Joint Effects of Obesity and Vitamin D Insufficiency on Insulin Resistance and Type 2 Diabetes

Results from the NHANES 2001–2006

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OBJECTIVE—The possible interaction of serum 25-hydroxyvitamin D [25(OH)D] and obesity in regard to type 2 diabetes and insulin resistance has not been well studied. To explore the effect modification of obesity on the association between 25(OH)D and insulin resistance/type 2 diabetes, data were examined from a nationally representative sample.

RESEARCH DESIGN AND METHODS—The analytic sample for the type 2 diabetes analysis (n = 12,900) was limited to participants from the National Health and Nutrition Examination Survey (NHANES) 2001–2006 over 20 years of age. Participants >20 years of age assigned to the morning session and free of diabetes were limited to the insulin resistance analysis (n = 3,806). Multiplicative interaction was assessed through a cross-product interaction term in a multiple logistic regression model. The presence of additive interaction between insufficient 25(OH)D and obesity (indicated by BMI or waist circumference) was evaluated by calculation of the relative excess risk due to interaction (RERI) and attributable proportion due to interaction (AP).

RESULTS—There was no multiplicative interaction of insufficient 25(OH)D and obesity on type 2 diabetes or insulin resistance. Furthermore, none of the RERI or AP values were statistically significant in the diabetes analysis. However, there was strong additive interaction between abdominal obesity and insufficient 25(OH)D (RERI 6.45 [95% CI 1.03–11.52]) in regard to insulin resistance. In addition, 47% of the increased odds of insulin resistance can be explained by interaction between insufficient 25(OH)D and high BMI (AP 0.47 [95% CI 0.08–0.87]).

CONCLUSIONS—Within a cross-sectional, nationally representative sample, abdominal obesity and insufficient 25(OH)D interact to synergistically influence the risk of insulin resistance.

Although the association between 25(OH)D and insulin resistance is consistently observed across multiple studies, this association may vary by obesity status. Serum 25(OH)D concentration was not associated with insulin sensitivity in obese Caucasian women either before bariatric surgery or 10 years postsurgery (17). Obesity may modify the association between 25(OH)D concentration and risk of type 2 diabetes. It has been demonstrated that the association between serum 25(OH)D concentration and A1C was stronger in British adults that had a high BMI compared with adults that had a low BMI after full covariate adjustment (15). Because of decreased bioavailability of vitamin D due to excess storage in body fat compartments, obesity may interact with vitamin D to synergistically influence risk of insulin resistance and type 2 diabetes (18). However, the possible interaction of vitamin D and obesity with regard to type 2 diabetes and insulin resistance has not been well studied. In a recently published study, the association of serum 25(OH)D concentration with insulin sensitivity was found to be stronger in overweight individuals than in normal-weight individuals (19). Although suggestive, this study was limited in that it featured a small sample of younger adults from a university campus with limited racial/ethnic groups. To further explore the effect modification of obesity on the association between 25(OH)D and insulin resistance/type 2 diabetes, we examined data from the National Health and Nutrition Examination Survey (NHANES), a large, nationally representative sample from across the U.S.
Prevention, for analysis. The NCHS ethics review board approved the survey, and participants were provided with informed consent prior to participation.

Data were analyzed from NHANES 2001–2006, and the analytic sample was limited to participants >20 years of age. Survey questions that assess smoking behavior were only asked to participants >20 years of age. The unweighted response rates for the years 2001–2006 were between 79 and 84% for the interviewed sample and between 76 and 80% for the MEC-examined sample.

**Serum 25(OH)D concentration**

In NHANES 2001–2006, serum 25(OH)D concentration was measured using a radioimmunoassay kit (DiaSorin, Stillwater, MN) (20). The coefficient of variation for the instrument for the years 2001–2006 was between 10 and 13%, and the sensitivity for the assay was 1.5 ng/mL (21). Serum 25(OH)D data files were updated in November 2010, and these data were used because NCHS has recommended that the adjusted data rather than the previously available, unadjusted data be used for all analyses of serum 25(OH)D concentration for NHANES 2001–2006 (22).

