Vitamin D during pregnancy and offspring body composition: A prospective cohort study

Natalie K Hyde^{1*}, Sharon L Brennan-Olsen^{1,2,3}, John D Wark^{4,5}, Sarah M Hosking¹, Kara L Holloway¹, Julie A Pasco^{1,6}

¹*Deakin University, Geelong, Victoria, Australia*

²*Australian Institute for Musculoskeletal Science (AIMSS), C/- The University of Melbourne and Western Health, St Albans, Victoria, Australia*

³*Institute for Health and Ageing, Australian Catholic University, Melbourne, Victoria, Australia*

⁴*University of Melbourne Department of Medicine (Royal Melbourne Hospital), Victoria, Australia;*

⁵*Bone and Mineral Medicine, Royal Melbourne Hospital, Parkville, Victoria, Australia*

⁶*Department of Medicine - Western Health, Melbourne Medical School, The University of Melbourne, St Albans, Victoria, Australia*

***Corresponding author**

Natalie Hyde

Epi-Centre for Healthy Ageing, IMPACT SRC, School of Medicine, Deakin University (Barwon Health), PO Box 281

Geelong, Victoria, Australia, 3220

Phone: +61 (3) 4215 3306 Fax: +61 (3) 4215 3491

Email: nhyde@barwonhealth.org.au

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Running title: Gestational vitamin D and body composition

What is already known about this subject?

- Some studies have suggested an association between maternal vitamin D status during pregnancy and offspring body composition in childhood
- However, the evidence to date is largely conflicting, and measurements of serum vitamin D have been taken at different stages of pregnancy

What this study adds?

- This study examines the association at two defined time points in pregnancy to examine the temporality of the association
- Interactions with maternal smoking status are also examined highlighting a potential role of maternal inflammation

Abstract

Background: Evidence regarding the association between gestational vitamin D status and offspring body composition during childhood is inconsistent. Therefore, we aimed to determine the association between maternal vitamin D and offspring lean and fat mass in the Vitamin D in Pregnancy (VIP) birth cohort.

Methods: Subjects were mother-child pairs recruited from the Australian-based VIP cohort study. Mothers were recruited before 16 weeks gestation and provided a blood sample at both recruitment and at 28-32 weeks gestation. Serum vitamin D (25(OH)D) was measured by radioimmunoassay (Tyne and Wear, UK). Offspring lean and fat mass were quantified using dual energy x-ray absorptiometry (GE Lunar Prodigy, Madison, WI, USA) at 11 years of age.

Results: Median maternal 25(OH)D levels were 55.9 (42.2-73.3) and 56.1 (43.6-73.9) at recruitment and 28-32 weeks gestation; respectively. Maternal smoking was identified as an effect modifier in the association between maternal vitamin D status at recruitment and offspring body composition. In smokers, but not non-smokers, serum 25(OH)D status at recruitment was negatively associated with offspring fat mass percentage and positively

associated with lean mass (both $p < 0.05$). There was no association with 25(OH)D status at 28-32 weeks gestation.

Conclusions: Maternal vitamin D status in early pregnancy, in smokers, is associated with offspring body composition. These important findings warrant confirmation in larger studies and trials.

Introduction

Vitamin D deficiency is recognised internationally as a substantial public health concern¹. Deficiency during pregnancy is of particular concern, not only for maternal health, but also for that of the offspring. The most recent nationwide study in Australia showed that a quarter of Australian women of child-bearing age were vitamin D-deficient ($<50\text{nmol/L}$)². Whilst there are some dietary sources, such as fatty fish and fortified margarines, the majority of vitamin D is obtained from the endogenous synthesis in the skin after exposure to ultraviolet radiation from the sun^{3,4}. However, sunlight exposure and ultraviolet absorbance varies by latitude, skin pigmentation, time of day and time spent outdoors, season, amount of clothing covering skin and sun-avoidance behaviours⁴. It is increasingly recognised that vitamin D plays an important role in skeletal muscle. Vitamin D receptors (VDR) have been found in the plasma membrane and nucleus of human skeletal muscle cells⁵. In animal models, maternal vitamin D has been shown to impact upon myogenesis and myoblast activity⁶⁻⁷. Furthermore, VDR polymorphisms have been linked to adiposity phenotypes, which supports the hypothesis that VDR may play a biological role in lipogenesis and adipocyte differentiation⁸. Vitamin D supplementation in infants has been associated with leaner body composition at 3 years of age⁹ and there have been several studies to-date that have examined associations between maternal serum 25-hydroxyvitamin D (25(OH)D) status in human cohorts and offspring body composition during childhood; however, these studies have provided conflicting results¹⁰⁻¹⁴. Moreover, to-date, none of these studies has examined maternal 25(OH)D status at two defined time-points to determine the temporality of the association.

