Pre-pregnancy habitual intake of vitamin D from diet and supplements in relation to risk of gestational diabetes mellitus: a prospective cohort study

Running title: Vitamin D intake and gestational diabetes risk

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Abbreviations: AHEI, alternate healthy eating index; BMI, body mass index; CI, confidence interval; GDM, gestational diabetes mellitus; MET, metabolic equivalent task; NHS, Nurses' Health Study; RR, relative risk; SSBs, sugar-sweetened beverages; UVB, ultraviolet B.

ABSTRACT

Background: Vitamin D may play a pivotal role in regulating insulin secretion and insulin sensitivity. However, the impact of vitamin D intake either from diet or from supplements on the development of gestational diabetes mellitus (GDM) remains unknown. We prospectively examined the association of pre-pregnancy habitual intake of vitamin D from diet and supplements with risk of incident GDM in a well-established cohort.

Methods: We included 21,356 singleton pregnancies from 15,225 women in the Nurses' Health Study II cohort. Diet information, including vitamin D intakes from food sources and supplements, was assessed in 1991 and every four years thereafter by validated food frequency

questionnaires. We used log-binomial models with generalized estimating equations to estimate the relative risks (RRs) and 95% confidence intervals (CIs).

Results: We documented 865 incident GDM cases during 10 years of follow-up. After adjustment for age, parity, race/ethnicity, family history of diabetes, dietary and lifestyle factors, and body mass index, the RRs (95% CIs) of GDM risk associated with supplemental vitamin D intake of 0, 1-399, ≥ 400 IU/d were 1.00 (reference), 0.80 (0.67-0.96), and 0.71 (0.56-0.90), respectively (P for trend = 0.002). Dietary and total vitamin D intakes were also inversely associated with GDM risk, but the associations were not statistically significant.

Conclusions: Pre-pregnancy supplemental vitamin D intake was significantly and inversely associated with risk of GDM. Our study indicates potential benefits of increasing vitamin D intake from supplements in the prevention of GDM in women of reproductive age.

HIGHLIGHTS

- Vitamin D insufficiency is common in pregnant women, and it has been associated with gestational diabetes. However, the impact of vitamin D intake either from diet or from supplements on the development of gestational diabetes mellitus (GDM) remains unknown.
- In a large prospective cohort study, we found that pre-pregnancy supplemental vitamin D intake was significantly and inversely associated with risk of GDM. These results indicate potential benefits of increasing vitamin D intake from supplements in the prevention of GDM.

KEYWORDS

Gestational diabetes mellitus; vitamin D; diet; nutrition; preconception

INTRODUCTION

Gestational diabetes mellitus (GDM), characterized by glucose intolerance with onset or first recognition during pregnancy, is a common pregnancy complication that affects approximately 9% of all pregnancies.[1] GDM is not only associated with adverse pregnancy and perinatal outcomes, but also related to an increased risk of long-term adverse health outcomes for both mother and child in later life, including type 2 diabetes, metabolic syndrome, and cardiovascular disease.[2] For example, women with a history of GDM have more than 7-fold increased risk of developing type 2 diabetes.[3] Thus, it is crucial to identify important modifiable risk factors that could prevent the development of GDM.

Vitamin D insufficiency is widespread around the world across various age groups.[4] In the United States, the prevalence of vitamin D insufficiency, defined as 25-hydroxyvitamin D (25[OH]D) level < 75 nmol/L, is 83% among pregnant women in the first trimester.[5] Moreover, 78% of non-pregnant women of childbearing age have vitamin D insufficiency.[5] These data indicate that a substantial number of women may enter pregnancy with suboptimal vitamin D status.

Evidence from previous studies in animals and humans suggests that vitamin D may play a pivotal role in regulating insulin secretion[6-8] and insulin sensitivity.[6 9] In addition, improved vitamin D status by vitamin D supplementation could normalize fasting glucose levels and attenuate insulin resistance in pregnant women.[10-12] Some, although not all, previous studies found that maternal low concentration of 25(OH)D during early pregnancy was associated with increased risk of GDM.[13 14] Interestingly, a recent animal study has shown that high vitamin D status before pregnancy, but not during pregnancy, is inversely associated with the development of GDM.[15] However, the impact of vitamin D intake either from diet or from supplements on the

development of GDM has not been investigated. Using data from a well-established prospective cohort, we examined the association between pre-pregnancy vitamin D intake and risk of GDM.

