted models (Table 5). Maternal 25OHD as a continuous variable was associated with a lower risk of the infant belonging to the stable high BMI growth class in the crude model (RR 0.99, 95% CI 0.99-1.00, $p = 0.06$) but not after adjustment (RR 1.00, 95% CI 0.99-1.00).

5 | DISCUSSION

Two main classes of infant BMI growth trajectories were identified, a stable normal and a stable high class. In the Norwegian MoBa cohort, maternal $25\text{OHD} \leq 75$ nmol/L in pregnancy was significantly associated with higher risk of the infant belonging to the stable high BMI growth class. In the Swedish GraviD cohort, no association between maternal 25OHD and stable high BMI growth class was found. However, in the pooled analysis including both MoBa and GraviD, maternal $25\text{OHD} \leq 75$ nmol/L in pregnancy was non-significantly associated with a higher risk of the infant belonging to the stable high BMI growth class. Our results thus suggest an association between lower maternal vitamin D status in pregnancy and risk of the infant belonging to the higher class of BMI growth trajectory, but the results were significant only in the cohort with the largest study sample and the lowest vitamin D status.

There are several suggested pathways for the mechanisms relating lower maternal vitamin D status to a stable high growth trajectory in infancy. For example, vitamin D deficiency during pregnancy in human studies may induce insulin resistance in the mother.⁴¹ If the fetus is exposed to hyperglycemia in utero, the fetal insulin production alters and the risk of later type 2 diabetes increase.⁴² Children of women with pregnancy affected by gestational diabetes mellitus are more likely to be overweight.⁴³ However, little is known about this link between maternal vitamin D, insulin resistance and risk of metabolic diseases in children of non-diabetic mothers. Another suggested pathway linking maternal vitamin D to the child's risk of later metabolic disease is through inflammation.⁴⁴ Vitamin D levels have been negatively associated with the inflammatory biomarker c-reactive protein levels in both mother and neonate.^{45,46} Possibly, exposure to environmental factors such as hyperglycemia or inflammation during fetal life can influence disease risk and program the child toward later metabolic conditions.⁴⁷

The hypothesis that maternal vitamin D status during pregnancy was associated with infant growth was supported by the results in MoBa and the pooled effect estimate. One possible explanation as to why no association was found in GraviD is insufficient variation in vitamin D status among the women. In MoBa, recruitment was conducted throughout the year, while only conducted during September to November and during February to June in GraviD. Thus, the lack of measurements during large parts of summer and winter in GraviD might lead to a lower capacity to find a possible association. Furthermore, gestational week at the time of blood sampling differed between the two cohorts. Since there are indications that 25OHD

TABLE 3 Median BMI (kg/m²) and corresponding BMI-for-age z-score² and BMI percentiles² derived from the Jenss–Bayley growth curve model³¹ by class of infant growth trajectory and sex in MoBa and GraviD (*n* = 3384)

Age	Class 1						Class 2						Class 3					
	Girls (<i>n</i> = 1467)			Boys (<i>n</i> = 1559)			Girls (<i>n</i> = 135)			Boys (<i>n</i> = 154)			Girls (<i>n</i> = 34)			Boys (<i>n</i> = 35)		
	BMI	BMlz	BMlp	BMI	BMlz	BMlp	BMI	BMlz	BMlp	BMI	BMlz	BMlp	BMI	BMlz	BMlp	BMI	BMlz	BMlp
1 month	14.0	−0.4	35	14.6	−0.3	39	15.3	0.6	71	15.8	0.7	74	13.1	−1.1	13	13.5	−1.1	14
6 months	17.0	0.1	52	17.5	0.1	53	19.1	1.4	91	19.8	1.6	94	16.4	−0.4	36	17.9	0.4	66
12 months	16.5	0.1	54	16.9	0.1	53	18.7	1.5	93	19.2	1.6	95	17.4	0.7	76	18.7	1.3	90
18 months	16.1	0.2	59	16.5	0.3	60	18.3	1.7	95	18.7	1.8	96	17.6	1.3	89	18.8	1.8	97
24 months	15.9	0.2	57	16.3	0.2	58	17.9	1.5	94	18.4	1.7	96	17.9	1.5	93	18.6	1.8	96

Abbreviations: BMI, body mass index; BMlp, BMI-for-age percentile; BMlz, BMI-for-age z-score.