Previously we have reported reduced mid-upper arm circumference and leg circumference with no associated changes in skinfold measures in the offspring of mothers with lower vitamin D levels¹⁵, suggestive that infants had a lower proportion of lean tissue mass. Given the paucity of data and conflicting results, we aimed to examine the associations between maternal vitamin D status at two defined time points in pregnancy and measures of offspring fat and lean tissue as components of offspring body composition.

Methods

Participants

Mothers were recruited at their initial antenatal visit, after receiving information about the study with their clinic booking. Women were recruited from the region's sole public tertiary hospital, the University Hospital Geelong (formerly the Geelong Hospital) in Australia, before 16 weeks gestation (n=475) from 2002-2004, as part of the Vitamin D in Pregnancy Study. This study was designed to investigate maternal vitamin D levels during pregnancy and offspring health. Women were excluded if they had multiple pregnancy or maternal disability or disease that would preclude participation in the study and/or effect offspring growth. There were 402 mother-child pairs at birth that provided at least one measure of maternal vitamin D and birth measures. All mother-child pairs were invited back to participate in the 11-year follow-up which took place from 2013-2016.

Maternal vitamin D measures

Maternal serum samples were collected both at recruitment and 28-32 weeks. Samples were analysed in batches by radioimmunoassay (Immunodiagnostic Systems, Tyne and Wear, UK). There is a reported cross-reactivity of 100% with 25(OH)D₃ 75% with 25(OH)D₂. The coefficient of variation at 100nmol/L was 10.1% and 10.2% at 30nmol/L

Offspring body composition measures

Lean and fat mass were measured by dual-energy X-ray absorptiometry (DXA; Lunar Prodigy Pro, GE, Madison, WI, USA) at the 11 year follow-up and analysed using paediatric specific software (eNCORE, v.14.1). Percent lean and fat mass were calculated as a fraction of total weight. Lean mass incorporates all remaining tissue mass after subtracting bone and fat tissue such as the lean component of adipose tissue, skin and muscle. All scans were performed by trained operators. For internal validity, all the scans were analysed by the same operator (NKH).

Other maternal and offspring measures

Maternal smoking status was self-reported at recruitment. Mothers were considered smokers if they reported currently smoking one or more cigarettes per day. Numbers of previous children were also self-reported at recruitment and mothers were considered nulliparous if they reported having no previous children.

Offspring were measured at birth and at the 11-year follow-up by trained personnel. At the 11-year follow-up, height (± 0.1 cm), with shoes removed, was measured on a wall-mounted stadiometer (Harpenden) and weight (± 0.1 kg) was measured in minimal clothing on

electronic scales. Offspring self-reported their pubertal stage (Tanner stage 1-5). Pubertal status was collapsed into a binary variable because of lower numbers in the higher stages, therefore stages 1 and 2 were considered earlier development and stages 3 and 4 were considered later.

All participants provided informed written consent, or optional assent. The study was approved by the Barwon Health Human Research Ethics Committee (Project 01/43).

