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Maternal birthweight is associated with subsequent risk of vitamin D deficiency in early pregnancy

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Abstract

Background—Maternal low birthweight and vitamin D deficiency in pregnancy are associated with a similar spectrum of adverse pregnancy outcomes including preeclampsia and gestational diabetes. However, the relationship between maternal birthweight and subsequent vitamin D concentrations in early pregnancy is largely unknown.

Methods—We assessed whether self-reported maternal birthweight was associated with risk of early pregnancy vitamin D deficiency (≥20 ng/mL) among a pregnancy cohort (n=658). Vitamin D (25[OH]D) was measured using liquid chromatography-tandem mass spectroscopy.

Results—Adjusting for maternal characteristics and month of blood draw, a 100-gram higher maternal birthweight was associated with a 5.7% decreased risk of early pregnancy 25[OH]D deficiency (OR = 0.94, [95% CI: 0.90, 0.99]). Low birthweight (<2,500 g) women were 3.7 times as likely to have early pregnancy 25[OH]D deficiency compared to normal birthweight women (OR = 3.69, [95% CI: 1.63, 8.34]). These relationships were not modified by either pre-pregnancy overweight status (BMI ≥25 kg/m^2) or adulthood weight trajectory (BMI change ≥2 kg/m^2 from age 18 to pre-pregnancy).

Conclusions—Further research on shared developmental mechanisms that determine birthweight and vitamin D homeostasis may help identify targets and related preventative measures for adverse pregnancy and birth outcomes.

Keywords

birthweight; vitamin d; pregnancy

Maternal low birthweight (<2500 g) has been associated with a wide range of adverse maternal pregnancy outcomes including gestational diabetes,[1,2] preeclampsia,[3,4] and preterm delivery,[5] as well as infant birth outcomes such as low birthweight,[6] small for gestational age,[7] and infant mortality[8]. However, neither the importance of intermediary risk factors nor the mechanisms by which poor maternal *in utero* growth affects risk factors and pregnancy outcomes have been fully described.

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Early pregnancy vitamin D deficiency (≥20 ng/mL) has also been associated with a spectrum of adverse pregnancy and birth outcomes similar to that of low birthweight mothers, including gestational diabetes,[9] preeclampsia,[10] low birthweight,[11] and small for gestational age.[12] Vitamin D and its associated cell-surface receptors have been increasingly implicated as important moderators of gene regulation in pregnancy,[13] fetal growth,[14] as well as cardio-metabolic risk development.[15]

Vitamin D deficiency may be a critical risk factor mechanistically linking maternal *in utero* growth and subsequent pregnancy outcomes. Suggestive evidence links *in utero* growth with future vitamin D homeostasis. Possible mechanisms for associations between poor *in utero* growth and adulthood vitamin D deficiency involve reduced vitamin D binding protein (DBP),[16] reduced renal function,[17] and genetic variations that influence both fetal growth and vitamin D homeostasis.[18–21] Evaluating maternal low birthweight (an indicator of suboptimal *in utero* growth) as a potential determinant of vitamin D concentration in pregnancy, particularly during early pregnancy, may enhance understanding of early life mechanisms of adverse pregnancy outcomes.

To our knowledge, no previous study has assessed the relationship between maternal birthweight and early pregnancy vitamin D concentrations. Two previous studies on maternal birthweight and post-menopausal bone health found inverse associations between birthweight and late-life vitamin D.[22, 23] One small case-control study of very low birthweight (VLBW) individuals found no association of birthweight with vitamin D status (at 22–25 years of age).[24] However, pregnant women were excluded in that study.[24]

Based on the hypothesis that maternal *in utero* growth may influence adult vitamin D homeostasis, we investigated whether birthweight was associated with risk of early pregnancy vitamin D (25[OH] D) deficiency. We additionally explored whether any such association was modified by pre-pregnancy overweight/obesity status or weight change in adulthood.

METHODS

Study setting

This study was conducted among participants of the Omega study, a prospective cohort study designed to examine maternal dietary risk factors of preeclampsia and other adverse pregnancy outcomes. Pregnant women were eligible for participation if they were 18 years or older, spoke and read English, initiated prenatal care at or prior to 20 weeks of gestation, and planned to deliver at either the Swedish Medical Center (Seattle, WA) or Tacoma General Hospital (Tacoma, WA). Between 1996 and 2008, 4000 participants were enrolled in the Omega study. The institutional review boards of Swedish Medical Center and Tacoma General Hospital approved the study protocols.

Study population

Study participants for the current analyses were drawn from a previous Omega case-cohort sub-study designed to investigate associations of 25[OH]D with pregnancy complications. The randomly selected sub-cohort of 750 women enrolled in the Omega study and delivered at the Swedish Medical Center constituted the study population for the current analyses. Of 676 mothers with singleton pregnancies, 13 (2%) were missing birthweight information and 5 others were missing serum 25[OH]D measurements (<1%), leaving 658 (97%) with complete data on maternal birthweight (exposure) and early pregnancy 25[OH]D concentrations (outcome).