Maternal 25OHD	MoBa (<i>n</i> = 2513)			GraviD (<i>n</i> = 802)		
	RR	95% CI	<i>p</i> -Value	RR	95% CI	<i>p</i> -Value
Crude model						
>75 nmol/L (ref) ^a	1.0			1.0		
50–75 nmol/L ^b	3.04	1.42, 6.51	0.004	0.91	0.56, 1.47	0.695
<50 nmol/L ^c	3.10	1.46, 6.60	0.003	0.85	0.49, 1.47	0.564
Adjusted model 1 ^d						
>75 nmol/L (ref)	1.0			1.0		
50–75 nmol/L	2.81	1.31, 6.02	0.008	0.90	0.55, 1.45	0.656
<50 nmol/L	2.67	1.25, 5.71	0.011	0.83	0.47, 1.47	0.531
Adjusted model 2 ^e						
>75 nmol/L (ref)	1.0			1.0		
50–75 nmol/L	2.70	1.26, 5.77	0.011	0.90	0.55, 1.45	0.653
<50 nmol/L	2.56	1.20, 5.47	0.016	0.84	0.48, 1.49	0.559

Abbreviations: 25OHD, 25-hydroxyvitamin D; CI, confidence interval; RR, risk ratio.

^{a–c}Children in the stable normal and the stable high class, respectively.

^a*n* = 264 and *n* = 7 in MoBa, and *n* = 114 and *n* = 19 in GraviD.

^b*n* = 961 and *n* = 82 in MoBa, and *n* = 389 and *n* = 58 in GraviD.

^c*n* = 1103 and *n* = 96 in MoBa, and *n* = 195 and *n* = 27 in GraviD.

^dMinimally adjusted model, including maternal education, origin, and pre-pregnancy BMI.

^eFully adjusted model, including maternal education, origin, pre-pregnancy BMI, maternal age, smoking during pregnancy, and parity.

vary throughout pregnancy,²⁴ the time point of blood sampling is likely of importance for the association studied. Also, different laboratories were used for analyses of 25OHD in the two cohorts and the measurements in GraviD were standardized. Thus, the values are not fully comparable. Finally, the study sample was three times larger in MoBa than in GraviD (*n* = 2513 and *n* = 802, respectively). Taken together, this can explain why an association between maternal 25OHD and infant growth was not found in GraviD. Future studies with data on 25OHD throughout all seasons and sufficiently large study samples are warranted to confirm the association between maternal 25OHD and infant's BMI growth trajectory suggested in this study.

TABLE 4 The association between maternal 25OHD and infant risk of belonging to the stable high BMI growth class during the first 2 years of life, using the stable normal BMI class as reference category, by cohort

The selection of a three-class model is consistent with results from a systematic review of studies using group-based trajectory modeling approaches to investigate BMI trajectories in early childhood.⁷ A stable normal and a stable high BMI growth class were found in most of the studies investigating BMI growth during infancy.^{9–11,47} To our knowledge, only one previous article has investigated the association between maternal vitamin D status and infant BMI trajectory class.²¹ However, none of the two classes identified in that study corresponded to the stable high class found in the current study. A systematic review and meta-analysis of randomized controlled trials concluded that vitamin D supplementation during pregnancy or infancy may be associated with reduced adiposity in

