Original Article

Age- and gender-specific associations between low serum 25-hydroxyvitamin D level and type 2 diabetes in the Korean general population: analysis of 2008-2009 Korean National Health and Nutrition Examination Survey data

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Introduction: We present data from the Korean National Health and Nutritional Examination Survey (KNHANES) 2008-2009 on the association between 25-hydroxyvitamin D[25(OH)D] status and type 2 diabetes in a representative sample of the adult Korean population. Methods: This study was based on data obtained from the KNHANES 2008–2009, which was conducted for 3 years (2007-2009) using a rolling sampling design that involved a complex, stratified, multistage, probability-cluster survey of a representative sample of the non-institutionalized civilian population of South Korea. Results: We showed that serum 25(OH)D concentration is inversely associated with type 2 diabetes in the Korean general population. In particular, low serum 25(OH)D concentration was associated with an increased prevalence of type 2 diabetes in young women and old men. The present study showed that 25(OH)D has a significant negative association with fasting insulin and insulin resistance. Conclusion: The age- and gender-specific association between low 25(OH)D level and type 2 diabetes may be related to interactions between vitamin D, sex hormone concentrations, and type 2 diabetes. In conclusion, we showed that low 25(OH)D concentration is associated with type 2 diabetes in the Korean general population in an age- and gender-specific pattern.

Key Words: vitamin D, diabetes, age, gender, 25-hydroxyvitamin D

INTRODUCTION

Socioeconomic development and changes in nutrition in Korea between the late 1980s and 2005 were accompanied by an increase in the prevalence of type 2 diabetes, from 3 to 7.3%, and increased concern about type 2 diabetes.[1]

Vitamin D plays an important role in bone and mineral metabolism, and deficiency of this vitamin is closely associated with the occurrence of metabolic bone diseases such as rickets in children and osteomalacia in adults. Recently, vitamin D has also attracted interest among medical researchers due to its nonskeletal effects[2] including type 2 diabetes,[3,4] cardiovascular diseases,[5-7] cancers,[8-11] infection,[12-14] and autoimmune diseases.[15]

Vitamin D from the skin and diet is metabolized in the liver to 25-hydroxyvitamin D [25(OH)D], which has no independent clinical activity as an intermediate form. Further hydroxylation of 25(OH)D in the kidneys yields the biologically active form of vitamin D, $1,25(OH)_2D$. The $1,25(OH)_2D$ ligand binds with high affinity to the vitamin D receptor and triggers an increase in intestinal absorption of both calcium and phosphorous. Circulating $1,25(OH)_2D$ reduces serum parathyroid hormone levels directly by decreasing parathyroid gland activity and indirectly by increasing serum calcium. A variety of factors, including serum phosphorus and parathyroid hormone regulate the renal production of $1,25(OH)_2D$. Although the assay for $1,25(OH)_2D$, an active form of vitamin D, is of value in evaluating the differential diagnosis for a variety of inborn and acquired disorders of calcium, vitamin D, and bone metabolism, $1,25(OH)_2D$ is not measured to determine vitamin D status, since patients with vitamin D deficiency and secondary hyperparathyroidism often have normal or increased concentrations of $1,25(OH)_2D$. However, serum level of 25(OH)D which reflects the amount

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of vitamin D entering the circulation is considered to be the standard clinical measure of vitamin D status, because 25-hydroxylation of vitamin D is not tightly regulated, and the level of 25(OH)D, which is the major circulating metabolite of vitamin D and has a half-life of 2 to 3 weeks, correlates with the clinical signs and symptoms of vitamin D deficiency. Vitamin D deficiency has been historically defined and recently recommended by the Institute of Medicine (IOM) as a 25(OH)D of less than 50 nmol/L.[2,16-21]

Several studies have suggested a link between low vitamin D level, as measured in terms of 25(OH)D level, and the occurrence of type 2 diabetes.[3,4,22,23] Scragg *et al.*[22] suggested ethnic variations in the risk of type 2 diabetes and vitamin D deficiency, determined by measuring the 25(OH)D level. Other studies from New Zealand,[24] Australia,[25] and the Netherlands [26] have shown an inverse association between vitamin D status (determined by measuring the 25(OH)D level) and type 2 diabetes. Renzaho *et al.*[27] observed ethnicity-, gender-, and age-related differences in a systematic review assessing the association between 25(OH)D and obesity/ type 2 diabetes in ethnic minority population groups. Looker [28] found that the relationship with percent body fat was stronger and significant in white women of all ages and significant in black women younger than 50 years old. Very few such reports have been published from Asian countries.[29-30] Lu *et al.*[29] reported a significant association between low serum 25(OH)D level and a high risk of the metabolic syndrome in Chinese people between 50 and 70 years of age. However, their study population was not representative of the general population. Recently, Choi *et al.*[30] reported an association between 25(OH)D and type 2 diabetes in an adult Korean population using Korean National Health and Nutritional Examination Survey (KNHANES) 2008 data. However, the authors analyzed the data using ordinary statistical methods with no consideration of sample weighting, which was recommended and explained in the KNHANES survey analysis manual.