Data collection

Study participants were asked to complete a questionnaire at or near the time of enrollment (median gestational age = 16 weeks; interquartile range: 13 to 17 weeks) regarding socio-demographics, anthropometric characteristics, and reproductive and medical history, as well as data on maternal birthweight, weight at 18 years, pre-pregnancy weight, and current height. Body mass index (BMI) at age 18 years and pre-pregnancy BMI were calculated as self-reported weights in kilograms divided by height in meters squared. BMI change was calculated by subtracting BMI at 18 years from pre-pregnancy BMI.

Vitamin D measurements

Study participants provided a 20 mL non-fasting sample of peripheral blood at or near the time of enrollment (16 weeks on average). The samples were immediately fractionated and stored at −80°C until analysis. Serum 25[OH]D concentrations were measured using liquid chromatography-tandem mass spectroscopy (LC-MS/MS) by ZRT Laboratory (ZRT Laboratory, Portland, OR). Both 25[OH]D2 and 25[OH]D3 concentrations were measured, with the sum giving total serum 25[OH] D concentration. Our analyses strictly refer to total serum 25[OH]D concentrations. The assay reportable range is 2–800 ng/ml with a coefficient of variation ranging between 6% and 11%. Measurements were conducted blinded to history of maternal birthweight.

Vitamin D deficiency

Vitamin D deficiency was defined as an early pregnancy 25[OH]D serum measurement < 20 ng/mL (50 nmol/L), in accordance with the 2011 Institute of Medicine report on vitamin D supplementation[25] and American College of Obstetricians and Gynecologists 2011 Committee Opinion.[40] This value is thought to be a conservative threshold in assessing adequacy of vitamin D for both skeletal and non-skeletal health.[26] With respect to dissenting opinion, we also categorized participants separately as severely deficient if total early pregnancy 25[OH]D was <12 ng/mL (30 nmol/L). This is a recognized threshold for risk of poor bone health[25] with some evidence of adverse non-skeletal outcomes including infant low birthweight.[27]

Statistical analyses

We fit three multiple logistic regression models with robust standard errors to estimate associations between maternal birthweight (grouped in 100 g increments) and vitamin D deficiency risk. The first model provided unadjusted estimates of associations. The second model was adjusted for self-reported race, age at assessment, parity, and month of blood draw. These are biological factors consistently found to be associated with vitamin D status.[28, 29] The final regression model was adjusted for these factors as well as other *a priori* covariates: infant sex, height, pre-pregnancy BMI, smoking status, marital status, and family income. These three models were repeated comparing vitamin D deficiency risk in normal birthweight mothers (2500 – 3999 g) to those who were low birthweight (<2500 g) or high birthweight (≥4000 g).

We also evaluated whether pre-pregnancy BMI or BMI trajectory modified this relationship using stratified analyses. Pre-pregnancy BMI ≥25 kg/m^2 and an increase in BMI of over 2 kg/m^2 between age 18 and pre-pregnancy were used as the respective cutoffs. All analyses were conducted using STATA 12 (StataCorp 2011).

RESULTS

The 658 women in our cohort tended to be white, primiparous, and around 33 years of age (Table 1). 25[OH] D concentrations were generally adequate and few had deficiency or

severe deficiency. Of the 658 mothers, 85 (12.9%) had early pregnancy vitamin D deficiency (25[OH]D serum concentration ≤20 ng/mL). With respect to birthweight, those that had normal or high birthweight (macrosomia) were more likely to be white, primiparous, married, non-smokers, and have sufficient early pregnancy 25[OH]D when compared to those born small. Mean early pregnancy serum 25[OH]D was 29.1 ng/mL (SD = 8.4) overall and was higher in normal birthweight women than those with low birthweight and macrosomia (29.2 versus 28.6 and 28.9 ng/mL, respectively). A greater proportion of low birthweight women had vitamin D deficiency and severe deficiency (serum 25[OH] D ≤12 ng/mL) than normal birthweight mothers (26.5% and 4.1% versus 11.7% and 2.0%, respectively).