25(OH)D concentration is generally understood to reflect total intake of vitamin D from cutaneous synthesis and dietary intake (23). The Institute of Medicine released a report in November 2010 on vitamin D status categorizing serum 25(OH)D: risk of deficiency, <12 ng/mL; risk of inadequacy, 12–19 ng/mL; sufficiency, 20–50 ng/mL; and possible harm, >50 ng/mL (3). For multiple regression analysis, vitamin D status will be reported as sufficient (20–50 ng/mL) or insufficient (<20 ng/mL). Few (~1%) participants are at risk for possible harm due to high serum 25(OH)D concentration.

**Outcomes**

Case definition of type 2 diabetes was based on fulfillment of the American Diabetes Association criteria (24) for diabetes diagnosis (fasting plasma glucose concentration ≥126 mg/dL, 2-h plasma glucose ≥200 mg/dL during an oral glucose tolerance test, or A1C ≥6.5%) or an answer of “yes” to any of the following questions.

1) Other than during pregnancy, have you ever been told by a doctor or other health professional that you have diabetes or sugar diabetes? 2) Are you taking insulin now? 3) Are you taking diabetic pills to lower your blood glucose?

Insulin resistance was estimated using the homeostatic model assessment for insulin resistance (HOMA-IR) by the following formula: (fasting serum insulin [μU/mL] × fasting plasma glucose [mg/dL])/405 (23). HOMA-IR correlates well with data using the hyperglycemic clamp technique (25,26), which is recognized to be the gold standard for measuring insulin resistance. Insulin sensitivity has been defined by the World Health Organization (WHO) as values below the highest quartile of the HOMA-IR index, as measured in subjects without diabetes (27). For this analysis, subjects in the highest quintile will be categorized as insulin resistant.

A fasting blood glucose test was performed on eligible participants who were examined in the morning session after a 9-h fast. Since an oral glucose tolerance test was added to the laboratory protocol in NHANES 2005–2006, the 2-h postload values (after a dose of 75 g of glucose) will be included in this analysis. Plasma glucose was measured using an enzyme hexokinase method for NHANES 2001–2006 surveys, and the 2005–2006 values (Hitachi 911) were corrected to the 2003–2004 values using the Roche Cobas Mira method. There were changes to the equipment and laboratory from NHANES 2003–2004. For NHANES 2005–2006, glucose and insulin measurements were performed by the Fairview Medical Center Laboratory at the University of Minnesota (Minneapolis, MN), and for NHANES 2003–2004, glucose and insulin measurements were performed by the Diabetes Diagnostic Laboratory at the University of Missouri (Columbia, MO). Insulin was measured using the Tosoh AIA-PACK IR1 immunoenzymometric assay in NHANES 2003–2004 and the Merocodia Insulin ELISA immunoassay in NHANES 2005–2006. A1C measurements were obtained using a high-performance liquid chromatography system. The Boronate Affinity high-performance liquid chromatography system determines total glycohemoglobin by measuring the 1,2-cis diol group found in A1C.

**Covariates**

Age, race/ethnicity, sex, education, season of examination, physical activity, and smoking were obtained by self-report. Season was assigned as winter if the period of examination was between 1 November and 30 April or summer if between 1 May and 31 October. The average level of physical activity was reported on a scale of 1–4 (least vigorous to most vigorous). Participants were asked whether they had smoked at least 100 cigarettes in their entire life to classify their smoking status. Those who answered “yes” were asked whether they now smoke cigarettes every day, some days, or not at all. Current smokers were those who had smoked at least 100 cigarettes during their lifetime and, at the time of the interview, reported smoking either every day or some days. Former smokers were those who reported smoking at least 100 cigarettes during their lifetime but currently did not smoke. Never smokers were those who reported never having smoked 100 cigarettes during their lifetime. Data on anthropometric measurements were obtained by health staff (28). BMI was calculated from measured weight and height according to a standardized protocol. For adults aged 20 years or older, normal weight was defined as a BMI of 18.5–24.99 kg/m², overweight was defined as a BMI of 25.0–29.99 kg/m², and obesity as a BMI of 30.0 kg/m² or higher. These definitions are consistent with those of the National Heart, Lung, and Blood Institute and the WHO (29,30). For multiple regression analysis, underweight adults will not be included because they comprise a small proportion of the sample (~2%). Waist circumference (WC) may correlate better with insulin resistance and type 2 diabetes because it is a better measure of body fat. Abdominal obesity was defined as WC ≥102 cm for men and ≥88 cm for women (31). WC was measured at a point immediately above the iliac crest on the midaxillary line at minimal respiration to the nearest 0.1 cm (32).

