Maternal milk consumption, fetal growth, and the risks of neonatal complications: the Generation R Study[1–3]

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ABSTRACT

Background: Maternal cow-milk consumption may increase birth weight. Previous studies did not assess the association of maternal milk consumption with trimester-specific fetal growth.

Objective: The objective was to assess associations of first-trimester maternal milk consumption with fetal growth characteristics in different trimesters and the risk of neonatal complications.

Design: In total, 3405 mothers participating in a prospective cohort study completed a 293-item semiquantitative food-frequency questionnaire to obtain information about dairy consumption during the first trimester of pregnancy. Fetal head circumference, femur length, and weight were estimated in the second and third trimesters by ultrasonography.

Results: Maternal milk consumption of >3 glasses/d was associated with greater fetal weight gain in the third trimester of pregnancy, which led to an 88-g (95% CI: 39, 135 g) higher birth weight than that with milk consumption of 0 to 1 glass/d. In addition, head circumference tended to be 2.3 cm (95% CI: −0.0, 4.6 cm) larger when mothers consumed >3 glasses/d. Maternal milk consumption was not associated with length growth. Maternal protein intake (*P* for trend = 0.01), but not fat or carbohydrate intake, from dairy products was associated with higher birth weight. This association appeared to be limited to milk (*P* for trend < 0.01), whereas protein intake from nondairy food or cheese was not associated with birth weight.

Conclusions: Maternal milk consumption is associated with greater fetal weight gain. The association seems to be due to milk protein, or milk components closely associated with protein, rather than to the fat or carbohydrate fraction of milk. *Am J Clin Nutr* 2011; 94:501–9.

INTRODUCTION

Maternal nutrition is one of the major environmental exposures influencing fetal growth and development (1–4). Maternal cow-milk consumption was associated with a higher neonatal weight, length, and abdominal and head circumferences in a Danish study (5). However, results from earlier studies on the associations of maternal milk consumption with birth weight are not consistent (6–12). Cow milk contains various nutrients considered to be beneficial for fetal growth and development, including protein, B vitamins, and minerals (13). In both children and adults, milk consumption increases blood concentrations of insulin growth factor I (IGF-I)—a peptide hormone and key regulator of postnatal growth (14–20). Results from a recent randomized clinical trial suggested that, specifically, the major protein fraction of milk, casein, increased IGF-I blood concentrations (21). In the Danish study, intake of protein from milk, but not from cheese, was associated with higher birth weight (5). However, most previous studies that assessed the associations of milk consumption and birth outcomes lacked information on specific intake of macronutrients from milk. Also, previous studies were not able to assess the associations between milk consumption and trimester-specific fetal growth characteristics, but focused on birth weight as outcome. However, different fetal growth patterns may result in the same birth weight. Assessing fetal growth characteristics in different periods of pregnancy may give information about specific critical periods.

Therefore, in a population-based prospective cohort study of 3405 mothers and their children, we assessed the associations of first-trimester maternal milk consumption and its constituents with fetal growth characteristics in different periods of pregnancy and the risks of neonatal complications.

SUBJECTS AND METHODS

Study design

The current study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life until young adulthood in the city of Rotterdam, the Netherlands (22). The study was conducted according to the guidelines of the Helsinki Declaration and approved by the Medical Ethics Committee of the

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Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all mothers. Mothers were enrolled during pregnancy between 2001 and 2005, and all children were born between April 2002 and January 2006. Of all eligible children in the study area, 61% participated at birth in the study (22). Enrollment was aimed at early pregnancy (gestational age <18 wk), at the routine fetal ultrasound examination in pregnancy, but was allowed until birth of the child. For the current study, we performed analyses in Dutch participants. Of the total group of enrolled Dutch mothers (n = 4057), 98% (n = 3979) were enrolled in the first or second trimester of pregnancy. From these mothers, 88% (n = 3482) fully completed the food-frequency questionnaire (FFQ). We excluded twin pregnancies (1.4%, n = 50) and pregnancies leading to intrauterine death (0.7%, n = 24) from the analyses and 0.1% (n = 3) were lost to follow-up. We performed the current study in the remaining 3405 mother-child pairs. (A flow chart is provided in Supplemental Figure 1 under "Supplemental data" in the online issue.)

