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Associations between lumbar bone mineral density, serum 25-hydroxyvitamin D and history of kidney stones in adults aged 30-69 years in US（NHANES 2011-2016）

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Abstract

Objectives: To examine the associations between lumbar bone mineral density （BMD）, serum 25-hydroxyvitamin D （25-OHD） and history of kidney stones in people aged between 30 and 69 years old.

Design: Cross-sectional study.

Setting: National Health and Nutrition Examination Survey 2011-2016

Participants: A total of 6817 participants between 2011 and 2016 from National Health and Nutrition Examination Survey (NHANES) were selected for this cross-sectional survey.

Main outcome measures: The result of this study is whether one had kidney stones.

Data analysis: Multivariable logistic regression model was conducted to estimate the relationship between lumbar BMD, serum 25-OHD and kidney stones. All models incorporated survey sample weights and adjusted for the Covariates.

Results Lumbar BMD was negatively correlated with the history of kidney stones in all three multivariable linear regression models, and there is a more stable negative association in men after adjusting for all confounding factors (OR = 0.387, 95% CI: 0.169, 0.888). In multiple regression analysis, there was an interaction between serum 25-OHD and lumbar BMD ($P < 0.05$) in the influence on kidney stones and the negative association between lumbar BMD and kidney stones is more obvious in the group of higher 25-OHD (≥50 nmol/L).

Conclusion This finding suggests that maintaining a high level of lumbar BMD may reduce the incidence of kidney stones. At the same time, maintaining a high serum 25-OHD level may be more beneficial to prevent the occurrence or recurrence of stones while ensuring high lumbar BMD.

Strengths and limitations of this study

1. Use of a large, nationally representative sample of the US population, increasing generalisability.
2. We introduce serum 25-OHD this variable, which is tightly associated with BMD, to explore whether the level of serum 25-OHD will affect the protective effect of BMD on stones.
3. the nature of the cross-sectional study limits the conclusions to associations and cannot assess the causal association of lumbar spine BMD and serum 25-OHD with the history of nephrolithiasis.
4. In view of the limitations of NHANES data, specificity for special groups such as adolescents, pregnant women, or those over 70 years people was poor.
5. due to the lack of data on urinary calcium and the analysis of stone composition, our study has limitations on the related effects of different kinds of stones and urinary calcium excretion.

Keywords

bone mineral density, 25-hydroxyvitamin D, kidney stones, NHANES

word counts for the manuscript: 1928

Introduction

Nephrolithiasis is a very common disease influenced by multiple factors. After entering twenty-first Century, the incidence rate of kidney stones showed a significant upward trend, and the male to female ratio 3:1 is narrowing.[1, 2] In a study of NHANES data from 2015 to 2018, it was found that the 12-month incidence of kidney stones was significantly higher than previous reports from the United States. The significant incidence rate and prevalence of stones are worrying, and had an impact on disease treatment and the allocation of public medical resources.[3] Therefore, it is very necessary to get up early and screen the high-risk groups with the risk of kidney stone disease or recurrence.

Most types of kidney stones contain calcium,[4] and Calcium is closely related to human bone health. So, we want to know the relationship between history of kidney stones and human bone health. Because many stone formers have hypercalciuria, clinicians have concerns that their BMD may be reduced. This concern has inspired many studies in recent years.[5-8] Although many studies have found that kidney stone disease is paralleled by decreased BMD, the results remain inconclusive.

It is considered that more than 20 years have passed since the last relevant study of NHANES data.[9] The purpose of this study was to measure the associations between lumbar BMD and kidney stones among 30-69 years adults using data from the National Health and Nutrition Examination Survey

(NHANES 2011–2016). We also introduce serum 25-OHD this variable, which is tightly associated with BMD, to explore whether the level of serum 25-OHD will affect the protective effect of BMD on stones.

METHOD

Data Sources

The data of this study are from NHANES. The National Health and Nutrition Examination Survey (NHANES) is a research program designed to assess the health and nutrition status of adults and children in the United States. It is a major project of the National Center for Health Statistics (NCHS). NHANES is an extensive, Consecutive cross-sectional survey designed to be nationally representative. Researchers worldwide can access to data from NHANES freely available via the Internet. In this study, we summarized the data of NHANES for three two-year cycles from 2011 to 2016(The data of lumbar bone mineral density is missing from the data from 2017 to now). From a total of 29902 participants, we excluded 18514 who were younger than 30 years or older than 69 years. Of the remaining 11388 participants, 4561 with missing lumbar BMD, 242 with missing serum 25-OHD, 310 with missing serum calcium and 25 with missing a history of kidney stones were excluded. After applying these exclusion criteria, 6507 participants were analyzed (Figure 1). The

survey plan was approved by the Institutional Review Board of the National Center for health statistics, and each participant provided written informed consent.

Exposures

The exposure is lumbar BMD which is an important index to measure bone quality, reflecting the degree of osteoporosis and predicting the risk of fracture. The measurement of lumbar BMD was provided by dual energy X-ray absorptiometry (DXA) scanning, and the software version apex 3.2 was used in hologic discovery type a densitometer (hologic, Inc., Bedford, Massachusetts). Trained and certified radiographers perform DXA examinations.

Outcome

The result of this study is whether one had kidney stones. Questions on kidney stones were asked in the home, by trained interviewers, using the Computer-Assisted Personal Interview (CAPI) system.

Covariates

Among covariates, we selected age, blood urea nitrogen, serum 25-OHD, serum calcium, serum creatinine, serum glucose, serum phosphorus, serum sodium, alkaline phosphatase, total cholesterol, serum uric acid, total protein,

serum potassium, serum triglycerides, BMI as a continuous variable; age, race, physical activities, smoking behavior, ratio of family income to poverty as a categorical variable. All the data was collected from the NHANES website.

Statistical Methods

The weight of the sample analysis package in this study was edited and considered in NCHS version 3.4(http://www.R-project.org) And Empowerstats software (http:// www.empowerstats.com). The confidence interval was 95%. The association of lumbar BMD, serum 25-OHD with history of renal calculi was evaluated by multivariable logistic regression models. We constructed three models: model 1, without adjusting covariates; Model 2, adjusted for age, gender, race and BMI; In model 3, the covariates in Table 1 were all adjusted. Subgroup analysis stratified by gender, lumbar BMD status and serum 25-OHD status was also performed.

Results

Table 1 shows the demographic and laboratory data of the participants. Women had significantly higher lumber BMD. Participants with higher lumber BMD have higher serum creatinine, total protein, BMI, education level, physical activity and ratio of family income to poverty, and lower alkaline

phosphatase, total cholesterol, serum triglyceride, smoking and stone incidence rate, compared with participants with lower lumber BMD.

1.Association between lumbar BMD and kidney stones

We found that lumbar BMD was negatively associated with the history of kidney stones in all three models (Table 2). The trend of different lumbar BMD quartile arrays was still significant ($P < 0.05$). This negative association existed only in men after adjusting for all confounding factors (OR= 0.387, 95%CI: 0.169, 0.888) in the subgroup analysis stratified by gender and race； as well as non-Hispanic whites. In addition, we use weighted generalized additive model and smooth curve fitting to solve the nonlinear relationship and confirm the results (Figure2). It is found that the results remain unchanged.

2. The interaction between serum 25-OHD and lumbar BMD

According to Michael's research[10], The Endocrine Society defined vitamin D deficiency as a 25-OHD < 20 ng/mL(50 nmol/L). So, we divide the continuous variable of serum 25-OHD into two groups with the tangent point of 50 nmol/L and conduct interaction analysis. As a result, we found that there was an interaction between serum 25-OHD and lumbar BMD ($P < 0.05$) in the influence on kidney stones in model 3 (Table 3). Further, we make stratified analysis with the above two groups of 25-OHD in the multiple regression analysis between lumbar BMD and kidney stones (Table 1). The results show

that the negative correlation between lumbar BMD and kidney stones is more obvious (OR= 0.280, 95%CI: 0.133, 0.592) in the group of higher 25-OHD (≥50 nmol/L).

Discussion

The overall purpose of this study was to explore the relationship between lumbar BMD and serum 25-OHD levels and the history of kidney stones in a nationally representative sample of people aged 30-69 in the United States. Our results suggest that low levels of lumbar BMD are correlated to the history of renal calculus, especially in men and non-Mexican whites. Although there were some nonlinear correlations between them, the trend was consistent with previous multivariable linear regression. The negative correlation between lumbar BMD and kidney stones is more obvious in the group of higher serum 25-OHD (≥50 nmol/L). This finding suggests that maintaining a high level of lumbar BMD may reduce the incidence of kidney stones. At the same time, while ensuring high lumbar BMD, maintaining a high serum 25-OHD level may be more beneficial to prevent the occurrence or recurrence of stones.