We hypothesized that serum 25(OH)D level may be inversely associated with type 2 diabetes in an age- and gender-specific pattern in the Korean general population. To test this hypothesis, we conducted a cross-sectional analysis of the association between 25(OH)D level and type 2 diabetes using KNHANES 2008–2009 data. The objective of this study was to evaluate whether serum 25(OH)D level is associated with type 2 diabetes in an age- and gender-specific pattern after adjusting for covariates in a representative sample of the adult Korean population.

METHODS

Design and data collection

This study was based on KNHANES 2008-2009 data, representing the second and third years of the KNHANES IV 2007-2009 survey, which was conducted for 3 years (2007-2009) using a rolling sampling design that involved a complex, stratified, multistage, probability-cluster survey of a representative sample of the noninstitutionalized civilian population of South Korea. Detailed information on the design of the survey has been provided previously. Briefly, the survey consisted of three components: a health interview survey, a health examination survey, and a nutrition survey.[31,32]

The present analysis was restricted to participants ≥20 years of age who completed the health examination survey, including measurements of serum 25(OH)D (n = 13,022). We excluded individuals who were pregnant, had liver cirrhosis or chronic liver diseases, or had chronic renal diseases. Therefore, the final analytical sample consisted of 12,336 participants. All participants provided written consent to participate in the study. Institutional Review Board requirement was waived because KNHANES was conducted by Korean government in accordance with the internationally agreed ethical principles for the conduct of medical research.

Information on age, education, smoking history, alcohol intake, and regular exercise or walking was collected during the health interview. Details on the categorization of body mass index, age, education level, smoking status, and alcohol consumption have been provided previously.[31,32] Regular walking was defined as indoor or outdoor walking for 30 or more minutes at a time at least five times per week. Regular exercise was defined as performing moderate exercise (swimming slowly, playing doubles tennis, volleyball, or occupational or recreational activity involving carrying light objects) for ≥30 min at a time at least five times per week, or vigorous exercise (running, climbing, cycling fast, swimming fast, football, basketball, jump rope, squash, playing singles tennis, or occupational or recreational activity involving carrying heavy objects) for ≥20 min at a time at least three times per week. Season was classified into four categories as spring (March-May), summer (June-August), fall (September-November), and winter (December-February).

Type 2 diabetes was defined as a fasting glucose level ≥7 mmol/L, current use of antidiabetic medications, or self-reported physician diagnosis of type 2 diabetes. Insulin resistance was determined using the homeostasis model assessment (HOMA) estimate of insulin resistance [HOMA-IR = fasting insulin (μIU/mL)×fasting glucose (mmol/L)/22.5] and fasting insulin levels.

Clinical laboratory tests

For clinical laboratory tests, blood samples were collected from individual participants during health examination surveys. Blood samples were centrifuged, aliquoted, and frozen at –70°C on-site. The frozen plasma and serum samples were transported on dry ice to the designated central laboratory of Neodin Medical Institute, a laboratory certified by the Korean Ministry of Health and Welfare in Seoul, South Korea.

Blood samples were analyzed within 24 h of transportation. Serum 25(OH)D levels were measured with a radioimmunoassay kit (DiaSorin, Stillwater, MN) using a 1470 Wizard gamma counter (Perkin-Elmer, Turku, Finland). The interassay coefficients of variation were 7.6 and 7.2% at 36.7 and 131.0 nmol/L, respectively. One possible limitation of the radioimmunoassay was that it used antibodies to measure 25(OH)D in unextracted serum. These antibodies may recognize other vitamin D metabolites, such as 24,25(OH)D. In contrast, liquid chromatography-mass spectroscopy can separate different vitamin D metabolites and is the preferred assay for clini-

cal trials.[21] However, the radioimmunoassay is usually used in mass surveys such as KNHANES, where the availability of serum is also limited.

A blood sample was taken in the morning after a fast of at least 8 hours for measurement of 25(OH)D, fasting blood glucose, and insulin levels. Serum glucose level was measured using a Hitachi 7600 autoanalyzer (Hitachi, Tokyo, Japan). Serum insulin level was measured by radioimmunoassay (INS-IRMA; Bio-Source, Nivelles, Belgium) using a 1470 Wizard gamma counter.

Statistical analysis

Statistical analyses were performed using SAS (version 9.22; SAS Institute, Cary, NC) and SUDAAN (release 10.0; Research Triangle Institute, Research Triangle Park, NC), a software package that incorporates sample weights and adjusts analyses for the complex sample design of the survey. Survey sample weights were used in all analyses to produce estimates that were representative of the non-institutionalized civilian Korean population.

Unadjusted mean (95% confidence interval, CI) serum 25(OH)D levels were calculated by gender, age group, residence location, region, season, educational level, smoking status, drinking status, BMI, regular exercise, regular walking, and diabetes using the Proc Descript function in SUDAAN. The adjusted means (95% CI) were also obtained by analysis of covariance, adjusted for all other variables in the tables using the Proc Regress function in SUDAAN.

Next, odds ratios (ORs) and 95% CI values for having type 2 diabetes were calculated for serum 25(OH)D as a continuous variable while controlling for covariates [model 1: age, sex, BMI, smoking status, drinking status, season, residence location, region, educational level, and regular walking; and model 2: model 1plus age (≥50), the interaction term for age (≥50) and serum 25(OH)D using the Proc Rlogist function to incorporate the sample weights and adjust the analyses for the complex sample design of the survey. For model 3, which has an interaction term for age and serum 25(OH)D, adjusted prevalence rates were calculated using conditional marginal probability analysis after covariate adjustment in men and women for comparison of prevalence rate by age category (<50 and ≥50 years) in men and women.