METHODS

Study Population

The Nurses' Health Study II (NHSII) is a prospective cohort study established in 1989, with 116,430 female nurses aged 24-44 years at study inception. The participants reported information regarding disease outcomes and lifestyle behaviors, such as smoking status and medication use on a biennial questionnaire. Follow-up for each questionnaire cycle was greater than 90%. This study has been approved by the Partners Human Research Committee (Boston, MA, USA), with participants' consent implied by the return of the questionnaires by mail.

We included NHSII participants in this analysis if they had at least one singleton pregnancy lasting longer than 6 months between 1991 and 2001. The 2001 questionnaire was the last time questions regarding GDM were included, as the majority of NHSII participants had passed reproductive age by then. Pregnancies became eligible if there was no prior GDM, or a prior diagnosis of T2DM, cardiovascular disease, or cancer. We excluded individuals who had missing information on vitamin D intake at baseline. Women with GDM in a previous pregnancy were not included because they may change their diet and lifestyle during the next pregnancy to prevent recurrent GDM.

Exposure Assessment

Intakes of dietary vitamin D, other nutrients, and alcohol were assessed in 1991 and every 4 years thereafter using an extensively validated food frequency questionnaire.[16-19] Information on current use and doses of specific vitamin D supplements and vitamin D-containing

multivitamins was collected biennially. Total vitamin D intake was calculated as the sum of dietary and supplemental vitamin D intakes from all sources.

Covariate Assessment

Data on age, race/ethnicity, residence, anthropometric measures, physical activity, and dietary intake, were collected using standardized questionnaires. Height and weight were reported in 1989 and weight was updated every two years. Self-reported body weight was highly correlated (r = 0.97) with technician-measured weight in a previous validation study.[20] Body mass index (BMI) was computed as weight in kilograms divided by height in meters squared. Physical activity was assessed by frequency of engaging in common recreational activities in 1991 and 1997. Total physical activity was calculated as metabolic equivalent task (MET)-hours per week. In a previous validation study, the questionnaire-based estimates of physical activity correlated well (r = 0.56) with detailed activity diaries.[21] We calculated the Alternate Healthy Eating Index 2010 (AHEI) as previously described[22] to represent overall diet quality. Previous studies have linked higher AHEI score, indicating a better diet quality, to a lower risk of major chronic diseases.[22] Race/ethnicity (Caucasians, African-American, Hispanic, Asian, others) was reported in 1989. Besides dietary and supplemental vitamin D intake, solar ultraviolet-B (UVB) radiation is considered a key source of circulating 25(OH)D, because UVB stimulates the conversion from 7-dehydrocholesterol to vitamin D3 in the epidermis of the skin. Average annual UVB flux, a composite measure of mean UVB radiation level on the earth's surface taking into account factors such as latitude, altitude and cloud cover, was approximated based on state of residence (i.e., mailing address) on each of the questionnaires.[23]

Outcome Ascertainment

On each of the biennial questionnaires from 1991 to 2001, the NHSII participants reported incident GDM as diagnosed by a physician. In the case of more than one pregnancy lasting longer than 6 months reported within a 2-year questionnaire period, GDM status was attributed to the first pregnancy. Self-reports on GDM diagnosis has been previously validated among a subgroup of in the NHSII cohort, with 94% of GDM self-reports confirmed by medical records.[24] In a random sample of parous women without GDM, a high level of GDM surveillance was observed, with 83% reporting a glucose screening test during pregnancy and 100% reporting frequent prenatal urine screenings during pregnancy.[24] During the period that GDM events were reported in the present study (1991-2001), the National Diabetes Data Group criteria[25] have been widely adopted for GDM diagnosis.