Statistical analyses

Characteristics are presented as mean ($\pm$ standard deviation, SD) or median (interquartile range, IQR) depending on the distributions; both the primary outcomes and exposure had a non-parametric distribution. T-tests, Mann-Whitney U tests or Chi-square tests were used to compare characteristics between groups. The association between maternal 25(OH)D and offspring body composition outcomes was explored using linear regression modelling. The best models were achieved using higher order polynomial terms for vitamin D, thereby optimising high R^2 and low Mallows' Cp values. The higher order polynomial terms were centred around the mean to reduce collinearity. Potential confounders and effect modifiers in the models that were tested but not included in the final model included maternal education, maternal and child age and maternal height. The multivariable model included the higher order polynomial vitamin D terms, child height, sex, maternal parity and smoking status at recruitment. All models were tested with and without season of serum sample to determine whether this altered associations. Season was entered into the model as a sinusoidal function

of the day of sample collection. All analyses were performed using Minitab version 17 (Minitab, State College, PA).

Results

Of the original mother-child sample, 209 (51.9%) participated in the most recent follow-up. Mothers who returned at the 11 year follow-up and had complete measures were older (30.1 vs 29.2 years, $p=0.02$), but no other differences were detected. Of the 209 (87.6%) mother-child pairs who returned for the 11-year follow-up, 183 provided both a maternal measure of 25(OH)D at recruitment and 28-32 weeks gestation and had a whole-body DXA scan of the offspring at follow-up. Median maternal vitamin D levels were 55.9 (42.2-73.3) and 56.1 (43.6-73.9) at recruitment and 28-32 weeks gestation; respectively. There were 67 (36.6%) mothers who were nulliparous at recruitment and 35 (19.3%; two missing information) who reported currently smoking at recruitment.

There was a significant interaction between maternal smoking and maternal vitamin D at recruitment and offspring body composition; hence, data for this time-point were stratified by maternal smoking status. Maternal and offspring characteristics are presented in Table 1 by offspring sex and maternal smoking status. There were 93 (50.8%) boys and 90 (49.2%) girls. Significant sex differences were observed in measures of body composition in the whole group. Although there was no sex difference detected for mean weight, boys had greater median percentage lean mass, whereas girls had greater median percentage body fat. However, in offspring whose mothers smoked ($n=13$ girls, 22 boys), differences in body composition were no longer significant (fat %: 27.3 (girls) vs 28.8 (boys), $p=0.75$; lean %:

68.6 (girls) vs 67.8 (boys), $p=0.90$). There were no differences in maternal or offspring characteristics between mothers who smoked in pregnancy and those who did not, with the exception of a trend for a lower 25(OH)D level at the later time point and higher offspring fat mass percentage in smokers.

Maternal 25(OH)D at recruitment

Results of models, stratified by maternal smoking status, are presented in Table 2. In smokers, higher maternal 25(OH)D level at recruitment was associated with higher offspring lean mass percentage and lower fat percentage. Mean lean and fat mass estimated from regression models for a range of 25OHD values (28, 50, 75nM) are presented in Table 3. For offspring whose mothers smoked, the most marked body composition differences were observed between 28 and 50nmol/L, with approximately a 10% increase in both lean mass percentage and fat mass percentage for both sexes; smaller differences were observed at higher 25OHD. Though the pattern of association was similar for non-smokers the differences were not significant.

Maternal 25(OH)D at 28-32 weeks

There were no smoking*vitamin D interactions observed in models for 25(OH)D at 28-32 weeks, thus data were not stratified by maternal smoking status for analyses. No associations were detected between maternal 25(OH)D and offspring body composition (Table 2).

Discussion

In this study, we report an association between maternal 25(OH)D and measures of offspring body composition. To our knowledge, these are the first findings to report a differential effect of maternal 25(OH)D status on offspring body composition according to maternal smoking status during pregnancy. Furthermore, these data are the first to demonstrate that the association only appears to be with maternal 25(OH)D in early pregnancy and not at a later stage of gestation.