In recent years, an increasing number of clinical investigators have noted the association between BMD and a history of kidney stones in patients. Consistent with the results of the present study, several studies have also verified from all aspects that there is an inverse association between history

of kidney stones and BMD.[5, 11-14] In a 2016 consensus statement experts recommended that BMD of patients with hypercalciuric stones or a predisposition to this condition should be measured by dual emission X-ray absorptiometry (DXA).[15] This noninvasive exam is convenient and efficient. But the mechanism of the effect between them is unclear. Stones are common in patients with high urinary calcium.[16] Hypercalciuria occurs because there is a net loss of calcium from the body, so patients usually excrete more calcium than is absorbed. Some researchers speculate that this extra urinary calcium is derived from bone.[17, 18] In another group, researchers found that sequence variants in the CLDN14 gene may be associated with kidney stones and bone mineral density.[19]

Vitamin D plays an important biological function in humans and Vitamin D deficiency is also associated with diseases caused by anemia and oxidative stress[20]. Although it was shown in some studies that vitamin D may be responsible for stone formation in some selected patients with certain genetic or clinical features,[21, 22] serum 25-OHD content did not differ in stone vs. non stone patients according to the previous cross-sectional study.[23, 24] Found in a 2019 interventional study that the use of regular doses of vitamin D supplementation in patients with vitamin D deficiency may not lead to an increased risk of hypercalciuria.[25] Several studies have also confirmed that raising the intake of vitamin D can indeed increase BMD and then improve bone quality, with significant beneficial effects on the risk of fracture.[26, 27]

So for patients with kidney stones or who have a tendency to develop stones, it is reasonable to assume that daily vitamin D supplementation might reduce their risk of stone recurrence or occurrence to achieve the goal of killing two birds with one stone by the interaction between serum 25-OHD and lumbar BMD. The studies by Susanna C Larsson, as well as Ian r Reid et al., suggest an insignificant causal relationship between chronically elevated serum 25-OHD concentrations and higher BMD in the general healthy population. 40 nmol/L is a sufficient concentration of serum 25-OHD.[28, 29] There are also some studies that suggest that vitamin D supplementation at lower amounts is safer in the normal population. The current findings do not support the beneficial effects of high-dose vitamin D supplements on bone health, and may even confers a substantial reduction in BMD, risk of falls, fractures or small increase of myocardial infarction. [30] According to the current available evidence, the benefits of vitamin D supplementation in humans are more biased towards a “U-shaped”. Therefore, although daily vitamin D supplementation may be beneficial in patients with kidney stones, the treatment measures should be adjusted at any time based on the change of condition to facilitate a positive balance between risks and benefits.

To make the current findings highly generalizable, the NHANES database strives to provide nationally representative estimates. But it still has certain limitations. First, the nature of the cross-sectional study limits the conclusions to associations and cannot assess the causal association of lumbar spine

BMD and serum 25-OHD with the history of nephrolithiasis. Second, due to the concentration of kidney stone patients in the middle-aged and older age groups, and pregnant women were excluded from DXA examination, individuals aged 30-69 years with nonpregnant status from the NHANES database were selected for study. So, specificity for special groups such as adolescents, pregnant women, or those over 70 years people was poor. Third, since we only assessed BMD at the lumbar spine without introducing BMD at other sites, it may have made the present study less broadly clinically representative. Finally, due to the lack of data on urinary calcium and the analysis of stone composition, our study has limitations on the related effects of different kinds of stones and urinary calcium excretion.

Conclusion

Our results suggest that low levels of lumbar BMD are associated with the history of renal calculus, especially in men and non-Mexican whites. This finding suggests that maintaining a high level of lumbar BMD may reduce the incidence of kidney stones. At the same time, the negative correlation between lumbar BMD and kidney stones is more obvious in the group of higher 25-OHD (≥50 nmol/L) which means that maintaining a high serum 25-OHD level may be more beneficial to prevent the occurrence or recurrence of stones while ensuring high lumbar BMD.

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Author contributions CXN, BS, LZY project development, data collection, manuscript writing. WSY, XKR, LMY project development, data collection, manuscript editing. LL, ZJY, LR data analysis.

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Data availability It is publicly available for people to collect data from the official website for users and researchers worldwide. (www.cdc.gov/nchs/ nhanes/).

Compliance with ethical standards

Disclosure and conflicts of interest None

Ethical statement This study was approved by the ethics review board of the National Center for Health Statistics and written informed consents were obtained from each participant.

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Figure legends

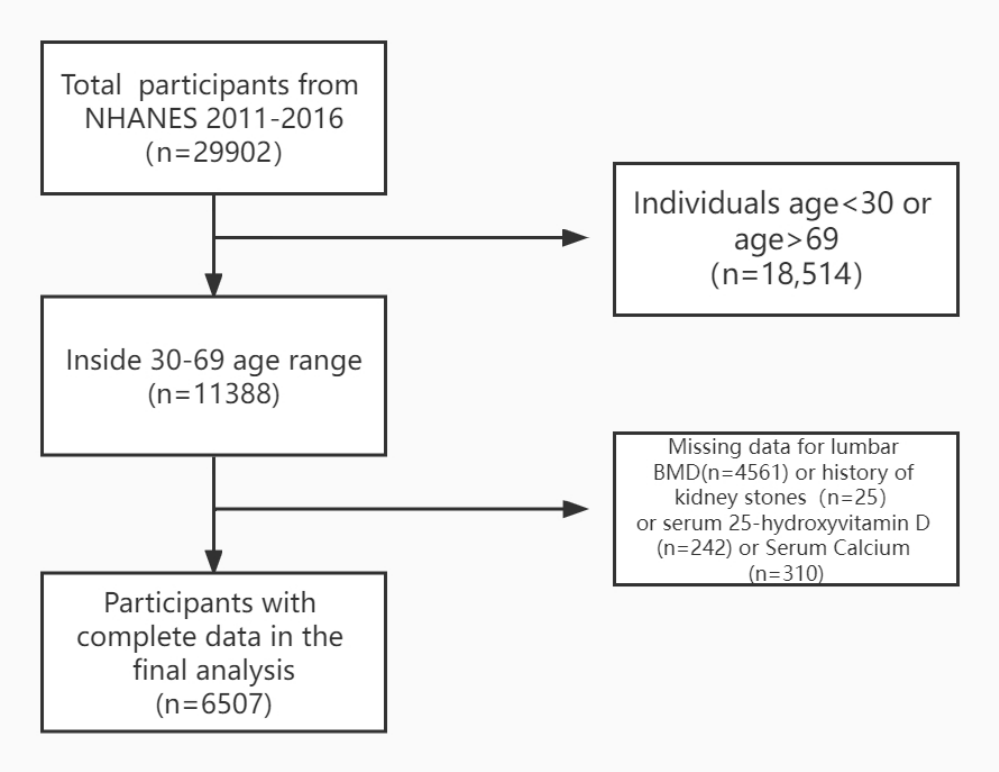
Figure 1: Flow chart of sample selection from the NHANES 2011–2016.

Figure2: The association between lumbar BMD and history of kidney stones. Each black point represents a sample. Solid rad line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit. Gender, age, race, BMI, education Level, BUN, serum calcium, Serum creatinine, serum glucose, serum phosphorus, serum sodium, physical activities, smoking behavior, poverty to income ratio, alkaline phosphatase, total cholesterol, total protein, serum uric acid, serum potassium, serum triglycerides were adjusted.

Table 1: Weighted Characteristics of Study Sample

Table 2. Association between lumbar BMD (g/cm²) and kidney stones.

Table 3: The interaction between serum 25-OHD (nmol/L) and lumbar BMD (g/cm²).



flow diagram

314x242mm (72 x 72 DPI)

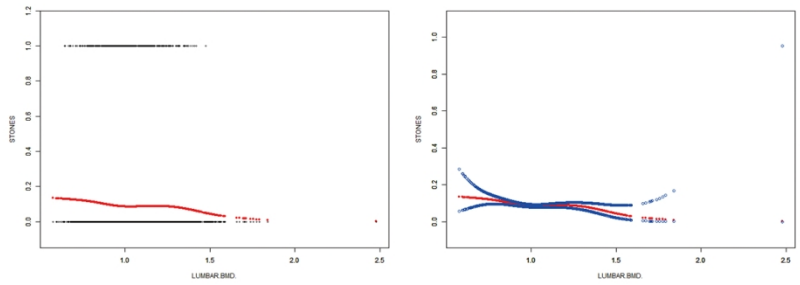


Figure 2

The association between lumbar BMD and history of kidney stones. Each black point represents a sample. Solid rad line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit. Gender, age, race, BMI, education Level, BUN, serum calcium, Serum creatinine, serum glucose, serum phosphorus, serum sodium, physical activities, smoking behavior, poverty to income ratio, alkaline phosphatase, total cholesterol, total protein, serum uric acid, serum potassium, serum triglycerides were adjusted.