Milk-consumption assessment

We assessed maternal dietary intake, including consumption of milk, at enrollment in the study (median: 13.5 wk of gestation; 95% CI: 10.8, 21.1) using a modified version of the validated semiquantitative FFQ of Klipstein-Grobusch et al (23). This FFQ considered food intake over the prior 3 months, thereby covering dietary intake within first trimester of pregnancy. The FFQ consists of 293 items structured according to meal pattern. Questions include consumption frequency, portion size, preparation method, and additions. Portion sizes were estimated by using Dutch household measures and photographs of foods showing different portion sizes (24). To calculate average daily nutritional values, we used the Dutch food composition table 2006 (13). For the assessment of milk consumption, additional questions were asked about their use of skimmed, semi-skimmed, and full-fat milk products; sweetened milk products; milk products with additional fruit; and milk products enriched with vitamins or extra calcium. To obtain frequency measures of milk consumption, we summed the consumption of milk and milk drinks. According to the Dutch household measures, one glass of milk on average contains 150 mL milk (24). For the analysis of dairy consumption, we added yogurt, yogurt drinks, cheese, butter, quark, pudding, ice cream (dairy cream based), and cream/creamers. Subsequently, we quantified daily intake of macronutrients from dairy consumption using the Dutch food composition table (13).

Fetal growth characteristics

Fetal ultrasound examinations were performed at 1 of the 2 research centers in each trimester of pregnancy. The medians (95% CIs) at these visits were 12.9 (11.0, 16.8), 20.5 (19.0, 22.6), and 30.4 (28.9 32.2) wk of gestation for the first, second, and third trimesters, respectively. Gestational age was established by the first fetal ultrasound examination, because the use of the last menstrual period has several limitations, such as the large number of mothers who do not know the exact date of their last menstrual period or have irregular menstrual cycles (25). In the second and third trimesters of pregnancy, we measured fetal head circumference, abdominal circumference, and femur length to the nearest millimeter using standardized ultrasound procedures (25). In this study we considered femur length as a proxy for length growth. Estimated fetal weight (EFW) was calculated with the formula from Hadlock et al (26) by using head circumference (HC), abdominal circumference (AC), and femur length (FL):

$$\log_{10}\mathrm{EFW} = 1.5662 - 0.0108(\mathrm{HC}) + 0.0468(\mathrm{AC}) + 0.171(\mathrm{FL}) + 0.00034(\mathrm{HC})^2 - 0.003685\left(\mathrm{AC}\times\mathrm{FL}\right) \quad (1)$$

Neonatal complications

Information about offspring sex, gestational age, weight, length, and head circumference at birth was obtained from medical records and hospital registries. Preterm birth was defined as a gestational age of <37 wk at delivery. Small size for gestational age at birth was defined as a sex and gestational age–adjusted birth weight below the 5th percentile in the study cohort [< −1.62 SD score (SDS)]. Large size for gestational age at birth was defined as a sex and gestational age–adjusted birth weight above the 95th percentile in the study cohort (>1.67 SDS).

Covariates

Maternal age was recorded at enrollment. Information about educational level, marital status, parity, and periconceptional folic acid supplement use was obtained by questionnaire at enrollment in the study. Frequency of nausea and vomiting and smoking and alcohol habits were assessed by questionnaires in each trimester. Maternal anthropometric data, including height and weight, were measured while the subjects were wearing heavy clothing and no shoes in the first, second, and third trimesters at the research center. Information about maternal weight just before pregnancy was obtained by questionnaire. Because enrollment in our study was in pregnancy, we were not able to measure maternal weight before pregnancy. Correlation of prepregnancy weight obtained by questionnaire and weight measured at enrollment was 0.97 ($P < 0.01$).

Statistical analysis

We analyzed milk consumption in 4 categories based on the distribution of milk consumption among mothers (0–1, >1–2, >2–3, and >3 glasses/d). We used the lowest category as the reference category in all models. First, we performed multivariate linear regression analyses to assess the association of milk consumption with fetal growth characteristics. Second, to assess potential nonlinear longitudinal effects, we used mixed-effect models with unstructured residual covariance to longitudinally model fetal growth SDS from 20 wk of pregnancy until birth by using natural cubic splines (27). We positioned interior knots of the spline based on moments of data collection (18, 23, 30, 37, and 43.4 wk). The models include a separate spline model for each milk consumption category. We performed a multivariate F test to detect a difference between the splines of each milk consumption category as compared with the lowest reference category. Third, we used multivariate logistic regression models to assess the association of milk consumption with the risk of neonatal complications (preterm birth, small or large for gestational age). Finally, we used multivariate linear regression models to assess the association of macronutrient (fat, protein, carbohydrate) intake from dairy products and protein intake from total diet, dairy products, nondairy products,

milk, and cheese with birth weight. We categorized macronutrient intake in quintiles and mutually adjusted the multivariate analyses for the intake of other macronutrients. We performed trend tests by using milk, dairy, or macronutrient consumption as continuous variable in the analyses. We adjusted models for potential confounders based on results from previous studies, including maternal age, height, body mass index, parity, educational level, marital status, alcohol use, smoking, use of folic acid supplements, paternal height, vomiting, nausea, daily energy intake, and consumption of fruit, vegetables, meat, fish, and coffee (5, 8–12, 28–32). We used multiple imputations to complete missing data on the covariates maternal prepregnancy BMI (14% missing), parity (0.2%), marital status (2%), educational level (0.6%), smoking (8%), alcohol use (7%), folic acid supplement use (17%), nausea (0.1%), vomiting (0.1%), and paternal height (11%) (33). Imputations were based on the relations between all covariates in the study. All measures of association are presented with their 95% CIs. *P* values are 2-sided. Spline regression analyses were performed by using the Statistical Analysis System (version 9.2; SAS Institute Inc, Cary, NC), and other analyses were performed