To evaluate the associations of 25(OH)D with fasting glucose, fasting insulin, and insulin resistance, fasting glucose was regressed to calculate regression coefficients and their 95% CIs against 25(OH)D after adjusting for covariates. After natural log transformation of fasting insulin and HOMA-IR because their distributions were skewed, log-transformed fasting insulin and HOMA-IR were regressed to calculate regression coefficients and 95% CIs against serum 25(OH)D after adjusting for all covariates.

RESULTS

The serum 25(OH)D levels of the study participants are listed according to category, ie, age, residence location, region, and season according to gender in Table 1.

Unadjusted and adjusted mean serum 25(OH)D levels are presented in the table along with their 95% CIs. Overall, the mean serum 25(OH)D levels in female participants (n = 6,926), male participants (n = 5,410), and all participants (n = 12,336) representing adult Koreans aged ≥20 years were 42.7 nmol/L (95% CI, 41.8-43.1 nmol/L), 49.3 nmol/L (95% CI, 48.2-49.9 nmol/L), and 46.1 nmol/L (95% CI, 45.2-46.6 nmol/L), respectively. The serum 25(OH)D level was significantly higher in male than in female participants, and increased significantly with age until ≥60 years old in both genders.

For both genders, mean 25(OH)D levels in participants living in rural areas were significantly higher than those in participants living urban areas. Compared to Seoul and the surrounding area comprising Kangwon Province, study participants of both genders in all other regions had higher serum 25(OH)D levels. In the seasons with less sunshine (ie, spring and winter), participants of both genders had significantly lower serum 25(OH)D levels than in seasons with higher levels of sunshine (ie, summer and fall).

Table 2 lists the serum 25(OH)D levels of study participants by categories, ie, educational level, smoking status, drinking status, BMI, regular exercise, regular walking, and diabetic status.

In adjusted analysis, men and total participants with higher educational levels had significantly lower serum 25(OH)D levels compared to less educated participants. On the other hand, current smokers had significantly lower serum 25(OH)D levels compared to never-smokers in the adjusted analysis of males and total participants, but heavy drinkers among male and total participants had significantly higher 25(OH)D levels compared to non-drinkers in adjusted analysis. BMI categorization showed no significant differences in mean serum 25(OH)D levels after adjustment for covariates.

Regular exercise and walking contributed significantly to increased mean serum 25(OH)D levels in participants. While diabetic status did not affect the mean serum 25(OH)D level in female participants in adjusted analysis. Significant mean differences in serum 25(OH)D levels were observed in male and total subjects in both unadjusted and adjusted analyses.

Next, adjusted ORs (95% CIs) for Korean adults with type 2 diabetes were calculated by logistic regression in all subjects, and separately by gender (Table 3).

The covariates for the adjusted OR calculation were age, sex, BMI, smoking status, and drinking status, and season, residence location, region, educational level, and regular walking in model 1; and covariates in model 1 plus age (<50 years) and interaction term for age (<50 years) and serum 25(OH)D in model 2. The ORs were significant only in model 2, which had an interaction term for age (≥50 years) and serum 25(OH)D. Model 2, with the interaction term for serum 25(OH)D and age (≥50 years), indicated that decreases in the prevalence of type 2 diabetes of 1.7% and 1.5% were associated with an increase of 1 unit in 25(OH)D in women <50 years of age and in men ≥50 years old, respectively.

In women <50 years old, the participants with higher serum 25(OH)D levels (75 nmol/L) showed a significantly lower type 2 diabetes prevalence rate than those with a lower serum 25(OH)D level (25 nmol/L). However, no significant differences in prevalence rates were observed among three different 25(OH)D groups in the older age

Table 1. Mean and 95% confidence interval (CI) values of blood 25-hydroxyvitamin D (nmol/L) by age group and other classification variables.