Statistical Analysis

We used log-binomial models[26] with generalized estimating equations (GEE) to estimate relative risks (RRs) and 95% confidence intervals (CIs). The GEE method allows us to account for correlations among repeated observations (pregnancies) contributed by a single participant.[27] We calculated the updated cumulative average vitamin D intake for each individual at each time period, in order to represent long-term usual vitamin D intake and reduce within-subject variation.[28]

For vitamin D intake, we fit multivariable models adjusting for age, parity, race/ethnicity, family history of diabetes, cigarette smoking, alcohol intake, physical activity, estimated UVB flux, BMI, total energy intake, and intakes of saturated fat, monounsaturated fat, polyunsaturated fat, trans fat, dietary cholesterol, glycemic load, dietary fiber, magnesium, calcium, and vitamin A. All of these variables were updated throughout the follow up, except family history of

diabetes and race/ethnicity that was reported in 1989. To test for a significant trend across quartiles, we modeled median values of each category as a continuous variable.

To evaluate effect modification, we conducted stratified analyses according to age (< 35 vs. ≥ 35 years), family history of diabetes (yes vs. no), overall diet quality (AHEI dietary pattern score < median vs. ≥ median), physical activity (< median vs. ≥ median), and overweight status (BMI < 25 vs. ≥ 25). We tested potential interactions via adding multiplicative interaction terms in the multivariable models. All statistical analyses were performed with SAS software (version 9.2; SAS Institute Inc.). $P < 0.05$ was considered statistically significant.

RESULTS

During 10 years of follow-up, we documented 865 incident GDM pregnancies among 21,356 eligible singleton pregnancies from 15,225 women. At baseline in 1991, women with higher total vitamin D intake were more likely to be white and nonsmokers, more physically active, consumed more carbohydrates, protein, dietary fiber, magnesium, potassium, calcium, vitamin A, vitamin C, vitamin E, fish, low-fat dairy, nuts, fruits, whole grains, and less alcohol, fat, red meat, sugar-sweetened beverages, and had an overall better diet quality (Table 1).

We observed a significant inverse association between supplemental vitamin D intake and the risk of GDM (Table 2). After adjustment for age, parity, non-dietary factors, and dietary factors including dietary vitamin D intake, the adjusted RRs (95% CIs) of GDM risk associated with supplemental vitamin D intake of 0, 1-399, ≥ 400 IU/d were 1.00 (reference), 0.80 (0.67-0.96), and 0.71 (0.56-0.90), respectively (P for trend = 0.002). Dietary and total vitamin D intakes were also inversely associated with GDM risk, but the associations were not statistically significant. The associations of total, dietary, and supplemental vitamin D intake with risk of

GDM were not significantly modified by other risk factors for GDM, including age, family history of diabetes, overall diet quality, physical activity, or overweight status.

DISCUSSION

In this large prospective cohort study, we found inverse associations of pre-pregnancy supplemental vitamin D intake with the risk of GDM. These associations remained statistically significant after adjustment for other major risk factors of GDM. Our results also suggested that dietary and total vitamin D intakes might be inversely associated with GDM risk, although the associations were not statistically significant.

To our knowledge, the present study is the first attempt to examine the association between pre-pregnancy vitamin D intake and GDM risk. Accumulating evidence suggests that most women with GDM may have a chronic beta-cell defect and insulin resistance before pregnancy.[29] Pregnancy itself is a process of progressive insulin resistance that begins near mid-pregnancy. The metabolic challenges occurring during pregnancy[29] serve to unmask a predisposition to glucose metabolic disorders in women who have a pre-existed compromised capacity to compensate for the progressive insulin resistance of pregnancy.[29] Therefore, pre-pregnancy risk factors implicated in glucose homeostasis may also be physiologically relevant to the development of GDM. In a previous study in female guinea pigs, high vitamin D status before pregnancy was inversely associated with the development of GDM.[15]