**Inclusion criteria**

A small number of participants (n = 900, 6.2%) >20 years of age who were interviewed and examined in a MEC did not have data on serum 25(OH)D concentration. Among the adults in this sample, all were eligible for the type 2 diabetes analysis, but only the participants randomly assigned to the morning session (n = 7,068, 51.8%) after an overnight fast were included in the insulin resistance analysis. The sample for the diabetes analysis had missing information for physical activity (n = 15, 0.11%), smoking status (n = 15, 0.12%), education (n = 17, 0.12%), BMI (n = 401, 2.9%), and WC (n = 590, 4.3%). However, the sample for the insulin resistance analysis was smaller and had missing information for physical activity (n = 10, 0.15%), smoking status (n = 8, 0.12%), education (n = 9, 0.14%), BMI (n = 170, 2.5%), and WC (n = 253, 3.9%). After excluding persons...
with missing information for covariates, the sample for the diabetes analysis comprised \( n = 12,900 \) individuals, and the sample for the insulin resistance analysis comprised \( n = 5,806 \) individuals. The flowchart of the excluded participants along with the reason is summarized in Fig. 1.

**Statistical analysis**

SAS 9.2 (SAS Institute, Cary, NC) was used for all calculations and analyses. Given the complex, stratified, multistage probability cluster sampling structure used in the NHANES survey design, data were analyzed using the SAS survey procedures. These include weight, cluster, and strata statements, which allow for the calculation of unbiased population-based estimates that reflect the unequal probability of selection, nonresponse adjustment, and adjustment to independent population controls. Since data from NHANES 2001–2006 were used for this analysis, 6-year sample weights were used to produce statistically reliable estimates, taking into account the complex survey design.

Differences in continuous variables were tested using a Student t test, and differences in categorical variables were assessed using a Pearson \( \chi^2 \) test. The reported means, standard errors, and proportions take into account NHANES design methodology. The association between 25(OH)D status (sufficient [20–50 ng/mL] or insufficient [<20 ng/mL]) and type 2 diabetes or insulin resistance was determined using multiple logistic regression. The results were stratified by BMI (overweight and obese versus normal, obese versus normal, or overweight versus normal) or WC (abdominally obese vs. not abdominally obese) and adjusted for age (continuous), sex (male or female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other), education level (less than high school, high school diploma, or some college education), season of examination (winter or summer), physical activity (continuous), and smoking status (never smoker, former smoker, or current smoker). Furthermore, the reference group in all models was sufficient 25(OH)D (20–50 ng/mL) and normal weight (BMI = 18.5–24.99 kg/m²) or not abdominally obese (WC <102 cm for men and <88 cm for women). A cross-product interaction term was included in the logistic regression model to assess multiplicative interaction. Odds ratios (ORs) and 95% CIs were calculated using the contrast statement in SAS 9.2. Variance was calculated using the Taylor series linearization method, which leads to an asymptotically unbiased estimate.

The expected interaction on the multiplicative and additive scale was also calculated. It has been argued that interaction on the additive scale better reflects biologic interaction (33). To assess additive interaction, the relative excess risk due to interaction (RERI) and attributable proportion due to interaction (AP) were calculated (34). In

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**Figure 1**—Flow diagram of NHANES 2001–2006 cohort and analytic sample. FPG, fasting plasma glucose; OGTT, oral glucose tolerance test.
Obesity and vitamin D on glucose homeostasis

the absence of additive interaction, RERI and AP are equal to 0 (33).

