Maternal vitamin D intake during pregnancy and early childhood wheezing[1–4]

Graham Devereux, Augusto A Litonjua, Stephen W Turner, Leone CA Craig, Geraldine McNeill, Sheelagh Martindale, Peter J Helms, Anthony Seaton, and Scott T Weiss

ABSTRACT

Background: Maternal intake of vitamin D in pregnancy is a potentially modifiable but understudied risk factor for the development of asthma in children.

Objective: We investigated whether maternal vitamin D intake in pregnancy is associated with decreased risks of wheezing symptoms in young children.

Design: Subjects were from a birth cohort recruited in utero with the primary objective of identifying associations between maternal diet during pregnancy and asthma and allergies in children. A random sample of 2000 healthy pregnant women was recruited while attending antenatal clinics at the Aberdeen Maternity Hospital, Scotland, at ≈12 wk gestation. Maternal vitamin D intake was ascertained from a food-frequency questionnaire completed at 32 wk of gestation. The main outcome measures were wheezing symptoms, spirometry, bronchodilator response, atopic sensitization, and exhaled nitric oxide at 5 y.

Results: Respiratory details through 5 y and maternal food-frequency-questionnaire data were available for 1212 children. In models adjusted for potential confounders, including the children's vitamin D intake, a comparison of the highest and lowest quintiles of maternal total vitamin D intake conferred lower risks for ever wheeze [odds ratio (OR): 0.48; 95% CI: 0.25, 0.91], wheeze in the previous year (OR: 0.35; 95% CI: 0.15, 0.83), and persistent wheeze (OR: 0.33; 95% CI: 0.11, 0.98) in 5-y-old children. In addition, lower maternal total vitamin D intakes in pregnancy were also associated with decreased bronchodilator response ($P = 0.04$). No associations were observed between maternal vitamin D intakes and spirometry or exhaled nitric oxide concentrations.

Conclusion: Increasing maternal vitamin D intakes during pregnancy may decrease the risk of wheeze symptoms in early childhood. *Am J Clin Nutr* 2007;85:853–9.

KEY WORDS Vitamin D intake, pregnancy, wheezing, asthma

INTRODUCTION

Antenatal and early life exposures are increasingly being recognized as determinants of a range of disorders throughout life (1). Although many early postnatal exposures have been studied for their association with asthma, maternal smoking during pregnancy is the only known antenatal modifiable risk factor for reduced lung function (2, 3), wheezing illnesses (3–5), and asthma (5, 6). Maternal diet during pregnancy is a modifiable exposure with the potential to influence the development of asthma and allergies. In 1994, Seaton et al (7) proposed that the recent increases in asthma prevalence could be explained by changes in diet. We subsequently showed, in 2 birth cohorts, that higher maternal dietary vitamin E and zinc intakes in pregnancy are associated with decreased risks of wheezing illnesses and asthma in young children (8–10), which highlights maternal diet as an exposure worth further study.

Vitamin D is both a nutrient and a hormone, and blood concentrations are dependent on dietary intakes and exposure to sunlight. Vitamin D deficiency is well-documented, not only in the elderly but in general populations around the world (11), and current recommended intakes may be inadequate for the maintenance of health (12), particularly in pregnant and lactating women (13, 14). This deficiency may contribute to the increased prevalence of both atopic and autoimmune disorders. Vitamin D and its receptor are important in immune function and development (15) and, therefore, could potentially have a role in the development of asthma and allergies. Initial direct evidence implicating vitamin D in asthma comes from studies showing that vitamin D receptor (VDR) gene polymorphisms are associated with asthma (16, 17) in 2 North American family-based studies. Additionally, recent cross-sectional studies have shown that vitamin D concentrations and vitamin D intakes are associated with lung function level in adults (18) and adolescents (19), respectively.

A separate analysis in a North American birth cohort showed that maternal intakes of vitamin D during pregnancy were inversely associated with wheezing illnesses in 3-y-old children (20). We therefore analyzed data from our Aberdeen cohort to investigate whether this relation is present in addition to those with vitamin E and minerals already reported. Thus, the aim of our study was to investigate the association between maternal vitamin D intake during pregnancy and asthma and wheezing

[1] From the Departments of Environmental and Occupational Medicine (GD, LCAC, GM, SM, and AS) and Child Health (SWT, GM, and PJH), University of Aberdeen, Aberdeen, United Kingdom, and the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (AAL and STW).

[2] GD and AAL contributed equally to this manuscript and are both first authors.

[3] Supported by Asthma UK (grant 02/017).

[4] Address reprint requests to AA Litonjua, Channing Laboratory, 181 Longwood Avenue, Boston, MA 02115. E-mail: augusto.litonjua@channing.harvard.edu.

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illnesses in 5-y-old children in a cohort with distinct demographic and dietary intakes from the North American birth cohort. We also investigated associations between maternal vitamin D intake in pregnancy and lung function, bronchodilator response (BDR), and exhaled nitric oxide in a subset of these children.