Our results were in general consistent with previous cohort studies relating dietary and supplemental vitamin D intake to type 2 diabetes risk.[30 31] Moreover, we concur with previous findings showing the effects vitamin D supplementation on improved glucose metabolism and insulin sensitivity in pregnant women.[10-12] Several epidemiological studies examining the

association between maternal circulating vitamin D levels during pregnancy and the risk of GDM have yielded equivocal results.[32 33] In line with our findings on the association between vitamin D intake and GDM risk, a meta-analysis of previous studies has demonstrated a significant association of vitamin D insufficiency during pregnancy and increased risk of GDM.[32] A recent randomized controlled trial also found a lower rate of GDM (13% vs 8%) after vitamin D supplementation during early pregnancy, although the difference was not statistically significant due to limited sample size.[34]

The observed inverse association of pre-pregnancy vitamin D intake with GDM risk is biologically supported by the direct and/or indirect effects of vitamin D on insulin secretion and insulin sensitivity. Traditionally, vitamin D is thought to act as a facilitator of intestinal calcium absorption, which in turn can normalize glucose intolerance.[35] However, increasing evidence suggests that the effect of vitamin D on beta-cells appears to be direct and independent of prevailing plasma calcium concentration.[6 36] For instance, inadequate vitamin D impairs insulin secretion,[7] and the impairment can be ameliorated by vitamin D supplementation.[37] Moreover, vitamin D receptor and vitamin D-dependent calcium-binding protein are present in human and rat pancreatic islet cells.[38] Vitamin D may regulate pancreatic beta-cell function and insulin secretion through the binding of circulating 1,25-dihydroxyvitamin D to beta-cell vitamin D receptor. The binding could regulate the balance between extracellular and intracellular calcium pools, which is critical for insulin-mediated intracellular processes in insulin-responsive tissues.[39] In addition, vitamin D can enhance insulin sensitivity by directly activating transcription of the human insulin receptor gene, peroxisome proliferator activator receptor-δ, and insulin-mediated glucose transport as well as modulation of cytokine expression and activity.[36 40]

Our study had several strengths. First, our study has a prospective study design with a long duration of follow-up, which establishes the temporal direction of the associations. Second, the questionnaires used to assess diet and lifestyle variables in this study have been extensively validated.[16-21] There were several limitations of this study. First, misclassification of dietary vitamin D intake is possible. However, due to the prospective nature of this study, the misclassification should be non-differential with regard to incident GDM status; therefore, our observed associations may underestimate the true relative risks. Furthermore, the use of cumulative averages of dietary intakes for participants with more than one pre-pregnancy FFQ reduces random error. Second, our study population consisted mostly of Caucasian American women. Thus, the generalizability of the observed associations may be limited to similar populations. However, the relative homogeneity of the study population reduces potential confounding due to unmeasured socio-economic variability. Because black and Hispanic women have higher prevalence of vitamin D insufficiency than white women do,[5] future studies across races/ethnicities are warranted. Third, the NHSII cohort did not specifically assess diet and lifestyle factors during pregnancy. Therefore, we were unable to assess the association of pre-pregnancy vitamin D intake with GDM risk, independent of vitamin D intake during pregnancy. Finally, because of observational nature of this study, a causal relation between pre-pregnancy vitamin D intake and GDM risk cannot be inferred.

In conclusion, pre-pregnancy supplemental vitamin D intake is significantly and inversely associated with risk of GDM. Our study indicates potential benefits of increasing vitamin D intake from supplements in the prevention of GDM in women of reproductive age. Large randomized controlled trials of pre-pregnancy vitamin D supplementation may be warranted to confirm our findings.