Classification variables	Women			Men			Total		
	n	Crude Mean (95% CI)	Adjusted † Mean (95% CI)	n	Crude Mean (95% CI)	Adjusted Mean (95% CI)	n	Crude Mean (95% CI)	Adjusted Mean (95% CI)
All subjects, age 20+ years	6926	42.7 (41.8-43.1)	42.5 (41.7-43.2)	5410	49.3 (48.2-49.9)	49.6 (48.7-50.4)	12336	46.1 (45.2-46.6)	
Age group									
20-29	895	37.9 (36.6-38.6)	39.1 (37.7-40.5)	735	42.6 (40.9-43.5)	44.0 (42.6-45.3)	1630	40.4 (39.1-41.1)	41.4 (40.3-42.5)
30-39	1458	41.7 (40.4-42.4)	43.0 (41.9-44.1)	1122	46.8 (45.2-47.6)	48.1 (46.9-49.3)	2580	44.4 (43.1-45.1)	45.6 (44.6-46.5)
40-49	1440	41.7 (40.5-42.3)	41.4 (40.4-42.4)	1129	51.0 (49.5-51.8)	51.0 (49.9-52.1)	2569	46.5 (45.3-47.1)	46.3 (45.4-47.2)
50-59	1153	46.6 (45.3-47.3)	45.7 (44.5-46.9)	914	54.3 (52.7-55.1)	52.7 (51.3-54.0)	2067	50.5 (49.3-51.2)	49.4 (48.4-50.4)
60+	1980	46.3 (44.8-47.0)	44.8 (43.4-46.1)	1510	54.6 (53.0-55.4)	52.5 (51.1-53.9)	3490	50.0 (48.6-50.7)	48.7 (47.6-49.8)
S_Waite chi-square		p<0.01	p<0.01		p<0.01	p<0.01		p<0.01	p<0.01
Residence location									
Urban	5171	41.6 (40.6-42.0)	42.1 (41.3-42.8)	4006	47.7 (46.5-48.4)	48.5 (47.6-49.3)	9177	44.7 (43.7-45.2)	45.3 (44.6-46.1)
Rural	1755	47.8 (45.7-48.9)	45.6 (43.9-47.3)	1404	56.4 (53.7-57.7)	53.3 (51.6-55.0)	3159	52.2 (50.0-53.4)	49.5 (48.0-51.1)
t-test		p<0.01	p<0.01		p<0.01	p<0.01		p<0.01	p<0.01
Region									
Seoul	1164	40.2 (38.2-41.3)	41.3 (39.7-42.9)	884	45.7 (43.2-46.9)	47.0 (45.4-48.5)	2048	43.0 (40.8-44.1)	44.2 (42.8-45.6)
Incheon, Kyunggi & Kangwon	1999	40.3 (38.9-41.0)	40.8 (39.8-41.7)	1618	47.2 (45.0-48.3)	47.5 (46.1-48.9)	3617	43.9 (42.2-44.7)	44.2 (43.1-45.2)
DaeJeon & Choongchung	813	43.9 (40.6-45.6)	43.0 (41.0-45.0)	637	52.7 (48.8-54.7)	51.0 (48.8-53.1)	1450	48.4 (44.9-50.2)	47.1 (45.1-49.0)
Daegu & Kyungbuk	812	44.2 (41.7-45.5)	43.7 (41.7-45.6)	634	51.7 (48.4-53.5)	51.4 (49.2-53.7)	1446	48.0 (45.3-49.4)	47.6 (45.7-49.5)
Pusan & Kyungnam	1065	46.0 (43.9-47.1)	45.7 (43.6-47.8)	816	51.8 (49.2-53.1)	51.5 (49.1-53.9)	1881	48.9 (46.7-50.1)	48.6 (46.5-50.8)
Kwanju, Honam & Jeju	1073	46.5 (43.9-47.9)	45.2 (43.4-47.0)	821	53.6 (50.5-55.1)	52.6 (50.7-54.4)	1894	50.1 (47.3-51.4)	48.9 (47.2-50.6)
S_Waite chi-square		p<0.01	p<0.01		p<0.01	p<0.01		p<0.01	p<0.01
Season									
Spring	1781	36.2 (35.0-36.9)	36.4 (35.3-37.5)	1476	41.8 (40.3-42.6)	42.1 (40.8-43.4)	3257	39.2 (37.9-39.8)	39.3 (38.2-40.4)
Summer	1906	48.4 (46.7-49.3)	48.3 (46.8-49.8)	1449	57.6 (55.6-58.6)	57.3 (55.5-59.0)	3355	53.1 (51.3-53.9)	52.8 (51.4-54.3)
Fall	1787	47.0 (45.5-47.7)	46.9 (45.4-48.3)	1365	55.1 (53.4-56.0)	55.1 (53.3-56.8)	3152	51.1 (49.6-51.8)	51.0 (49.6-52.5)
Winter	1452	38.1 (36.9-38.8)	38.2 (37.1-39.3)	1120	41.9 (40.6-42.6)	42.0 (40.9-43.1)	2572	40.1 (38.9-40.7)	40.2 (39.2-41.1)
S_Waite chi-square		p<0.01	p<0.01		p<0.01	p<0.01		p<0.01	p<0.01

† Covariates: gender, age, residence location, region, smoking status, drinking status, body mass index, educational level, season, regular exercise and regular walking. S_Waite chi-square: Satterthwaite's adjusted chi-square test

Table 2. Mean and 95% confidence interval (CI) values of 25-hydroxyvitamin D (nmol/L) by classification of study variables. Unit: nmol/L