SUBJECTS AND METHODS

Study subjects and protocol

Procedures concerning the recruitment of pregnant women and the follow-up of their children were described previously (8, 9). Briefly, 2000 healthy pregnant women were recruited over 19 mo during 1997 and 1999 while attending a hospital antenatal clinic at ≈12 wk (median) of gestation [interquartile range (IQR): 11–13 wk). The women were recruited irrespective of their asthma or atopic status and, other than expected slight biases, were representative of the local obstetric population (8). The women were characterized by an interviewer-administered questionnaire, and atopic status was ascertained by skin-prick testing.

At 32 wk of gestation, dietary intake over the preceding 3 mo was assessed by using version 5.4 of the Scottish Collaborative Group Food Frequency Questionnaire (FFQ). Vitamin D intake was expressed as International Units (IU), with 1 IU equating to 0.025 μg cholecalciferol. In 40 women of childbearing age, the Spearman rank correlation coefficients for intakes of vitamin D and calcium derived from this questionnaire and 4-d weighed records were 0.37 ($P < 0.05$) and 0.75 ($P < 0.001$) (21).

Assessment of children

Singletons born to the cohort of women were followed up at 2 and 5 y. Six weeks before the children's second and fifth birthdays, a questionnaire based on the format of the International Study of Asthma and Allergies in Childhood (8, 9) was mailed to all participating families; no more than 2 reminders were sent. Wheeze was defined by an affirmative response to the question, "Has your child had wheezing or whistling in the chest in the last 12 mo? " Similar questions inquired about whether the children had ever wheezed, had ever been asthmatic, and had ever had doctor-diagnosed asthma.

Parents responding to the 5-y questionnaire were invited to participate in assessments of the children's diet, ventilatory function, and atopic status. Version C1 of the Scottish Collaborative Group FFQ was used to assess the study children's dietary intake. This FFQ is based on the questionnaire used for the mothers, but was modified for use in children aged 3–5 y by simplifying the response choices and changing the food list and portion sizes to be appropriate for preschool children. In 74 children aged 3–5 y who were recruited from local nurseries, the rank correlation coefficients for intakes of vitamin D and calcium derived from this FFQ and from 4-d nonweighed food diaries were 0.31 ($P = 0.007$) and 0.38 ($P = 0.001$) (9).

At 5 y, the responding parents were invited to bring their children to the hospital for an assessment of spirometry, atopic status, and exhaled nitric oxide (FE_{NO}). The methods used were described previously (9) Briefly, spirometry was measured with a pneumotachograph (Spirotrac IV version 4.22; Vitalograph, Maids Moreton, United Kingdom) with onscreen incentive software. The spirometric values presented were the best from ≥2 technically acceptable expiratory maneuvers (22). BDR was expressed as the percentage change in forced expiratory volume in 1 s (FEV_1) 15 min after inhalation of 400 μg albuterol. BDR was not included in the original study protocol but was introduced for the last 510 children. A NIOX analyzer (Aerocrine, Solna, Sweden) was used to measure FE_{NO} in accordance with international guidelines (23). Measurements of FE_{NO} were not included in the original study protocol but were included in the last 262 assessments after a methodologic study showed that FE_{NO} measurements could be obtained in 65% of children aged 5 y with good reproducibility (24). Atopy was defined as at least one positive skin-prick response (mean weal diameter ≥3 mm larger than the negative control) to the allergens cat, timothy grass, egg, and house dust mite (ALK, Hungerford, United Kingdom). The Grampian Research Ethics Committee approved the study, and written parental consent was obtained.

Statistical analysis

The primary outcome variables of interest were the prevalence of wheeze and asthma. In addition to the wheeze outcomes at 2 and 5 y of age, wheezing data for the children at these ages were combined to classify children into wheezing phenotypes analogous to those used in other birth cohorts, namely, never wheezed, early-transient (wheezing at 0–2 y but not at 5 y of age), late-onset (no wheezing at 0–2 and at 5 y of age), and early persistent wheezers (wheezing at 0–2 and at 5 y of age) (25, 26). At 5 y, the secondary outcome variables were FEV_1, BDR, FE_{NO}, and atopic status. The primary exposure of interest was maternal vitamin D intake. Maternal and children's dietary and supplemental vitamin D intakes were summed to give a total intake, logarithmically transformed, energy adjusted, and divided into fifths (27). To aid the extrapolation of results to the general population, the quintiles of vitamin D intake were derived from the data for all of the women who completed the FFQ and not merely from those who responded at 2 or 5 y. Univariate associations between outcome variables and explanatory variables were assessed with Mantel-Haenszel odds ratios (OR); multivariate analysis was carried out by using appropriate multivariate regression with adjustment for potentially confounding covariates. Similar analyses related children's vitamin D intake to respiratory outcomes. Analyses were performed with the use of SPSS version 13.0 (SPSS Inc, Chicago, IL).