Previous studies of maternal 25(OH)D and offspring adiposity have shown inconsistent results. Our results concur with the largest two studies that report negative associations with measures of fat mass^{10,13} in primarily Caucasian populations, and a further study in an Indian population¹⁴. However, another study reported that at age 9 years there were no associations seen¹¹. The magnitude of the association reported by our study appears to be greater than those who had previously reported negative associations with fat mass. Though our findings are not directly comparable to those of Crozier et al. as they reported on absolute measures of fat mass as opposed to percentages, they found that there was a 0.16 standard deviation decrease in fat mass per 1 standard deviation increase in maternal 25(OH)D. However, the time-point at which 25(OH)D was assessed was 34 weeks gestation, whereas at a comparable time-point of 28-32 weeks gestation, we detected no association. Hrudey et al. demonstrated an approximate 0.13% decrease in fat mass per 10nmol/L increase of 25(OH)D in early pregnancy. A notable difference in the two aforementioned studies, is that the children were aged approximately 6 years. Therefore, it is plausible that the magnitude of the association may increase as children age. Certainly, Crozier et al. demonstrated a positive association

between offspring fat mass and maternal 25(OH)D at birth, a null association at 4 years of age, and a negative association in children aged 6 years. We cannot exclude the possibility that differences comparable with our study might be observed if the children are assessed at a similar age, 11 years.

In accordance with our findings for fat mass, Gale et al.¹¹ detected no association between lean mass and maternal 25(OH)D in late pregnancy. However, it was noted that lean mass tended to be lower in those in the lowest quarter of the 25(OH)D distribution ($p=0.09$). A larger cohort from the same study demonstrated associations between percentage lean mass in the offspring and maternal 25(OH)D during late pregnancy in unadjusted models¹²; however, the associations were explained after accounting for confounders. The only study to report a positive association with lean mass was by Krishnaveni et al. in their study of Indian children¹⁴. However, lean mass was measured as arm muscle area, taking into account arm circumference and skinfold measurement. Thus, robust findings have not been previously reported with objective measures of lean mass, such as by DXA.

An important difference in previous studies that have examined the associations between maternal 25(OH)D in pregnancy and offspring body composition is the timing of the 25(OH)D measurement. It is plausible that 25(OH)D may have differential effects depending on the stage of development in utero. In animal models, maternal nutritional deficiency during early-mid gestation reduces the number of muscle fibres and muscle mass in the offspring; however, restriction in later gestation has been shown to reduce muscle fibre size¹⁶. Moreover, offspring adiposity has been associated more strongly with maternal nutritional restriction in early-mid gestation, rather than late¹⁷. A clear epidemiological example of this

is the Dutch famine cohort. Maternal dietary restriction during early pregnancy of women aged 50 years was shown to have a more marked association with offspring obesity, than that of restriction in late pregnancy¹⁸. In line with this, our data suggest that early gestation is a critical time point for the programming of offspring lean and fat mass.

Furthermore, maternal smoking has been shown to be independently associated with maternal smoking¹⁹, with the exception of the study in Indian children¹³, the studies reporting a negative association with fat mass had adjusted for maternal smoking during pregnancy^{10,13}, yet it is unclear whether they had identified smoking as an effect modifier in their models. In adult populations, there is evidence to suggest that smoking influences vitamin D status²⁰; however, one small study in Iran reported no significant effect of smoking on vitamin D status in pregnant women²¹. In our study, we detected no difference in 25(OH)D levels between smokers and non-smokers. However, similar interactions have been described between maternal 25(OH)D status and gestational diabetes^{22,223}. The authors of these studies postulated a role for the anti-inflammatory²⁴ and antioxidant effects of vitamin D²⁵ that might mediate the association between 25(OH)D and gestational diabetes. Certainly, markers of inflammation have been shown to be associated with offspring adiposity independently²⁶. Given that smokers have a higher level of systemic inflammation and oxidative stress²⁷, perhaps this is why a differential effect is seen between smokers and non-smokers. This same conceptual framework may also apply to measures of offspring body composition. In the case of adiposity, maternal low-grade systemic inflammation during pregnancy has been associated with childhood measures of obesity at age 8 years²⁸. Given the relatively low

numbers of smokers in our cohort, however, these findings need to be replicated in larger cohorts.

