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*Research Article*

# Multivariate Path Analysis of Serum 25-Hydroxyvitamin D Concentration, Inflammation, and Risk of Type 2 Diabetes Mellitus

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*Background and Aims.* Despite growing interest in the protective role that vitamin D may have in health outcomes, little research has examined the mechanisms underlying this role. This study aimed to test two hypotheses: (1) serum 25-hydroxyvitamin D [25(OH)D] is inversely associated with type 2 diabetes mellitus (T2DM) and elevated hemoglobin A1c; (2) these associations are mediated by serum C-reactive protein (CRP). *Methods.* Participants aged 20 and older in 2001–2006 National Health and Nutrition Examination Surveys ($n$ = 8,655) with measures of serum 25(OH)D, CRP, hemoglobin A1c, and other important covariates were included in the present study. Logistic regression and path analysis methods were applied to test the study hypotheses. *Results.* Decreased serum 25(OH)D concentration was significantly associated with increased odds of T2DM. In males, an estimated 14.9% of the association between 25(OH)D and hemoglobin A1c was mediated by serum CRP. However, this mediation effect was not observed in females. *Conclusion.* Using a nationally representative sample, the present study extends previous research and provides new evidence that the effect of decreased serum vitamin D concentration on T2DM may proceed through increased systemic inflammation in males. Longitudinal studies and randomized control trials are needed to confirm the present findings.

## 1. Introduction

Systematic review studies indicate that high serum 25(OH)D concentration (a biomarker of vitamin D status in blood) may be associated with lower risk of T2DM [1–4]. Although the mechanism by which decreased serum 25(OH)D concentration increases risk of T2DM remains obscure, it has been suggested that vitamin D deficiency may cause diabetes through various pathways including impaired pancreatic $\beta$-cell function, insulin resistance, and systemic inflammation [5, 6]. Furthermore, the presence of vitamin D receptors on inflammatory cells suggests that there is a potential role for vitamin D in inflammation [7]. Because the activation of inflammatory pathways may downregulate insulin signaling which can cause insulin resistance, vitamin D might impact the risk of diabetes through the inflammatory response [8–14]. A recent randomized controlled trial found that among 100 diabetes patients, vitamin D supplementation led to an increase in 25(OH)D concentration and decrease in measured inflammatory biomarkers [12]. However, other studies found no association between vitamin D supplementation and inflammatory biomarkers [11–14]. Studies to date have limited generalizability due to using small samples [11, 12, 14]. In the present study, we used data from a nationally representative sample to explore the association between 25(OH)D and T2DM and HbA1c and test whether these associations were mediated by serum systemic inflammation.

## 2. Methods

*2.1. Study Design.* Data from 2001–2006 National Health and Nutrition Examination Survey (NHANES) were used. The NHANES are conducted by the National Center for Health Statistics (NCHS), part of the Centers for Disease Control and Prevention (CDC). Survey participants from the US

noninstitutionalized civilian population were selected using a stratified multistage probability sample design. Participants were interviewed and invited for a clinical examination. Physical examinations and collection of blood samples were conducted in a mobile examination clinic (MEC) [15]. All serum specimens were processed, stored, and shipped to the Division of Laboratory Sciences, National Center for Environmental Health, CDC, using standardized measurement and analysis. The unweighed response rates for 2001–2006 NHANES were ≥76% [16]. The NCHS Ethics Review Board approved the survey, and participants provided written informed consent [17].

Serum 25(OH)D concentration was measured using a radioimmunoassay kit (DiaSorin, Stillwater, MN) [18]. Serum 25(OH)D concentration is used to estimate total intake of vitamin D from cutaneous synthesis and dietary intake [19]. Serum HbA1c was measured using a high-performance liquid chromatography system. T2DM was defined on the basis of the American Diabetes Association criteria [20]. Patients who have fasting plasma glucose concentration ≥126 mg/dL or two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or HbA1c ≥6.5% or an answer of "yes" to any of the following questions were diagnosed as having T2DM: (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 sugar?" Serum CRP was measured by latex-enhanced nephelometry using a Behring Nephelometer Analyzer System (Behring Diagnostics Inc., Somerville, NJ).