Classification variables	Women			Men			Total		
	n	Crude Mean (95 %CI)	Adjusted† Mean (95 %CI)	n	Crude Mean (95 %CI)	Adjusted Mean (95 %CI)	n	Crude Mean (95 %CI)	Adjusted Mean (95 %CI)
Education level									
Less than High School	2961	46.2 (45.0-46.9)	43.6 (42.4~44.7)	1598	55.8 (54.0~56.7)	52.0 (50.7~53.4)	4559	49.9 (48.6~50.6)	47.6 (46.5~48.7)
High School	2031	42.0 (40.9-42.6)	42.7 (41.7-43.7)	1583	50.0 (48.6-50.8)	49.7 (48.7-50.7)	3614	46.0 (44.9-46.6)	46.3 (45.5-47.1)
College and more	1934	39.6 (38.6-40.2)	41.8 (40.8-42.7)	2229	46.1 (44.9-46.8)	48.0 (47.0-48.9)	4163	43.6 (42.5-44.1)	44.9 (44.1-45.7)
S_Waite chi-square		p<0.01	NS		p<0.01	p<0.01		p<0.01	p<0.01
Smoking status									
Non-Smoker	6075	43.0 (42.1-43.4)	42.8 (42.1-43.4)	1010	48.6 (47.1-49.4)	50.6 (49.4-51.8)	7085	44.0 (43.1-44.5)	46.5 (45.7-47.2)
Past Smoker	389	42.1 (40.0-43.2)	43.2 (41.4-45.1)	1961	51.8 (50.5-52.5)	50.7 (49.6-51.7)	2350	50.3 (49.0-51.0)	47.4 (46.3-48.4)
Current Smoker	458	40.3 (38.1-41.3)	41.6 (39.7-43.4)	2435	47.9 (46.6-48.6)	48.0 (47.1-48.9)	2893	46.9 (45.7-47.6)	44.6 (43.6-45.5)
S_Waite chi-square		p<0.05	NS		NS	p<0.01		p<0.01	p<0.01
Drinking status									
No Drink	2601	43.4 (42.2-44.0)	42.0 (41.0-43.0)	905	49.0 (47.3-49.9)	46.5 (45.1-47.9)	3506	45.1 (43.9-45.7)	44.5 (43.5-45.4)
Mild Drink	2265	43.3 (42.2-43.8)	42.9 (42.0-43.8)	740	50.0 (48.2-51.0)	47.9 (46.3-49.4)	3005	45.1 (44.0-45.7)	45.6 (44.7-46.5)
Moderate Drink	1074	42.9 (41.6-43.5)	44.1 (43.0-45.1)	860	49.8 (48.1-50.7)	49.1 (47.7-50.5)	1934	46.2 (45.0-46.9)	46.8 (45.9-47.7)
Heavy Drink	986	40.1 (38.9-40.7)	42.4 (41.2-43.5)	2905	49.2 (47.9-49.8)	50.3 (49.5-51.2)	3891	47.2 (46.1-47.8)	47.0 (46.3-47.8)
S_Waite chi-square		p<0.01	p<0.05		NS	p<0.01		p<0.01	p<0.01
Body Mass Index									
Lean	375	40.5 (38.5-41.5)	41.9 (40.1-43.6)	195	48.0 (44.4-49.8)	47.0 (44.2-49.7)	570	43.2 (41.2-44.2)	45.0 (43.5-46.6)
Normal	4579	42.3 (41.4-42.8)	42.6 (41.9-43.4)	3319	49.3 (48.0-50.0)	49.4 (48.5-50.3)	7898	45.7 (44.7-46.3)	46.1 (45.4-46.8)
Obese	1949	44.2 (43.1-44.8)	43.1 (42.2-44.0)	1868	49.5 (48.3-50.1)	49.5 (48.6-50.4)	3817	47.3 (46.3-47.9)	46.2 (45.5-47.0)
S_Waite chi-square		p<0.01	NS		NS	NS		p<0.01	NS
Regular exercise									
Yes	1040	45.8 (44.2-46.7)	44.4 (43.0-45.7)	837	52.3 (50.5-53.2)	51.2 (49.8-52.7)	1877	49.2 (47.7-49.9)	47.8 (46.6-48.9)
No	5886	42.2 (41.3-42.6)	42.4 (41.8-43.1)	4573	48.8 (47.7-49.4)	49.0 (48.3-49.8)	10459	45.6 (44.6-46.1)	45.8 (45.2-46.5)
t-test		p<0.01	p<0.01		p<0.01	p<0.01		p<0.01	p<0.01
Regular walking									
Yes	3069	43.8 (42.8-44.3)	43.6 (42.8-44.3)	2660	50.1 (48.7-50.7)	49.9 (49.0-50.8)	5729	47.2 (46.1-47.7)	46.8 (46.1-47.5)
No	3857	41.8 (40.9-42.3)	42.0 (41.2-42.8)	2750	48.7 (47.4-49.3)	48.8 (47.9-49.7)	6607	45.2 (44.2-45.7)	45.5 (44.8-46.2)
t-test		p<0.01	p<0.01		p<0.05	p<0.05		NS	NS
Diabetes									
Yes	580	44.4 (42.5-45.4)	41.9 (40.3-43.6)	550	51.1 (49.3-52.0)	47.6 (45.9-49.2)	1130	48.0 (46.5-48.8)	44.9 (43.6-46.1)
No	6346	42.6 (41.7-43.0)	42.8 (42.1-43.4)	4860	49.2 (48.0-49.8)	49.5 (48.7-50.3)	11206	45.9 (45.0-46.4)	46.2 (45.5-46.9)
t-test		p<0.05	NS		p<0.05	p<0.05		p<0.05	p<0.05

† Covariates: gender, age, residence location, region, smoking status, drinking status, body mass index, educational level, season, regular exercise and regular walking. NS: not significant. S_Waite chi-square: Satterthwaite's adjusted chi-square test

Table 3. Adjusted OR (95% CI) of Korean adults with diabetes mellitus by serum 25-hydroxyvitamin D level

	Women (n=6926)	Men (n=5410)	Total (n=12336)
Model 1	0.999 (0.992-1.007)	0.995 (0.989-1.002)	0.997 (0.992-1.002)
Model 2	1.017 (1.001-1.003)	0.985 (0.972-0.998)	0.998 (0.988-1.009)