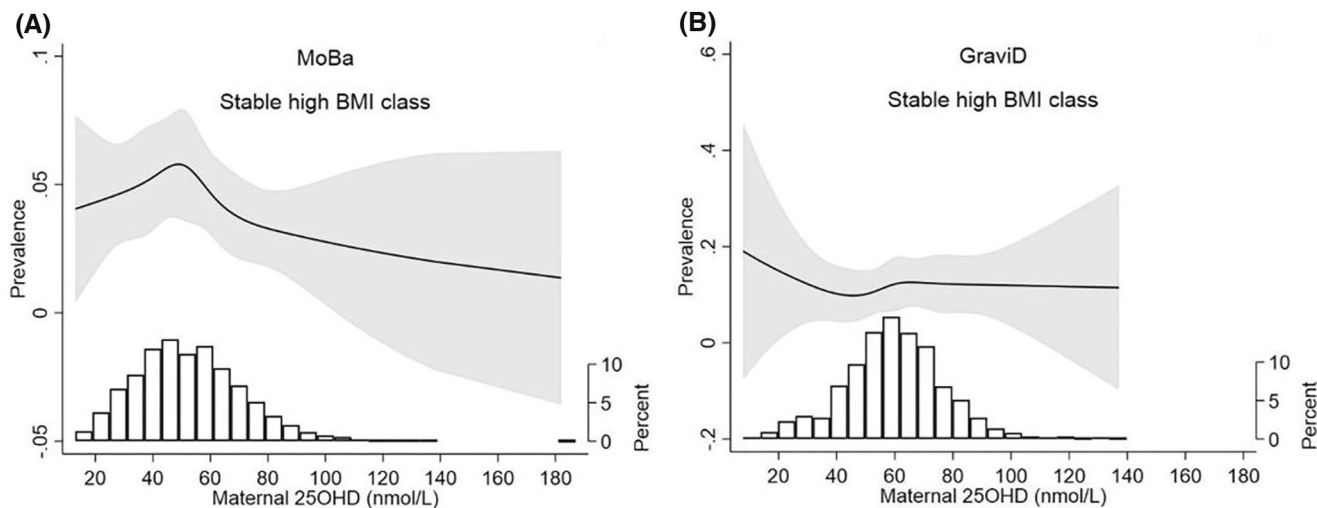


FIGURE 3 Maternal 25-hydroxyvitamin D (25OHD) and prevalence of infant stable high BMI growth class during the first 2 years of life in; (A) MoBa ($n = 2513$) and (B) GraviD ($n = 802$). Knots were located at 24, 40, 51, 62, and 85 nmol/L in MoBa, and 30, 50, 60, 70, and 89 nmol/L in GraviD in a log-link generalized linear model, adjusted for maternal education, origin, pre-pregnancy BMI, maternal age, smoking during pregnancy, and parity

childhood.⁴⁸ The results showed that vitamin D supplementation during pregnancy or infancy was associated with increased length-for-age z-score at 1 year of age, and lower BMI and BMI-for-age z-score at 3–6 years of age. Although the results from these studies are not comparable with the current study, the results from MoBa overall agree with the results of the meta-analysis. In the observational study by Leffelaar et al.,⁴⁹ children of vitamin D deficient (25OHD < 30 nmol/L) mothers had an increased growth velocity in both weight and length during the first year of life, compared with children of women with 25OHD ≥ 39 nmol/L. Although BMI was not investigated as an outcome, the findings suggested an association between maternal vitamin D deficiency and accelerated growth in childhood, as the current study also implies. In another observational study conducted in Greece,⁵⁰ children of women with 25OHD < 37.7 nmol/L during pregnancy had higher BMI SD score at 4 years of age. In contrast, other observational studies⁵¹ found no difference in BMI-for-age z-score at 4 or 12 months of age between children of mothers with 25OHD < 30 nmol/L compared with ≥ 30 nmol/L, nor an association between maternal vitamin D status and child's weight or height at 9 months of age.⁵² Evidently, the results from both previous studies and the current study investigating the association between maternal vitamin D status and childhood growth are inconsistent. Thus, these inconsistent findings pinpoint the need of further studies to clarify the role of maternal vitamin D status during pregnancy for the growth trajectories in infancy.

