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Original Contribution

Maternal Calcium Intake During Pregnancy and Blood Pressure in the Offspring at Age 3 Years: A Follow-up Analysis of the Project Viva Cohort

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A previous analysis of the Project Viva cohort (eastern Massachusetts, 1999–2002 recruitment) found an association between higher second-trimester supplemental maternal calcium intake and lower systolic blood pressure in offspring at 6 months. The authors analyzed 5,527 systolic blood pressure measurements from 1,173 mother-child pairs from this same cohort when the children were aged 3 years. They estimated the change in offspring blood pressure for a 500-mg difference in maternal total, dietary-only, and supplemental-only calcium intake during the first 2 trimesters of pregnancy. Mean daily total calcium intake was 1,311 mg (standard deviation, 421) in the first trimester and 1,440 mg (standard deviation, 386) in the second trimester. Mean systolic blood pressure of the offspring at age 3 years was 92.1 mm Hg (standard deviation, 10.3). None of the maternal calcium intake measures during the first and second trimesters was associated with systolic blood pressure in the offspring. For example, for each 500-mg increment in maternal total elemental calcium intake in the second trimester, child's 3-year systolic blood pressure was 0.1 mm Hg lower (95% confidence interval: −0.9, 0.6). Maternal calcium intake during pregnancy was not associated with offspring blood pressure at the age of 3 years.

blood pressure; calcium; cardiovascular diseases; child; pregnancy

Abbreviations: BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; SD, standard deviation.

More than one-quarter of US adults have hypertension (1), a major cardiovascular risk factor (2). Small blood pressure differences in children may progress to larger differences at older ages (3): blood pressure increases with age and tracks over time (2, 4, 5). Thus, finding predictors of childhood blood pressure may aid in preventing hypertension over the long term.

Several studies in children have suggested that higher calcium intake is related to lower blood pressure (6–8), particularly in children whose calcium intake is low (9–11). One mechanism by which a diet low in calcium could increase blood pressure is through an increase in 1,25-dihydroxyvitamin D level, which could increase vascular smooth muscle cell intracellular calcium and thus peripheral vascular resistance (12). In addition, the benefits of calcium intake on blood pressure may start in utero (13–17). A recent systematic review and meta-analysis by Bergel and Barros (18) estimated that higher maternal calcium intake during pregnancy was associated with 1.92 mm Hg (95% confidence interval (CI): −3.14, −0.71) lower blood pressure in offspring ranging in age from 1 to 9 years. Two randomized controlled trials (13, 15) and 3 observational studies (13, 19, 20) were included in the review. An experiment in rats (15) also showed that a deficit in maternal dietary calcium intake during pregnancy had an increasing effect over age on the offspring's blood pressure. However, a dietary calcium intake much higher than recommended provided no benefits.

Of the studies included in the systematic review by Bergel and Barros (18), 4 had sample sizes smaller than our previously published cohort analysis of 936 children aged 6 months (20). We found that a 500-mg increment in maternal second-trimester calcium intake from supplements was associated with a change in systolic blood pressure of −3.0 mm Hg (95% CI: −4.9, −1.1). However, we found no effect of calcium from foods, and 6 months is a relatively young age at which to study blood pressure outcomes.

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Accordingly, the objective of this study was to investigate the association between 1) maternal calcium intake and blood pressure in the offspring at a later age and 2) calcium intake from both foods and supplements in early and midgestation.

MATERIALS AND METHODS

Subjects

The subjects for this study were participants in Project Viva, a prospective cohort study of gestational factors, pregnancy outcomes, and offspring health. Between April 1999 and July 2002, we recruited women attending their initial prenatal visit at 1 of 8 urban and suburban obstetric offices of a multispecialty group practice in eastern Massachusetts.

Eligibility criteria included fluency in English, gestational age less than 22 weeks at the initial prenatal clinical appointment, and singleton pregnancy. Details of recruitment and retention procedures are available elsewhere (21).

Data collection

The first study visit immediately followed recruitment at the woman's initial clinical prenatal visit. During this first visit, we obtained informed consent, carried out a brief interview, and provided a take-home, self-administered questionnaire that included a validated food frequency questionnaire (FFQ) to assess the woman's diet during the first trimester (22). We gathered information about first-trimester vitamin and supplement use during a brief interview.

We performed the second study visit at 26–28 weeks of gestation. During this visit, we again conducted a brief interview and provided a questionnaire that included a similar FFQ about the woman's diet during the second trimester. At that time, the FFQ itself included questions about vitamin and supplement use during the second trimester.