Adjusting for maternal characteristics and month of draw, a 100-gram higher maternal birthweight was associated with a 5.7% lower odds of vitamin D deficiency during pregnancy (odds ratio = 0.94, [95% confidence interval: 0.89, 0.99]; Table 2). Similarly, a 100-gram higher maternal birthweight was associated with a 24.1% lower odds of severe vitamin D deficiency during pregnancy (OR = 0.76, [95% CI: 0.65, 0.88]). Low birthweight women were 3.7 times as likely to have early pregnancy vitamin D deficiency compared to normal birthweight women (OR = 3.69, [95% CI: 1.63, 8.34]; Table 3). Women who were macrosomic at birth did not have higher risk of vitamin D deficiency. The relationship between birthweight and risk of deficiency was not modified by pre-pregnancy BMI or weight gain since age 18 (P-interaction for fully adjusted models were 0.964 and 0.879, respectively; Table 4). However, among women who were not overweight before pregnancy (BMI <25 kg/m^2) or who maintained weight between age 18 and pregnancy (BMI change <2 kg/m^2), low birthweight was associated with higher odds of vitamin D deficiency relative to normal birthweight (Table 5). These odds ratios were not statistically different from one among women who were overweight or obese before pregnancy (BMI ≥ 25 kg/m^2) or who gained weight between age 18 and pregnancy (BMI gain ≥2 kg/m^2). However, the differences in odds ratios were not statistically significant (both interaction P-values > 0.05; Table 5).

COMMENT

Our study suggests that higher birthweight is related to a reduced risk of vitamin D deficiency in early pregnancy, a period in pregnancy that is critical for placental and fetal development. More specifically, a 5–6% lower risk of vitamin D deficiency was observed for each 100 g greater birthweight. In addition, a 3-fold higher risk of vitamin D deficiency was observed among low birthweight women relative to normal birthweight women. Our findings also suggest that this relationship exists independent of attained BMI and other determinants of adult vitamin D status.

While there are no previous studies specifically relating maternal birthweight to early pregnancy vitamin D status, three previous studies have assessed the relationship between birthweight and adult or post-menopausal vitamin D. Two studies on bone health in post-menopausal women[22, 23] suggested an inverse relationship between birthweight and late-life serum 25[OH]D concentrations. Recently, a case-control study of skeletal health in very low birthweight (VLBW) individuals found no difference in mean 25[OH]D between VLBW (< 1500 g) cases and normal controls at 22–25 years of age.[24] However, 25[OH]D was not their primary outcome of interest and, due to their sample size (n = 64), their study may not have been powered to find a difference. Furthermore, it is possible that VLBW survivors may different both biologically and behaviorally[24] from our low-risk cohort. Finally, pregnant women were excluded from their analysis, further limiting comparability.

Despite the lack of comparable previous studies, there are several compelling pathways that may explain the association observed between maternal birthweight and adult, early pregnancy vitamin D deficiency. Suboptimal fetal growth, manifested by low birthweight is associated with *in utero* protein restriction and reduced expression of vitamin D binding protein (DBP) in the offspring.[30] Since circulating vitamin D is almost entirely bound to DBP,[16] fetal programming that produces reduced DBP may be a reason for lower future serum 25[OH]D reserves. DBP may also have as yet uncharacterized role(s) in fetal programming.[31, 32] Suboptimal fetal growth may also act to limit adult 25[OH]D reserves through its impact on metabolic processes such as renal dysfunction,[33] obesity,[34] and insulin resistance.[35] Additionally, experimental models suggest metabolic dysfunction causes vitamin D deficiency through reduced renal reabsorption and increased urinary excretion of vitamin D due to inhibited expression of accessory transport proteins.[17] Finally, polymorphisms in vitamin D metabolism-related genes, including *CYP2R1*, *DHCR7*, and *VDBP*, may also be related to both suboptimal growth and low birthweight[18, 19] and abnormal lifetime vitamin D homeostasis.[20,21]

We explored potential modification of associations of birthweight with vitamin D deficiency by overweight/obesity status or adult weight trajectory. Low birthweight is associated with postnatal catch-up growth and later adiposity.[34] In addition, high birthweight (≥4000 g) has also been associated with adult obesity.[36] Due to lipid-solubility of vitamin D and sequestration in fat deposits or other mechanisms,[25] mothers with higher adiposity during pregnancy may have lower serum concentrations.[37] Mothers of high or low birthweight and subsequently greater adiposity may have correspondingly lower serum 25[OH]D. In their review of vitamin D supplementation, the IOM suggests that observational studies investigating associations between serum 25[OH]D concentrations and increased risk of type II diabetes or metabolic syndrome may be confounded by overweight and obesity.[25] Similarly, smaller maternal birthweight may be related to vitamin D deficiency solely through its relation to obesity. Since adjusting for pre-pregnancy BMI did not greatly reduce our risk estimates, our findings suggest that attained weight can not fully explain the observed relationship between birthweight and early pregnancy 25[OH]D. However, it is important to note here that recent methodological work suggests that adjusting for intermediates in analyses (*e.g.*, attained BMI) may not be appropriate to assess for an independent effect, due to the introduction of bias resulting from unmeasured intermediate-outcome confounding.[38] However, we do not anticipate any strong unadjusted confounders between the obesity-serum 25[OH]D relationships in our case. Nevertheless, we evaluated our assumption through a basic sensitivity analysis by re-fitting our models among strata of propensity scores defined by overweight/obesity (≥25 kg/m^2) status. By dichotomizing at the 80th percentile for propensity of overweight/obesity status, we can estimate odds ratios for those who would likely become overweight regardless of the influences of birthweight. Among those with a “high” propensity for overweight/obesity (n = 144) using our maximum model, we found a 15% reduced risk of vitamin D deficiency for each 100 g higher maternal birthweight (OR = 0.85, [95% CI 0.74, 0.98]). Had the relationship been due solely to the likelihood of low birthweight women to become overweight or obese, this relationship would not be so consistently observed. This conclusion was not surprising as our cohort consisted of few overweight and obese women.