*2.2. Measurements of Covariates.* Information on age, race/ethnicity, sex, education level, physical activity, and family history of diabetes was obtained using standard survey questionnaires. Season of examination was classified as winter if the period of examination was between November 1 and April 30 or summer if between May 1 and October 31. Physical activity per day was grouped on a scale of 1 to 4 (least vigorous to most vigorous). Family history of diabetes was defined if a participant answered "yes" to the following question: including living and deceased, were any of your biological relatives, that is, blood relatives, including grandparents, parents, brothers, and sisters, ever told by a health professional that they had diabetes?

Anthropometric measurements and blood pressure (BP) were obtained by trained researchers during a physical examination [15]. Waist circumference (WC) was measured at a point immediately above the iliac crest on the midaxillary line at minimal respiration to the nearest 0.1 cm [17]. Resting systolic and diastolic BP (SBP and DBP) were measured three to four times with a mercury sphygmomanometer. When more than one BP measurements were available, the average SBP and DBP were calculated. Serum high-density lipoprotein (HDL) cholesterol was measured using a direct immunoassay method.

*2.3. Inclusion and Exclusion Criteria.* Participants who were interviewed and examined in MEC and did not have data on age, sex, season, education, serum 25(OH)D concentration, CRP, and HbA1c were excluded from the present study ($n = 1090$). Participants missing covariate information (WC, education, physical activity, family history of diabetes, HDL, SBP, and DBP) were excluded as well ($n = 1,407$).

Race/ethnicity was adjusted in multivariate analysis due to the strong association between skin pigmentation and lower 25(OH)D concentration [21, 22] and associations with socioeconomic status and behaviors [23]. The final analyzed sample was 8,655 participants.

*2.4. Statistical Analysis.* First we examined associations between 25(OH)D and T2DM before and after adjustment for CRP. Serum 25(OH)D status was classified as insufficient (<50 nmol/L) and sufficient (50–125 nmol/L). To test the association between 25(OH)D status and T2DM, we used multivariate logistic regression models. Second, further adjustment analysis was conducted in order to control for multiple confounders. In this analysis, we adjusted for age (years), race/ethnicity (non-Hispanic White or non-Hispanic Black), season of examination (winter or summer), education level (less than high school, high school diploma, or some college education), physical activity (1 to 4), smoking status (never smoker, former smoker, or current smoker), SBP (mm Hg), HDL (mmol/L), WC (cm), and family history of diabetes (yes or no). We repeated the analysis with adjustment for log-CRP (nmol/L) to evaluate the mediation effect of inflammation. Third, multivariate path analysis was performed in order to examine direct and indirect associations between 25(OH)D (nmol/L) and HbA1c (%). In the study, a theoretical path model was specified based on prior theory [24] and standard procedures were followed to test whether the data fit the theoretical model including ensuring that conditions were satisfied for unbiased parameter estimation and interpretation of path model fit [25]. Standardized summary of the average covariance residuals (root mean square error of approximation (RMSEA)), standardized difference between the observed correlation and the predicted correlation (standardized root mean square residual (SRMSR)), Bentler comparative fit index (BCFI), the proportion of the observed covariance, and adjusted goodness of fit index (AGFI) were used to evaluate whether a multivariate model meets the modeling requirement. Generally accepted values for fit indices are RMSEA < 0.10 [26], SRMSR < 0.08 [27], BCFI > 0.90 [28], and AGFI > 0.90 [29].

Figure 1 depicts the hypothesized relationships in the present study. Single-headed arrows indicate a direct effect from exogenous to endogenous variable, and a double-headed arrow indicates a correlation among exogenous variables (Figure 1). Three endogenous variables are HbA1c, 25(OH)D concentration, and log-CRP. Values of CRP were log-transformed to improve normality. Six exogenous variables were race/ethnicity (non-Hispanic Black versus non-Hispanic White), family history of diabetes (yes or no), age (years), WC (cm), SBP (mm Hg), and HDL (mmol/L). Season, education, physical activity, and DBP were dropped from the path model because of nonsignificance. In order to