Within 3 days after delivery, we conducted a brief interview with the mother in the hospital. We also took anthropometric and blood pressure measurements of the newborn.

When the children reached 3 years of age, we invited all mothers with their eligible children for an in-person visit. During this visit, we updated information on the mother; took anthropometric, skinfold thickness, and blood pressure measurements from both mother and child; and administered an FFQ to the mother about the child's diet.

The human subject review committees of Harvard Pilgrim Health Care, Brigham and Women's Hospital, and Beth Israel Deaconess Medical Center (all in Boston, Massachusetts) approved the study protocols.

Measurements

Details of the data collected for Project Viva during pregnancy are described elsewhere (21). In summary, in addition to the FFQ assessment, we obtained demographic, social, economic, behavioral, and health information at the 2 prenatal visits. At the first prenatal visit, we administered a brief maternal interview to collect information on prepregnancy weight and height as well as father's weight and height. We used these data to calculate prepregnancy body mass index (BMI; weight (kg)/height $(m)^2$) of the mother and BMI of the father. We estimated gestational age at birth from the number of days between the first day of the last menstrual period and the date of delivery, and we compared these estimates with ultrasound measurements made between 16 and 20 weeks of gestation. If the difference was more than 10 days, we used the ultrasound-based gestational age. At the 3-year visit, we measured the BMI of the child.

We measured systolic and diastolic blood pressures in both mother and child with a Dinamap (Critikon, Inc., Tampa, Florida) Pro 100 automated oscillometric recorder. For each of 5 measurements of the child taken 1 minute apart, we recorded child position (sitting, semireclining, reclining, or standing), arm used, cuff size, child state (asleep, quiet awake, crying, or active awake), ambient temperature, blood pressure machine used, pulse, and which research assistant obtained the readings.

We measured nutrient intake with a validated FFQ during the first and second trimesters of pregnancy (23). The dietary period assessed during the first-trimester FFQ was "during this pregnancy" (the date of the last menstrual period until the date of assessment). For the second-trimester FFQ, the dietary period was "in the past 3 months." We also assessed the child's diet with a validated FFQ during the 3-year visit (24). To calculate calcium intake from foods and supplements, we used the Harvard nutrient database, which contains food composition values from the US Department of Agriculture, supplemented by other sources (25). From the maternal and child's FFQs, we also estimated intakes of vitamin D, which is important in calcium absorption. We used the nutrient residuals method to energy-adjust nutrients (26).

Statistical analysis

The main explanatory variable in this study was maternal calcium intake. We studied 3 different calcium estimates for both the first and second trimesters: total calcium intake, calcium intake from foods only, and calcium intake from supplements only.

Our main outcome was systolic blood pressure in the offspring at age 3 years. We focused on systolic blood pressure rather than diastolic blood pressure because it is a better predictor of later outcomes and is more accurately measured (3, 27). Although the first blood pressure measurement tends to be higher than the following ones, we did include the first measurement in the analysis because it tends to improve precision when absolute levels are not as important as differences (28).

We used mixed models to assess associations between predictors and blood pressure (29). The mixed-model method fits each of the as many as 5 blood pressure measurements of every child as repeated outcome measures. An advantage of this modeling approach over using the average measure for each child as an outcome is that children with more measurements and less variability in their measurements are assigned more weight than those with fewer measurements, more variability, or both.

We evaluated confounding by examining the association of calcium intake with systolic blood pressure before and after adding covariates to the regression model. All models were controlled for blood pressure measurement conditions of body position, child state, arm used, cuff size, measurement sequence number, and blood pressure machine to increase precision of the measurements. The ''crude'' models were also adjusted for child's age and sex. Ambient temperature did not add information, so we did not include it in the models. We used energy-adjusted nutrients for total and food-derived calcium intake only (25). The reason for not adjusting for energy intake at the supplement nutrients level is because supplements do not contribute to total daily caloric intake.

In subsequent models, we adjusted for ethnicity, education, prepregnancy BMI, and third-trimester systolic blood pressure of the mother; BMI of the father; and child's BMI z score at the 3-year visit. We calculated linear regression effect estimates and 95% confidence intervals for a 500-mg increment in elemental calcium intake, which approximates the difference in total elemental calcium intake between the 25th and 75th percentiles during the first and second trimesters (20). We used SAS version 9.1 software (SAS Institute, Inc., Cary, North Carolina) for all analyses.