Similarly, our secondary findings suggest that attained adult BMI does not modify the relationship between low birthweight and early pregnancy serum 25[OH] D concentrations. In fact, our results suggest that those who gained weight from early adulthood until pregnancy may have lower risk associated with low birthweight than those who maintained weight. However, these differences were not statistically significant and likely due to differences in underlying risks of deficiency and propensity for weight gain. Nonetheless,

due to the small sizes of our sub-strata, we can not rule out a lack of power to detect true interaction.

Our study has several important strengths. A major strength is the prospective cohort design and absence of differential recall based on outcome status. Additionally, our patient population was well characterized with little missing data. Another notable strength is the use of liquid chromatography-tandem mass spectrometry (LC-MS/MS) to measure serum 25[OH]D, as it is considered the gold standard. An assessment of laboratory methods found other methods of measuring 25[OH]D (e.g. automated assays and radioimmunoassays) to be biased and sensitive to concentrations of vitamin D binding protein when compared to LC-MS/MS.[39]

Several limitations of our study deserve mention. First, there is a possibility that participants missing birthweight and 25[OH]D measurements may have differed (non-white, primiparous, non-smoking, unmarried, and poor) from the individuals included in our analysis leading to biased estimates. However, the number of individuals missing exposure and outcome measures was likely too few (2% and less than 1%, respectively) to significantly influence our estimates. As a sensitivity analysis, we used the *mi impute* function in Stata to perform multiple imputations by chained equations (ICE) to generate 100 simulated complete data sets (*i.e.* complete information for all 676 participants) under the assumption of multivariate normality.

We then estimated odds ratios for risk of vitamin D deficiency using *mi estimate*, which generates point estimates and standard errors using the weighted sum of within- and between-simulation variances described by Rubin.[41] Findings were similar to our main results (Maximum Model OR of vitamin D deficiency per 100 g higher birthweight = 0.94, [95% CI: 0.90, 0.99]).

Our study relied on self-report for birthweight and historical BMI, thus misclassification may bias these results. While these measures are imprecise, past studies comparing self-reported birthweight and birth certificates of US women of childbearing age show moderate to good reliability[42,43] with the best recall amongst white women of higher educational attainment and income.[44] Our participants were mostly non-Hispanic white, well educated, and with high income. Therefore, we believe these women to be relatively good historians. In addition, this misclassification is more likely to be non-differential as women do not know their own vitamin D status, and assays of vitamin D ere conducted independently of mothers' interviews. Moreover, the relationship between birthweight and subsequent vitamin D is not well known. Finally, past studies have been successful in identifying associations between maternal birthweight and pregnancy outcomes using either self-report[1,2,4,5] or birth records[6,7,8] increasing our confidence in the measure.

A recent review of vitamin D in pregnancy suggested at least 26% of pregnant women worldwide were vitamin D deficient.[12] In our study, it was less than 13%. This may have resulted due to difference in racial/ethnic composition and socio-economic status. Therefore, generalizability of our findings may be limited. However, it is unlikely the relationship, if it truly exists, would differ strictly on the basis of socioeconomic status or other medical comorbidities. Similarly, the rarity of low birthweight in our cohort (7.4% of births) makes disentangling the role of preterm delivery versus intrauterine growth retardation difficult. Additionally, self-report of gestational age, in contrast to birth weight, has been shown to be unreliable[45]. We did not collect information on gestational age at birth. An analysis excluding low birthweight women found a similar reduction in risk of vitamin D deficiency per 100 gram increase in birthweight, albeit of borderline statistically significance (OR = 0.95, 95% CI 0.87, 1.04). Given the potential importance of in-utero developmental

signaling, future studies that pay particular attention to the experience of low weight, term birth, are warranted. Finally, the literature on the adequate level of 25[OH]D remains nascent. We chose 20 ng/mL as our cutoff for vitamin D deficiency in line with much of the literature[12] including American College of Obstetrics and Gynecology committee opinion (ACOG). However, the definition of adequate 25[OH]D concentrations, particularly during pregnancy remains contested, with recommendation as high as 32 ng/mL or as low as 12 ng/mL.[12] Therefore, we reported our results using the lowest threshold reported (12 ng/mL), and still observed a similar inverse relationship between maternal birthweight and risk of vitamin D deficiency (Tables 2 and 3). However, it should be noted that there were only 13 participants with early pregnancy serum 25[OH] D ≤12 ng/mL and estimates may not be stable. However, similarities of findings from these analyses using different cutoffs minimize our concern.