119x160mm (300 x 300 DPI)

Table 1. Weighted Characteristics of Study Sample

	Lumbar BMD Q1 (g/cm²) (1625)	Lumbar BMD Q2 (g/cm²) (1622)	Lumbar BMD Q3 (g/cm²) (1627)	Lumbar BMD Q4 (g/cm²) (1633)	P value
Age (years)	46.1 ± 8.6	44.6 ± 8.6	43.8 ± 8.6	44.6 ± 8.6	<0.05
Gender					<0.05
Men/Women	55.1/44.9	50/50	49.4/50.6	49.7/50.3	
Race					<0.05
Mexican American	12.4	12.1	9.4	5.4	
Other Hispanic	7.7	6.7	5.8	5.2	
Non-Hispanic White	65	62.7	65.7	63.6	
Non-Hispanic Black	5.8	8.3	11.3	18.8	
Other Race - Including Multi-Racial	9.2	10.2	7.8	6.9	
BUN (mmol/L)	4.6 ± 1.6	4.6 ± 1.5	4.5 ± 1.5	4.6 ± 1.8	0.28
Serum calcium (mmol/L)	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	1
Serum creatinine (μmol/L)	74.8 ± 20.3	75.5 ± 22.5	76.2 ± 28.3	78.5 ± 34.1	<0.05
Serum glucose (mmol/L)	5.5 ± 1.8	5.5 ± 2.0	5.5 ± 1.9	5.6 ± 2.2	0.3
Serum phosphorus (mmol/L)	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	<0.05
Serum sodium (mmol/L)	139.1 ± 2.2	139.1 ± 2.1	139.0 ± 2.1	138.9 ± 2.1	0.01
Serum 25-hydroxyvitamin D (nmol/L)	66.6 ± 26.6	67.3 ± 25.3	68.7 ± 26.6	67.8 ± 28.0	0.14
Alkaline phosphatase (U/L)	70.7 ± 26.0	66.9 ± 20.9	63.7 ± 19.2	62.9 ± 23.4	<0.05
Total cholesterol (mmol/L)	5.3 ± 1.0	5.2 ± 1.2	5.1 ± 1.0	5.0 ± 1.0	<0.05
Total protein (g/L)	70.8 ± 4.6	70.8 ± 4.3	71.1 ± 4.5	71.2 ± 4.3	0.04
Serum uric acid (μmol/L)	319.1 ± 78.2	322.0 ± 82.3	315.4 ± 80.8	321.4 ± 83.3	0.08
Serum potassium (mmol/L)	4.0 ± 0.3	4.0 ± 0.3	3.9 ± 0.3	4.0 ± 0.3	0.02
BMI (kg/m2)	29.3 ± 6.0	29.7 ± 6.5	29.1 ± 6.6	30.3 ± 7.4	<0.05
Serum triglycerides (mmol/L)	2.0 ± 1.5	2.0 ± 2.5	1.8 ± 1.4	1.8 ± 1.7	<0.05
Education level					<0.05
Less than 9th grade	7.8	5	4.1	4.4	
9-11th grade (Includes 12th grade with no diploma)	12	10.1	8.5	8.8	
High school graduate/GED or equivalent	20	21.7	18.5	19.7	
Some college or AA degree	30.6	30.6	31.2	31.2	
College graduate or above	29.6	32.6	37.8	35.9	
Vigorous recreational activities					<0.05
Yes	22.7	28.4	30.7	33	
No	77.3	71.6	69.3	67	
Smoked at least 100 cigarettes in life					<0.05
Yes	48.2	43	43.4	47	
No	51.8	57	56.6	53	
Stones					<0.05
Yes	12.4	9.4	9.3	11.7	
No	87.6	90.6	90.7	88.3	
Ratio of family income to poverty					<0.05
<1.99	34.8	30.6	27.5	33.2	
1.99-3.49	19.1	21.8	20.6	20.5	
>3.49	40.2	40.5	47	46.2	

Notes: Mean ± SD for continuous variables: P-value was calculated by weighted linear regression model.% for categorical variables: P-value was calculated by weighted chi-square test

Table 2. Association between lumbar BMD (g/cm²) and kidney stones.

	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Lumbar BMD (g/cm²)	0.406 (0.232, 0.710)	0.491 (0.274, 0.881)	0.455 (0.249, 0.830)
Quintiles of lumbar BMD			
Lowest quintile	Reference	Reference	Reference
Q2	0.751 (0.595, 0.949)	0.788 (0.622, 0.998)	0.787 (0.620, 0.999)
Q3	0.731 (0.578, 0.924)	0.791 (0.622 1.005)	0.776 (0.608, 0.990)
Q4	0.710 (0.561, 0.899)	0.777 (0.608, 0.993)	0.767 (0.596, 0.986)
P for trend	0.005	0.046	0.038
Stratified by 25-OHD			
<50	0.863 (0.341, 2.186)	1.311 (0.481, 3.575)	1.159 (0.410, 3.272)
>=50	0.273 (0.135, 0.551)	0.300 (0.146, 0.618)	0.280 (0.133, 0.592)
Total	0.410 (0.234, 0.719)	0.486 (0.271, 0.873)	0.449 (0.246, 0.822)
Stratified by gender			
Men	0.443 (0.206, 0.953)	0.479 (0.215, 1.068)	0.387 (0.169, 0.888)
Women	0.368 (0.163, 0.831)	0.416 (0.173, 0.999)	0.468 (0.189, 1.158)
Stratified by race			
Mexican American	1.783 (0.346, 9.185)	2.056 (0.387, 10.915)	1.267 (0.211, 7.609)
Other Hispanic	1.256 (0.245, 6.450)	1.154 (0.217, 6.131)	0.710 (0.109, 4.623)
Non-Hispanic White	0.244 (0.101, 0.590)	0.233 (0.097, 0.559)	0.249 (0.101, 0.613)
Non-Hispanic Black	0.965 (0.254, 3.661)	1.090 (0.284, 4.183)	1.111 (0.270, 4.564)
Other Race - Including Multi-Racial	0.290 (0.052, 1.620)	0.233 (0.040, 1.348)	0.195 (0.030, 1.289)

Model 1 Adjust For: None
Model 2 Adjust For: Gender, age, race, BMI
Model 3 Adjust For: Gender, age, race, BMI, education Level, BUN, serum calcium, Serum creatinine, serum glucose, serum phosphorus, serum sodium, physical activities, smoking behavior, poverty to income ratio, alkaline phosphatase, total cholesterol, total protein, serum uric acid, serum potassium, serum triglycerides.

Table 3. The interaction between serum 25-OHD (nmol/L) and lumbar BMD (g/cm²).

	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Serum 25-OHD (nmol/L)			
<50	0.863 (0.341, 2.186)	1.160 (0.440, 3.058)	1.090 (0.408, 2.911)
>=50	0.273 (0.135, 0.551)	0.312 (0.152, 0.638)	0.284 (0.136, 0.592)
P interaction	0.05	0.03	0.03

Model 1 Adjust For: None

Model 2 Adjust For: Gender, age, race, BMI

Model 3 Adjust For: Gender, age, race, BMI, education Level, BUN, serum calcium, Serum creatinine, serum glucose, serum phosphorus, serum sodium, physical activities, smoking behavior, poverty to income ratio, alkaline phosphatase, total cholesterol, total protein, serum uric acid, serum potassium, serum triglycerides.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5, 6
Methods			
Study design	4	Present key elements of study design early in the paper	6, 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6, 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7, 8
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*e*) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, 9
		(b) Indicate number of participants with missing data for each variable of interest	6
Outcome data	15*	Report numbers of outcome events or summary measures	9, 10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, 10
		(*b*) Report category boundaries when continuous variables were categorized	9, 10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9, 10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9, 10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12, 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12, 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Associations between lumbar bone mineral density, serum 25-hydroxyvitamin D, and history of kidney stones in adults aged 30-69 years in United States (NHANES 2011–2018)

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Associations between lumbar bone mineral density, serum 25-hydroxyvitamin D, and history of kidney stones in adults aged 30-69 years in United States (NHANES 2011–2018)

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Keywords

Bone mineral density, 25-hydroxyvitamin D, kidney stones, NHANES

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Abstract

Objectives: Most kidney stones contain calcium, which is closely associated with human bone health. Therefore, we aimed to determine the relationship between the history of kidney stones and human bone health. This study examined the associations between lumbar bone mineral density (BMD), serum 25-hydroxyvitamin D (25-OHD), and a history of kidney stones in individuals aged between 30 and 69 years.

Design and data analysis: A multivariate logistic regression model was used to estimate the relationship between lumbar BMD, serum 25-OHD levels, and kidney stones in this cross-sectional study. All models incorporated survey sample weights and were adjusted for covariates.

Setting: National Health and Nutrition Examination Survey (NHANES) 2011–2018. The exposure and outcomes of this study included the lumbar BMD and presence of kidney stones.

Participants: All the 7500 participants for this cross-sectional survey were selected from the NHANES between 2011 and 2018.

Main outcome measures: The main outcome of this study was the presence of kidney stones. The interviewers asked the questions on kidney stones while the respondents were at home, using a CAPI system.