RESULTS

Of the 2,128 women who delivered live infants, 1,579 were eligible for 3-year follow-up by virtue of having prenatal FFQ data and consent available for child follow-up. We collected follow-up information on 1,402 participants, including in-person examinations of 1,294. For this analysis, we excluded 101 participants with missing blood pressure data (7 because the machine was not working and 94 because the participant declined blood pressure measurement), 1 with invalid blood pressure measurements, and 19 with no or an invalid FFQ during pregnancy (energy intake lower than 600 or higher than 6,000 kcal). Thus, the cohort for analysis comprised 1,173 mother-child pairs (74% of 1,579). In total, 1,017 children had 5 systolic blood pressure measurements, 67 had 4, 28 had 3, 29 had 2, and 32 had 1, for a total of 5,527 measurements.

Compared with mothers eligible for the 3-year in-person visit but excluded from the analysis ($n = 406$), mothers in this analysis had a higher educational status (34% vs. 24% had a graduate degree), were more likely to be white (73% vs. 57%), were more likely to be married or cohabitating (94% vs. 87%), and reported higher household income (>$70,000: 65% vs. 52%), but they were similar regarding parity ($\geq$1: 53% vs. 50%). Age at enrollment (32.5 vs. 30.8 years), prepregnancy BMI (24.6 vs. 25.3 kg/m^2), gestational age at delivery (39.5 vs. 39.3 weeks), and birth weight (3.499 vs. 3.414 kg) were slightly different.

Mean first-trimester maternal daily total calcium intake was 1,311 mg (standard deviation (SD), 421; 5th–95th percentile: 684–2,037). Mean calcium intake was 1,109 mg/day (SD, 338; 5th–95th percentile: 592–1,676) from foods only and 195 mg/day (SD, 237; 5th–95th percentile: 0–643) from supplements only. Second-trimester intakes were slightly higher; daily total calcium intake was 1,440 mg (SD, 386), with 1,170 mg/day (SD, 341) from foods only and 264 mg/day (SD, 191) from supplements only. Total mean caloric intake increased from 2,095 kcal/day (SD, 657) in the first trimester to 2,158 kcal/day (SD, 645) in the second trimester (Table 1). These results were similar to those for the cohort as a whole (30).

About half of the children were girls. Mean gestational age at birth was 39.5 weeks (SD, 1.8). Approximately 6% of the children were born at a gestational age of less than 37 weeks. Mean birth weight was 3.499 kg (SD, 0.558). At the follow-up visit, the mean age of the children was 3.3 years (SD, 0.3). Mean systolic blood pressure was 92.1 mm Hg (SD, 10.3), which is similar to published blood pressure levels at this age (31). Mean calcium intake of the children at the 3-year visit was 968 mg/day (SD, 273), and mean vitamin D intake was 245 μg/day (SD, 111) (Table 1).

Crude models showed no association between first- or second-trimester total maternal calcium intake and systolic blood pressure in the child at age 3 years: the change associated with a 500-mg difference in calcium intake was 0.2 mm Hg (95% CI: −0.4, 0.8) during the first trimester and −0.2 mm Hg (95% CI: −0.9, 0.4) during the second trimester) (Table 2). This lack of association persisted after covariate adjustment (first trimester: 0.1 mm Hg (95% CI: −0.5, 0.7), second trimester: −0.1 mm Hg (95% CI: −0.9, 0.6)) (Table 2). We found no associations between calcium from supplements only or from foods only in the first (data not shown) or second trimester (adjusted model for calcium from supplements: −0.1 mm Hg (95% CI: −1.4, 1.2), adjusted model for calcium from foods only: −0.2 mm Hg (95% CI: −1.0, 0.6)) (Table 3). We repeated the same analysis for diastolic blood pressure measurements of the children; we also found no association with maternal calcium intake (data not shown).

Additional adjustment for total maternal vitamin D intake again revealed no association between total maternal calcium intake and systolic blood pressure in the offspring (fully adjusted model, first trimester: −0.1 mm Hg (95% CI: −0.8, 0.7), second trimester: −0.3 mm Hg (95% CI: −1.2, 0.6)) or for diastolic blood pressure (fully adjusted model, first trimester: 0.1 mm Hg (95% CI: −0.5, 0.7), second trimester: −0.2 mm Hg (95% CI: −0.9, 0.5)). Similarly, adjusting for calcium intake and vitamin D intake of the child at age 3 years did not change the estimates (data not shown).