Model 1: adjusted for age, sex, body mass index, smoking status, drinking status, season, residence location, region, education, and regular exercise
Model 2: adjusted as in model 1 plus young and interaction term of young×serum 25-hydroxyvitamin D level

Table 4. Adjusted regression coefficient (SE) of 25-hydroxyvitamin D on fasting glucose, fasting insulin and HOMA_IR , adjusted for covariates†

Outcome variables	Female		Male		Total	
	β (SE)	*p* value	β (SE)	*p* value	β (SE)	*p* value
Fasting glucose	-0.0003 (0.0007)	0.702	0.0006 (0.0008)	0.438	0.0003 (0.0006)	0.570
Log-transformed fasting insulin	-0.0012 (0.0005)	0.032	-0.0026 (0.0006)	<0.001	-0.0020 (0.0004)	<0.001
Log-transformed HOMA_IR	-0.0011 (0.0006)	0.068	-0.0023 (0.0006)	<0.001	-0.0018 (0.0005)	<0.001

†: age, gender, residence location, region, smoking status, drinking status, body mass index, regular exercise, and season

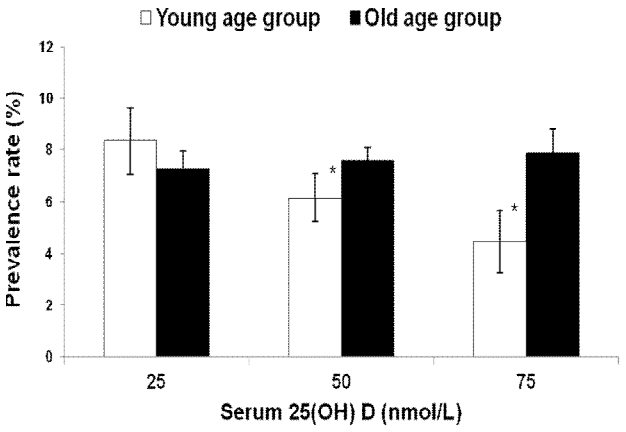

Figure 1. Adjusted prevalence rate (%) of diabetes mellitus by level of serum 25(OH)D by young and old age group in female subjects. *p<0.01 compared with 25 nmol/L

group (≥50 years) (Figure 1). In contrast, the opposite was observed in men. The adjusted prevalence rate in men ≥50 years old showed a significant decrease according to increasing 25(OH)D level, but no differences were observed in the younger age group (age <50 years) (Figure 2).

Finally, to evaluate the associations between serum 25(OH)D and fasting glucose, log-transformed fasting insulin, and log-transformed HOMA-IR in multiple regression analysis after controlling for covariates, the beta coefficient and its 95% CI were calculated in all participants as well as separately in female and male participants (Table 4). While 25(OH)D showed no significant association with fasting glucose, significant negative associations were observed with log-transformed fasting insulin and log-transformed HOMA-IR.

DISCUSSION

Several cross-sectional studies have suggested an association between low serum 25(OH)D level and the occurrence of type 2 diabetes.[4,22-26] Several cohort studies also noted an association between low 25(OH)D level and type 2 diabetes.[3,33-35] In a Finish cohort study by Mattila *et al.*[3] the relative risk (RR) between the highest and lowest serum 25(OH)D quartile was 0.60 (95% CI 0.36-0.98; *p*-trend; 0.01) (4097 participants). However, this association was attenuated after further adjustments for BMI, leisure-time exercise, smoking, and education (RR 0.70 [95% CI 0.42-1.16]; *p* trend; 0.07). The association is not very strong. The incident type 2 diabetes cases were identified from a nationwide registry of patients receiving diabetes medication reimbursement. The register does not include diabetic patients undergoing dietary therapy only. Thus, the identified diabetic patients had more severe disease than diabetic patients on average.

The nested case-control study by Knekt *et al.,*[33] which pooled data from two cohorts in Finland (total of 7503 available participants) included 412 cases who developed type 2 diabetes during the follow-up period and 986 matched controls. After multivariate adjustment men in the highest quartile (mean 25(OH)D; 75 nmol/L) had a 72% lower risk of developing type 2 diabetes compared with men in the lowest quartile (mean 25(OH)D; 25 nmol/L); there was no significant association among women. The incident type 2 diabetes cases were identified from a nationwide registry of patients receiving diabetes medication reimbursement as in the study by Mattila *et al.*

The second nested case-control study[34] was conducted using data from 608 women with newly diagnosed type 2 diabetes and 559 controls who were enrolled in the Nurses' Health Study. After multivariate adjustment, higher levels of plasma 25(OH)D were associated with a lower risk for type 2 diabetes. The OR for incident type 2 diabetes in the top (median 25(OH)D; 83.4 nmol/L) versus the bottom (median 25(OH)D; 35.9 nmol/L) quartile was 0.52 (95% CI; 0.33-0.83). Incident cases of type 2 diabetes were identified by validated self-report.