TABLE 1
Maternal and fetal characteristics according to maternal milk consumption during pregnancy: the Generation R Study Cohort, Rotterdam, Netherlands[1]

		Milk consumption (glasses/d)				
	All (n = 3405)	0–1 (reference) (n = 990)	>1–2 (n = 805)	>2–3 (n = 940)	>3 (n = 670)	*P* value
Maternal characteristics						
Age (y)	31.4 ± 4.4	31.4 ± 4.4	31.8 ± 4.3*	31.4 ± 4.3	30.9 ± 4.6*	0.01*
Height (cm)	170.9 ± 6.4	170.5 ± 6.4	171.2 ± 6.4*	170.9 ± 6.3	171.0 ± 6.5	0.25
BMI (kg/m^2)	23.2 ± 3.9	23.0 ± 3.9	23.1 ± 3.8	23.4 ± 3.9*	23.5 ± 4.2*	<0.01*
Total energy intake (kJ)	2145 ± 511	1953 ± 503	2101 ± 479*	2185 ± 471*	2424 ± 482*	<0.01*
Parity ≥1 (%)	39.8	38.3	36.9	43.9*	39.7	0.11
Missing	0.2	0.4	0.1	0	0	
Married/living together (%)	91.3	90.0	92.3	93.1*	89.4	0.61
Missing	1.9	2.1	1.5	1.7	2.5	
High education (%)	58.9	59.3	65.6*	58.6	50.6*	<0.01*
Missing	0.6	0.5	0.2	1.0	0.4	
Smoking (%)						
Never	69.6	71.2	69.9	71.7	63.7*	0.01*
First trimester	8.1	7.9	8.6	7.9	8.1	0.97
Continued	14.7	13.5	13.7	13.4	19.6*	<0.01*
Missing	7.6	7.4	7.8	7.0	8.7	
Alcohol use (%)						
Never	31.3	31.6	26.7*	33.0	33.9	0.08
First trimester only	15.4	16.0	14.0	14.4	17.5	0.52
Continued	46.0	45.2	52.2*	46.0	40.0	0.03*
Missing	7.3	7.3	7.1	6.7	6.9	
Folic acid supplement use (%)						
Preconception start	46.4	43.8	48.2	48.3	45.4	0.64
Postconception start	27.2	27.9	26.8	26.5	27.5	0.49
None	8.9	9.2	8.0	8.7	9.9	0.78
Missing	17.5	19.1	17.0	16.5	17.3	
Fetal characteristics						
Second trimester						
Head circumference (mm)	179 ± 13	179 ± 13	179 ± 13	180 ± 13	180 ± 14	0.48
Femur length (mm)	33.4 ± 3.3	33.4 ± 3.3	33.3 ± 3.3	33.4 ± 3.3	33.3 ± 3.4	0.96
Estimated fetal weight (g)	379 ± 87	377 ± 83	379 ± 86.9	381 ± 86	380 ± 92	0.42
Third trimester						
Head circumference (mm)	286 ± 12	285 ± 12	286 ± 12	287 ± 12*	285 ± 11	0.64
Femur length (mm)	57.5 ± 2.9	57.5 ± 3.0	57.5 ± 2.8	57.5 ± 2.9	57.3 ± 2.9	0.47
Estimated fetal weight (g)	1632 ± 256	1626 ± 254	1635 ± 253	1645 ± 256	1621 ± 262	0.84
Birth outcomes						
Males (%)	50.5	48.5	49.4	53.3*	50.6	0.13
Gestational age (wk)	40.0 ± 1.7	40.0 ± 1.7	39.9 ± 1.7	40.0 ± 1.7	39.9 ± 1.7	0.71
Birth weight (g)	3489 ± 556	3446 ± 554	3489 ± 558	3521 ± 548*	3508 ± 563*	<0.01*
Birth length (cm)	50.5 ± 2.4	50.4 ± 2.4	50.5 ± 2.5	50.5 ± 2.3	50.4 ± 2.9	0.46
Head circumference (cm)	34.0 ± 1.6	33.9 ± 1.7	34.0 ± 1.7	34.1 ± 1.6	34.1 ± 1.7	0.12
Preterm birth (%)	4.7	4.7	5.3	3.9	4.9	0.74
Small for gestational age (%)	5.0	5.3	5.1	4.4	5.2	0.72
Large for gestational age (%)	5.4	4.0	5.3	6.5*	6.1*	0.02*

[1] Values are means ± SDs for continuous variables and percentages for categorical variables. *$P < 0.05$ (univariate regression models).

by using the Predictive Analytic Software version 17.0 for Windows (PASW Inc, Chicago, IL).