DISCUSSION

We found no association between maternal calcium intake during the first or second trimester of pregnancy and blood pressure in the child at age 3 years. With the relatively large sample size, the confidence intervals were narrow enough to rule out any clinically meaningful association. In no analysis of total calcium intake was a 95% confidence limit greater than 1.3 or less than −1.5 mm Hg (Table 3). Thus, the inverse association we previously found between second-trimester supplemental calcium intake and systolic blood pressure at the age of 6 months in the same cohort (20) was not present when the children were 2.5 years older.

One of the reasons for this difference could be the change in the child's diet between the age of 6 months and 3 years.

Table 1. Characteristics of 1,173 Mother-Child Pairs Participating in Project Viva, Eastern Massachusetts, 1999–2002 and Analyzed for Any Relation Between Maternal Calcium Intake During Pregnancy and Systolic Blood Pressure in the Offspring at Age 3 Years

Characteristics	Mean (SD)	No.	%
Prenatal maternal characteristics			
Daily calcium intake, mg			
First trimester			
Total	1,311 (421)		
From foods only	1,109 (338)		
From supplements only	195 (237)		
Second trimester			
Total	1,440 (386)		
From foods only	1,170 (341)		
From supplements only	264 (191)		
Calorie intake, kcal			
First-trimester total	2,095 (657)		
Second-trimester total	2,158 (645)		
Daily vitamin D intake, μg			
First-trimester total	277 (165)		
Second-trimester total	368 (138)		
Other maternal factors			
Age at enrollment, years	32.5 (5.0)		
Prepregnancy body mass index, kg/m^2	24.6 (5.2)		
Mean third-trimester systolic blood pressure, mm Hg	111.5 (8.3)		
Race/ethnicity			
White		856	73
Black		136	12
Hispanic		71	6
Asian		58	5
Other		51	4
Educational level			
High school diploma at most		86	7
Some college		243	21
Bachelors degree		439	37
Graduate degree		404	34
Marital status			
Married or cohabitating		1,099	94
Divorced/separated/never married/other		72	6
Parity			
0		550	47
1		423	36
2		153	13
≥3		47	4
Household income, $			
<40,000		136	12
40,001 to 70,000		249	23
>70,000		719	65
Paternal characteristics			
Body mass index, kg/m^2	26.4 (3.9)		
Child characteristics			
Gestational age at birth, weeks	39.5 (1.8)		
Birth weight, kg	3.499 (0.558)		
Boys		590	50
Breastfeeding duration, months			
0		131	11
>0 to <12		668	57
≥12		313	27
Unknown		61	5
Child characteristics at 3-year visit			
Age, years	3.3 (0.3)		
Anthropometrics			
Body mass index, kg/m^2	16.5 (1.5)		
Body mass index *z* score	0.46 (1.04)		
Blood pressure			
Systolic blood pressure, mm Hg	92.1 (10.3)		
Diastolic blood pressure, mm Hg	58.2 (8.1)		
Pulse, beats/minute	106 (12)		
Nutrient intake			
Total calcium, mg	968 (273)		
Total vitamin D, μg	245 (111)		

Abbreviation: SD, standard deviation.

At age 6 months, a substantial proportion of children were receiving their entire calcium intake from breast milk or infant formula. At age 3 years, the amounts of calcium consumed through the child's own diet could overwhelm any prenatal influence. However, adjusting for 3-year calcium intake made no difference in our results. Additionally, we did not find a cross-sectional association between children's 3-year calcium intake and their blood pressures (data not shown).

Another possible explanation for the lack of an association could be that the effect of maternal calcium intake on offspring blood pressure reappears after 3 years. In rats, Bergel and Belizán (15) found that a maternal diet deficit in calcium during pregnancy had an increasing effect over age on the offspring's blood pressure. In humans, Silverman et al. (32) found early (at birth) and late (after 4 years), but not intermediate, effects of diabetes in utero on obesity in childhood. Therefore, an association between maternal calcium intake and blood pressure in the offspring might become evident again when the children are older.

Table 2. Estimates From Multivariate Mixed Regression Models Predicting Offspring Blood Pressure From Maternal Total Dietary Calcium Intake During Pregnancy in 1,173 Mother-Child Pairs Participating in Project Viva, Eastern Massachusetts, 1999–2002

Model Covariates	Estimated Change in Systolic Blood Pressure at Age 3 Years for a 500-mg Difference in Maternal Calcium Intake, mm Hg			
	First Trimester		Second Trimester	
	Change	95% CI	Change	95% CI
Adjusted for maternal energy intake[a] and child's blood pressure measurement conditions,[b] sex, and age at 3-year visit	0.2	−0.4, 0.8	−0.2	−0.9, 0.4
Model 1 + maternal ethnicity, education, prepregnancy BMI, third-trimester systolic blood pressure, and paternal BMI	0.0	−0.6, 0.7	−0.2	−0.9, 0.5
Model 2 + child BMI *z* score at 3-year visit	0.1	−0.5, 0.7	−0.1	−0.9, 0.6

Abbreviations: BMI, body mass index; CI, confidence interval.