RESULTS

Characteristics of mother-infant pairs

Of the 2000 pregnant women recruited, 1751 (87.6%) completed the FFQ. The questionnaire response rates at 2 and 5 y were 1374 (71.4%) and 1253 (65.1%); estimates of maternal vitamin D intake from the FFQ were available for 1335 (97.2%) and 1212 (96.7%) of these groups, respectively, and 1924 singletons were born to the cohort.

Of the 1253 children with symptom questionnaire data at 5 y, dietary data were available for 1120 (89%) and 797 (64%) children who had attended the hospital for assessment. All of the children attempted to perform spirometry; 639 were successful and 478 were able to provide a prebronchodilator FEV_1 measurement. Five hundred two children attempted postbronchodilator spirometry; 383 were successful and 238 were able to provide a postbronchodilator measurement. Skin-prick reactivity

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TABLE 1
Energy-adjusted total vitamin D intakes of mothers by response status of children at 2 and 5 y

		Response at 2 y		Response at 5 y	
Vitamin D	32 wk gestation (n = 1751)	Responder (n = 1335)	Nonresponder (n = 416)	Responder (n = 1212)	Nonresponder (n = 539)
Median intake (IU/d)[1]	128 (99–170)	131[2] (101–175)	118[2] (92–158)	131 (102–173)	122[2] (92–167)
5th–95th Centiles (IU/d)	67–445	68–468	60–389	70–486	61–364

[1] North American Adequate Intake for pregnant women = 200 IU/d. Interquartile range in parentheses.
[2] $P < 0.001$ (Mann-Whitney U test).

and FE_{NO} were determined in 700 (56%) and 167 (7%) children, respectively.

The characteristics of the mothers and children responding at 2 and 5 y were described previously (8, 9). Mothers responding to the 2- and 5-y questionnaire were less likely to smoke, were older, were of higher socioeconomic status (SES), were less likely to have wheezed or to have had asthma, and had slightly higher vitamin D intakes than did the women who failed to respond (**Table 1**) (8, 9). The participating children were slightly larger at birth, were more likely to have had a cesarean delivery, were more likely to have been breastfed (8, 9). The mothers and children who attended the hospital for the assessment of spirometry, FE_{NO}, and atopic status were representative of those responding to the questionnaire (9).

The characteristics of the mothers and children at recruitment and delivery and at the follow-up of the children at 2 and 5 y are outlined in **Table 2**. For more details of the cohort characteristics, *see* Table A under "Supplemental data" in the current online issue at www.ajcn.org. Maternal total vitamin D intake was negatively associated with smoking and was positively associated with age, SES, breastfeeding of child, other children in the home at 5 y, use of vitamin D supplements, and intakes of vitamin E, zinc, and calcium. Total vitamin D intake by the children was positively associated with maternal total vitamin D intake (rank correlation coefficient = 0.16, $P < 0.001$). No independent significant associations were observed between maternal vitamin D intake and wheezing symptoms in the children at 2 y of age.

TABLE 2
Characteristics of mother-infant pairs at recruitment and delivery and of the children responding at 5 y[1]

Mothers (n = 1751)	
Median energy-adjusted intake (IU/d)[2]	128
Interquartile range (IU/d)	103–165
5th–95th percentile (IU/d)	67–445
Use of vitamin D supplements (%)	10.5
Use of any vitamin supplements (%)	45
Geometric mean calcium intake, (mg/d)	1232 (1209, 1255)
Maternal age at enrollment (y)	29.2 (28.9, 29.4)
Partner of nonmanual social class (%)	57.9
Maternal smoking during pregnancy (%)	26.7
Ever asthma (%)	16.1
Atopic sensitisation (%)	35.8
LMP during winter or a spring vs summer or autumn (%)	41.2
Children (n = 1751)	
Boys (%)	51.2
Mean birth weight (g)	3099 (2974, 3233)
Ever breastfed (%)	72.0
Children at 5 y (n = 1253)	
Smoker in home (%)	24.5
One adult smoker in home (%)	16.2
≥2 Smokers in home (%)	8.3
Median energy-adjusted vitamin D intake (IU/d)	47
Interquartile range (IU/d)	35–88
5th–95th percentile (IU/d)	22–242
Use of vitamin D supplements (%)	24.1

[1] 95% CI in parentheses.
[2] North American Adequate intake for pregnant women = 200 IU/d.