Results: Lumbar BMD was negatively correlated with a history of kidney stones in all three multivariate linear regression models; the negative association existed in all gender after adjusting for all confounding factors. In

the multiple regression analysis, there was an interaction between serum 25-OHD and lumbar BMD ($P < 0.05$) regarding the influence on kidney stones; the negative association between lumbar BMD and kidney stones was more obvious in the higher 25-OHD group (≥ 50 nmol/L).

Conclusion: The study results suggest that maintaining a high lumbar BMD may reduce the incidence of kidney stone formation. Simultaneously, maintaining a high serum 25-OHD level may be more beneficial in preventing the occurrence or recurrence of stones while ensuring a high lumbar BMD.

Strengths and limitations of this study

1. Use of a large, nationally representative sample of the US population, increasing generalizability.
2. The content of calcium would affect BMD, and serum 25-OHD in turn was one of the important factors affecting calcium metabolism. Therefore, we introduced serum 25- hydroxyvitamin D (25-OHD), which is closely associated with BMD, to explore whether serum 25-OHD levels affect the protective effect of BMD on kidney stones.
3. The nature of the cross-sectional study limits the conclusions to associations and cannot assess the causal association of lumbar spine BMD and serum 25-OHD with the history of nephrolithiasis.
4. In view of the limitations of NHANES data, specificity for special groups

such as adolescents, pregnant women, or those over 70 years people was poor.

5. Due to the lack of data on urinary calcium and the analysis of stone composition, our study has limitations on the related effects of different kinds of stones and urinary calcium excretion.

Introduction

Nephrolithiasis is a common disease that is influenced by multiple factors. After entering 21st century, the incidence rate of kidney stones showed a significant upward trend, and the male-to-female ratio of 3:1 narrowed.[1, 2] In a study of the National Health and Nutrition Examination Survey (NHANES) data from 2015 to 2018, the researchers found that the 12-month incidence of kidney stones was significantly higher than that stated in previous reports from the United States. The significantly higher incidence and prevalence of stones are concerning, which have an impact on disease treatment and the allocation of public medical resources.[3] Therefore, it is necessary to screen those at high-risk of kidney stone disease or recurrence.

Most kidney stones contain calcium,[4] which is closely related to human bone health. Therefore, we aimed to determine the relationship between a history of kidney stones and human bone health. As many patients with kidney stones have hypercalciuria, clinicians are concerned that their bone mineral density (BMD) may be reduced, which has inspired several recent studies.[5-8] Although many studies have found that the occurrence of kidney stones is associated with a decreased BMD, the results remain inconclusive.

More than 20 years have passed since the last relevant study on the NHANES data.[9] The main objective of this study was to measure the relationship between lumbar BMD and kidney stones among adults aged 30–69 years using data from the NHANES (2011–2018). We also introduced serum 25-

hydroxyvitamin D (25-OHD), which is closely associated with BMD, to explore whether serum 25-OHD levels affect the protective effect of BMD on kidney stones.

Methods

Data Sources

The data used in this study was obtained from the NHANES, which is a research program designed to assess the health and nutritional status of adults and children in the United States. This was a major project of the National Center for Health Statistics (NCHS). The NHANES is an extensive, consecutive, cross-sectional survey designed to be nationally representative. Researchers worldwide can access data from the NHANES, which is freely available via the internet.

The National Center for Health Statistics Research Ethics Review Board approved the study design, and informed consent was provided by all participants. The data used in this study has been de-identified and has been made publicly available (https://www.cdc.gov/nchs/nhanes/index.htm).

In our research, we summarized the data of the NHANES for four 2-year cycles from 2011 to 2018 (lumbar BMD data is missing from 2019 to present). From a total of 39,156 participants, we excluded 24,073 who were younger than 30 years or older than 69 years, 5983 with missing lumbar BMD, 1319 with missing data or refusal to answer the questionnaire about the history of

kidney stones, and 281 participants without data on serum 25-OHD, serum calcium, and other continuous variables. Finally, 7500 participants were analyzed (Figure 1).

Exposures

Lumbar BMD, an important index for measuring bone quality, reflects the degree of osteoporosis and predicts the risk of fracture. Measurement of lumbar BMD was performed by dual energy X-ray absorptiometry (DXA) scanning, and the software version apex 3.2 was used in a hologic discovery type a densitometer (hologic, Inc., Bedford, Massachusetts). The DXA examinations were performed by trained and certified radiologists

Outcome

The main outcome of this study was the presence of kidney stones. The question used to investigate the presence of kidney stones was: Have you ever had kidney stones? Participants can choose from four answers: “yes”, “no”, “refused”, or “don’t know”. The trained interviewers asked the questions on kidney stones while the respondents were at home, using a Computer-Assisted Personal Interview (CAPI) system. Even though many of NHANES interviewers had prior interviewing experience, they still have to complete a comprehensive training program. The training included general interview techniques, role-playing exercises, and hands-on interviews with on-site

respondents. The NCHS and contractor staff were responsible for the above training program. Besides interview administration, the interviewers also participated in a series of cultural competency training sessions to help them recognize and respect cultural differences.

CAPI is a technique used for data collection using portable devices. In the last decade, CAPI has been widely used in social research because of its cost-effectiveness, ease of use, and the immediate availability of data.[10-12] The usual working form of a CAPI system is that the questionnaire is managed and presented by a computer, and visitors can access and work according to the questions on the computer screen and input the answers given by the interviewees directly into the computer. If the interviewee is unwilling to answer through the interviewer, the interviewee can also input the answer directly into the computer to protect the interviewee's privacy. When the interview ends, the interviewer directly transmits the questionnaire results to the organizer through the internet. The organizer can then analyze the results immediately after receiving them. The CAPI system was programmed with built-in consistency checks to reduce data entry errors. The CAPI also uses online help screens to assist interviewers in defining the key terms used in the questionnaire.[12]

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Covariates

Among the covariates, we selected age, blood urea nitrogen, serum 25-OHD, serum calcium, serum creatinine, serum glucose, serum phosphorus, serum sodium, serum uric acid, alkaline phosphatase, total cholesterol, total protein, serum potassium, serum triglycerides, and body mass index (BMI) as continuous variables; gender, race, physical activities(consist of high-intensity exercise, fitness, or recreational activities, such as running or basketball, that cause large increases in respiration or heart rate, lasting at least 10 min), smoking behavior, and ratio of family income to poverty (calculated by dividing family (or individual) income by the poverty guidelines specific to the survey year; if the income reported by the respondent was < $20,000 or ⩾ $20,000, the value was not calculated; if the family income was reported as a more detailed category, the midpoint of the range was used to compute the ratio; values at or above 5.00 were coded as 5.00 or more because of disclosure concerns; values were not computed if income data were missing) were considered categorical variables. All data were collected from the National Health and NHANES website.

Statistical Methods

The weight of the sample analysis package in this study was edited and considered using NCHS version 3.4 (http://www.R-project.org) and Empowerstats software (http://www. empowerstats. com). The confidence interval (CI) was set at 95%. The association between lumbar BMD, serum 25-OHD levels, and a history of renal calculi was evaluated using multivariable logistic regression models. We constructed three models: model 1, no covariates were adjusted; model 2, only adjusted for age, sex, race, and BMI; and model 3, all the covariates listed in Table 1 were adjusted. We also performed the subgroup analyses stratified according to sex, lumbar BMD status, and serum 25-OHD status.

Table 1. Weighted Characteristics of Study Sample：the cohort of the 30-69 aged adults (7500)

	Lumbar BMD Q1 (g/cm²) (1873)	Lumbar BMD Q2 (g/cm²) (1869)	Lumbar BMD Q3 (g/cm²) (1882)	Lumbar BMD Q4 (g/cm²) (1876)	P value
Age (years)	46.4 ± 8.7	44.5 ± 8.6	44.0 ± 8.7	44.2 ± 8.6	<0.05
Gender					<0.05
Men/Women	55.6/44.4	49.8/50.2	48.9/51.1	50.7/49.3	
Race					<0.05
Mexican American	11.2	11.5	9.0	4.9	
Other Hispanic	8.0	6.7	5.6	4.9	
Non-Hispanic White	64.6	62.6	66.5	64.5	
Non-Hispanic Black	5.9	8.4	10.8	17.7	
Other Race - Including Multi-Racial	10.3	10.8	8.1	8.0	
BUN (mmol/L)	4.7 ± 1.6	4.7 ± 1.5	4.6 ± 1.5	4.7 ± 1.7	0.19
Serum calcium (mmol/L)	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	0.92
Serum creatinine (μmol/L)	74.9 ± 19.6	75.8 ± 23.6	75.9 ± 28.8	78.7 ± 32.0	<0.05
Serum glucose (mmol/L)	5.5 ± 1.6	5.5 ± 2.0	5.5 ± 1.9	5.6 ± 2.3	0.15
Serum phosphorus (mmol/L)	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	<0.05
Serum sodium (mmol/L)	139.2 ± 2.3	139.3 ± 2.3	139.1 ± 2.3	139.1 ± 2.2	0.19
Serum 25-hydroxyvitamin D (nmol/L)	67.3 ± 26.6	67.5 ± 25.8	70.1 ± 27.6	68.2 ± 26.4	<0.05
Alkaline phosphatase (U/L)	73.3 ± 27.0	69.1 ± 22.3	65.4 ± 20.1	64.2 ± 23.1	<0.05
Total cholesterol (mmol/L)	5.3 ± 1.1	5.2 ± 1.1	5.1 ± 1.0	5.0 ± 1.0	<0.05
Total protein (g/L)	71.0 ± 4.5	70.9 ± 4.3	71.1 ± 4.5	71.1 ± 4.1	0.61