[a] The nutrient residuals method was used to energy-adjust total calcium intake.

[b] Blood pressure measurement conditions are body position, child state (asleep, quiet awake, crying, or active awake), arm used, cuff size, measurement sequence number, and blood pressure machine.

Our null results were similar to those of at least 1 other study. Morley et al. (19) found no association between maternal calcium supplementation and blood pressure in twins at age 9 years. However, whether data from twin studies can be generalized to singletons is still debated (33, 34).

Misleading null associations between diet and disease can occur in several circumstances (26). Nutrients can interact. Vitamin D interacts with calcium, affecting calcium absorption in the intestines, and it may affect the development of cardiovascular disease (26, 35). Chan et al. (36) found that calcium supplementation during pregnancy is associated with increased cord blood 25-hydroxyvitamin D levels, the active part of vitamin D. However, adjusting the multivariate models for vitamin D intake in the first and second trimesters of the mother did not change our results. Also adjusting for child's dietary vitamin D intake did not change our results.

Another possibility is that the range of calcium intake was too narrow to see an effect. Calcium supplementation has the greatest blood-pressure-lowering effect in individuals with the lowest habitual intakes of calcium, in most

Table 3. Estimates From Multivariate Mixed Regression Models Predicting Offspring Blood Pressure From Maternal Calcium Intake From Foods Only and Supplements Only During the Second Trimester of Pregnancy in 1,173 Mother-Child Pairs Participating in Project Viva, Eastern Massachusetts, 1999–2002

Model Covariates	Estimated Change in Systolic Blood Pressure at Age 3 Years for a 500-mg Difference in Maternal Calcium Intake, mm Hg			
	Second-Trimester Calcium Intake From Supplements Only		Second-Trimester Calcium Intake From Foods Only	
	Change	95% CI	Change	95% CI
Adjusted for maternal energy intake[a] and child's blood pressure measurement conditions,[b] sex, and age at 3-year visit	−0.1	−1.5, 1.3	−0.3	−1.0, 0.5
Model 1 + maternal ethnicity, education, prepregnancy BMI, third-trimester systolic blood pressure, and paternal BMI	−0.1	−1.5, 1.3	−0.2	−1.0, 0.6
Model 2 + child BMI *z* score at 3-year visit	−0.1	−1.4, 1.2	−0.2	−1.0, 0.6

Abbreviations: BMI, body mass index; CI, confidence interval.

[a] The nutrient residuals method was used to energy-adjust calcium intake from foods only.

[b] Blood pressure measurement conditions are body position, child state (asleep, quiet awake, crying, or active awake), arm used, cuff size, measurement sequence number, and blood pressure machine.

studies less than about 900 mg/day (9, 11, 37). Approximately 19% of women in the first trimester and 16% in the second trimester had such low intakes. However, the lowest calcium intakes found in our data were not associated with higher blood pressures.

One of the strengths of this study was the prospective data collection, which started in early pregnancy. None of the other observational studies (13, 19) collected dietary data during pregnancy; rather, they collected recalled nutrient and covariate data after delivery. Another strength was collection of a wider range of potential confounding factors than in previous studies. In addition, we had a relatively large sample size of 1,173 participants. Published studies were conducted in smaller samples, varying from 57 children (16) to 591 children (14), as reviewed by Bergel and Barros (18). We measured maternal calcium intake in both the first and second trimesters. In addition, the blood pressure measurements in this study were very precise. For 87% of the children at the age of 3 years, we collected 5 blood pressure measurements. Finally, the FFQ is an appropriate method to measure calcium intake in large studies measuring long-term dietary intake.

Several limitations of this study should be mentioned. The participating mothers in this study were relatively older and highly educated, and all were residents of eastern Massachusetts. Thus, findings may not be generalizable to other populations (38). Loss to follow-up may cause selection bias; several characteristics were different between the analysis group and the participants not included in this analysis.

In conclusion, the results of this study do not confirm findings from earlier studies that higher maternal calcium intake is associated with lower childhood blood pressure. Nevertheless, following the children in this and other cohorts is warranted to investigate whether an association between maternal calcium intake and offspring blood pressure exists at later stages of the life course.

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