In this study, we demonstrate a relationship between maternal birthweight and risk of vitamin D deficiency during early pregnancy. Given previous studies that have implicated vitamin D in gene regulation, growth, insulin resistance, and other related metabolic pathways, our findings suggest some effort should also be directed towards understanding mechanisms by which *in utero* growth and development may lead to changes in vitamin D homeostasis. This understanding may enhance targeted interventions for preventing both adverse pregnancy outcomes and future metabolic diseases. Studies targeting potential mechanisms by assessing the relationships in the context of genetic variations, vitamin D binding protein, and, pregnancy cardiometabolic comorbidities are also warranted.

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References

1. Dubé MC, Morisset AS, Tchernof A, Weisnagel SJ. Impact of a mother's weight history on her offspring. Journal of Obstetrics and Gynaecology Canada. 2012; 34(1):34–38. [PubMed: 22260761]
2. Seghieri G, Anichini R, De Bellis A, Alviggi L, Franconi F, Breschi MC. Relationship between gestational diabetes mellitus and low maternal birth weight. Diabetes Care. 2002; 25(10):1761–1765. [PubMed: 12351474]
3. North RA, McCowan LM, Dekker GA, Poston L, Chan EH, Stewart AW, et al. Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort. BMJ. 2011; 342:d1875. [PubMed: 21474517]
4. Dempsey JC, Williams MA, Luthy DA, Emanuel I, Shy K. Weight at birth and subsequent risk of preeclampsia as an adult. American Journal of Obstetrics and Gynecology. 2003; 189(2):494–500. [PubMed: 14520224]
5. De B, Lin S, Lohsoonthorn V, Williams MA. Risk of preterm delivery in relation to maternal low birth weight. Acta Obstetricia et Gynecologica Scandinavica. 2007; 86(5):565–571. [PubMed: 17464585]
6. Stein AD, Lumey LH. The relationship between maternal and offspring birth weights after maternal prenatal famine exposure: the Dutch Famine Birth Cohort Study. Human Biology. 2000; 72(4):641–654. [PubMed: 11048791]
7. Tocharoen A, Thompson S, Addy C, Sargent R, Best R, Shoob H. Intergenerational and environmental factors influencing pregnancy outcomes. Annals of Epidemiology. 2000; 10(7):475–476. [PubMed: 11018415]
8. Masho SW, Archer PW. Does maternal birth outcome differentially influence the occurrence of infant death among African Americans and European Americans? Maternal and Child Health Journal. 2011; 15(8):1249–1256. [PubMed: 21057863]