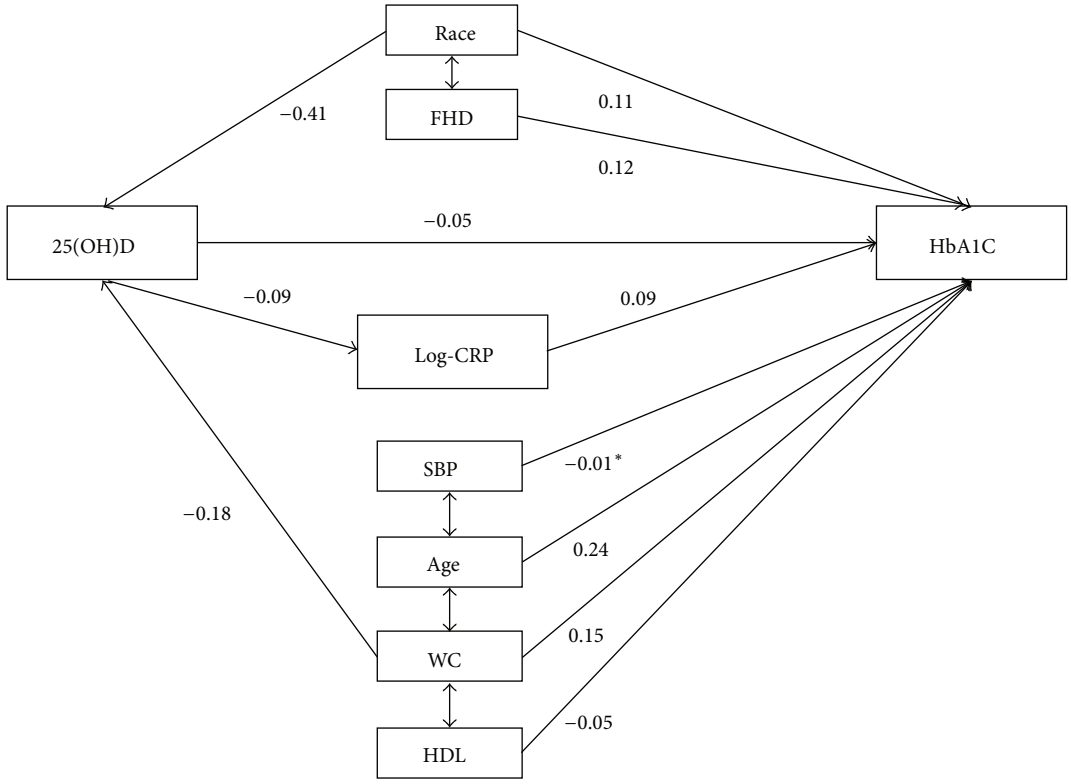


Figure 1: Path analysis diagram shown with standardized coefficients from the model for males, NHANES 2001–2006.

assess the sensitivity of results to departures from multivariate normality when using maximum likelihood estimation (MLE), we retested our path model using weighted-least squares regression (a robust estimation procedure) [30]; however, the results were the same. It is likely due to the large sample size [31], thus the latter are not reported here.

All data analyses were stratified by sex because of sex difference in serum 25(OH)D concentration and T2DM rate [32–34]. SAS 9.2 (SAS Institute, Cary, NC) was used in all data analyses.

## 3. Results

Table 1 shows the characteristics of participants stratified by sex. Males tended to be older, less educated, more physically active, and less likely to have a blood relative with diabetes. In addition, males were more likely to have a greater WC, lower serum 25(OH)D concentration, higher HbA1c, lower serum CRP, lower HDL, higher systolic blood pressure, and higher diastolic blood pressure.

Results from multiple logistic regression analyses indicate that 25(OH)D insufficiency was significantly associated with a 20.7% (OR = 1.207, 95% CI: 1.203, 1.210) and 77.3% (OR = 1.773, 95% CI: 1.731, 1.740) increased odds of T2DM in females and males, respectively (Table 2). Adjustment for log-CRP in males slightly attenuated the association (OR = 1.736, 95% CI: 1.731, 1.740), but we observed no change in females.

Table 3 shows the model fit statistics of path models. In males, the path models fitted well indicated by RMSEA = 0.09, SRMSR = 0.05, AGFI = 0.91, and BCFI = 0.90. However, the path model did not fit well for females as compared to the model for males. The results from path analysis suggest that there was no or a weak mediation effect of CRP on the association between serum 25(OH)D and HbA1c (path coefficient = 0.004, 95% CI: −0.03, 0.03, $P = 0.28$, Table 4).

Figure 1 shows the proposed path model and standardized coefficients. All path coefficients were statistically significant except for the path between SBP and HbA1c (path coefficient = −0.01, 95% CI: −0.04, 0.02). Serum 25(OH)D concentration had a negatively direct association with HbA1c (path coefficient = −0.05, 95% CI: −0.08, −0.02). The indirect association of 25(OH)D with HbA1c was statistically significant (path coefficient = −0.008, $P < 0.0001$). By dividing the indirect effect by the total effect, a 14.9% of the association between 25(OH)D and HbA1c could be attributable to CRP (i.e., a mediated effect).