RESULTS—Table 1 displays the characteristics of the participants >20 years of age from NHANES 2001–2006 in the analytic sample separated by diabetes and insulin resistance status. Individuals with diabetes or insulin resistance were more likely to be overweight or obese compared with those without diabetes or insulin-sensitive individuals. The proportion of 25(OH)D sufficiency was higher for individuals without diabetes or insulin-sensitive individuals. Smoking status was marginally different across the insulin-sensitive and insulin-resistant groups but was retained in the multiple regression models for adjustment. Individuals with diabetes and insulin resistance were more likely to be older, male, non-Hispanic black and Mexican American, a former smoker, less educated, and less physically active than participants without diabetes.

Insulin resistance
Results from the multiple logistic regression models adjusted for age, sex, race/ethnicity, education level, season of examination, physical activity, and smoking status are shown in Table 2. The results are presented to assess interaction using a joint effects method, with the P value of the interaction term indicating statistical significance of multiplicative interaction. Obese individuals with insufficient vitamin D had a significantly increased risk of insulin resistance compared with normal-weight individuals with sufficient vitamin D (OR 32.13 [95% CI 22.49–45.89]). In addition, overweight, and obese, and abdominally obese individuals had a significantly higher risk of insulin resistance compared with the reference group. However, there was no evidence of multiplicative interaction of

Table 1—Characteristics of participants ≥20 years of age stratified by type 2 diabetes or insulin resistance status (NHANES 2001–2006)

| Characteristic                          | Diabetes present | Diabetes absent | P*  | Insulin-resistant participants | Insulin-sensitive participants | P*  |
|----------------------------------------|------------------|----------------|-----|--------------------------------|--------------------------------|-----|
| Unweighted sample size                 | 991              | 11,909         |     |                                | 1,939                          | 4,413|     |
| Age (years)                            | 57.1 ± 12.8      | 45.2 ± 17.2    | <0.0001 | 47.1 ± 15.7                  | 45.0 ± 17.0                   | <0.0001|
| Sex (%)                                |                  |                | 0.0015 |                              | 0.02                           |     |
| Male                                   | 523 (52.8)       | 6,567 (47.5)   |     |                                | 708 (50.8)                     | 2,008 (47.5) |
| Female                                 | 468 (47.2)       | 6,232 (52.5)   |     |                                | 685 (49.2)                     | 2,325 (52.7) |
| Race/ethnicity (%)                     |                  |                | <0.0001 |                              | <0.0001                        |     |
| Non-Hispanic white                     | 362 (36.5)       | 6,393 (53.7)   |     |                                | 664 (47.7)                     | 2,464 (55.8) |
| Non-Hispanic black                     | 261 (26.3)       | 2,267 (19.0)   |     |                                | 322 (23.1)                     | 786 (17.8) |
| Mexican-American                      | 291 (29.4)       | 2,386 (20.0)   |     |                                | 327 (23.5)                     | 836 (18.9) |
| Other                                  | 77 (7.8)         | 863 (7.3)      |     |                                | 80 (5.7)                       | 327 (7.4) |
| Education (%)                          |                  |                | <0.0001 |                              | <0.0001                        |     |
| Less than high school                  | 443 (44.7)       | 3,193 (26.8)   |     |                                | 429 (30.8)                     | 1,132 (25.7) |
| High school diploma                   | 210 (21.2)       | 2,903 (24.4)   |     |                                | 360 (25.8)                     | 1,050 (23.8) |
| Some college education                | 338 (34.1)       | 5,813 (48.8)   |     |                                | 604 (43.4)                     | 2,231 (50.6) |
| BMI categories (%)                     |                  |                | <0.0001 |                              | <0.0001                        |     |
| Underweight                            | 3 (0.3)          | 206 (1.7)      |     |                                | 2 (0.1)                        | 89 (2.0) |
| Normal                                 | 141 (14.2)       | 3,700 (31.1)   |     |                                | 84 (6.0)                       | 1,693 (38.4) |
| Overweight                             | 316 (31.9)       | 4,300 (36.1)   |     |                                | 419 (30.1)                     | 1,699 (38.5) |
| Obese                                  | 531 (53.6)       | 3,703 (31.1)   |     |                                | 888 (63.8)                     | 932 (21.1) |
| WC (%)                                 |                  |                | <0.0001 |                              | <0.0001                        |     |
| Abdominally obese                      | 767 (77.4)       | 6,314 (53.0)   | <0.0001 | 1,140 (81.8)                  | 1,980 (44.9)                   | <0.0001|
| Not abdominally obese                  | 224 (22.6)       | 5,595 (47.0)   |     |                                | 253 (18.2)                     | 2,433 (55.1) |
| Average level of physical activity each day | 1.9 ± 0.7     | 2.1 ± 0.8      | <0.0001 | 2.0 ± 0.8                     | 2.2 ± 0.8                      | <0.0001|
| Smoking status (%)                     |                  |                | <0.0001 |                              | 0.07                           |     |
| Current smoker                         | 466 (47.0)       | 6,142 (51.6)   |     |                                | 713 (51.2)                     | 2,247 (50.9) |
| Former smoker                          | 346 (34.9)       | 3,054 (25.6)   |     |                                | 393 (28.2)                     | 1,142 (25.9) |
| Never smoked                           | 179 (18.1)       | 2,713 (22.8)   |     |                                | 287 (20.6)                     | 1,024 (23.2) |
| Vitamin D status (%)                   |                  |                | <0.0001 |                              | <0.0001                        |     |
| Possibly harmful (>50 ng/mL)           | 393 (39.7)       | 7,004 (58.8)   |     |                                | 657 (47.2)                     | 2,800 (63.5) |
| Sufficiency (20–50 ng/mL)              |                  |                | <0.0001 |                              | <0.0001                        |     |
| At risk for inadequacy (12–19 ng/mL)   | 353 (35.6)       | 3,042 (25.5)   |     |                                | 434 (31.2)                     | 1,005 (22.8) |
| Risk of deficiency (<12 ng/mL)         | 245 (24.7)       | 1,783 (15.0)   |     |                                | 299 (21.5)                     | 570 (12.9) |
| Season of examination (%)              |                  |                | 0.02  |                              | 0.06                           |     |
| Winter                                 | 533 (53.8)       | 5,433 (45.8)   |     |                                | 692 (49.7)                     | 2,008 (45.5) |
| Summer                                 | 458 (46.2)       | 6,456 (54.2)   |     |                                | 701 (50.3)                     | 2,405 (54.5) |