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Table 1. Age-standardized characteristics of the study population (n=15,225) in 1991, according to categories of total vitamin D intake

Characteristics	Total vitamin D intake (IU/d)			
	< 200	200-399	400-599	≥ 600
Number of participants	2812	4967	3582	3864
Age, years	31.9 (3.3)	31.9 (3.3)	31.9 (3.2)	32.2 (3.3)
White, %	91.5	93.2	93.3	94.3
Family history of diabetes, %	11.1	11.5	10.4	10.5
Nulliparous, %	39.2	36.0	36.9	33.2
Current smoking, %	14.2	9.5	7.6	5.8
Alcohol, g/day	3.6 (6.0)	3.3 (5.3)	3.1 (5.0)	2.3 (4.3)
UVB flux, $\times 10^{-4}$ R-B units	125.2 (24.4)	122.8 (23.4)	123.6 (24.4)	124.4 (24.8)
BMI, kg/m²	23.4 (4.6)	23.4 (4.3)	23.4 (4.3)	23.6 (4.1)
Physical activity, MET-h/wk	20.3 (25.8)	23.3 (29.8)	24.0 (28.5)	24.8 (29.9)
Total calories, kcal/d	1756.9 (556.7)	1871.3 (561.6)	1949.2 (560.9)	1730.1 (495.6)
Carbohydrate, %E	49.7 (8.3)	50.2 (7.0)	51.3 (7.0)	51.3 (6.7)
Protein, %E	17.9 (3.4)	19.2 (3.1)	19.2 (3.2)	20.2 (3.2)
Total fat, %E	32.7 (6.0)	31.3 (5.3)	30.3 (5.2)	29.7 (5.0)
Saturated fat, %E	11.5 (2.6)	11.3 (2.4)	11.0 (2.3)	10.9 (2.2)
Monounsaturated fat, %E	12.6 (2.5)	11.8 (2.2)	11.4 (2.2)	11.0 (2.2)
Polyunsaturated fat, %E	5.7 (1.4)	5.5 (1.3)	5.3 (1.3)	5.2 (1.2)
Trans fat, %E	1.8 (0.7)	1.6 (0.6)	1.5 (0.6)	1.4 (0.5)
Cholesterol, mg/d*	234.0 (69.2)	239.1 (62.2)	236.6 (62.8)	238.1 (64.2)

Glycemic Index*	55.3 (3.2)	54.0 (3.0)	53.7 (3.2)	53.2 (3.3)
Glycemic Load*	124.7 (23.7)	122.4 (20.1)	123.9 (20.2)	123.8 (19.7)
Total fiber, g/d*	17.3 (5.5)	18.0 (5.0)	18.3 (5.4)	18.4 (5.9)
Magnesium, mg/d*	265.9 (57.7)	302.0 (53.7)	332.0 (67.3)	365.8 (78.5)
Heme iron, mg/d*	1.1 (0.4)	1.1 (0.4)	1.0 (0.4)	1.0 (0.4)
Potassium, mg/d*	2644.6 (522.9)	2873.5 (472.9)	2934.0 (495.9)	3023.3 (483.5)
Calcium, mg/d*	703.0 (217.8)	969.3 (285.6)	1148.1 (363.3)	1397.8 (465.4)
Vitamin A, μg/d*	840.6 (636.0)	1196.8 (785.6)	1903.4 (935.8)	2870.7 (1376.9)
Vitamin C, mg/d*	167.0 (195.9)	197.5 (218.7)	267.8 (257.7)	349.5 (352.1)
Vitamin E, mg/d*	12.6 (36.5)	15.2 (37.1)	22.5 (42.3)	30.9 (56.1)
Red meat, servings/d	0.9 (0.6)	0.8 (0.6)	0.8 (0.5)	0.6 (0.4)
Poultry, servings/d	0.4 (0.3)	0.5 (0.3)	0.5 (0.3)	0.4 (0.3)
Fish, servings/d	0.1 (0.1)	0.2 (0.2)	0.3 (0.2)	0.3 (0.3)
Eggs, servings/d	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)
Low-fat dairy, servings/d	0.6 (0.5)	1.5 (1.0)	1.8 (1.3)	2.2 (1.4)
High-fat dairy, servings/d	1.0 (0.9)	1.1 (1.0)	1.1 (1.0)	0.9 (0.8)
Nuts, servings/d	0.2 (0.3)	0.3 (0.3)	0.3 (0.4)	0.2 (0.3)
Legumes, servings/d	0.3 (0.3)	0.4 (0.3)	0.4 (0.4)	0.3 (0.3)
Vegetables, servings/d	3.0 (2.1)	3.3 (2.0)	3.4 (2.0)	3.0 (1.8)
Fruits, servings/d	1.0 (0.9)	1.2 (1.0)	1.4 (1.0)	1.3 (1.0)
Whole grains, servings/d	0.9 (1.0)	1.1 (1.0)	1.3 (1.1)	1.1 (1.0)
SSBs, servings/d	0.8 (1.1)	0.5 (0.8)	0.6 (0.9)	0.4 (0.6)
AHEI score	40.3 (10.3)	43.6 (10.2)	43.9 (10.5)	45.2 (10.0)