9. Zhang C, Qiu C, Hu FB, David RM, van Dam RM, Bralley A, et al. Maternal plasma 25-hydroxyvitamin D concentrations and the risk for gestational diabetes mellitus. PLoS One. 2008; 3(11):e3753. [PubMed: 19015731]
10. Wei SQ, Audibert F, Hidiroglou N, Sarafin K, Julien P, Wu Y, et al. Longitudinal vitamin D status in pregnancy and the risk of pre-eclampsia. BJOG. 2012; 119:832–839. [PubMed: 22462640]
11. Morley R, Carlin JB, Pasco JA, Wark JD, Ponsonby AL. Maternal 25-hydroxyvitamin D concentration and offspring birth size: effect modification by infant VDR genotype. European Journal of Clinical Nutrition. 2009; 63(6):802–804. [PubMed: 19018272]
12. Dror DK. Vitamin D status during pregnancy: maternal, fetal, and postnatal outcomes. Current Opinion in Obstetrics and Gynecology. 2011; 23(6):422–426. [PubMed: 21986726]
13. Enquobahrie DA, Williams MA, Qiu C, Siscovick DS, Sorensen TK. Global maternal early pregnancy peripheral blood mRNA and miRNA expression profiles according to plasma 25-hydroxyvitamin D concentrations. Journal of Maternal-Fetal and Neonatal Medicine. 2011; 24(8): 1002–1012. [PubMed: 21219104]
14. Novakovic B, Sibson M, Ng HK, Manuelpillai U, Pakyan V, Down T, et al. Placenta-specific methylation of the vitamin D 24-hydroxylase gene: implications for feedback autoregulation of active vitamin D levels at the fetomaternal interface. The Journal of Biological Chemistry. 2009; 284(22):14838–14848. [PubMed: 19237542]
15. Muldowney S, Kiely M. Vitamin D and cardiometabolic health: a review of the evidence. Nutrition Research Reviews. 2010 Dec 1.:1–20. [PubMed: 21118613]
16. Powe CE, Seely EW, Rana S, Bhan I, Ecker J, Karumanchi SA, et al. First trimester vitamin D, vitamin D binding protein, and subsequent preeclampsia. Hypertension. 2010; 56(4):758–763. [PubMed: 20733087]
17. Anderson RL, Ternes SB, Strand KA, Rowling MJ. Vitamin D homeostasis is compromised due to increased urinary excretion of the 25-hydroxycholecalciferol-vitamin D-binding protein complex in the Zucker diabetic fatty rat. American Journal of Physiology Endocrinology and Metabolism. 2010; 299(6):E959–967. [PubMed: 20876762]
18. Steffen KM, Cooper ME, Shi M, Caprau D, Simhan HN, Dagle JM, et al. Maternal and fetal variation in genes of cholesterol metabolism is associated with preterm delivery. Journal of Perinatology. 2007; 27(11):672–680. [PubMed: 17855807]
19. Swamy GK, Garrett ME, Miranda ML, Ashley-Koch AE. Maternal vitamin D receptor genetic variation contributes to infant birthweight among black mothers. American Journal of Medical Genetics (Part A). 2011; 155A(6):1264–1271. [PubMed: 21548019]
20. Wang TJ, Zhang F, Richards JB, Kestenbaum B, van Meurs JB, Berry D, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. Lancet. 2010; 376(9736):180–188. [PubMed: 20541252]
21. Gozdzik A, Zhu J, Wong BY, Fu L, Cole DE, Parra EJ. Association of vitamin D binding protein (VDBP) polymorphisms and serum 25(OH)D concentrations in a sample of young Canadian adults of different ancestry. The Journal of Steroid Biochemistry and Molecular Biology. 2011; 127(3–5):405–412. [PubMed: 21684333]
22. Arden NK, Major P, Poole JR, Keen RW, Vaja S, Swaminathan R, et al. Size at birth, adult intestinal calcium absorption and 1,25(OH)(2) vitamin D. QJM: An International Journal of Medicine. 2002 Jan; 95(1):15–21. [PubMed: 11834768]
23. Arden NK, Syddall HE, Javaid MK, Dennison EM, Swaminathan R, Fall C, et al. Early life influences on serum 1,25 (OH) vitamin D. Paediatric and Perinatal Epidemiology. 2005 Jan; 19(1): 36–42. [PubMed: 15670107]
24. Smith CM, Wright NP, Wales JK, Mackenzie C, Primhak RA, Eastell R, et al. Very low birth weight survivors have reduced peak bone mass and reduced insulin sensitivity. Clinical Endocrinology (Oxford). 2011; 75(4):443–449. [PubMed: 21635277]
25. Institute of Medicine (IOM). Dietary reference intakes for calcium and vitamin D. Washington, DC: National Academies Press; 2011. p. 13-14.
26. Heaney RP, Holick MF. Why the IOM recommendations for vitamin D are deficient. Journal of Bone and Mineral Research. 2011; 26(3):455–457. [PubMed: 21337617]

