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Nutritional Epidemiology

Association between Serum 25-Hydroxyvitamin D Concentrations and Respiratory Infection among United States Adults

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A B S T R A C T

Background: Vitamin D plays an essential role in immune responses to infections. However, the association between serum 25(OH)D concentrations and respiratory infection remains unclear.

Objectives: The current study aimed to examine the association between serum 25(OH)D concentrations and respiratory infection among the United States adults.

Methods: This cross-sectional study used data from the NHANES 2001–2014. Serum 25(OH)D concentrations were measured by radioimmunoassay or liquid chromatography-tandem mass spectrometry and were classified as ≥75.0 nmol/L (sufficiency), 50.0–74.9 nmol/L (insufficiency), 30.0–49.9 nmol/L (moderate deficiency), and <30 nmol/L (severe deficiency). The respiratory infections included self-reported head or chest cold as well as influenza, pneumonia, or ear infection within the last 30 d. The associations between serum 25(OH)D concentrations and respiratory infections were examined using weighted logistic regression models. Data are presented as ORs and 95% CIs.

Results: This study included 31,466 United States adults ≥20 y of age (47.1 y, 55.5% women) with a mean serum 25(OH)D concentration of 66.2 nmol/L. After adjusting for sociodemographic characteristics, season of examination, lifestyle and dietary factors, and body mass index, compared with participants with a serum 25(OH)D concentration ≥75.0 nmol/L, those with a serum 25(OH)D concentration <30 nmol/L had higher risk of head or chest cold (OR: 1.17; 95% CI: 1.01, 1.36) and other respiratory diseases, including influenza, pneumonia, and ear infections (OR: 1.84; 95% CI: 1.35, 2.51). In the stratification analyses, lower serum 25(OH)D concentrations were associated with a higher risk of head or chest cold in obese adults but not in nonobese adults.

Conclusions: Serum 25(OH)D concentrations are inversely associated with respiratory infection occurrence among United States adults. This finding may shed light on the protective effect of vitamin D on the respiratory health.

Keywords: serum 25-hydroxyvitamin D, vitamin D deficiency, respiratory infection, head or chest colds, influenza and pneumonia

Introduction

Respiratory infections, including upper and lower respiratory tract infections, are one of the most common causes of mortality in the United States and other countries worldwide [1]. Common cold and influenza are major upper respiratory infections with a high incidence among people of all ages. Lower respiratory tract infections, such as bronchitis and pneumonia, have a high fatality rate in older and frail people. These lower respiratory infections have high incidence and mortality rates that cause a substantial burden on individuals, families, and the society, with significant direct and indirect medical costs [2]. The annual economic burden of influenza on the United States health care system was ~11.2 billion dollars in 2015 [3].

Vitamin D is essential in maintaining the life activities of the human body. Vitamin D insufficiency and deficiency are associated with elevated proinflammatory cytokine levels in the lung and decreased antiviral activity in individuals with viral respiratory infections [4]. Observational studies have revealed an inverse association between serum 25(OH)D concentrations and

Abbreviations used: $25(OH)D_2$, 25-hydroxyergocalciferol; $25(OH)D_3$, 25-hydroxycholecalciferol; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MET, metabolic equivalent of task.

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the development of respiratory infections [5–7] and lung function in adults with obesity [8]. A Japanese cohort study revealed that low circulating 25(OH)D concentrations are associated with a high risk of respiratory infection-related mortality [9]. Similarly, a German cohort study found an inverse association between serum 25(OH)D concentrations and respiratory disease-related mortality [10]. A meta-analysis of 46 clinical trials showed that vitamin D supplementation has a minimal protective effect against acute respiratory infections [11]. Notably, the prevalence of vitamin D insufficiency was >20% among United States adults [12, 13]. However, current evidence on the association between serum 25(OH)D concentrations and respiratory infections in the American population is limited.

The current study aimed to investigate the association between serum 25(OH)D concentrations and respiratory infections in a nationally representative sample of United States adults.

Methods

Study population

NHANES is a nationally representative health survey program of the civilian noninstitutionalized resident population in the United States [14]. It is administered by the NCHS at the Centers for Disease Control and Prevention. The NHANES program not only collects questionnaire data through in-person interviews but also performs health examinations in the mobile examination center and collects specimens for laboratory tests [15]. The NHANES protocol has been approved by the Ethics Review Board of the NCHS. Written informed consent was obtained from all participants.