RESULTS

The median reported milk consumption was 2.6 glasses/d (interquartile range: 2.1 glass/d). As indicated in **Table 1**, mothers with higher milk consumption tended to have a higher energy intake, lower age, and higher BMI and more frequently smoked, but less frequently finished higher education (all $P < 0.01$). Of all births, 4.7% were born preterm, 5.0% were small, and 5.0% were large for gestational age at birth. Fetal growth characteristics measured during the second and third trimesters of pregnancy were available in 98.6% and 98.1% of the mothers, respectively.

Milk consumption, fetal growth, and neonatal outcomes

Results from the linear regression analyses, which are given in the **Tables 2–4** showed that some milk intake categories were associated with increased fetal head circumference or estimated fetal weight in the second and third trimesters of pregnancy. However, we found no evidence of a dose-response relation, because the *P* for trend of these findings was not significant. Maternal milk consumption of >2–3 glasses was associated with a 2.2-cm (95% CI: 0.2, 4.2) larger head circumference at birth (*P* for trend = 0.03). Maternal milk consumption was not associated with fetal length characteristics or length at birth. Maternal milk consumption was positively associated with birth weight (*P* for trend < 0.01). The birth weight difference between the highest and lowest categories of milk consumption was 88 g (95% CI: 39, 135).

The associations of maternal milk consumption with longitudinally measured fetal growth (head circumference, length, and weight) between the gestational ages of 20 and 40 wk are shown in **Figure 1**, A–C. To easily compare effect estimates throughout pregnancy, the results are presented as differences in gestational age–adjusted SDS. We found no consistent associations of maternal milk consumption with longitudinally measured fetal head circumference or length (Figure 1A and 1B). Compared with the lowest reference category of milk consumption (0–1 glasses/d), maternal milk intakes of >1–2 glasses/d ($P < 0.01$), 2–3 glasses/d ($P = 0.01$), and >3 glasses/d ($P = 0.06$) were associated with increased fetal weight gain (Figure 1C). (The effect estimates of fetal growth differences at 40 wk of pregnancy are presented in Supplemental Table 1 under "Supplemental data" in the online issue). Differences in fetal weight gain appeared from 20 wk onward, but became most evident in the last part of the third trimester.

Maternal milk consumption was not associated with the risk of preterm birth or with the risk of a small or large size for gestational age at birth in the offspring (**Table 5**). Results of the unadjusted analyses are presented elsewhere (*see* Supplemental Tables 2 and 3 under "Supplemental data" in the online issue). To exclude a potential effect of parity, we performed a sensitivity analysis by restricting the study population to nulliparous women. The effect estimates were only slightly changed. In addition, performing a complete case analysis did not significantly change our results (data not shown).

Macronutrient intake from dairy products and birth weight

The associations of macronutrient intake from dairy products with birth weight are shown in **Figure 2**A. Protein intake, but not fat or carbohydrates intake, from dairy products was associated with higher birth weight (*P* for trend = 0.01). Positive effect estimates for the association of maternal total protein intake with birth weight (*P* for trend = 0.15) are shown in Figure 2B. Because nondairy protein intake showed negative effect estimates for the association with birth weight, the association of total protein intake seems more likely to be driven by protein intake from dairy products than by a general protein effect. The association of maternal protein intake from dairy products with birth weight was further restricted to protein intake from milk (*P* for trend < 0.01; Figure 2C). The difference in birth weight between the lowest and highest quintiles was 115 g (95% CI: 20, 209). Protein intake from cheese was not associated with birth weight; the corresponding effect estimates are presented elsewhere (*see* Supplemental Tables 4, 5, and 6 under "Supplemental data" in the online issue). We performed a sensitivity analysis to assess the possibility of a general effect of animal protein. Maternal total intake of animal protein was not associated with birth weight. Because the removal of intake of milk protein from total animal protein turned the direction of the association, the association of milk protein intake is

TABLE 2
Associations of maternal daily milk consumption with fetal head circumference: the Generation R Study Cohort, Rotterdam, Netherlands[1]

	Head circumference								
	Second trimester (*n* = 3331)			Third trimester (*n* = 3301)			Birth (*n* = 1936)		
Milk consumption	Subjects	Difference	95% CI	Subjects	Difference	95% CI	Subjects	Difference	95% CI
	n	*mm*	*mm*	*n*	*mm*	*mm*	*n*	*mm*	*mm*
0–1 glass/d	959	Reference	—	969	Reference	—	564	Reference	—
>1–2 glasses/d	784	0.8	0.1, 1.4*	773	1.0	0.0, 1.9*	455	0.9	−1.2, 3.0
>2–3 glasses/d	926	0.3	−0.3, 0.9	911	1.0	0.1, 1.9*	551	2.2	0.2, 4.2*
>3 glasses/d	662	0.4	−0.3, 1.1	648	0.2	−0.8, 1.2	366	2.3	−0.0, 4.6
P for trend	—	0.86	—	—	0.38	—	—	0.03*	—