There are important implications to these findings, as body composition is an intrinsic risk factor for a wealth of other health conditions and accidents. Decreased muscle mass increases the risk of childhood falls, which can result in bruising, sprains, fractures and contusions²⁹. Injuries, arising from accidental childhood falls are costly³⁰ and present significant burden to the healthcare system. Childhood adiposity is associated with a number of physical and psychosocial health outcomes³¹. Furthermore, obesity-induced comorbidities that arise in childhood, such as hypertension and type 2 diabetes, frequently persist into adulthood and are associated with increased mortality^{32,33}.

There are several strengths and limitations to our study. A major strength is the prospective cohort study design, using objective measures of 25(OH)D and offspring body composition. However, this study design also is limited by loss to follow-up which may introduced bias in the retained sample, although we did not detect any differences in the smoking and vitamin D status of mothers who returned versus those lost to follow-up. We also did not collect pre-pregnancy weight and thus were unable to account for pre-pregnancy maternal adiposity. Low 25(OH)D status has been described in both underweight and obese pregnant women. It has therefore been hypothesised that there may be an interaction between pre-pregnancy BMI and 25(OH)D in cardio-metabolic outcomes in the offspring¹⁴. However, while interactions with measures of insulin resistance have been shown in associations with 25(OH)D and measures of insulin, the same is not true in models predicting offspring adiposity. However, in our analyses, we found that the association with 25(OH)D in early pregnancy was not

explained by maternal BMI as measured at recruitment (supplementary table), suggesting that the observed associations are independent of maternal adiposity. We also did not collect maternal smoking status information at the 28-32 week visit. Thus, it is plausible that some women who were smokers during early pregnancy discontinued during late pregnancy and thus the interaction with smoking may have been obscured at 28-32 weeks gestation. Moreover, the smoking data were collected by self-report, thus some women may have reported smoking status inaccurately. Detailed data on passive smoking exposure was not collected either and so the influence of cigarette smoke may have been under-estimated. Though we cannot draw causal conclusions due to the observational nature of this study, these findings suggest that there is an association between maternal 25(OH)D in early pregnancy and body composition in offspring of mothers who smoke during pregnancy. These findings warrant confirmation in larger cohorts. Mothers who smoke during pregnancy, should be encouraged to quit smoking, and optimise their vitamin D levels from early pregnancy.

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NKH, SMH, KLH and JAP all declare no conflict of interest. SLB-O has received non-related speaker fees from Amgen Australia and JDW received in-kind support from Swisse Wellness for an unrelated clinical trial.

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Table 1: Maternal and offspring characteristics by maternal smoking status.

Characteristic	Smokers n=35	Non-smokers n=146	p for difference
<i>Maternal</i>			
Age ^a (yr)	41.7 (4.7)	41.4 (5.3)	0.75
Height ^a (cm)	164.2 (6.5)	165.3 (5.8)	0.37
Weight ^{a,b} (kg)	71.0 (63.2-87.0)	75.6 (64.3-90.6)	0.41
25(OH)D recruitment	55.9 (40.2-83.6)	55.8 (42.2-72.5)	0.76
25(OH)D 28-32 wk	51.8 (35.2-68.7)	57.3 (45.3-72.6)	0.08
<i>Offspring</i>			
Age (ys)	10.9 (10.7-11.5)	10.9 (10.9-11.3)	0.96
Height (cm)	146.9 (143.2-154.8)	147.7 (144.3-153.4)	0.83
Weight (kg)	43.0 (39.6-73.5)	39.6 (40.4-83.0)	0.24
Pubertal status n (% low)	28 (80.0)	125 (85.6)	0.38
%lean mass	68.6 (58.7-75.4)	71.1 (64.2-76.5)	0.15
%fat mass	27.3 (21.2-38.3)	24.2 (19.2-32.4)	0.08

^a measured at 11-year follow-up ^b 3 missing information

25(OH)D= serum 25-hydroxyvitamin D (measured in nmol/L)

NB: Maternal age and height were compared using t-test, pubertal status was compared using a Chi-squared test. All other characteristics were compared using a Mann-Whitney U test. All data is presented as mean (standard deviation) or median (interquartile range)