Maternal vitamin D intake and symptoms in children aged 5 y

Maternal total vitamin D intake from the diet and supplements was negatively associated with the symptoms "ever wheeze", "wheeze in the previous year," and "persistent wheeze" at 2 and 5 y of age (**Table 3**) but not with asthma in children aged 5 y (OR per quintile of maternal energy-adjusted vitamin D intake 0.99, 95% CI: 0.83, 1.17, $P = 0.98$). We previously reported in this cohort that maternal vitamin E and zinc intakes are associated with 5-y outcomes; however, the associations with maternal total vitamin D intake remained significant even after adjustment for maternal vitamin E and zinc intakes. Separate analyses in which maternal smoking status during pregnancy was replaced with parental smoking status or with the number of smokers in the 5-y-old child's house (24.5% of 5-y-olds were from a smoking household) did not change the nature or the strength of the associations with vitamin D. The associations between maternal total vitamin D intake and 5-y outcomes were independent of total vitamin D intake by the children.

Associations similar to those seen for total intakes were seen for maternal dietary vitamin D intake during pregnancy. No associations between children's symptoms at 5 y and maternal calcium intake were observed.

Maternal vitamin D intake and atopy and FE_{NO} in children aged 5 y

Maternal total and dietary vitamin D intakes were not associated with atopic sensitization (700 children) or with FE_{NO} (167 children).

Maternal vitamin D intake and spirometry in children aged 5 y

Maternal total and dietary vitamin D intake were not associated with prebronchodilator $FEV_{0.5}$, $FEV_{0.75}$, FEV_1, $FEF_{25–75}$, FEF_{50}, PEF, and FVC in univariate or multivariate analyses. The median BDR in 238 children was 4.4% (interquartile range: 0-8.4). The distribution of BDR was normal for this population. In a univariate analysis, BDR was 3.6% in the 39 children whose

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TABLE 3
Univariate and multivariate analyses of total maternal vitamin D intake and likelihood of wheezing symptoms in children aged 5 y[1]

	Quintile of energy-adjusted maternal vitamin D intake					
	1 (n = 213)	2 (n = 246)	3 (n = 237)	4 (n = 261)	5 (n = 255)	P for trend[2]
Median energy-adjusted intake (IU/d)[3]	77	104	128	157	275	
5th–95th percentile (IU/d)	46–92	94–115	117–139	142–182	189–751	—
Ever wheeze (n = 20.1%)						
Unadjusted	1	0.85 (0.55, 1.31)[4]	0.85 (0.55, 1.32)	0.65 (0.42, 1.01)	0.53 (0.34, 0.85)	0.004
Multivariate model 1[5]	1	0.84 (0.51, 1.37)	0.77 (0.46, 1.27)	0.65 (0.39, 1.11)	0.56 (0.31, 1.01)	0.04
Multivariate model 2[6]	1	0.86 (0.51, 1.47)	0.70 (0.41, 1.20)	0.57 (0.32, 1.01)	0.48 (0.25, 0.91)	0.01
Wheeze in previous year (n = 12.8%)						
Unadjusted	1	1.033 (0.62, 1.72)	0.98 (0.58, 1.65)	0.82 (0.49, 1.38)	0.40 (0.22, 0.75)	0.004
Multivariate model 1[5]	1	1.09 (0.61, 1.95)	0.98 (0.54, 1.80)	0.80 (0.42, 1.52)	0.45 (0.21, 0.97)	0.04
Multivariate model 2[6]	1	1.27 (0.68, 2.37)	0.95 (0.49, 1.82)	0.70 (0.35, 1.41)	0.35 (0.15, 0.83)	0.009
Persistent wheeze at 2 and 5 y (n = 7.6%) vs never wheeze						
Unadjusted	1	0.86 (0.45, 1.66)	0.81 (0.42, 1.56)	0.63 (0.32, 1.24)	0.39 (0.18, 0.84)	0.01
Multivariate model 1[5]	1	0.91 (0.44, 1.88)	0.75 (0.35, 1.61)	0.51 (0.22, 1.20)	0.43 (0.16, 1.12)	0.04
Multivariate model 2[6]	1	1.10 (0.51, 2.35)	0.63 (0.27, 1.45)	0.43 (0.17, 1.11)	0.33 (0.11, 0.98)	0.01

[1] n = 1212.
[2] The Wald test was used to compute P for trend across the quintiles of vitamin D intake, from logistic regression models.
[3] North American Adequate Intake for pregnant woman = 200 IU/d.
[4] Odds ratio; 95% CI in parentheses (all such values).
[5] Adjusted for maternal atopy, maternal age, maternal smoking, maternal age at termination of full-time education, paternal social class, deprivation index based on area of residence, breastfeeding, infant sex, infant antibiotic use in first year, birth weight, birth order, season of last menstrual period, and maternal intakes of vitamin E, zinc, and calcium.
[6] Adjusted for model 1 variables plus energy-adjusted children's vitamin D intake at 5 y.

mothers had the lowest quintile of total vitamin D intake, 2.5% for the 57 children in the second quintile, 3.2% for the 34 children in the third quintile, 5.0% for the 50 children in the fourth quintile, and 6.1% for the 50 children in the highest tertile ($P = 0.115$, analysis of variance). After the adjustment for confounders (including sex, atopy, baseline prebronchodilator FEV_1, and maternal vitamin E intake), lower maternal vitamin D intake was associated with a decreased BDR ($P = 0.036$; **Table 4**).