[1] Values are based on multivariate linear regression models and reflect the differences and 95% CIs for each amount of daily milk consumption compared with the lowest reference group. Models were adjusted for maternal age, height, BMI, parity, educational level, marital status, alcohol use, smoking, use of folic acid supplements, vomiting, nausea, daily energy intake, paternal height, fetal sex, gestational age at measurement, and consumption of fruit, vegetables, meat, fish, and coffee. *$P < 0.05$.

TABLE 3
Associations of maternal daily milk consumption with fetal femur length and birth length: the Generation R Study Cohort, Rotterdam, Netherlands[1]

	Femur length (n = 3330)			Femur length (n = 3334)			Birth length (n = 2321)		
Milk consumption	Subjects	Difference	95% CI	Subjects	Difference	95% CI	Subjects	Difference	95% CI
	n	*mm*	*mm*	*n*	*mm*	*mm*	*n*	*mm*	*mm*
0–1 glass/d	965	Reference	—	974	Reference	—	663	Reference	—
>1–2 glasses/d	783	0.1	−0.1, 0.3	784	−0.0	−0.3, 0.2	545	2.2	−0.3, 4.8
>2–3 glasses/d	922	0.1	−0.0, 0.3	919	0.0	−0.2, 0.3	653	1.7	−0.8, 4.2
>3 glasses/d	660	−0.1	−0.3, 0.1	657	−0.2	−0.4, 0.1	460	1.9	−0.9, 4.8
P for trend	—	0.72	—	—	0.35	—	—	0.37	—

[1] Values are based on multivariate linear regression models and reflect the differences and 95% CIs for each amount of daily milk consumption compared with the lowest reference group. Models were adjusted for maternal age, height, BMI, parity, educational level, marital status, alcohol use, smoking, use of folic acid supplements, vomiting, nausea, daily energy intake, paternal height, fetal sex, gestational age at measurement, and consumption of fruit, vegetables, meat, fish, and coffee.

unlikely to be driven by a general animal protein effect. (The results are presented in Supplemental Table 7 and Supplemental Figure 2 under "Supplemental data" in the online issue.)

DISCUSSION

Main findings

In this prospective cohort study of pregnant women in the Netherlands, we found that maternal milk consumption during pregnancy was associated with a greater fetal weight gain, resulting in a higher birth weight. It seems that the growth-promoting effect of milk may have an effect on fetal growth throughout pregnancy, but it tends to have the greatest effect on fetal growth in the third trimester of pregnancy. Furthermore, we specifically found that a higher intake of protein from milk, but not intake of fats or carbohydrates from milk, was associated with a higher birth weight.

Methodologic considerations

To our knowledge, this was the first study that assessed the associations of first-trimester maternal milk consumption with fetal growth characteristics measured in the second and third trimesters. The strength of this study was that we assessed fetal growth characteristics by actually measuring fetal growth instead of using birth outcomes as a proxy for fetal growth. In total, 88% of all eligible mothers fully completed the FFQ. The mean maternal age was 31.4 y, which is slightly higher than the mean maternal age of 29.4 y in the study area (34). Our study population was relatively highly educated; 59% finished higher education, as compared with 31% in the study area (35). This difference may have largely been due to restriction of the study population to white women. Selective participation may thereby have led to biased estimates. However, it has been shown that selection bias in cohort studies primarily arises from loss to follow-up rather than to nonresponse at baseline (36). We prospectively collected detailed information on milk and dairy consumption, which enabled separate analyses. Also, we extensively collected information on many potential confounding variables. However, as in any observational study, residual confounding might still have been an issue. Nonetheless, adjustment for confounders only marginally influenced the studied associations. Another limitation of the study was that the FFQ that was used was validated in an older white population. Also, we assessed maternal milk consumption only once during pregnancy. Therefore, we were unable to determine whether the associations were primarily due to milk consumption in the first trimester or later in pregnancy.