Data are presented as means ± SD or n (%) and account for the complex sampling design used by NHANES. *P value represents differences in means ± SD or proportions using Student t test or Pearson χ² test.
25(OH)D and general obesity on increasing the risk of insulin resistance ($P = 0.44$).

RERI and AP were calculated as measures of additive interaction and presented in Table 3. There is strong additive interaction between abdominal obesity and insufficient 25(OH)D (RERI 6.45 [95% CI 1.03–11.52]). In other words, the OR of being insulin resistant in abdominally obese adults who have insufficient 25(OH)D is 6.45 times higher as a result of the additive interaction between obesity and insufficient 25(OH)D.

**Type 2 diabetes**

Obese individuals with insufficient vitamin D had an increased risk of type 2 diabetes compared with the reference group (OR 6.78 [95% CI 4.54–10.12]). In addition, overweight, overweight and obese, and abdominally obese individuals had a significantly higher risk of type 2 diabetes compared with the reference group. There was no evidence of multiplicative interaction of insufficient 25(OH)D and general obesity on increasing the risk of type 2 diabetes ($P = 0.65$).

RERIs derived from the relation with type 2 diabetes were significantly lower than those derived from the relation with insulin resistance. The highest RERI for type 2 diabetes was observed for obesity and vitamin D insufficiency. None of the RERI or AP values were statistically significant in the type 2 diabetes analysis. In addition, AP was lower in the diabetes analysis as compared with the insulin resistance analysis.