Values are means (SD) unless otherwise specified.

* Value is energy-adjusted.

%E, % of energy; AHEI indicates alternate healthy eating index; BMI, body mass index; IU, international unit; MET, metabolic equivalent; SSBs, sugar-sweetened beverages; UVB, ultraviolet B.

All comparisons were significant across categories, except family history of diabetes and BMI.

Table 2. Risk of gestational diabetes in association with pre-pregnancy vitamin D intake

	Total vitamin D intake (IU/d)				P for trend
	< 200	**200-399**	**400-599**	**≥ 600**	
GDM/pregnancies	174/3,618	307/6,948	188/5,459	196/5,331	
Model 1	1.00	0.90 (0.75, 1.08)	0.69 (0.57, 0.85)	0.76 (0.62, 0.93)	0.002
Model 2	1.00	0.98 (0.82, 1.17)	0.78 (0.64, 0.95)	0.85 (0.70, 1.04)	0.03
Model 3	1.00	0.95 (0.76, 1.19)	0.77 (0.58, 1.03)	0.86 (0.61, 1.20)	0.31
	Dietary vitamin D intake (IU/d)[1]				**P for trend**
	< 200	**200-399**	**≥ 400**		
GDM/pregnancies	163/3,224	195/4,381	37/1,016		
Model 1	1.00	0.88 (0.72, 1.08)	0.72 (0.51, 1.03)		0.05
Model 2	1.00	0.97 (0.79, 1.19)	0.83 (0.58, 1.17)		0.34
Model 3	1.00	0.89 (0.69, 1.16)	0.78 (0.49, 1.26)		0.28
	Supplemental vitamin D intake (IU/d)[2]				**P for trend**
	0	**1-399**	**≥ 400**		
GDM/pregnancies	395/8,621	280/7,174	190/5,561		
Model 1	1.00	0.79 (0.68, 0.92)	0.76 (0.64, 0.90)		< 0.001
Model 2	1.00	0.83 (0.71, 0.96)	0.78 (0.66, 0.92)		0.002
Model 3[2]	1.00	0.80 (0.67, 0.96)	0.71 (0.56, 0.90)		0.002

Model 1: Adjusted for age (months).

Model 2: Model 1 + additionally adjusted for parity (0, 1, 2, 3+), race/ethnicity (Caucasian, African-American, Hispanic, Asian, others), family history of diabetes (yes, no), cigarette

smoking (never, past, current), alcohol intake (0, 0.1-4.9, 5.0-9.9, ≥ 10.0 g/d), physical activity (quartiles), estimated UVB flux (quartiles), and BMI (nine categories, < 21, 21-22.9, 23.0-24.9, 25.0-26.9, 27.0-28.9, 29.0-30.9, 31.0 -32.9, 33.0-34.9 and ≥ 35.0 kg/m^2).

Model 3: Model 2 + additionally adjusted for total energy intake (quartiles), and intakes of saturated fat (quartiles), monounsaturated fat (quartiles), polyunsaturated fat (quartiles), trans fat (quartiles), dietary cholesterol (quartiles), glycemic load (quartiles), dietary fiber (quartiles), magnesium (quartiles), calcium (quartiles), and vitamin A (quartiles).

[1] The analytic population consisted of women who did not consume specific vitamin D supplements or vitamin D-containing multivitamins at baseline and during follow-up.

[2] Additionally adjusted for dietary vitamin D intake in the entire analysis of supplemental vitamin D intake.