The other nested case-control study by Deleskog *et al.*[35] very recently, showed that low serum 25(OH)D level predicts progression to type 2 diabetes in individuals with pre-diabetes at follow-up 8-10 years in a Swedish cohort . They defined pre-diabetes as impaired fasting glucose (fasting plasma glucose ≥5.6 mmol/L) or impaired glu-

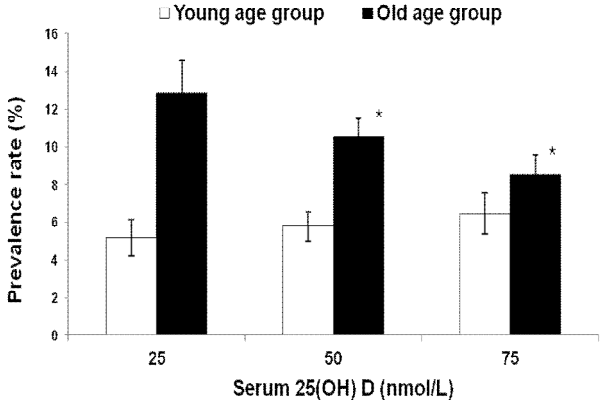

Figure 2. Adjusted prevalence rate (%) of diabetes mellitus by level of serum 25(OH)D by young and old age group in male subjects. *p<0.01 compared with 25 nmol/L

cose tolerance test (7.8 mmol/L ≤ 2-h plasma glucose < 11 mmol/L). Type 2 diabetes was defined as fasting plasma glucose >7.0 mmol/L or 2-h plasma glucose >11 mmol/L.

Scragg *et al.*[22] suggested ethnic variation in an association of type 2 diabetes with vitamin D deficiency (as determined by measuring 25(OH)D levels) in the Third National Health and Nutrition Examination Survey (6228 participants). They showed a strong inverse trend between the odds of developing type 2 diabetes and serum 25(OH)D among white and Mexican Americans, after adjusting for age, sex, BMI, physical activity, and season. However, no such association was observed among African Americans, which is suggestive of ethnic variation in the association of type 2 diabetes with low serum 25(OH)D levels, possibly due to decreased sensitivity to vitamin D. Type 2 diabetes was defined as fasting glucose ≥7.0 mmol/L or 2-h glucose ≥11.1 mmol/L.[22] American, European, and Australian studies have demonstrated that migrants and members of ethnic minorities with dark skin exhibit low serum 25(OH)D concentrations.[36-42] Several studies performed in the United States included participants from non-Hispanic black, Hispanic, and non-Hispanic white, or equivalent ethnic groups.[22,37,40,43,44] Less commonly included ethnicities were Asian Americans. In addition, few studies reported such an association in the Asian population.[29,30] Recently, Choi *et al.*[30] reported an association between serum 25(OH)D level and type 2 diabetes in the Korean adult population using KNHANES 2008 data, which indicated that a low serum 25(OH)D concentration was associated with a high risk of type 2 diabetes in Korean adults. However, the authors analyzed the data using ordinary statistical methods with no consideration of sample weighting, which was recommended and explained in the survey analysis manual from KNHANES. Without the application of appropriate statistical methods, reaching definitive conclusions is difficult. The weighted analysis of Choi *et al.*[30] showed no significant association between serum 25(OH)D level and type 2 diabetes, unlike the results of unweighted analysis. Due to the nature of survey data, weighted analyses tend to produce larger CIs than ordinary statistical analyses typically used for data collected through simple random sampling.[45]

In the present study, we analyzed data for 2 years from KNHANES 2007–2009 to validate the possible association between 25(OH)D level and type 2 diabetes. We also showed that serum 25(OH)D concentration is inversely associated with type 2 diabetes in the Korean general population. In particular, the association showed an age- and gender-specific pattern: low serum 25(OH)D level was associated with type 2 diabetes in women <50 years old and in men ≥50 years old. To our knowledge, this is the first report of an age- and gender-specific association between serum 25(OH)D level and type 2 diabetes. This association may be related to the interaction between vitamin D and circulating sex hormone concentrations. It is possible that the observed effects of vitamin D are related to testosterone, which circulates at lower levels in young females and older men than in older females and younger men, respectively. Alternatively, it may be related to estrogen/testosterone ratios. Younger women have a higher estrogen/testosterone ratio than their older counterparts, whereas older men have a higher estrogen/testosterone ratio than their younger counterparts (as a result of the decrease in testosterone levels resulting from increased aromatization with increased body fat levels and normal decrease in testosterone levels).[46-48] Our data suggest that this may be the case. However, no significant effect modification was observed with age or gender in other studies.[35,49] There is currently little or no research to support a link between vitamin D status, sex hormones, and diabetes. Levels of sex hormones were not available in the present study, and further studies are therefore required.

Vitamin D may directly enhance insulin action by stimulating the expression of the insulin receptor, thereby enhancing insulin responsiveness for glucose transport.[50] The present study showed that 25(OH)D was significantly negatively associated with fasting insulin and HOMA-IR. Associations between low 25(OH)D level and decreased insulin sensitivity have been reported in previous cross-sectional studies.[22,26,37,51-54]

The mechanisms underlying the potential association between type 2 diabetes and 25(OH)D are unclear. The 25(OH)D level may have an impact on many factors, including pancreatic beta cell function, insulin action, and systemic inflammation.[50] Accumulating evidence indicates that vitamin D may be useful in the prevention and treatment of type 2 diabetes. Vitamin D supplementation in participants with vitamin D deficiency has been shown to result in improved glucose tolerance, whereas that in participants with sufficient vitamin D yielded conflicting results.[56]