**CONCLUSIONS**—In a large, nationally representative sample of adults $>20$ years of age, we found evidence that being overweight or obese modified the associations of 25(OH)D with insulin resistance. The magnitude of the effect modification was large; for example, obese individuals with low 25(OH)D had 32.13 times the risk for insulin resistance, which was still much higher than the 19.97-fold increase among obese individuals with sufficient 25(OH)D. No statistically significant additive interaction was found in regard

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Table 2—Odds ratios for the association between serum 25(OH)D concentration and type 2 diabetes or insulin resistance stratified by obesity among participants $>20$ years of age (NHANES 2001–2006)

| Obesity                | 25(OH)D status | Type 2 diabetes | Insulin resistance |
|------------------------|----------------|-----------------|--------------------|
|                        |                | OR (95% CI)     | $P^*$              | OR (95% CI)     | $P^*$ |
| BMI category           |                |                 |                    |                 |       |
| Normal                 |                |                 |                    |                 |       |
| Normal Sufficient      | 1.00           | 0.65            | 1.00               | 0.44            |
| Normal Insufficient    | 1.49 (0.93–2.37)|                | 1.31 (0.81–2.11)   |                |
| Obese Sufficient       | 3.97 (2.49–6.33)| 19.97 (14.12–28.25)| 32.13 (22.49–45.89)|                |
| Obese Insufficient     | 6.78 (4.54–10.12)|                |                    |                |
| Normal Sufficient      | 1.00           | 0.21            | 1.00               | 0.17            |
| Normal Insufficient    | 1.27 (0.80–2.00)| 1.33 (0.79–2.23) |                    |                |
| Overweight Sufficient  | 1.63 (1.11–2.39)| 4.44 (3.11–6.36) |                    |                |
| Overweight Insufficient| 2.89 (1.95–4.26)|                | 9.17 (6.31–13.30)  |                |
| Normal Sufficient      | 1.00           | 0.28            | 1.00               | 0.17            |
| Normal Insufficient    | 1.42 (0.90–2.23)|                | 1.34 (0.83–2.17)   |                |
| Overweight and obese Sufficient | 2.56 (1.70–3.84)|                | 9.49 (6.86–13.12)  |                |
| Overweight and obese Insufficient | 4.81 (3.28–7.07)|                | 18.64 (13.46–25.61)|                |

WC category

| WC category             | 25(OH)D status | Type 2 diabetes | Insulin resistance |
|-------------------------|----------------|-----------------|--------------------|
| Not abdominally obese   |                |                 |                    |                 |
| Sufficient              | 1.00           | 0.30            | 1.00               | 0.28            |
| Insufficient            | 1.48 (1.06–2.07)|                | 1.62 (1.19–2.22)   |                |
| Abdominally obese       |                |                 |                    |                 |
| Sufficient              | 2.98 (2.11–4.22)|                | 7.46 (5.07–9.18)   |                |
| Insufficient            | 5.42 (3.85–7.63)|                | 14.53 (11.53–18.30)|                |

Models were adjusted for age, sex, race/ethnicity, education level, season of examination, physical activity, and smoking status. *P value represents significance of interaction from weighted logistic regression model.

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Table 3—Interaction of 25(OH)D and obesity with regard to type 2 diabetes and insulin resistance among participants $>20$ years of age (NHANES 2001–2006): estimate of measures of additive interaction and associated CIs

| Type 2 diabetes         | Obese versus normal | Overweight versus normal | Obese and overweight versus normal | Abdominally obese versus not abdominally obese |
|-------------------------|---------------------|--------------------------|-----------------------------------|-----------------------------------------------|
| RERI (95% CI)           | 2.32 (–3.15 to 7.80)| 0.99 (–1.28 to 3.29)     | 1.84 (–1.70 to 5.42)              | 1.96 (–1.28 to 5.21)                          |
| AP (95% CI)             | 0.34 (–0.33 to 1.00)| 0.34 (–0.31 to 1.01)     | 0.37 (–0.21 to 0.98)              | 0.36 (–0.12 to 0.83)                          |