Interpretation of main results

Our results suggest that the growth-promoting effect of maternal milk consumption mainly affects fetal weight gain in the third trimester of pregnancy. The effect of milk consumption on head

TABLE 4
Associations of maternal daily milk consumption with estimated fetal weight and birth weight: the Generation R Study Cohort, Rotterdam, Netherlands[1]

	Estimated fetal weight (n = 3314)			Estimated fetal weight (n = 3322)			Birth weight (n = 3392)		
Milk consumption	Subjects	Difference	95% CI	Subjects	Difference	95% CI	Subjects	Difference	95% CI
	n	*g*	*g*	*n*	*g*	*g*	*n*	*g*	*g*
0–1 glass/d	961	Reference	—	969	Reference	—	987	Reference	—
>1–2 glasses/d	779	5.5	1.0, 9.9*	780	10.8	−8.4, 30.0	800	63.8	20.3, 107*
>2–3 glasses/d	921	5.2	0.9, 9.6*	917	15.0	−3.6, 33.6	939	63.8	21.7, 106*
>3 glasses/d	653	2.4	−2.5, 7.3	656	−5.7	−26.9, 15.6	666	87.5	39.3, 135*
P for trend	—	0.36	—	—	0.57	—	—	<0.01*	—

[1] Values are based on multivariate linear regression models and reflect the differences and 95% CIs for each amount of daily milk consumption compared with the lowest reference group. Models were adjusted for maternal age, height, BMI, parity, educational level, marital status, alcohol use, smoking, use of folic acid supplements, vomiting, nausea, daily energy intake, paternal height, fetal sex, gestational age at measurement, and consumption of fruit, vegetables, meat, fish, and coffee. *$P < 0.05$.

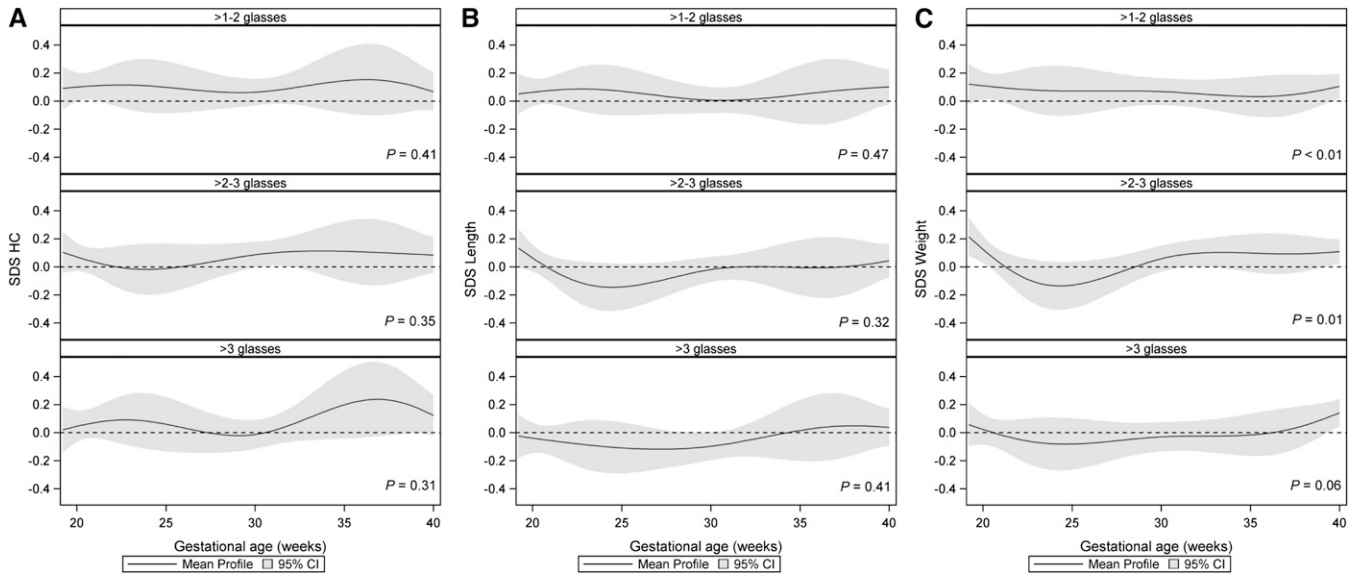

FIGURE 1. Associations of maternal daily milk consumption with longitudinally measured fetal growth characteristics: the Generation R Study, Rotterdam, Netherlands. The panels are based on spline regression models of longitudinally measured head circumference (HC) growth (n = 8542), length growth (n = 8947), and weight growth (n = 10,025) for each level of daily milk consumption compared with the lowest reference group. P values are based on multivariate F tests and reflect the difference between the spline of each milk-consumption category and the lowest reference category. Models were adjusted for maternal age, height, BMI, parity, educational level, marital status, alcohol use, smoking, use of folic acid supplements, vomiting, nausea, daily energy intake, paternal height, fetal sex, and consumption of fruit, vegetables, meat, fish, and coffee. The effect estimates of fetal growth differences at 40 wk of pregnancy based on these models are presented elsewhere (*see* Supplemental Table 1 under "Supplemental data" in the online issue). SDS, SD score.