Serum uric acid (μmol/L)	319.8 ± 78.3	321.5 ± 83.5	314.4 ± 82.6	321.2 ± 83.6	<0.05
Serum potassium (mmol/L)	4.0 ± 0.3	4.0 ± 0.3	3.9 ± 0.3	4.0 ± 0.3	<0.05
BMI (kg/m2)	29.3 ± 6.1	29.7 ± 6.6	29.2 ± 6.7	30.3 ± 7.3	<0.05
Serum triglycerides (mmol/L)	1.9 ± 1.4	1.9 ± 1.9	1.8 ± 1.3	1.7 ± 1.4	<0.05
Education level					<0.05
Less than 9th grade	6.9	4.3	3.1	2.0	
9-11th grade (Includes 12th grade with no diploma)	11.2	9.3	7.8	7.9	
High school graduate/GED or equivalent	21.5	22.1	19.0	19.5	
Some college or AA degree	30.5	30.6	32.0	32.0	
College graduate or above	29.9	33.7	38.1	38.6	
Vigorous recreational activities					<0.05
Yes	22.7	28.8	31.6	33.3	
No	77.3	71.2	68.4	66.7	
Smoked at least 100 cigarettes in life					<0.05
Yes	47.6	42.6	42.1	42.8	
No	52.4	57.4	57.9	57.2	
Stones					<0.05
Yes	13.7	9.2	9.4	8.6	
No	86.3	90.8	90.6	91.4	
Ratio of family income to poverty					<0.05
<1.99	35.8	33.7	28.9	28.9	
1.99-3.49	21.0	22.8	21.0	21.6	
>3.49	43.2	43.5	50.1	49.5	

Notes: Mean ± SD for continuous variables: P-value was calculated by weighted linear regression model. % for categorical variables: P-value was calculated by weighted chi-square test

Results

Table 1 presents the demographic and laboratory data of the participants. Women had a significantly higher lumbar BMD. Participants with higher lumbar BMD had a higher serum creatinine level, BMI, education level, level of physical activity, and ratio of family income to poverty, as well as lower

alkaline phosphatase, total cholesterol, serum triglyceride, smoking rate, and stone incidence rate than participants with lower lumbar BMD.

1. Association between lumbar BMD and kidney stones

We found that lumbar BMD was negatively associated with a history of kidney stone formation in all three models (Table 2). The trend in the different lumbar BMD quartile arrays remained significant ($P < 0.05$). This negative association existed in both men and women after adjusting for all confounding factors (odds ratio (OR) = 0.281, 95% CI: 0.131, 0.601; odds ratio (OR) = 0.299, 95% CI: 0.129, 0.693) in the subgroup analysis stratified by sex and race, as well as in non-Hispanic whites. In addition, a weighted generalized additive model and smooth curve fitting was used to solve the non-linear relationship and confirm the results (Figure 2). This is one of the modules of the Empowerstats software for statistical applications. This module examines non-linear relationships between outcome variables and risk factors (exposure) using generalized additive models. It is helpful to determine the relationship between non-straightness and determine whether there is a threshold effect. The outcome variable in this study was dichotomous; therefore, the smooth curve fitting of Empowerstats software was performed using the gam() function in the mgcv package of R, with the curve fitting term defined by the s() function. The model automatically determined the degree of freedom according to the minimum GCV method.[13]After the above analytical tests,

Table 2. Association between lumbar BMD (g/cm²) and kidney stones.

	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Lumbar BMD (g/cm²)	0.324 (0.193, 0.543)	0.374 (0.219, 0.641)	0.321 (0.184, 0.560)
Quintiles of lumbar BMD			
Lowest quintile	Reference	Reference	Reference
Q2	0.695 (0.562, 0.860)	0.725 (0.585, 0.900)	0.699 (0.562, 0.869)
Q3	0.685 (0.554, 0.848)	0.733 (0.590, 0.911)	0.697 (0.559, 0.870)
Q4	0.669 (0.540, 0.829)	0.716 (0.573, 0.896)	0.681 (0.542, 0.855)
P for trend	<0.001	0.004	0.001
Stratified by 25-OHD			
<50	0.512 (0.209, 1.253)	0.721 (0.277, 1.873)	0.534 (0.199, 1.438)
>=50	0.263 (0.139, 0.497)	0.277 (0.144, 0.534)	0.249 (0.126, 0.489)
Total	0.328 (0.195, 0.550)	0.249 (0.126, 0.489)	0.249 (0.126, 0.489)
Stratified by gender			
Men	0.363 (0.180, 0.733)	0.360 (0.173, 0.749)	0.281 (0.131, 0.601)
Women	0.284 (0.133, 0.606)	0.291 (0.129, 0.658)	0.299 (0.129, 0.693)
Stratified by race			
Mexican American	0.678 (0.139, 3.300)	0.799 (0.161, 3.970)	0.341 (0.059, 1.954)
Other Hispanic	1.069 (0.231, 4.960)	0.979 (0.204, 4.692)	0.635 (0.117, 3.448)
Non-Hispanic White	0.223 (0.098, 0.504)	0.220 (0.098, 0.494)	0.214 (0.093, 0.495)
Non-Hispanic Black	0.537 (0.162, 1.778)	0.615 (0.184, 2.059)	0.612 (0.170, 2.203)
Other Race - Including Multi-Racial	0.285 (0.063, 1.283)	0.222 (0.048, 1.035)	0.175 (0.034, 0.910)

Model 1 Adjust For: None
Model 2 Adjust For: Gender, age, race, BMI
Model 3 Adjust For: Gender, age, race, BMI, education Level, BUN, serum calcium, Serum creatinine, serum glucose, serum phosphorus, serum sodium, physical activities, smoking behavior, poverty to income ratio, alkaline phosphatase, total cholesterol, total protein, serum uric acid, serum potassium, serum triglycerides.

the negative linear relationship between BMD and stone formation remained unchanged.

2. The interaction between serum 25-OHD and lumbar BMD

According to Michael et al.,[14] the Endocrine Society defines vitamin D deficiency as a 25-OHD level < 20 ng/mL (50 nmol/L). Therefore, we divided the serum 25-OHD level into two groups with a tangent point of 50 nmol/L and conducted an interaction analysis. We found an interaction between serum 25-OHD and lumbar BMD (P < 0.05) that influenced kidney stones in model 3 (Table 3). Furthermore, we performed a stratified analysis of the above two 25-OHD groups in the multiple regression analysis between lumbar BMD and kidney stones (Table 2). The results showed that the negative correlation between lumbar BMD and kidney stones is more obvious (OR = 0.249, 95% CI: 0.126, 0.489) in the higher 25-OHD group (≥ 50 nmol/L).

Table 3. The interaction between serum 25-OHD (nmol/L) and lumbar BMD (g/cm²).

	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Serum 25-OHD (nmol/L)			
<50	0.512 (0.209, 1.253)	0.718 (0.278, 1.854)	0.670 (0.254, 1.767)
>=50	0.263 (0.139, 0.497)	0.278 (0.145, 0.534)	0.282 (0.144, 0.551)
P interaction	0.23	0.11	0.03

Model 1 Adjust For: None

Model 2 Adjust For: Gender, age, race, BMI

Model 3 Adjust For: Gender, age, race, BMI, education Level, BUN, serum calcium, Serum creatinine, serum glucose, serum phosphorus, serum sodium, physical activities, smoking behavior, poverty to income ratio, alkaline phosphatase, total cholesterol, total protein, serum uric acid, serum potassium, serum triglycerides.

Discussion

The overall purpose of this study was to explore the relationship between lumbar BMD, serum 25-OHD levels, and a history of kidney stones in a

nationally representative sample of people of the US population aged 30–69 years. Our results suggest that a low lumbar BMD is correlated with a history of renal calculus both in men and women, and particularly in non-Hispanic whites. Although there were some non-linear correlations, the trend was consistent with that of a previous multivariable linear regression analysis. The negative correlation between lumbar BMD and kidney stones is more obvious in the higher serum 25-OHD group (≥ 50 nmol/L). This finding suggests that maintaining a high lumbar BMD may reduce the incidence of kidney stone formation. Simultaneously, while ensuring a high lumbar BMD, maintaining a high serum 25-OHD level may be more beneficial for preventing the occurrence or recurrence of stones.