## 4. Discussion

Using data from a large, nationally representative sample of adults aged 20 and older, the main findings of the present study not only support that decreased serum 25(OH)D concentration is significantly associated with prevalent T2DM and elevated HbA1c but also extend previous studies by examining and identifying that there is a possible mediation effect of systemic inflammation on the association between 25(OH)D and metabolic dysfunction in males. This result is independent of a set of covariates, including

Table 1: Characteristics of participants by sex, NHANES 2001–2006.

| Characteristic | Male | Female | $P$ value* |
|---|---|---|---|
| Unweighed sample size | 4181 | 4474 | |
| Age (years) | 51.2 (18.6) | 49.1 (19.2) | <0.0001 |
| Sample recruited by season | | | 0.69 |
| Winter | 1589 (38.0) | 1682 (37.6) | |
| Summer | 2592 (62.0) | 2792 (62.4) | |
| Race/ethnicity | | | 1.0 |
| Non-Hispanic White | 3070 (73.4) | 3285 (73.4) | |
| Non-Hispanic Black | 1111 (26.6) | 1189 (26.6) | |
| Education | | | 0.02 |
| Less than high school | 858 (20.5) | 822 (18.4) | |
| High school diploma | 1100 (26.3) | 1157 (25.9) | |
| Some college | 2223 (53.2) | 2495 (55.8) | |
| Physical activity (1: least vigorous, 4: most vigorous) | 2.2 ± 0.9 | 2.0 ± 0.7 | <0.0001 |
| Waist circumference (cm) | 100.8 ± 14.9 | 95.3 ± 15.7 | <0.0001 |
| Serum 25(OH)D (nmol/L) | 56.5 ± 21.8 | 57.6 ± 25.9 | 0.03 |
| Hemoglobin HbA1c (%)** | 5.4 (5.2–5.7) | 5.3 (5.1–5.6) | <0.0001 |
| Serum C-reactive protein (nmol/L)** | 16.2 (6.7–36.2) | 26.7 (10.5–59.0) | <0.0001 |
| Family history of diabetes | | | <0.0001 |
| Yes | 1785 (42.7) | 2225 (49.7) | |
| No | 2396 (57.3) | 2249 (50.3) | |
| HDL cholesterol (mmol/L) | 1.27 ± 0.36 | 1.57 ± 0.44 | <0.0001 |
| Systolic blood pressure (mmHg) | 127.0 ± 17.6 | 124.5 ± 22.4 | <0.0001 |
| Diastolic blood pressure (mmHg) | 72.42 ± 12.5 | 69.2 ± 12.4 | <0.0001 |

Data are presented as means ± SD or median (IQR)** or $n$ (%).
* $P$ value represents differences in means ± SD or median (IQR) or proportions using $t$-test or Wilcoxon rank-sum test or Pearson's chi-squared test, respectively, using a two-tailed test.

Table 2: Odds ratios of the association between serum 25(OH)D sufficiency and T2DM before and after adjustment for C-reactive protein by sex, NHANES 2001–2006.

| Sex | Model | Odds ratio (95% CI) |
|---|---|---|
| Females | Model 1 | 1.207 (1.203, 1.210) |
| | Model 2 | 1.207 (1.203, 1.210) |
| Males | Model 1 | 1.773 (1.769, 1.778) |
| | Model 2 | 1.736 (1.731, 1.740) |

[1]Model 1: adjusted for age, race/ethnicity, season of examination, education level, physical activity, smoking status, systolic BP, high-density lipoprotein cholesterol, waist circumference, and family history of diabetes.
[2]Model 2: adjusted for log-CRP in addition to the variables from Model 1.

age, race/ethnicity, season of examination, education, lipid profiles, and behavior risk factors.

In the present study, we did not observe a significant mediation effect of serum CRP on the associations of serum 25(OH)D with T2DM and HbA1c in females. Although we are unable to further test this sex difference using the present limited data, there may be more complex predictors in females, such as reproductive history, female hormone use, and the degree of sensitivity to a certain disease and medication. Additional studies will be required to further address these questions.