Children's vitamin D intake and symptoms at 5 y of age

No significant associations were observed between the total and dietary vitamin D intakes of children and respiratory symptoms, atopic sensitization, spirometry, or FE_{NO}.

TABLE 4
Results of linear regression analysis relating bronchodilator response (%) to maternal daily total vitamin D intake during pregnancy (IU/d)[1]

	Regression coefficient (95% CI)	P
Lowest quintile maternal vitamin D	−4.0 (−7.4, −0.7)	—
Second quintile maternal vitamin D	−4.3 (−7.3, −1.2)	—
Third quintile maternal vitamin D	−4.4 (−7.9, −1.0)	0.04[2]
Fourth quintile maternal vitamin D	−2.2 (−5.3, 0.9)	—
Fifth quintile maternal vitamin D	0	
Male sex	2.2 (0.2, 4.1)	0.04
Atopy	−2.4 (−4.7, −0.1)	0.04
FEV_1 (L)	−6.2 (−11.8, −0.7)	0.03

[1] FEV_1, forced expiratory volume in 1 s.
[2] For trend across quintiles.

DISCUSSION

Our analyses showed that low maternal dietary and total vitamin D intakes during pregnancy are associated with increased wheezing symptoms in children at the age of 5 y. These associations were independent of maternal smoking status and maternal intakes of vitamin E, zinc, calcium, and vitamin D by the 5-y-old children.

Vitamin D is important for the regulation of calcium homeostasis, bone formation, and resorption. However, VDRs (28, 29) and vitamin D metabolic enzymes (11, 30) have been identified in many tissues other than bone and the intestine, which suggests involvement in the metabolism and function of many cell types. Specifically, VDRs are expressed in cells of the immune system, such as T cells (31), activated B cells (32), and dendritic cells (33). Indeed, vitamin D has been linked with a diverse group of disorders characterized by immunologically mediated inflammation, such as type 1 diabetes mellitus (34, 35), multiple sclerosis (36), and rheumatoid arthritis (37). Additionally, vitamin D has been implicated in the susceptibility to mycobacterial (38, 39) and HIV (40) disease and with antimicrobial innate immune responses (41). With regard to the development of asthma and allergies, experimental models of asthma have shown that vitamin D may alter the balance between T helper subset 1 cell and T helper subset 2 cell cytokine secretion (42, 43). Reduced secretion of the T helper subset 1 cell cytokines interleukin (IL) 2 and interferon (IFN) γ (43, 44) and an increase in the T helper subset 2 cell cytokine IL-4 (45, 46) have been observed after treatment with 1,24-dihydroxyvitamin D. In contrast, Pichler et al (47) showed that in human $CD4^+$ and $CD8^+$ cord blood cells, vitamin D inhibits not only IL-12–generated

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IFN-γ production, but also suppresses T helper subset 2 cell–related IL-4 and IL-4–induced expression of IL-13. Although seemingly contradictory, it is possible that the effects of vitamin D on these cells are dependent on the timing of exposure (ie, prenatal compared with postnatal); thus, the response to vitamin D exposure of naïve T cells in the fetus or neonate may differ from that of mature cells (48). Because vitamin D deficiency has been documented in populations around the world, we speculate that this may contribute to the rise in prevalence of both T helper subset 1 cell and T helper subset 2 cell diseases.

Vitamin D has been linked to fetal lung development in animal models (49, 50), and higher vitamin D concentrations and intakes are associated with higher lung function in adults (18) and adolescents (19), respectively. Although we did not find any association between maternal vitamin D intake and lung function at 5 y, we did see a positive association with BDR in a subset of the children. This association should be interpreted with caution because, although the children able to achieve a post-BDR were representative of those attending for clinical evaluation, they were relatively small in number ($n = 238$). The positive association with BDR appears contradictory to our wheeze findings; however, a greater BDR in early childhood asthmatics has been shown to predict higher FEV_1 values after 4 y (51), which suggests that a larger BDR in childhood may be a marker of greater potential lung growth as the child gets older. Further follow-up of the cohort is needed to clarify this association.

Initial evidence implicating vitamin D in asthma and allergy development came from studies of genetic associations in humans. Significant associations between polymorphisms in the VDR gene with asthma have been reported in 2 family-based studies of North American subjects (16, 17). However, 2 subsequent German studies found no significant associations (52, 53). In addition to genetics, evidence indicates that vitamin D may have a therapeutic role in asthma by enhancing responsiveness to glucocorticoids for induction of IL-10 (54). A birth cohort from Northern Finland has shown that vitamin D supplementation in the first year of life increased the risk of asthma and atopy at 31 y of age (55). However, this study did not assess maternal or childhood vitamin D intakes and did not assess childhood asthma and atopy. The results of the present study are consistent with only one other study (20) to date that has assessed maternal vitamin D intakes during pregnancy; both studies indicated that childhood vitamin D intake is not associated with recurrent wheezing in childhood and that prenatal mechanisms probably underlie the effect of vitamin D.