In recent years, an increasing number of clinical investigators have noted an association between BMD and history of kidney stones in patients. Consistent with the results of the present study, several studies have also verified, from all aspects, that there is an inverse association between history of kidney stones and BMD.[5, 15-18] In a 2016 consensus statement, experts recommended that the BMD of patients with hypercalciuric stones or a predisposition to this condition should be measured by DXA.[19] This noninvasive examination is convenient and efficient; however, the mechanisms underlying this effect remain unclear. Stones are common in patients with high calcium levels in the urine.[20] Hypercalciuria occurs because of a net loss of calcium from the body; therefore, patients usually

excrete more calcium than they absorb. Some researchers have speculated that this extra urinary calcium is derived from bone.[21, 22] In another group, researchers found that sequence variants in the *CLDN14* gene may be associated with kidney stones and BMD.[23] A study published in 2022 also demonstrated that for adults, the risk of developing kidney stones and osteoporosis increases mutually.[24] We have attached the table of this large cohort studies to the supplementary materials as a comparative table for this study (supplementary material 1).

Vitamin D plays an important biological role in humans, and vitamin D deficiency is associated with diseases caused by anemia and oxidative stress.[25] Although it has been shown that vitamin D may be responsible for stone formation in selected patients with certain genetic or clinical features,[26, 27] serum 25-OHD content did not differ between patients with and without stones, according to a previous cross-sectional study.[28, 29] An interventional study in 2019 found that regular doses of vitamin D supplementation in patients with vitamin D deficiency may not increase the risk of hypercalciuria.[30] Several studies have also confirmed that increasing the intake of vitamin D can increase BMD and improve bone quality, with significant beneficial effects on the risk of fractures.[31-33] Therefore, for patients with kidney stones or those with a tendency to develop stones, it is reasonable to assume that daily vitamin D supplementation might reduce the risk of stone recurrence or occurrence through the interaction between serum

25-OHD and lumbar BMD. Studies by Larsson et al. and Reid et al. suggested an insignificant causal relationship between chronically elevated serum 25-OHD concentrations and higher BMD in the general healthy population. 40 nmol/L is a sufficient concentration of serum 25-OHD.[34, 35] There are also some studies that suggest that vitamin D supplementation at lower amounts is safer in the normal population. The current findings do not support the beneficial effects of high-dose vitamin D supplements on bone health, which may even confer a substantial reduction in BMD, risk of falls, fractures, or a small increase in myocardial infarction.[36] Excluding people with normal renal function, in kidney transplant recipients, a recent study showed that supplementation with inactive vitamin D did not modify the urinary calcium nor the BMD, Z-score, or T-score at lumbar bodies and the femoral neck in kidney transplant recipients.[37] According to the current available evidence, the benefits of vitamin D supplementation in humans are more biased towards a "U-shaped" association. Therefore, although daily vitamin D supplementation may be beneficial in patients with kidney stones, treatment measures should be adjusted at any time based on changes in the condition to facilitate a positive balance between risks and benefits.

To make the current findings highly generalizable, the NHANES database aims to provide nationally representative estimates. However, this method has certain limitations. First, the character of this cross-sectional study limits the conclusions to associations and cannot assess the causal association of

lumbar spine BMD and serum 25-OHD with a history of nephrolithiasis. Second, due to kidney stone patients being concentrated in the middle-aged and older age groups, and because pregnant women were excluded from DXA examination, individuals aged 30–69 years with a non-pregnant status from the NHANES database were selected for the study. Therefore, the specificity for certain groups, such as adolescents, pregnant women, or those > 70 years of age, was poor. Third, as we only assessed BMD at the lumbar spine without introducing BMD at other sites, the present study may have been less clinically representative. Finally, owing to the lack of data on urinary calcium and analysis of stone composition, our study has limitations regarding the related effects of different types of stones and urinary calcium excretion.

Conclusion

Our results suggest that low lumbar BMD is associated with a history of renal calculus, both in men and women and particularly in non-Hispanic whites. This finding suggests that maintaining a high lumbar BMD may reduce the incidence of kidney stone formation. At the same time, the negative correlation between lumbar BMD and kidney stones is more obvious in the higher 25-OHD group (≥ 50 nmol/L), which means that maintaining a high serum 25-OHD level may be more beneficial to prevent the occurrence or recurrence of kidney stones while ensuring a high lumbar BMD.

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Data availability It is publicly available for people to collect data from the official website for users and researchers worldwide. (www.cdc.gov/nchs/nhanes/). Data are available upon reasonable request.

Compliance with ethical standards

Disclosure and conflicts of interest None

Ethical statement This study was approved by the ethics review board of the National Center for Health Statistics and written informed consents were obtained from each participant.

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Figure Legends

Figure 1: Flow chart of sample selection from the National Health and Nutrition Examination Survey (NHANES) 2011–2018.

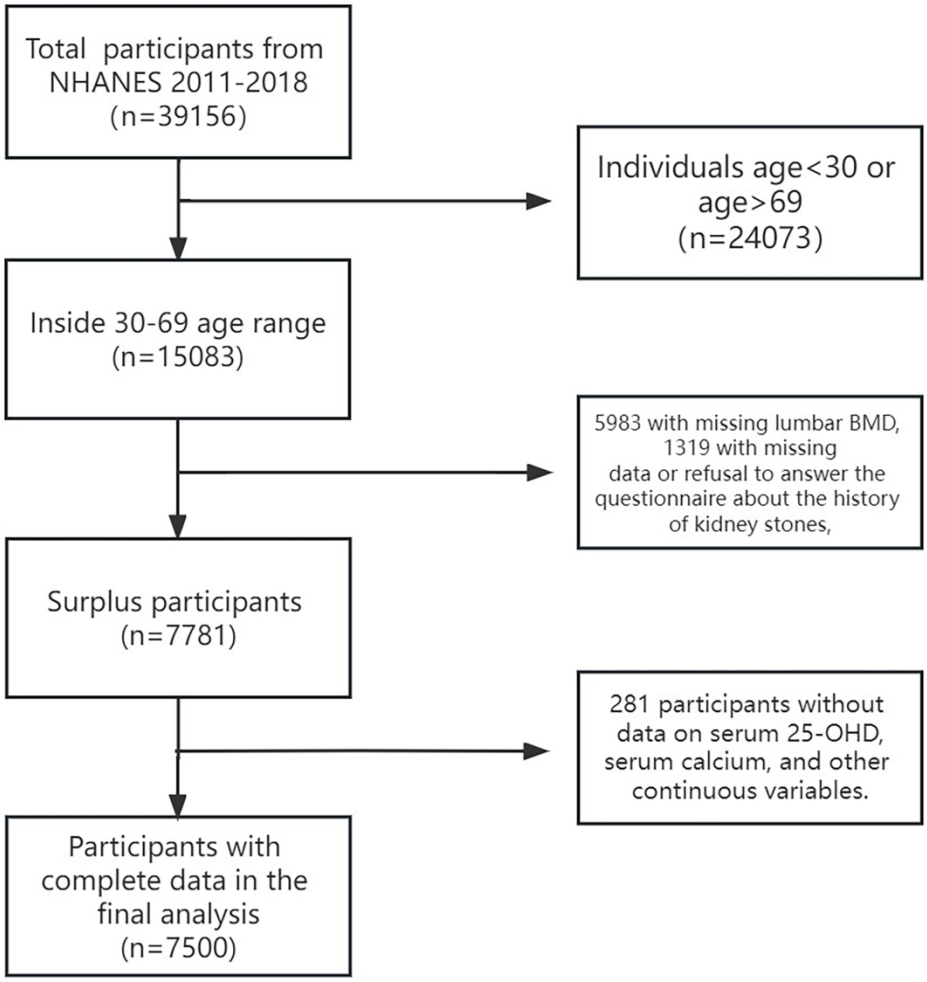
Figure 2: The association between lumbar bone mineral density (BMD) and history of kidney stones. Each black point represents a sample. The solid red line represents the smooth curve fit between variables. Blue bands represent the 95% confidence interval from the fit. Gender, age, race, body mass index, education level, blood urea nitrogen, serum calcium, serum creatinine, serum glucose, serum phosphorus, serum sodium, physical activities, smoking behavior, poverty to income ratio, alkaline phosphatase, total cholesterol, total protein, serum uric acid, serum potassium, and serum triglycerides were adjusted.

Table 1: Weighted characteristics of the study sample.

Table 2: Association between lumbar bone mineral density (g/cm²) and kidney stones.