Table 2: Regression modelling of offspring fat and lean mass percentage

25(OH)D Recruitment				
Predictor	Smokers n=35			
	Fat % r ² =56.3		Lean % r ² =54.0	
	β (95% CI)	p	β (95% CI)	p
(25(OH)D-mean ^a)	-0.21 (-0.32,-0.07)	<0.05*	0.20 (0.08,0.31)	<0.05*
(25(OH)D-mean ^a) ²	0.01 (0.002,0.009)		-0.01 (-0.01,-0.002)	
Child height	0.36 (0.02,0.70)	0.04	-0.36 (-0.69,-0.02)	0.04
Child sex	2.40 (-3.02,7.82)	0.37	-1.87 (-7.4,3.50)	0.48
Parity	7.29 (0.68,13.89)	0.03	-6.62 (-13.17,-0.08)	0.047
Predictor	Non-smokers n=146			
	Fat % r ² =19.6		Lean % r ² =18.5	
	β (±SE)	p	β (±SE)	p
(25(OH)D-mean ^a)	-0.06 (-0.12,0.01)	>0.05	0.05 (-0.01,0.12)	>0.05
(25(OH)D-mean ^a) ²	0.0002 (-0.001,0.001)		-0.0001 (-0.001,0.001)	
Child height	0.34 (0.16,0.51)	<0.001	-0.29 (-0.46,-0.12)	0.001
Child sex	-5.03 (-7.65,-2.42)	<0.001	5.03 (2.48,7.59)	<0.001
Parity	2.00 (-0.72,4.71)	0.15	-2.02 (-4.67,0.63)	0.15
25(OH)D 28-32 weeks				
Predictor	Smokers and non-smokers pooled n=181			
	Fat % r ² = 20.1		Lean % r ² =19.0	
	β (95% CI)	p	β (95% CI)	p
(25(OH)D-mean ^b)	-0.12 (-0.32,0.06)	>0.05	-0.12 (-0.06,0.31)	>0.05
(25(OH)D-mean ^b) ²	0.001 (-0.001,0.002)		0.001 (-0.002,0.001)	
Child height	0.37 (0.21,0.53)	<0.001	-0.33 (-0.48,-0.17)	<0.001
Maternal smoking	3.11 (-0.06,6.28)	0.06	-2.71 (-5.80,0.38)	0.06
Child sex	-4.05 (-6.53,-1.58)	0.001	4.14 (1.73,6.55)	0.001
Parity	2.89 (0.30,5.48)	0.03	-2.71 (-5.33,-0.28)	0.03

^aMean serum 25-hydroxyvitamin D 25(OHD)=60.15 nmol/L^bMean serum 25-hydroxyvitamin D 25(OHD)=60.84 nmol/L*p considered less than 0.05 when F>F_c at α 0.05

Table 3: Lean and fat mass of boys and girls predicted from regression equations for maternal 25(OH)D levels at recruitment of 28, 50 and 75nmol/L

Smokers				
25(OH)D nmol/L	% Fat mass		% Lean mass	
	Boys	Girls	Boys	Girls
28	36.5 (3.2)	34.1 (3.0)	60.3 (3.3)	62.2 (3.0)
50	26.3 (2.0)	23.9 (2.4)	70.0 (2.0)	71.9 (2.4)
75	21.8 (2.1)	19.4 (2.7)	74.2 (2.1)	76.1 (2.7)
Non-smokers				
25(OH)D nmol/L	% Fat		% Lean	
	Boys	Girls	Boys	Girls
28	24.5 (1.6)	29.6 (1.6)	71.5 (1.6)	66.4 (1.5)
50	23.1 (1.0)	28.2 (1.0)	72.8 (1.0)	67.8 (0.9)
75	21.7 (1.2)	26.8 (1.2)	74.2 (1.2)	69.1 (1.1)

Data presented as mean (standard error)

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Author/s:

Hyde, NK;Brennan-Olsen, SL;Wark, JD;Hosking, SM;Holloway-Kew, KL;Pasco, JA

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