In the current analysis, we included 31,466 United States adults aged ≥20 y who participated in NHANES 2001–2014 and who had available data on serum total 25(OH)D concentrations. Supplementary Figure 1 shows the flowchart of participant inclusion in the analysis.

Assessment of serum 25(OH)D concentrations

The serum total 25(OH)D concentrations were measured by radioimmunoassay (DiaSorin assay kit) in NHANES 2001–2006. From NHANES 2007–2014, liquid chromatography-tandem mass spectrometry (LC-MS/MS), a fully validated and standardized method, was used to measure the concentrations of 25-hydroxyergocalciferol [25(OH)D_2], 25-hydroxycholecalciferol [25(OH)D_3], and the C3 epimer of 25(OH)D_3 in all eligible participants. Using LC-MS/MS, the total 25(OH)D concentration was examined and defined as the sum of 25(OH)D_2 and 25(OH)D_3, excluding the C3 epimer of 25(OH)D_3. Due to the difference in detection methods, data on serum 25(OH)D concentrations measured by radioimmunoassay from NHANES 2001–2006 have been converted to LC-MS/MS-equivalent data. Detailed information on the conversion to LC-MS/MS-equivalent data and the serum 25(OH)D standardization program can be found elsewhere [16].

Outcomes

During the in-person interviews, the participants reported the presence of a head or chest cold (yes or no) and a respiratory infection, including influenza, pneumonia, or ear infection (yes or no) within the last 30 d [17, 18].

Covariates

Information on age, sex, race and ethnicity, educational level, family income, smoking status, alcohol consumption, physical activity, and dietary intake was collected using questionnaires. According to the 1997 United States Federal Office of Management and Budget Standards, race and ethnicity was categorized into Hispanic (including Mexican and non-Mexican Hispanic), non-Hispanic White, non-Hispanic Black, and others. The season of examination was divided into 2 periods, from 1 November to 30 April and from 1 May to 31 October 31. Family income was defined as the ratio of family income to the federal poverty level (<1.0, 1.0–1.9, 2.0–3.9, and ≥4.0) [19]. A high income to poverty ratio indicated a better family income status. Self-reported educational levels were classified as less than high school, high school, and college or higher. In accordance with the NCHS classifications, individuals who smoked <100 cigarettes in their lifetime were considered as never smokers, those who smoked ≥100 cigarettes but did not smoke during the survey as former smokers, and those who smoked ≥100 cigarettes in their lifetime and smoked cigarettes during the survey as current smokers [20]. Alcohol intake was categorized as none (0 g/d), moderate drinking (0.1–27.9 g/d in men and 0.1–13.9 g/d in women), and heavy drinking (≥28 g/d in men and ≥14 g/d in women) [21]. In terms of physical activity, the participants were asked a series of questions related to daily activities in the questionnaire, from which metabolic equivalent (MET) of task minutes per week was calculated. There have been some changes in the physical activity questionnaires since NHANES 2007–2008. Therefore, the physical activity of each participant was categorized according to the standards appropriate for each cycle, which are as follows: *1)* below, <600 MET min/wk or 150 min/wk of moderate-intensity exercise; *2)* meet, 600–1200 MET min/wk or 150–300 min/wk of moderate-intensity exercise; and *3)* exceed, >1200 MET min/wk or 300 min/wk of moderate-intensity exercise [22]. Dietary information was collected through 24-h dietary recall interviews. Total energy intake was calculated using the USDA Automated Multiple-Pass Method [23, 24]. The Healthy Eating Index-2010 was used to indicate the overall diet quality (scores ranging from 0 to 100, with 100 indicating the best-quality diet) [24]. Body weight and height were measured according to the NHANES Anthropometry Procedures Manual. BMI was calculated as weight in kilograms divided by height in meters squared and 3 categories were defined (kg/m^2, <25, underweight; 25–29.9, normal; ≥30, overweight or obese).