The original study population of 2000 pregnant women was very similar demographically to the local obstetric population (8), but there has been some loss to follow-up with time (9). Of particular concern were the lower response rates of women with a lower SES, who were more likely to smoke during pregnancy and to have lower intakes of vitamin D during pregnancy. Accordingly, several measures of smoking exposure (maternal smoking status during pregnancy and number of smokers in the household at age 5 y) and SES status (maternal age of leaving full time education, paternal social class, ad deprivation score based on area of residence) were included in the regression analysis; however, the inclusion of these measures had a minimal effect on the association between maternal vitamin D intake and wheezing outcomes. Although the evidence indicated response biases typical of this type of study, it is unlikely that these biases accounted for our observations because the nature of the biases would be to weaken the observed negative associations rather than to augment them. (*See* "Supplemental data" in the current online issue at www.ajcn.org for a full discussion of these potential biases.)

At the time of inception of the study, it was not standard practice to recommend universal vitamin supplementation during pregnancy; thus, only 45% of the women were taking any vitamin supplements, and 10.5% were taking supplements containing vitamin D. The vitamin D intakes of the women participating in the study were slightly higher ($\bar{x}$: 137 IU/d) than the average vitamin D intake by women in the United Kingdom ($\bar{x}$: 112 IU/d) reported by the UK National Diet and Nutrition Survey (56), which possibly reflects the enrichment of our study sample by women of a higher SES. These means are still below the current recommended intakes for pregnant women in North America (Adequate Intake = 200 IU/d) (57).

The North American study (20) and the present study have identified similar associations in 2 geographically disparate areas (Boston, MA, 42 °N; Aberdeen, Scotland, 57 °N) in 2 populations that differ demographically. When compared with their North American counterparts, mothers in the present study had a lower vitamin D intake (137 compared with 548 IU/d in the North American study), were younger, were more likely to smoke during pregnancy, were less likely to have a degree, and were almost universally white (98%), which reflected the local population. Although the demonstration of similar associations in 2 distinct populations increases confidence in the validity and biological relevance of the associations, we cannot entirely eliminate the possibility that the observed associations are a consequence of residual confounding by factors associated with a higher SES and a healthy lifestyle.

In the United Kingdom, margarine is fortified with vitamin D and common sources of dietary vitamin D for UK women are fish (25%), meat and meat products (22%), cereals and grains (21%), spreads (17%), and eggs (9%). There is some overlap with the food groups that are sources of dietary vitamin E intake, spreads (18%), cereals and grains (17%), potato products (13%), vegetables (13%), meat and meat products (11%), fish (5%), and eggs (3%) (52). It seems unlikely that the associations between maternal vitamin D intakes and childhood wheezing could be a consequence of confounding by maternal vitamin E intake, because the associations with vitamin D persisted after adjustment for maternal vitamin E intake. Although we did not observe a statistically significant association between maternal vitamin D intakes and childhood asthma, we did find an inverse association with asthma treatment (data not shown). Thus, further follow-up of this cohort will clarify this association.

In summary, we report an inverse association between maternal vitamin D intake in pregnancy and risk of recurrent wheezing in 5-y-old children. Our results are of great public health significance because they could lead to relatively low cost interventions of vitamin D supplementation that would have a large effect on the future prevalence of asthma in children.

GD, AS, PJH, and GM designed the overall study, obtained funding, and provided critical reviews of the manuscript. GD defined the variables, analyzed the data, and wrote and revised the manuscript. AAL conceived and designed the analysis plans, assisted in the data analysis, and wrote and revised the manuscript. SWT supervised the clinical follow-up of the children, analyzed the spirometry and FE_{NO} data, and provided critical reviews. LCAC managed the study database, ensured quality control of the data, validated the children's FFQ, and provided critical reviews of the manuscript. GM provided nutritional advice and critical reviews of the manuscript. SM

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recruited the cohort of mothers, conducted the follow-up of the children at 2 y, and provided critical reviews. STW helped conceive the analysis plans, provided critical reviews, and helped revise the manuscript. The authors had no conflicts of interest to report related to the data in the manuscript.