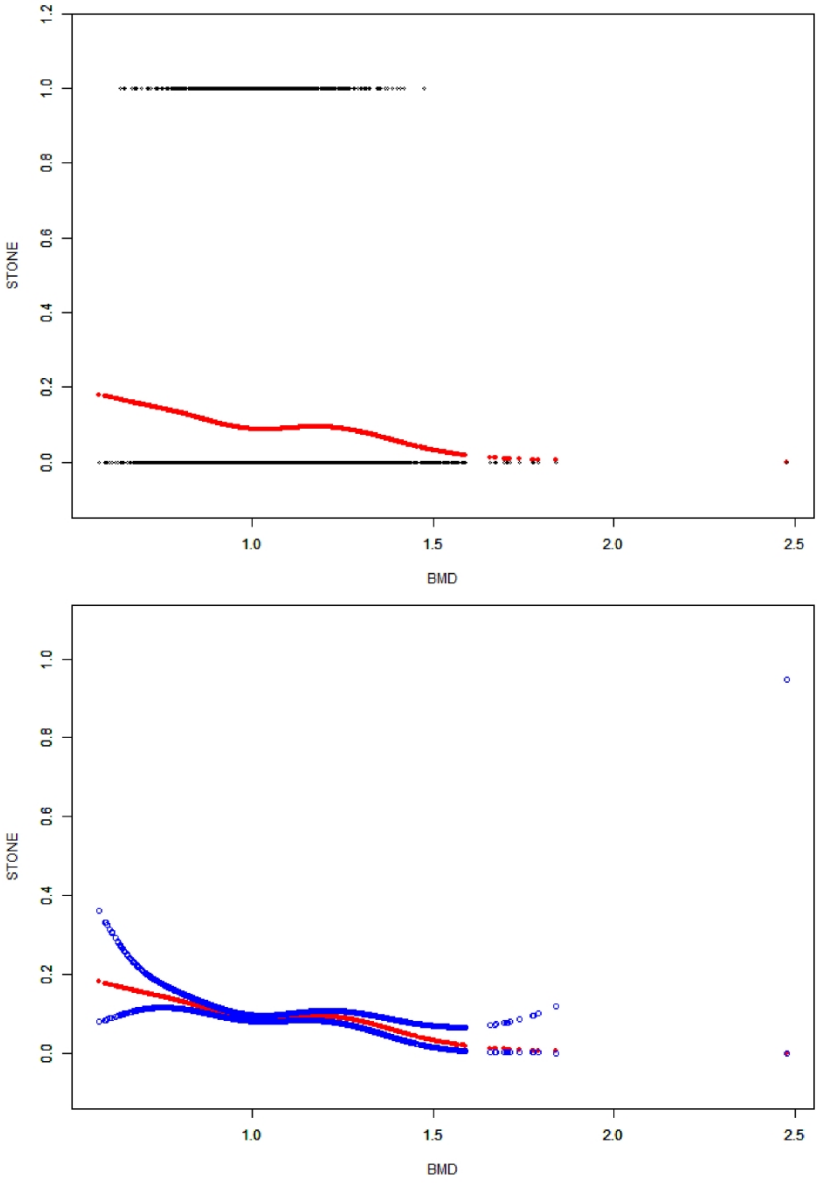
Table 3: The interaction between serum 25-hydroxyvitamin D (nmol/L) and lumbar bone mineral density (g/cm²).

Supplementary material 1: some comparative tables of other large cohort study.



Flow chart of sample selection from the National Health and Nutrition Examination Survey (NHANES) 2011–2018.

209x220mm (300 x 300 DPI)



The association between lumbar bone mineral density (BMD) and history of kidney stones. Each black point represents a sample. The solid red line represents the smooth curve fit between variables. Blue bands represent the 95% confidence interval from the fit. Gender, age, race, body mass index, education level, blood urea nitrogen, serum calcium, serum creatinine, serum glucose, serum phosphorus, serum sodium, physical activities, smoking behavior, poverty to income ratio, alkaline phosphatase, total cholesterol, total protein, serum uric acid, serum potassium, and serum triglycerides were adjusted.

209x297mm (300 x 300 DPI)

Table 1

General Characteristics of Participants.

Characteristics	Total Participants		
	Osteoporosis (*n* , %)	Control (*n* , %)	Standardized Difference
Total number	67,811 (100.0)	67,811 (100.0)	
Age (years old)			0
40–44	1025 (1.5)	1025 (1.5)	
45–49	5110 (7.5)	5110 (7.5)	
50–54	12,051 (17.8)	12,051 (17.8)	
55–59	15,211 (22.4)	15,211 (22.4)	
60–64	13,563 (20.0)	13,563 (20.0)	
65–69	7263 (10.7)	7263 (10.7)	
70–74	6944 (10.2)	6944 (10.2)	
75–79	4458 (6.6)	4458 (6.6)	
80–84	1826 (2.7)	1826 (2.7)	
85+	360 (0.5)	360 (0.5)	
Sex			0
Male	12,306 (18.2)	12,306 (18.2)	
Female	55,505 (81.9)	55,505 (81.9)	
Income			0
1 (lowest)	12,855 (19.0)	12,855 (19.0)	
2	10,246 (15.1)	10,246 (15.1)	
3	11,083 (16.3)	11,083 (16.3)	
4	13,786 (20.3)	13,786 (20.3)	
5 (highest)	19,841 (29.3)	19,841 (29.3)	
Region of residence			0
Urban	28,576 (42.1)	28,576 (42.1)	
Rural	39,235 (57.9)	39,235 (57.9)	
Obesity †			0.18
Underweight	2400 (3.5)	1632 (2.4)	
Normal	27,361 (40.4)	23,234 (34.3)	
Overweight	17,731 (26.2)	17,716 (26.1)	
Obese I	18,530 (27.3)	22,309 (32.9)	
Obese II	1789 (2.6)	2920 (4.3)	
Smoking status			0.5
Nonsmoker	60,277 (88.9)	59,566 (87.8)	
Past smoker	3451 (5.1)	3572 (5.3)	
Current smoker	4083 (6.0)	4673 (6.9)	
Alcohol consumption			0.05
<1 time a week	56,281 (83.0)	55,306 (81.6)	
≥1 time a week	11,530 (17.0)	12,505 (18.4)	
Systolic blood pressure			0.13
<120 mmHg	23,007 (33.9)	20,459 (30.2)	
120–139 mmHg	30,208 (44.6)	29,831 (44.0)	
≥140 mmHg	14,596 (21.5)	17,521 (25.8)	
Diastolic blood pressure			0.11
<80 mmHg	34,028 (50.2)	31,177 (46.0)	

80–89 mmHg	22,243 (32.8)	22,738 (33.5)	
≥90 mmHg	11,540 (17.0)	13,896 (20.5)	
Fasting blood glucose			0.13
<100 mg/dL	47,274 (69.7)	43,952 (64.8)	
100–125 mg/dL	16,240 (24.0)	17,471 (25.8)	
≥126 mg/dL	4297 (6.3)	6388 (9.4)	
Total cholesterol			0.04
<200 mg/dL	33,542 (49.5)	32,588 (48.1)	
200–239 mg/dL	23,440 (34.6)	23,523 (34.7)	
≥240 mg/dL	10,829 (16.0)	11,700 (17.3)	
CCI score			0.13
0	37,311 (55.0)	40,827 (60.2)	
1	12,535 (18.5)	10,550 (15.6)	
≥2	17,965 (26.5)	16,434 (24.2)	
Renal stone	2276 (3.4)	1696 (2.5)	0.05

Abbreviation: CCI, Charlson comorbidity index; † Obesity (BMI, body mass index, kg/m$_2$) was categorized as <18.5 (underweight), ≥18.5 to <23 (normal), ≥23 to <25 (overweight), ≥25 to <30 (obese I), and ≥30 (obese II).

Table 2

Crude and adjusted hazard ratios of osteoporosis for renal stones by subgroup according age, sex, income, and region.