Insulin resistance

| RERI (95% CI)           | 11.85 (–9.82 to 34.71)| 4.40 (–1.42 to 10.10) | 8.81 (–0.79 to 18.48) | 6.45 (1.03–11.52) |
| AP (95% CI)             | 0.37 (–0.16 to 0.95)  | 0.48 (0.01 to 0.95)    | 0.47 (0.08–0.87)      | 0.44 (0.15–0.74) |

Reference group is sufficient 25(OH)D (20–50 ng/mL) and normal weight (BMI = 18.5–24.99 kg/m²) or not abdominally obese (WC <102 cm for men and <88 cm for women).
to diabetes. The stronger interaction of 25(OH)D with obesity in regard to insulin resistance as compared with diabetes may be related to the direct impact of vitamin D deficiency on insulin resistance. Animal and in vitro studies provide evidence that vitamin D indirectly impacts diabetes through insulin resistance, which may explain the weaker additive interaction (4).

We believe that our results are biologically plausible. Evidence for deposition of fat-soluble vitamin D in adipose tissues (14,18) may explain the joint effect of vitamin D insufficiency and obesity on increasing risk of insulin resistance. Abdominal obesity is more highly correlated with the presence of adipose tissue than general obesity, which provides a rationale for the differences in additive interaction. The storage of vitamin D in fat tissues can result in lower vitamin D bioavailability for influencing pancreatic β-cell function or activating vitamin D receptors, thereby increasing the risk of adverse glycemic outcomes (5). In addition, the presence of a vitamin D response element in the insulin gene promoter is another potential mechanism for the observed interaction (35).

Although our study features a large, nationally representative sample that enhances generalizability, a limitation of this study is its cross-sectional nature. Information on vitamin D, obesity, insulin resistance, and diabetes was collected at the same point in time, so temporality is not assured. However, cohort studies with longitudinal follow-up have shown that obesity is a risk factor for low 25(OH)D concentration (16) and insulin resistance/diabetes (1,2,4), which supports a temporal link for the observed interaction. Although not adjusting for geographic region may be a potential limitation in this study, because data are collected in the south during the winter and north during the summer, adjustment for season would also take into account some of the geographic variation. On a separate note, use of the OR may overestimate the risk ratio when assessing additive interaction for an outcome as common as type 2 diabetes. But a simulation study has shown that AP is the most robust to direct substitution of the OR for risk ratio (36). Finally, a sensitivity analysis was conducted with undiagnosed cases so that participants who were under treatment with pharmacological agents (insulin or oral antidiabetic pills) and physician-diagnosed cases of diabetes were excluded, but the overall results were similar.

The results of this study are consistent with those reported by two other studies. Hyppönen and Power (15) found that among obese participants, there was a stronger association between serum 25(OH)D concentration and A1C compared with normal-weight patients. Ou et al. (19) reported a stronger association between serum 25(OH)D concentration and insulin sensitivity in overweight individuals compared with normal-weight individuals. However, it is difficult to generalize the results of Ou et al. due to the limited age range and racial diversity and the fact that the participants in the study were not obese. Furthermore, Ou et al. defined obesity with different cut points than what is conventionally accepted. In contrast, the current study used standard definitions of weight categories (using both BMI and WC cut points) (30,31), vitamin D status based on serum 25(OH)D concentration (3), insulin resistance (27), and type 2 diabetes diagnosis (24) based on laboratory reports.

Although our study is a cross-sectional observational study, we believe that our results have large public health significance. In fully adjusted models, we estimated that 47% of the cases of insulin resistance can be explained by interaction between low 25(OH)D and high BMI. This statistical evidence supports the notion that the burden of insulin resistance in obese individuals may be reduced by making improvements in serum 25(OH)D concentration. Given the difficulty in management of overweight or obese status in certain individuals (37), recommendations to improve vitamin D status may be an inexpensive and practical means of reducing the burden of diabetes. Indeed, it was found in a meta-analysis that vitamin D supplementation reduced the risk of type 2 diabetes (2) and improved insulin resistance (38,39) to a small extent. Future randomized, controlled trials should focus on the impact of vitamin D supplementation among obese individuals. If results are positive, vitamin D may be an avenue for obese individuals to improve glucose homeostasis.

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