A major strength of the current study was the use of two population-based mother–child cohorts from two different Nordic countries. In addition, the use of the Jenss–Bayley growth curve model cleaned the dataset from implausible growth data, compen-

TABLE 5 The association between maternal 25OHD and infant risk of belonging to the stable high BMI growth class during the first 2 years of life, using the stable normal BMI class as reference category, in pooled analyses of MoBa and GraviD

Maternal 25OHD	RR ($n = 3315$)	95% CI	p -Value
Crude model			
>75 nmol/L (ref) ^a	1.0		
50–75 nmol/L ^b	1.24	1.00, 1.54	0.052
<50 nmol/L ^c	1.24	1.00, 1.56	0.052
Adjusted model 1 ^d			
>75 nmol/L (ref)	1.0		
50–75 nmol/L	1.22	0.80, 1.51	0.079
<50 nmol/L	1.19	0.95, 1.49	0.133
Adjusted model 2 ^e			
>75 nmol/L (ref)	1.0		
50–75 nmol/L	1.20	0.96, 1.50	0.098
<50 nmol/L	1.17	0.94, 1.47	0.161

Note: Effect estimates derive from multilevel mixed effects logistic regression model, with random intercept by cohort.

Abbreviations: 25OHD, 25-hydroxyvitamin D; CI, confidence interval; RR, risk ratio.

^{a–c}Children in the stable normal and the stable high class, respectively.

^a $n = 378$ and $n = 26$.

^b $n = 1350$ and $n = 140$.

^c $n = 1298$ and $n = 123$.

^dMinimally adjusted model, including maternal education, origin, and pre-pregnancy BMI.

^eFully adjusted model, including maternal education, origin, pre-pregnancy BMI, maternal age, smoking during pregnancy, and parity.

sated the loss to follow-up, and modeled predictions of weights and heights at the same ages for all children. Another strength is the ability of the GMM used to identify sub-groups.⁶ Other statistical methods to characterize early growth, such as residual growth model and SuperImposition by Translation And Rotation, assume absence of sub-groups.⁵³ However, as evident by the current results, some children do have a very different growth pattern and thus, sub-groups can be present. Further, a GMM model also allows for heterogeneity within classes.

Limitations include the complexity of the GMM to fit the data. As the model requires several parameters (e.g., variance-covariance matrix of random effects), some assumptions needed to be made. This can have affected the model fit and the predictions. The identified classes of BMI growth trajectories are model-derived growth curves based on the predictions from the Jenss–Bayley growth curve model, and not on the children's actual BMI growth trajectories. Thus, the results reflect associations between the maternal 25OHD concentrations and the predicted classes. Another limitation associated with using GMM to model growth was the difference in derived class-size between study populations. The identified classes will be different for each new study population and not always comparable between cohorts, which complicates replication of results. Other limitations were the mentioned differences in cohort protocols and lack of data on some covariates identified as important (i.e., child's vitamin D intake from supplements, paternal height, and BMI). Finally, the findings in the current study might be explained by residual confounding or any other nutrient, foods, or metabolite.

Maternal vitamin D status (25OHD) below 75 nmol/L during pregnancy may be associated with a higher class of BMI growth trajectory during the first 2 years of life. Some inconsistencies between cohorts pinpoint the need of further studies to confirm the suggested association.

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Data sharing statement The consent given by the participants does not open for storage of data on an individual level in repositories or journals. Researchers who want access to data sets for replication should submit an application to datatilgang@fhi.no. Access to data sets requires approval from The Regional Committee for Medical and Health Research Ethics in Norway and an agreement with MoBa.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Hanna Augustin initiated the study, Hanna Augustin, Linnea Bärebring, Eleni Papadopoulou, and Anna Amberntsson planned the study, Hanna Augustin and Anne-Lise Brantsæter is responsible for data protection and access, Anna Amberntsson conducted the statistical analyses and wrote the first version of the manuscript, Hanna Augustin, Linnea Bärebring, and Eleni Papadopoulou assisted with the statistical analyses. All authors (Hanna Augustin, Linnea Bärebring, Anna Amberntsson, Eleni Papadopoulou, Anne-Lise Brantsæter, Lauren Lissner, Anna Winkvist, and Helle M. Meltzer) were involved in interpretation of the results and writing of the final manuscript.

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