REFERENCES

1. Gillman MW. Developmental origins of health and disease. N Engl J Med 2005;353:1848–50.
2. Hanrahan JP, Tager IB, Segal MR, et al. The effect of maternal smoking during pregnancy on early infant lung function. Am Rev Respir Dis 1992;145:1129–35.
3. Tager IB, Hanrahan JP, Tosteson TD, et al. Lung function, pre- and post-natal smoke exposure, and wheezing in the first year of life. Am Rev Respir Dis 1993;147:811–7.
4. Gold DR, Burge HA, Carey V, Milton DK, Platts MT, Weiss ST. Predictors of repeated wheeze in the first year of life. The relative roles of cockroach, birth weight, acute lower respiratory illness, and maternal smoking. Am J Respir Crit Care Med 1999;160:227–36.
5. Gilliland FD, Li YF, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. Am J Respir Crit Care Med 2001;163:429–36.
6. Skorge TD, Eagan TM, Eide GE, Gulsvik A, Bakke PS. The adult incidence of asthma and respiratory symptoms by passive smoking in uterus or in childhood. Am J Respir Crit Care Med 2005;172:61–6.
7. Seaton A, Godden DJ, Brown KM. Increase in asthma: a more toxic environment or a more susceptible population? Thorax 1994;49:171–4.
8. Martindale S, McNeill G, Devereux G, Campbell D, Russell G, Seaton A. Antioxidant intake in pregnancy in relation to wheeze and eczema in the first two years of life. Am J Respir Crit Care Med 2005;171:121–8.
9. Devereux G, Turner SW, Craig LCA, et al. Reduced maternal vitamin E intake during pregnancy is associated with asthma in 5-year-old children. Am J Respir Crit Care Med 2006;174:499–507.
10. Litonjua AA, Rifas-Shiman SL, Ly NP, et al. Maternal antioxidant intake in pregnancy and wheezing illnesses at 2 y of age. Am J Clin Nutr 2006;84:903–11.
11. Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc 2006;81:353–73.
12. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr 2005;135:317–22.
13. Hollis BW, Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. Am J Clin Nutr 2004; 80(suppl):1752S–8S.
14. Hollis BW, Wagner CL. Nutritional vitamin D status during pregnancy: reasons for concern. CMAJ 2006;174:1287–90.
15. Griffin MD, Xing N, Kumar R. Vitamin D and its analogs as regulators of immune activation and antigen presentation. Annu Rev Nutr 2003; 23:117–45.
16. Raby BA, Lazarus R, Silverman EK, et al. Association of vitamin D receptor gene polymorphisms with childhood and adult asthma. Am J Respir Crit Care Med 2004;170:1057–65.
17. Poon AH, Laprise C, Lemire M, et al. Association of vitamin D receptor genetic variants with susceptibility to asthma and atopy. Am J Respir Crit Care Med 2004;170:967–73.
18. Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin d and pulmonary function in the third national health and nutrition examination survey. Chest 2005;128:3792–8.
19. Burns JS, Dockery DW, Speizer FE. Low levels of dietary vitamin D intake and pulmonary function in adolescents. Proc Am Thoracic Soc 2006;3:A526(abstr).
20. Camargo CAJ, Rifas-Shiman SL, Litonjua AA, et al. Prospective study of maternal intake of vitamin D during pregnancy and risk of wheezing illnesses in children at age 2 years. J Allergy Clin Immunol 2006;117: 721–2(abstr).
21. Masson LF, McNeill G, Tomany JO, et al. Statistical approaches for assessing the relative validity of a food-frequency questionnaire: use of correlation coefficients and the kappa statistic. Public Health Nutr 2003; 6:313–21.
22. Aurora P, Stocks J, Oliver C, et al. Quality control for spirometry in preschool children with and without lung disease. Am J Respir Crit Care Med 2004;169:1152–9.
23. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. Am J Respir Crit Care Med 2005;171:912–30.
24. Napier E, Turner SW. Methodological issues related to exhaled nitric oxide measurement in children aged four to six years. Pediatr Pulmonol 2005;40:97–104.
25. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;332:133–8.
26. Henderson J, North K, Griffiths M, Harvey I, Golding J. Pertussis vaccination and wheezing illnesses in young children: prospective cohort study. The Longitudinal Study of Pregnancy and Childhood Team. BMJ 1999;318:1173–6.
27. Willett WC. Future directions in the development of food-frequency questionnaires. Am J Clin Nutr 1994;59(suppl):171S–4S.
28. Dickson I. New approaches to vitamin D. Nature 1987;325:18.
29. Minghetti PP, Norman AW. 1,25$(OH)_2$-vitamin D_3 receptors: gene regulation and genetic circuitry. FASEB J 1988;2:3043–53.
30. Akeno N, Saikatsu S, Kawane T, Horiuchi N. Mouse vitamin D-24-hydroxylase: molecular cloning, tissue distribution, and transcriptional regulation by 1alpha,25-dihydroxyvitamin D3. Endocrinology 1997; 138:2233–40.
31. Mahon BD, Wittke A, Weaver V, Cantorna MT. The targets of vitamin D depend on the differentiation and activation status of CD4 positive T cells. J Cell Biochem 2003;89:922–32.
32. Heine G, Anton K, Henz BM, Worm M. 1alpha,25-dihydroxyvitamin D_3 inhibits anti-CD40 plus IL-4-mediated IgE production in vitro. Eur J Immunol 2002;32:3395–404.
33. Adorini L, Penna G, Giarratana N, et al. Dendritic cells as key targets for immunomodulation by Vitamin D receptor ligands. J Steroid Biochem Mol Biol 2004;89–90:437–41.
34. Zella JB, DeLuca HF. Vitamin D and autoimmune diabetes. J Cell Biochem 2003;88:216–22.
35. Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 2001;358:1500–3.
36. Munger KL, Zhang SM, O'Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. Neurology 2004;62:60–5.
37. Oelzner P, Muller A, Deschner F, et al. Relationship between disease activity and serum levels of vitamin D metabolites and PTH in rheumatoid arthritis. Calcif Tissue Int 1998;62:193–8.
38. Bellamy R, Ruwende C, Corrah T, et al. Tuberculosis and chronic hepatitis B virus infection in Africans and variation in the vitamin D receptor gene. J Infect Dis 1999;179:721–4.
39. Roy S, Frodsham A, Saha B, Hazra SK, Mascie-Taylor CG, Hill AV. Association of vitamin D receptor genotype with leprosy type. J Infect Dis 1999;179:187–91.
40. Barber Y, Rubio C, Fernandez E, Rubio M, Fibla J. Host genetic background at CCR5 chemokine receptor and vitamin D receptor loci and human immunodeficiency virus (HIV) type 1 disease progression among HIV-seropositive injection drug users. J Infect Dis 2001;184:1279–88.
41. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006;311:1770–3.
42. Cantorna MT, Zhu Y, Froicu M, Wittke A. Vitamin D status, 1,25-dihydroxyvitamin D_3, and the immune system. Am J Clin Nutr 2004; 80(suppl):1717S–20S.
43. Matheu V, Back O, Mondoc E, Issazadeh-Navikas S. Dual effects of vitamin D-induced alteration of TH1/TH2 cytokine expression: enhancing IgE production and decreasing airway eosinophilia in murine allergic airway disease. J Allergy Clin Immunol 2003;112:585–92.
44. Reichel H, Koeffler HP, Tobler A, Norman AW. 1 alpha,25-Dihydroxyvitamin D3 inhibits gamma-interferon synthesis by normal human peripheral blood lymphocytes. Proc Natl Acad Sci U S A 1987; 84:3385–9.
45. Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HF, O'Garra A. 1alpha,25-Dihydroxyvitamin D_3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. J Immunol 2001;167: 4974–80.
46. Cantorna MT, Woodward WD, Hayes CE, DeLuca HF. 1,25-dihydroxyvitamin D_3 is a positive regulator for the two anti-encephalitogenic cytokines TGF-beta 1 and IL-4. J Immunol 1998; 160:5314–9.
47. Pichler J, Gerstmayr M, Szepfalusi Z, Urbanek R, Peterlik M, Willheim M. 1 alpha,25$(OH)_2D_3$ inhibits not only Th1 but also Th2 differentiation in human cord blood T cells. Pediatr Res 2002;52:12–8.