Statistical analysis

The NHANES program uses a complex, multistage probability sampling design to represent a national, civilian, noninstitutionalized population in the United States. Therefore, sampling weights, strata, and primary sampling units were applied according to the NHANES Analytic Guidelines to account for the unequal probability of selection, oversampling of certain subpopulations, and nonresponse adjustment [25]. Specifically, the sample weights of the participants were constructed and designated *WTMEC14YR*. Subsequently, *SDMVSTRA, SDMVPSU, and WTMEC14YR* were used to reflect stratum, primary sampling units, and final sample weight, respectively, for all analyses.

According to previous studies and guidelines [26–28], the serum 25(OH)D concentrations were divided into <30.0 nmol/L (severe deficiency), 30.0–49.9 nmol/L (moderate deficiency), 50.0–74.9 nmol/L (insufficiency), and ≥75.0 nmol/L (sufficiency; reference group). The means and proportions of the basic characteristics across serum 25(OH)D categories were compared using the χ^2 test for categorical variables and linear regression for continuous variables. The associations between serum 25(OH)D concentrations and the occurrence of head or chest cold and influenza, pneumonia, or ear infection were examined using multivariate logistic regression models, and presented as ORs and 95% CIs. Linear trend tests were applied in the logistic models using the median in each serum 25(OH)D category as the continuous variable. In the fully-adjusted model, adjustments were made for age, sex, race/ethnicity, season of examination, educational level, family income, smoking status, alcohol intake, physical activity, total energy intake, overall diet quality based on the Healthy Eating Index-2010 score, and BMI. Furthermore, stratification and interaction analyses were performed to examine whether these associations differed by age groups (20–59 y or ≥60 y), sex, race/ethnicity (non-Hispanic White or others), season of examination, educational level (high school or lower, college or higher), family income level (ratio <2 or ≥2), smoking status (current smoker or nonsmoker), alcohol intake

Table 1

Basic characteristics of the study population according to serum 25(OH)D concentrations among United States adults in NHANES 2001–2014[1]