The mechanisms by which serum 25(OH)D may have a protective effect on risk of metabolic dysfunction are still being studied. It has been suggested that vitamin D may influence the nuclear transcription factors necessary for the generation and action of cytokines [35]. Appropriate levels of serum vitamin D concentration may have a direct effect to help cells less sensitive to particular nuclear factors which might cause insulin resistance [36]. Insulin resistance and decreased pancreatic $\beta$-cell function are the primary pathways by which vitamin D is suggested to impact glucose homeostasis [5]. Vitamin D may also have a function by reducing the risk effect of inflammation on metabolic diseases. In the present study, the associations between serum 25(OH)D and T2DM and HbA1c were significantly reduced after adjustment for serum CRP; in other words, CRP may have a mediation effect on the association between vitamin D and metabolic dysfunction in males.

Increasing evidence supports the hypothesis that vitamin D may play a pivotal role in the pathophysiology of glucose metabolism. Although these mechanisms are not fully understood, pathways may include impaired pancreatic $\beta$-cell function, insulin resistance, and systemic inflammation. Evidence for an inverse association between serum 25(OH)D and type 2 diabetes has been derived from many cross-sectional studies. However, the results have not been internally and externally consistent. Depending on the outcome

Table 3: Model fit indices for path analysis models by sex, NHANES 2001–2006.

| Model fit index | Good fit threshold levels | Model fit statistic value | |
|---|---|---|---|
| | | Males | Females |
| Root mean square error approximation (RMSEA) | <0.10 | 0.09 | 0.14 |
| Standardized root mean square residual (SRMSR) | <0.08 | 0.05 | 0.07 |
| Adjusted goodness of fit (AGFI) | >0.90 | 0.91 | 0.83 |
| Bentler comparative fit index (BCFI) | >0.90 | 0.90 | 0.86 |

Table 4: Standardized path coefficients and 95% confidence intervals by sex.

| Path | Path coefficient | 95% CI | | $P$ value* |
|---|---|---|---|---|
| | | Males | | |
| Standardized effects on HbA1c | | | | |
| 25(OH)D → HbA1c | −0.05 | −0.08 | −0.02 | 0.003 |
| Log-CRP → HbA1c | 0.09 | 0.06 | 0.12 | <0.0001 |
| Standardized effects on log-CRP | | | | |
| 25(OH)D → Log-CRP | −0.09 | −0.12 | −0.06 | <0.0001 |
| Standardized effects on 25(OH)D | | | | |
| WC → 25(OH)D | −0.18 | −0.21 | −0.15 | <0.0001 |
| Race → 25(OH)D | −0.41 | −0.44 | −0.39 | <0.0001 |
| | | Females | | |
| Standardized effects on HbA1c | | | | |
| 25(OH)D → HbA1c | 0.004 | −0.03 | 0.03 | 0.28 |
| Log-CRP → HbA1c | 0.05 | 0.02 | 0.07 | 0.0004 |
| Standardized effects on Log-CRP | | | | |
| 25(OH)D → Log-CRP | −0.13 | −0.16 | −0.10 | <0.0001 |

25(OH)D: 25-hydroxyvitamin D, WC: waist circumference, log-CRP: log C-reactive protein.
* $P$ value based on two-tailed test.

measures, results may vary within a study. For example, in the Baynes et al. study [37], serum 25(OH)D was found to be associated with 1-hour glucose after a standard 75 g oral glucose tolerance test (OGTT) but not fasting plasma glucose. Findings from the Kuopio Ischaemic Heart Disease Risk Factor Study indicate that serum 25(OH)D concentration was inversely associated with OGTT 2-hour glucose concentration after adjustment for age, sex, and year of examination [38]. However, other important covariates, such as race, SBP, and obesity, were not adjusted in their study. In our present study, taking the advantage of data from a large-scale nationally representative sample, we were able to take account of all these covariates in our multivariate and path analysis models. The findings of our study extend previous studies and add new evidence to the research field.

Most previous studies had been limited to their case definitions, including T2DM which they defined on the basis of participants' self-reported data. This approach may lead to a serious underestimation of the true prevalence of T2DM because of possible information bias and the classifications without support from blood sample tests [14]. In our present study, we were able to use results from blood tests to classify the prevalence of T2DM. The main limitation of our present study is that the findings are driven from a study with cross-sectional design. Therefore, all results from the present study cannot be interpreted as a cause-effect association, although this association has been supported by few longitudinal studies [38–43]. In conclusion, using a large community-based general population sample, the present study adds new evidence to the literature on the association between decreased vitamin D and risk of T2DM, and this association may be mediated by systemic inflammation in males. Further longitudinal prospective and randomized clinical trials are needed to confirm the present findings.

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