27. Leffelaar ER, Vrijkotte TG, van Eijsden M. Maternal early pregnancy vitamin D status in relation to fetal and neonatal growth: results of the multi-ethnic Amsterdam Born Children and their Development cohort. British Journal of Nutrition. 2010; 104(1):108–117. [PubMed: 20193097]
28. Carpenter TO, Herreros F, Zhang JH, Ellis BK, Simpson C, Torrealba-Fox E, et al. Demographic, dietary, and biochemical determinants of vitamin D status in inner-city children. American Journal of Clinical Nutrition. 2012; 95(1):137–146. [PubMed: 22170368]
29. Perampalam S, Ganda K, Chow KA, Opie N, Hickman PE, Shadbolt B, et al. Vitamin D status and its predictive factors in pregnancy in 2 Australian populations. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2011; 51(4):353–359. [PubMed: 21806574]
30. Polberger SK, Fex GA, Axelsson IE, Räihä NC. Eleven plasma proteins as indicators of protein nutritional status in very low birth weight infants. Pediatrics. 1990; 86(6):916–921. [PubMed: 2251030]
31. Bolland MJ, Grey AB, Ames RW, Horne AM, Mason BH, Wattie DJ, et al. Age-, gender-, and weight-related effects on levels of 25-hydroxyvitamin D are not mediated by vitamin D binding protein. Clinical Endocrinology (Oxford). 2007; 67(2):259–264. [PubMed: 17547688]
32. Chun RF. New perspectives on the vitamin D binding protein. Cell Biochemistry and Function. 2012; 30(6):445–456. [PubMed: 22528806]
33. Mu M, Wang SF, Sheng J, Zhao Y, Li HZ, Hu CL, et al. Birth weight and subsequent blood pressure: a meta-analysis. Archives of Cardiovascular Diseases. 2012; 105(2):99–113. [PubMed: 22424328]
34. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. BMJ. 2000; 320(7240):967–971. Erratum in: BMJ 2000, 320, 7244-1244. [PubMed: 10753147]
35. Tsubahara M, Shoji H, Mori M, Matsunaga N, Ikeno M, Hisata K, et al. Glucose metabolism soon after birth in very premature infants with small- and appropriate-for-gestational-age birth weights. Early Human Development. 2012; 88(9):735–738. [PubMed: 22503438]
36. Zhao Y, Wang SF, Mu M, Sheng J. Birth weight and overweight/obesity in adults: a meta-analysis. European Journal of Pediatrics. 2012; 171(12):1737–1746. [PubMed: 22383072]
37. Song Q, Sergeev IN. Calcium and vitamin D in obesity. Nutrition Research Reviews. 2012:1–12. [PubMed: 22309781]
38. VanderWeele TJ, Mumford SL, Schisterman EF. Conditioning on intermediates in perinatal epidemiology. Epidemiology. 2012; 23(1):1–9. Erratum in: *Epidemiology*.2012; 23(3): 507. [PubMed: 22157298]
39. Heijboer AC, Blankenstein MA, Kema IP, Buijs MM. Accuracy of 6 routine 25-hydroxyvitamin D assays: influence of vitamin D binding protein concentration. Clinical Chemistry. 2012; 58(3): 543–548. [PubMed: 22247500]
40. American College of Obstetricians and Gynecologists. Vitamin D: screening and supplementation during pregnancy. Committee Opinion No. 495. Obstetrics and Gynecology. 2011; 118:197–198. [PubMed: 21691184]
41. Rubin, DB. Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons, Inc; 2008.
42. Sanderson M, Williams MA, White E, Daling JR, Holt VL, Malone KE, et al. Validity and reliability of subject and mother reporting of perinatal factors. American Journal of Epidemiology. 1998; 147:136–140. [PubMed: 9457002]
43. Troy LM, Michels KB, Hunter DJ, Spiegelman D, Manson JE, Colditz GA, et al. Self-reported birthweight and history of having been breastfed among younger women: an assessment of validity. International Journal of Epidemiology. 1996; 25(1):122–127. [PubMed: 8666479]
44. Tehranifar P, Liao Y, Flom JD, Terry MB. Validity of self-reported birth weight by adult women: sociodemographic influences and implications for life-course studies. American Journal of Epidemiology. 2009; 170(7):910–917. [PubMed: 19748903]
45. Little RE. Birthweight and gestational age: mothers' estimates compared with state and hospital records. American Journal of Public Health. 1986; 76(11):1350–1351. [PubMed: 3766839]

Table 1

Study participant characteristics by maternal birthweight

	Overall	Low Birthweight (<2500 g)	Normal Birthweight (2500 to 3999 g)	Macrosomia (≥4000 g)
	Mean (SD) (*n* = 658)	**Mean (SD) (*n* = 49)**	**Mean (SD) (*n* = 556)**	**Mean (SD) (*n* = 53)**
Birthweight (kg)	3.31 (0.5)	--	--	--
Age (years)	32.9 (4.5)	33.0 (5.1)	32.8 (4.5)	33.5 (4.5)
Prepregnancy BMI (kg/m^2)	23.8 (5.4)	24.2 (4.5)	23.7 (5.4)	25.1 (5.8)
BMI at 18 years (kg/m^2)	20.8 (3.0)	20.3 (2.3)	20.8 (3.0)	21.5 (3.5)
BMI change (kg/m^2)	3.0 (4.1)	3.9 (3.8)	2.9 (4.2)	3.3 (3.8)
Serum vitamin D (ng/mL)	29.1 (8.4)	28.6 (11.1)	29.2 (8.2)	28.9 (8.0)
	% (n)	% (n)	% (n)	% (n)
% white	90.7 (567)	80.0 (36)	91.1 (481)	96.2 (50)
% previous pregnancies	37.7 (248)	28.6 (14)	38.3 (213)	39.6 (21)
% ever smoked	29.2 (192)	32.7 (16)	29.1 (162)	26.4 (14)
% unmarried	10.5 (69)	14.3 (7)	10.1 (56)	11.3 (6)
% family income <$30K	3.5 (23)	6.3 (3)	3.7 (20)	0.0 (0)
% vitamin D ≤20 ng/mL	12.9 (85)	26.5 (13)	11.7 (65)	13.2 (7)
% vitamin D ≤ 2 ng/mL	2.0 (13)	4.1 (2)	2.0 (11)	0.0 (0)

Table 2

Association between maternal birthweight and early pregnancy vitamin D

	Odds Ratio [95% CI]	P-value
2a. Risk of vitamin D deficiency (≤20 ng/mL), per 100 g higher maternal birthweight		
Unadjusted	0.96 [0.91, 1.00]	0.067
Minimum Model *	0.96 [0.92, 1.01]	0.147
Maximum Model *	0.94 [0.90, 0.99]	0.026
2b. Risk of severe vitamin D deficiency (≤12 ng/mL), per 100 g higher maternal birthweight		
Unadjusted	0.89 [0.82, 0.96]	0.004
Minimum Model *	0.82 [0.74, 0.92]	0.001
Maximum Model *	0.76 [0.65, 0.88]	0.001