The present study showed that, in both genders, the mean 25(OH)D levels in subjects living in rural areas were significantly higher than those in urban areas. This study also showed that serum 25(OH)D levels were significantly lower in seasons with less sunshine (ie, spring and winter) than in those with higher levels of sunshine (ie, summer and fall) in both genders. Regular exercise and walking were significantly associated with increased mean serum 25(OH)D levels in participants in the present study. A role of 25(OH)D in type 2 diabetes was suggested by the seasonal variations in glycemic control reported in patients who have type 2 diabetes, with control being worse in winter,[57-59] which may be due at least in part to

prevalent hypovitaminosis D in winter. As increasing numbers of people live in cities and spend the majority of their time indoors, this will lead to insufficient sunlight exposure for adequate cutaneous production of vitamin D. Thus, vitamin D insufficiency has become a major health concern in modern society. In a recent study performed in 7,441 postmenopausal osteoporotic women from 29 countries participating in a clinical trial on bazedoxifene, the prevalence rates of 25(OH)D levels of <50 nmol/L were as high as 35.3% in winter and 25.2% in summer, while the prevalence rates of 25(OH)D levels in excess of 75 nmol/L were 21.2% in winter and 27.5% in summer.[60] Higher educational status in men may mean that they work in offices and are exposed to less sunlight, which may result in vitamin D insufficiency.

Whereas current smokers had significantly lower serum 25(OH)D levels compared with never-smokers in the adjusted analysis of males and total participants, heavy drinkers among male and total participants had significantly higher 25(OH)D levels compared with nondrinkers in the adjusted analysis. The opposite directions of these associations may be related to lifestyle. For example, males with more stress tend to smoke and may not perform outdoor activities. Additionally, heavy drinking is easily observed among agricultural or manual workers, who are exposed to more sunlight compared with office workers. However, no clear explanation is available.

The present study had several important strengths. First, we used serum 25(OH)D concentration as an indicator of vitamin D status, reflecting vitamin D obtained from the diet, supplements, and cutaneous synthesis. Second, age- and gender-specific analyses were performed. Adjusted prevalence rates were calculated using conditional marginal probability analysis, with the addition of an interaction term for age and serum 25(OH)D, in men and women for comparison of prevalence rates by age category (<50 and ≥50 years) and gender. Third, the study was carried out on a representative sample of the general Korean population. Finally, rigorous quality control of study procedures was ensured in the KNHANES.

However, the present study also had some limitations. First, our associations were obtained by cross-sectional analysis. We cannot completely exclude the possibility of reverse causality. An unknown third factor might be the common link which produces the association. Therefore, a causal relationship between serum 25(OH)D level and type 2 diabetes cannot be inferred from our correlational data. However, several cohort studies support our results,[3,33-35,61] although further randomized controlled clinical trials or prospective studies are needed to clarify causality. Second, although serum level of 25(OH)D is used to be the standard clinical measure of vitamin D status, the clinical implication of the 25(OH)D level as an intermediate form of vitamin D is not determined, compared to $1,25(OH)_2D$, a biologically active form of vitamin D.

Third, data on sun exposure and dietary vitamin D intake were not available. Instead, we obtained data about the participants' exercise and walking habits, which were presumed to provide an estimate of each subject's sunlight exposure.[8] We also adjusted for season. Fourth, we did not obtain data regarding behavioral factors that could affect cutaneous synthesis of vitamin D, such as sunscreen use or clothing. Fifth, we did not obtain data regarding each individual's vitamin D intake through diet and supplements, which may have affected serum 25(OH)D levels to some extent.

In conclusion, we showed an age- and gender-specific association between low 25(OH)D concentration and type 2 diabetes in the Korean general population.

AUTHOR DISCLOSURES

The authors declare that there are no conflicts of interest.

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Original Article

Age- and gender-specific associations between low serum 25-hydroxyvitamin D level and type 2 diabetes in the Korean general population: analysis of 2008-2009 Korean National Health and Nutrition Examination Survey data

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韓國人民之低血清 25-羥基維生素 D 濃度和第 2 型糖尿病在不同年齡及性別之相關性： 2008-2009 韓國國民健康營養調查資料之分析

前言：我們呈現的資料是來自 2008-2009 韓國國民健康營養調查，針對韓國成年人中一群具代表性樣本，探討 25-羥基維生素 D(25(OH)D)狀況和第 2 型糖尿病之相關性。方法：本篇研究是根據 2008-2009 韓國國民健康營養調查的資料，調查之執行於 2007 至 2009 共 3 年的時間，利用滾動式抽樣設計，為一個複雜、分層、多步驟、集束的調查，所得到的樣本是一個南韓具代表性非機構住民之群體。結果：由分析資料顯示，韓國人民之血清 25(OH)D 濃度與第 2 型糖尿病呈負相關。尤其在年輕女性和老年男性，其低血清 25(OH)D 與第 2 型糖尿病發生率的增加有相關。本研究亦顯示，25(OH)D 與禁食胰島素濃度和胰島素抗性有顯著負相關。結論：低 25(OH)D 濃度與第 2 型糖尿病在不同年齡、性別之相關性，可能受維生素 D、性荷爾蒙濃度和第 2 型糖尿病之間的交互作用影響。總之，韓國人民之低 25(OH)D 濃度與第 2 型糖尿病之相關性在不同性別、年齡呈現不一樣的模式。

關鍵字：維生素 D、糖尿病、年齡、性別、25-羥基維生素 D