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48. Annesi-Maesano I. Perinatal events, vitamin D, and the development of allergy. Pediatr Res 2002;52:3–5.
49. Nguyen M, Trubert CL, Rizk-Rabin M, et al. 1,25-Dihydroxyvitamin D_3 and fetal lung maturation: immunogold detection of VDR expression in pneumocytes type II cells and effect on fructose 1,6 bisphosphatase. J Steroid Biochem Mol Biol 2004;89–90:93–7.
50. Nguyen TM, Guillozo H, Marin L, Tordet C, Koite S, Garabedian M. Evidence for a vitamin D paracrine system regulating maturation of developing rat lung epithelium. Am J Physiol 1996;271:L392–9.
51. Tantisira KG, Fuhlbrigge AL, Tonascia J, et al. Bronchodilation and bronchoconstriction: predictors of future lung function in childhood asthma. J Allergy Clin Immunol 2006;117:1264–71.
52. Vollmert C, Illig T, Altmuller J, et al. Single nucleotide polymorphism screening and association analysis—exclusion of integrin beta 7 and vitamin D receptor (chromosome 12q) as candidate genes for asthma. Clin Exp Allergy 2004;34:1841–50.
53. Wjst M. Variants in the vitamin D receptor gene and asthma. BMC Genet 2005;6:2.
54. Xystrakis E, Kusumakar S, Boswell S, et al. Reversing the defective induction of IL-10-secreting regulatory T cells in glucocorticoid-resistant asthma patients. J Clin Invest 2006;116:146–55.
55. Hypponen E, Sovio U, Wjst M, et al. Infant vitamin D supplementation and allergic conditions in adulthood: northern Finland birth cohort 1966. Ann N Y Acad Sci 2004;1037:84–95.
56. Henderson L, Irving K, Gregory J, et al. The National Diet and Nutrition Survey: adults aged 19 to 64 years. London, United Kindom: HMSO, 2003.
57. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D and fluoride. Washington, DC: National Academy Press, 1997.

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