* Minimum Model: Adjusted for race, age, parity, and month of blood draw

Maximum Model: Also adjusted for infant sex, maternal height, BMI, smoking, marital status, and family income

Table 3

Association between maternal birthweight categories and early pregnancy vitamin D

	Normal Weight (Odds Ratio [95% CI])	Low Birthweight (Odds Ratio [95% CI])	Macrosomia (Odds Ratio [95% CI])
3a. Risk of vitamin D deficiency (≤20 ng/mL), relative to normal birthweight (2500 to 3999 g)			
Unadjusted	1.00 [Reference]	2.73 [1.37, 5.41]	1.15 [0.50, 2.65]
Minimum Model*	1.00 [Reference]	2.84 [1.30, 6.18]	1.19 [0.53, 2.70]
Maximum Model*	1.00 [Reference]	3.69 [1.63, 8.34]	1.07 [0.46, 2.52]
3b. Risk of severe vitamin D deficiency (≤12 ng/mL), relative to normal birthweight (2500 to 3999 g)‡			
Unadjusted	1.00 [Reference]	2.11 [0.45, 9.81]	--
Minimum Model*	1.00 [Reference]	6.46 [1.01, 41.27]	--
Maximum Model*	1.00 [Reference]	15.3 [2.44, 95.98]	--

*Minimum Model: Adjusted for race, age, parity, and month of blood draw;

Maximum Model: Also adjusted for infant sex, maternal height, BMI, smoking, marital status, and family income

‡Estimates for risk of severe deficiency unstable due to small cell counts: 3 LBW mothers and 0 macrosomic mothers with severe deficiency.

Table 4

Potential modification of vitamin D deficiency risk associated with birthweight, by BMI

4a. Risk of Vitamin D Deficiency (≤20 ng/mL) per 100 g higher maternal birthweight, by pre- pregnancy BMI			
	Pre-pregnancy BMI <25 (OR [95% CI]) (*n* = 483)	**Pre-pregnancy BMI ≥25 (OR [95% CI]) (*n* = 192)**	**P-value for interaction**
Unadjusted	0.952 [0.896, 1.01]	0.962 [0.892, 1.04]	0.828
Minimum Model *	0.960 [0.908, 1.02]	0.970 [0.887, 1.06]	0.850
Maximum Model *	0.946 [0.893, 1.00]	0.948 [0.863, 1.04]	0.964
4b. Risk of Vitamin D Deficiency (≤20 ng/mL) per 100 g higher maternal birthweight, by BMI change from age 18 to pre-pregnancy			
	BMI gain <2 kg/m^2 (OR [95% CI]) (*n* = 324)	BMI gain ≥2 kg/m^2 (OR [95% CI]) (*n* = 342)	P-value for interaction
Unadjusted	0.939 [0.829, 1.06]	0.960 [0.912, 1.01]	0.738
Minimum Model *	0.941 [0.884, 1.00]	0.990 [0.919, 1.07]	0.311
Maximum Model *	0.958 [0.856, 1.07]	0.948 [0.895, 1.00]	0.879

* Minimum Model: Adjusted for race, age, parity, and month of blood draw

Maximum Model: Also adjusted for infant sex, maternal height, BMI, smoking, marital status, and family income

Table 5

Potential modification of vitamin D deficiency risk associated with low birthweight relative to normal birthweight mothers, by BMI

5a. Risk of vitamin D deficiency (≤ 20 ng/mL), by pre-pregnancy BMI			
	Pre-pregnancy BMI <25 (OR [95% CI]) (*n* = 483)	**Pre-pregnancy BMI ≥25 (OR [95% CI]) (*n* = 192)**	**P-value for interaction**
Unadjusted	3.67 [1.59, 8.50]	1.47 [0.443, 4.87]	0.219
Minimum Model *	3.35 [1.37, 8.18]	2.04 [0.510, 8.13]	0.551
Maximum Model *	3.87 [1.49, 10.1]	2.84 [0.719, 11.2]	0.708
5b. Risk of vitamin D deficiency (≤20 ng/mL), by BMI change from age 18 to pre-pregnancy			
	BMI gain <2 kg/m^2 (OR [95% CI]) (*n* = 324)	BMI gain ≥2 kg/m^2 (OR [95% CI]) (*n* = 342)	P-value for interaction
Unadjusted	3.79 [1.41, 10.2]	2.05 [0.775, 5.44]	0.387
Minimum Model *	4.54 [1.74, 11.8]	1.74 [0.487, 6.21]	0.240
Maximum Model *	4.26 [1.48, 12.2]	2.51 [0.716, 8.78]	0.525

* Minimum Model: Adjusted for race, age, parity, and month of blood draw;

Maximum Model: Also adjusted for infant sex, maternal height, BMI, smoking, marital status, and family income