growth remains uncertain. Several studies assessed the associations of maternal milk consumption with birth outcomes; however, not with fetal growth characteristics. In a large cohort in Denmark, higher maternal milk consumption was associated with higher neonatal weight, length, and abdominal and head circumferences (5). Likewise, we observed an association of milk consumption with offspring birth weight and a tendency toward an association of milk consumption with head circumference at birth. However, we did not observe an association of maternal milk consumption with length. This difference in results may have been due to the smaller size of our study population, or, less likely, to a slightly higher intake of milk in the Danish population than in the Dutch population. A retrospective cohort in Sweden reported a birth weight increase of 75 and 134 g in the offspring of mothers who consumed >2 dL and >1 L milk daily, respectively (11). In a prospective study in India, frequency of milk consumption at 18 wk of gestation was positively associated with birth weight, birth length, head circumference, and placental weight (8). In a prospective study in Canada, maternal daily consumption of an additional 1 cup (≈237 mL) of milk was associated with a 41-g increase in offspring birth weight (12). A prospective Australian study in 557 mothers found that protein intake from dairy products was associated with higher offspring birth weight (10). In a small randomized controlled trial of 72 adolescent pregnant mothers, 25 mothers were counseled to consume >4 servings of dairy products a day, which resulted in a 240-g higher birth weight in this group than in the control group (37). In a case-control study of 844 small-for-gestational age cases and 870 normal-weight controls in New Zealand, no significant association of dairy consumption and a lower risk of being small for gestational age was observed (9).

Our findings on macronutrient intakes from milk suggest that the growth-promoting effect was specifically driven by protein

TABLE 5
Associations of maternal daily milk consumption with the risks of neonatal complications: the Generation R Study Cohort, Rotterdam, Netherlands[1]

	Neonatal complications											
	Preterm birth (n = 160)				Small for gestational age (n = 169)				Large for gestational age (n = 185)			
Milk consumption	n	Cases	Odds ratio	95% CI	n	Cases	Odds ratio	95% CI	n	Cases	Odds ratio	95% CI
0–1 glass/d	943	47	Reference	—	938	52	Reference	—	951	40	Reference	—
>1–2 glasses/d	761	43	1.12	0.68, 1.83	765	41	0.81	0.49, 1.34	762	43	1.21	0.73, 2.01
>2–3 glasses/d	903	37	0.82	0.49, 1.38	899	41	0.79	0.28, 2.19	879	61	1.56	0.97, 2.49
>3 glasses/d	636	33	1.15	0.66, 2.00	635	35	0.84	0.49, 1.43	629	41	1.59	0.94, 2.70
P for trend	—	—	0.68	—	—	—	0.25	—	—	—	0.17	—

[1] Values are based on multivariate logistic regression models and reflect the odds ratios and 95% CIs for pregnancy complications for each amount of daily milk consumption compared with the lowest reference group. Models were adjusted for maternal age, height, BMI, parity, educational level, marital status, alcohol use, smoking, use of folic acid supplements, vomiting, nausea, daily energy intake, paternal height, fetal sex, gestational age at measurement, and consumption of fruit, vegetables, meat, fish, and coffee.