Independent Variables	IR per 1000 Person-Year	IRD per 1000 Person-Years (95% CI)	Hazard Ratios for Renal Stone (95% Confidence Interval)			
			Crude †	*p* Value	Adjusted †,‡	*p* Value
Total participants (*n* = 135,622)						
Osteoporosis	3.2	0.70 (0.52 to 0.88)	1.30 (1.22 to 1.39)	<0.001 *	1.36 (1.28 to 1.45)	<0.001 *
Control	2.5		1		1	
Age < 60 (*n* =66,794)						
Osteoporosis	3.7	0.93 (0.68 to 1.19)	1.34 (1.24 to 1.46)	<0.001 *	1.41 (1.29 to 1.53)	<0.001 *
Control	2.7		1		1	
Age ≥ 60 (*n* = 68,828)						
Osteoporosis	2.3	−0.46 (−0.70 to −0.21)	1.24 (1.12 to 1.37)	<0.001 *	1.30 (1.17 to 1.44)	<0.001 *
Control	2.7		1		1	
Men (*n* = 24,612)						
Osteoporosis	4	0.54 (−0.04 to 1.12)	1.17 (1.00 to 1.37)	0.044 *	1.37 (1.15 to 1.64)	0.001 *
Control	3.4		1		1	
Women (*n* = 111,010)						
Osteoporosis	3.1	0.72 (0.53 to 0.91)	1.33 (1.24 to 1.42)	<0.001 *	1.36 (1.27 to 1.46)	<0.001 *
Control	2.4		1		1	
Low income (*n* = 68,368)						
Osteoporosis	3.1	0.77 (0.52 to 1.01)	1.35 (1.24 to 1.48)	<0.001 *	1.38 (1.26 to 1.51)	<0.001 *
Control	2.4		1		1	
High income (*n* = 67,254)						
Osteoporosis	3.3	0.63 (0.37 to 0.89)	1.25 (1.15 to 1.37)	<0.001 *	1.29 (1.18 to 1.41)	<0.001 *
Control	2.7		1		1	
Urban residents (*n* = 57,152)						
Osteoporosis	3.2	0.67 (0.40 to 0.94)	1.33 (1.24 to 1.42)	<0.001 *	1.31 (1.19 to 1.44)	<0.001 *
Control	2.5		1		1	
Rural residents (*n* = 78,470)						
Osteoporosis	0.1	−0.18 (−0.23 to −0.12)	1.28 (1.16 to 1.41)	<0.001 *	1.35 (1.24 to 1.47)	<0.001 *
Control	0.2		1		1	

Abbreviations; IR, incidence rate; IRD, incidence rate difference; * Stratified Cox proportional hazard regression model, Significance at $p < 0.05$; † Models were stratified by age, sex, income, and region of residence. ‡ The model was adjusted for obesity, smoking, alcohol consumption, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, and CCI scores.

Table 3

General Characteristics of Participants.

Characteristics	Total Participants		
	Renal Stone (*n* , %)	Control (*n* , %)	Standardized Difference
Total number	25,261 (100.0)	101,044 (100.0)	
Age (years old)			0
40–44	1162 (4.6)	4648 (4.6)	
45–49	3498 (13.9)	13,992 (13.9)	
50–54	5134 (20.3)	20,536 (20.3)	
55–59	5557 (22.0)	22,228 (22.0)	
60–64	4289 (17.0)	17,156 (17.0)	
65–69	2738 (10.8)	10,952 (10.8)	
70–74	1651 (6.5)	6604 (6.5)	
75–79	857 (3.4)	3428 (3.4)	
80–84	289 (1.1)	1156 (1.1)	
85+	86 (0.3)	344 (0.3)	
Sex			0
Male	18,200 (72.1)	72,800 (72.1)	
Female	7061 (28.0)	28,244 (28.0)	
Income			0
1 (lowest)	3428 (13.6)	13,712 (13.6)	
2	2950 (11.7)	11,800 (11.7)	
3	3916 (15.5)	15,664 (15.5)	
4	5528 (21.9)	22,112 (21.9)	
5 (highest)	9439 (37.4)	37,756 (37.4)	
Region of residence			0
Urban	11,219 (44.4)	44,876 (44.4)	
Rural	14,042 (55.6)	56,168 (55.6)	
Obesity †			0.18
Underweight	309 (1.2)	2063 (2.0)	
Normal	6969 (27.6)	34,846 (34.5)	
Overweight	7322 (29.0)	28,527 (28.2)	
Obese I	9729 (38.5)	32,905 (32.6)	
Obese II	932 (3.7)	2703 (2.7)	
Smoking status			0.14
Nonsmoker	15,012 (59.4)	67,025 (66.3)	
Past smoker	4800 (19.0)	16,222 (16.1)	
Current smoker	5449 (21.6)	17,797 (17.6)	
Alcohol consumption			0.07
<1 time a week	15,185 (60.1)	64,127 (63.5)	
≥1 time a week	10,076 (39.9)	36,917 (36.5)	
Systolic blood pressure			0.02
<120 mmHg	7180 (28.4)	30,437 (30.1)	
120–139 mmHg	13,006 (51.5)	50,408 (49.9)	
≥140 mmHg	5075 (20.1)	20,199 (20.0)	
Diastolic blood pressure			0.03
<80 mmHg	10,932 (43.3)	45,395 (44.9)	

80–89 mmHg	9652 (38.2)	37,229 (36.8)	
≥90 mmHg	4677 (18.5)	18,420 (18.2)	
Fasting blood glucose			0.04
<100 mg/dL	14,854 (58.8)	61,919 (61.3)	
100–125 mg/dL	7698 (30.5)	29,732 (29.4)	
≥126 mg/dL	2709 (10.7)	9393 (9.3)	
Total cholesterol			0.04
<200 mg/dL	13,284 (52.6)	55,208 (54.6)	
200–239 mg/dL	8454 (33.5)	33,059 (32.7)	
≥240 mg/dL	3523 (14.0)	12,777 (12.6)	
CCI score			0.15
0	15,210 (60.2)	67,732 (67.0)	
1	4452 (17.6)	14,943 (14.8)	
≥2	5599 (22.2)	18,369 (18.2)	
Osteoporosis	2319 (9.2)	7658 (7.6)	0.06

Abbreviation: CCI, Charlson comorbidity index; † Obesity (BMI, body mass index, kg/m$_2$) was categorized as <18.5 (underweight), ≥18.5 to <23 (normal), ≥23 to <25 (overweight), ≥25 to <30 (obese I), and ≥30 (obese II).

Table 4

Crude and adjusted hazard ratios of renal stones for osteoporosis stratified by age, sex, income, and region.

Independent Variables	IR per 1000 Person-Year	IRD per 1000 Person-Years (95% CI)	Hazard Ratios for Osteoporosis (95% Confidence Interval)			
			Crude †	*p* Value	Adjusted †,‡	*p* Value
Total participants (*n* = 126,305)						
Renal stone	11.3	1.98 (1.50 to 2.46)	1.24 (1.18 to 1.29)	<0.001 *	1.26 (1.21 to 1.32)	<0.001 *
Control	9.3		1		1	
Age < 60 (*n* = 76,755)						
Renal stone	7.8	1.55 (1.09 to 2.01)	1.28 (1.20 to 1.37)	<0.001 *	1.31 (1.23 to 1.40)	<0.001 *
Control	6.2		1		1	
Age ≥ 60 (*n* = 49,550)						
Renal stone	20.4	3.00 (1.77 to 4.22)	1.19 (1.12 to 1.28)	<0.001 *	1.22 (1.14 to 1.30)	<0.001 *
Control	17.4		1		1	
Men (*n* = 91,000)						
Renal stone	3.5	0.80 (0.50 to 1.10)	1.29 (1.17 to 1.42)	<0.001 *	1.38 (1.25 to 1.53)	0.001 *
Control	2.7		1		1	
Women (*n* = 35,305)						
Renal stone	34.4	6.41 (4.77 to 8.05)	1.22 (1.16 to 1.29)	<0.001 *	1.24 (1.17 to 1.30)	<0.001 *
Control	28		1		1	
Low income (*n* = 51,470)						
Renal stone	14.3	2.92 (2.07 to 3.76)	1.29 (1.21 to 1.38)	<0.001 *	1.32 (1.23 to 1.41)	<0.001 *
Control	11.4		1		1	
High income (*n* = 74,835)						
Renal stone	9.3	1.39 (0.82 to 1.95)	1.19 (1.11 to 1.27)	<0.001 *	1.21 (1.14 to 1.30)	<0.001 *
Control	8		1		1	
Urban residents (*n* = 56,095)						
Renal stone	10.6	2.31 (1.64 to 2.98)	1.30 (1.21 to 1.40)	<0.001 *	1.33 (1.24 to 1.43)	<0.001 *
Control	8.3		1		1	
Rural residents (*n* = 70,210)						
Renal stone	11.9	1.70 (1.02 to 2.37)	1.28 (1.12 to 1.26)	<0.001 *	1.22 (1.14 to 1.29)	<0.001 *
Control	10.2		1		1	

Abbreviations; IR, incidence rate; IRD, incidence rate difference; * Stratified Cox proportional hazard regression model, Significance at $p < 0.05$. † Models were stratified by age, sex, income, and region of residence. ‡ The model was adjusted for obesity, smoking, alcohol consumption, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, and CCI scores.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5, 6
Methods			
Study design	4	Present key elements of study design early in the paper	6, 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6, 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6, 7
Bias	9	Describe any efforts to address potential sources of bias	7, 8
Study size	10	Explain how the study size was arrived at	7,8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6, 7, 8, 9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9, 10
		(*b*) Describe any methods used to examine subgroups and interactions	9, 10
		(*c*) Explain how missing data were addressed	9, 10
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	9, 10
		(*e*) Describe any sensitivity analyses	9, 10
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, 7
		(b) Give reasons for non-participation at each stage	6, 7
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, 9
		(b) Indicate number of participants with missing data for each variable of interest	6, 7
Outcome data	15*	Report numbers of outcome events or summary measures	9, 10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 11
		(*b*) Report category boundaries when continuous variables were categorized	10, 11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10, 11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11, 12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.