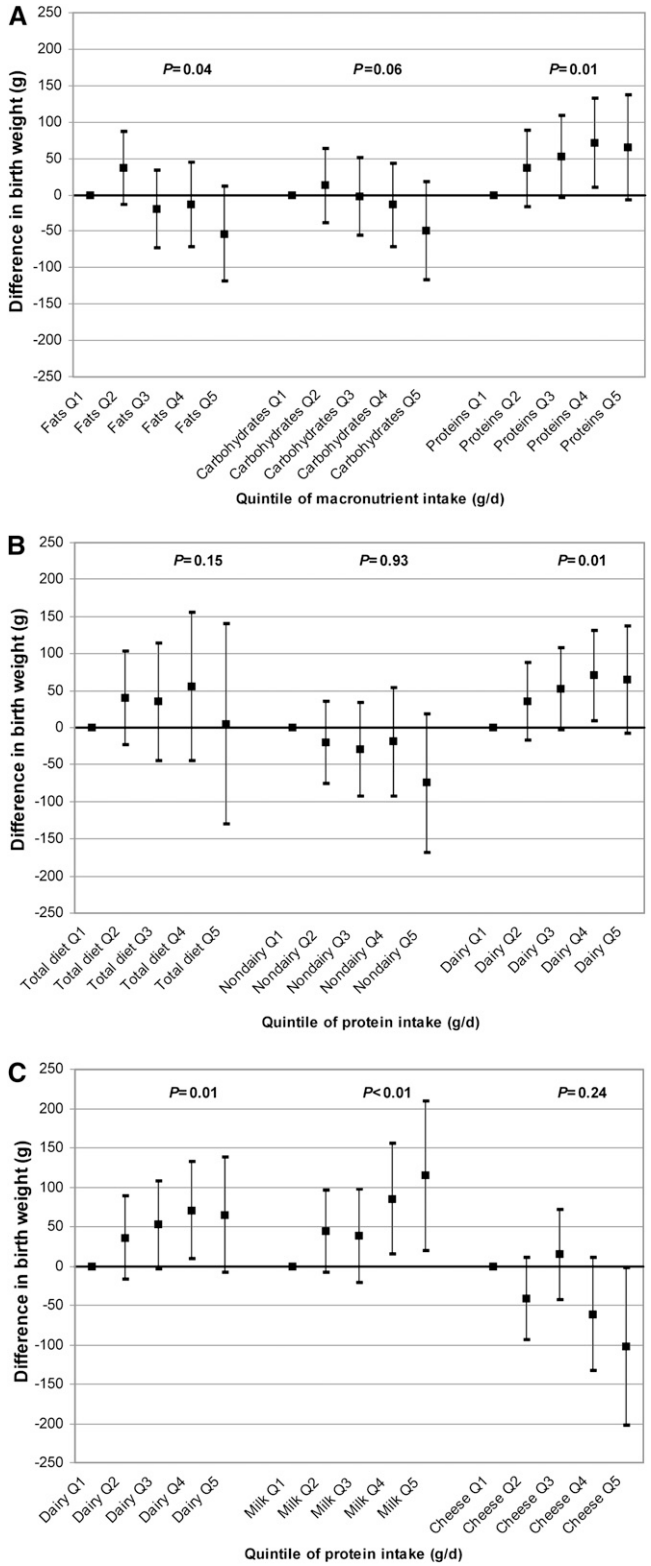

FIGURE 2. Associations of maternal macronutrient intake with offspring birth weight: the Generation R Study, Rotterdam, Netherlands. Results are based on multivariate linear regression models and reflect the difference and 95% CI for each level of daily macronutrient intake from dairy products (A); protein intake from total diet, nondairy products, or dairy products (B); and protein intake from dairy products, milk, or cheese consumption (C) compared with the lowest reference group. Models were adjusted for maternal age, height, BMI, parity, educational level, marital status, alcohol use, smoking, use of folic acid supplements, vomiting, nausea, daily energy intake, paternal height, fetal sex, gestational age at measurement and mutually for the other macronutrients, and consumption of fruit, vegetables, meat, fish, and coffee. The corresponding effect estimates and CIs are presented elsewhere (*see* Supplemental Tables 2, 3, and 4 under "Supplemental data" in the online issue). Q, quintile.

intake from milk, not by protein intake from cheese or other foods. In line with our findings, protein intake, but not fat intake, from dairy products was associated with higher birth weight in the Danish study (5). A high intake of protein from dairy products resulted in a 65-g higher birth weight, which is comparable with our findings. Likewise, protein intake from nondairy products and cheese was not associated with birth weight in the Danish study. The explanation for the difference between the effects of protein from milk and cheese on fetal growth is unknown. A methodologic explanation may be that reported milk consumption is a better predictor of intake of beneficial constituents in dairy products and thus leads to higher effect estimates. Alternatively, from a biological perspective, alteration of the structure of casein proteins or loss of whey proteins during the process of cheese production may lead to a different biological activity of its constituents (38).

Potential underlying mechanisms

Milk contains various nutrients potentially beneficial for fetal growth. Milk consumption is known to increase IGF-I blood concentrations in both adults and children (17, 18, 39–41). Some of the previous studies that reported an association of milk protein intake with IGF-I also reported an association of calcium intake with IGF-I concentrations (14, 15, 21, 39). Because we did not measure IGF-I or calcium blood concentrations, additional studies are needed to explore whether IGF-I or calcium concentrations involved in the underlying mechanism responsible for the associations between maternal milk consumption and fetal growth. Vitamin D has also been suggested to contribute to the association between milk consumption and fetal growth (12). However, vitamin D is unlikely to explain our findings because, in the Netherlands, milk is not enriched with vitamin D and naturally occurring concentrations of vitamin D in milk are negligible (42).

Conclusions

In a Dutch population-based cohort, we observed an association between higher milk consumption and greater fetal weight gain, particularly in the third trimester of pregnancy. Our results suggest that this association is mediated by the protein fraction and not by the fat or carbohydrate fraction of milk. Additional research is needed to clarify the mechanisms underlying these associations and the long-term consequences.

The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and the Faculty of Social Sciences at the Erasmus University, Rotterdam, the Municipal Health Service, Rotterdam area, and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (Star-MDC), Rotterdam. We gratefully acknowledge the contribution of general practitioners, hospitals, midwives, and pharmacies in Rotterdam.

The authors' responsibilities were as follows—DHMH and VWVJ: designed the study; DHMH, SPW, and HdB: performed the statistical analyses; DHMH, RMvD, HR, AH, EAPS, and VWVJ: wrote the manuscript; and DH: had primary responsibility for the final content. None of the authors had a financial or personal conflict of interest related to the content of the study.

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