Variables	Serum 25(OH)D concentrations				*P* value
	≥75.0 nmol/L (Sufficiency)	50.0–74.9 nmol/L (Insufficiency)	30.0–49.9 nmol/L (Moderate deficiency)	<30.0 nmol/L (Severe deficiency)	
Participants, *n*	8516	12,123	8116	2711	
Age, y, mean (SE)	49.5 (0.3)	46.4 (0.3)	45.3 (0.3)	44.0 (0.4)	
Sex, % (SE)					<0.001
Men	44.7 (0.7)	53.7 (0.6)	48.3 (0.7)	40.3 (1.2)	
Women	55.3 (0.7)	46.3 (0.6)	51.7 (0.7)	59.7 (1.2)	
Race/ethnicity, % (SE)					<0.001
Hispanic	5.7 (0.6)	14.3 (1.0)	20.2 (1.3)	16.4 (1.6)	
Non-Hispanic White	87.7 (0.8)	74.1 (1.2)	50.5 (1.7)	30.3 (1.9)	
Non-Hispanic Black	2.9 (0.2)	6.2 (0.4)	20.7 (1.2)	44.1 (2.0)	
Other	3.7 (0.3)	5.4 (0.3)	8.7 (0.6)	9.2 (1.0)	
Season of examination, % (SE)					<0.001
November–30 April	30.8 (2.3)	39.6 (2.2)	53.7 (2.8)	64.3 (2.9)	
May–31 October	69.2 (2.3)	60.4 (2.2)	46.3 (2.8)	35.7 (2.9)	
Education, % (SE)					<0.001
Less than high school	12.9 (0.8)	17.2 (0.6)	22.5 (0.7)	23.9 (1.0)	
High school	23.4 (0.6)	23.3 (0.6)	24.1 (0.8)	26.7 (1.1)	
College or higher	63.6 (1.1)	59.5 (0.9)	53.4 (0.9)	49.2 (1.3)	
Family income to poverty ratio, % (SE)					<0.001
<1	9.1 (0.5)	12.1 (0.5)	17.6 (0.7)	20.9 (1.1)	
1–1.9	15.5 (0.6)	19.2 (0.5)	22.9 (0.6)	26.7 (1.2)	
2–3.9	27.4 (0.9)	28.6 (0.6)	27.2 (0.8)	27.0 (1.2)	
≥4	42.5 (1.1)	35.1 (1.0)	26.5 (1.0)	19.1 (1.2)	
Missing	5.4 (0.3)	5.1 (0.3)	5.8 (0.4)	6.2 (0.6)	
Cigarette smoking, % (SE)					<0.001
Never smoker	52.0 (0.9)	52.9 (0.8)	54.5 (0.7)	53.2 (1.2)	
Current smoker	28.5 (0.8)	26.2 (0.7)	20.3 (0.6)	15.9 (0.9)	
Ever smoker	19.5 (0.7)	20.9 (0.5)	25.1 (0.7)	30.8 (1.2)	
Alcohol drinking[2], % (SE)					<0.001
Nondrinker	67 (1.0)	70.3 (0.7)	74.2 (0.7)	75.2 (1.1)	
Moderate drinking	9.6 (0.5)	10.0 (0.4)	8.0 (0.4)	6.1 (0.6)	
Heavy drinking	21.4 (0.8)	17.7 (0.6)	15.5 (0.6)	16 (1.0)	
Missing	2.1 (0.2)	2.0 (0.2)	2.3 (0.2)	2.7 (0.4)	
Meeting the physical activity guidelines[3], % (SE)					<0.001
Below	31.9 (0.8)	36.4 (0.6)	46.9 (0.8)	51.9 (1.4)	
Meet	12.6 (0.4)	13.9 (0.4)	12.8 (0.6)	12.9 (0.8)	
Exceed	55.5 (0.9)	49.4 (0.6)	40.2 (0.9)	35.0 (1.3)	
Total energy intake, kcal/d	2194 (13.7)	2244 (13.8)	2167 (14.1)	2075 (25.2)	<0.001
Healthy Eating Index-2010	51.8 (0.4)	49.1 (0.2)	46.7 (0.3)	44.6 (0.4)	<0.001
BMI categories, % (SE)					<0.001
<25.0 kg/m^2	39.0 (0.8)	29.1 (0.7)	24.4 (0.6)	24.2 (1.0)	
25–29.9 kg/m^2	35.6 (0.6)	35.2 (0.5)	30.3 (0.8)	24.3 (0.9)	
≥30.0[3] kg/m^2	24.6 (0.6)	34.7 (0.8)	43.9 (0.8)	49.3 (1.2)	
Missing	0.8 (0.1)	1.1 (0.1)	1.3 (0.2)	2.3 (0.4)	

[1] Values are presented as means (SE) or percentages (SE), and are adjusted for NHANES weights to reflect the nationally representative estimates, except that sample size in cells reflected the participants in this study. Numbers may not add to 100% due to missing data.

[2] Nondrinker: 0 g/d; Moderate drinking: 0.1–27.9 g/d in men and 0.1–13.9 g/d in women; Heavy drinking: ≥28 g/d in men and ≥14 g/d in women.

[3] Below, <600 MET min/wk or 150 min/wk of moderate-intensity exercise; Meet, 600–1200 MET min/wk or 150–300 min/wk of moderate-intensity exercise; Exceed, >1200 MET min/wk or 300 min/wk of moderate-intensity exercise.

(current drinker or nondrinker), and obesity status (non-obesity, BMI <30 kg/m^2; obesity, BMI ≥30 kg/m^2), after adjusting for covariates in the fully-adjusted model except the stratified variables. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc.). A two-sided *P* value of <0.05 was considered statistically significant.

Results

Characteristics of the participants

We included 31,466 United States adults aged ≥20 y [weighted mean (SE) age: 47.1 (0.2) y; 16,036 women (weighted: 55.5%)]. Their weighted mean serum 25(OH)D concentration was 66.19 nmol/L. Among them, 5587 reported a head or chest cold, and 1335 had a respiratory infection, including influenza, pneumonia, or ear infection, within the last 30 d. As shown in Table 1, participants with high serum 25(OH)D concentrations were more likely to be old and non-Hispanic White, examined from 1 May to 31 October, and have high educational level, family income, and physical activity, good dietary quality, and low BMI.

Association between serum 25(OH)D concentrations and respiratory infection

The associations between serum 25(OH)D concentrations and respiratory infection are presented in Table 2. After adjusting for sociodemographic characteristics, lifestyle and dietary factors, BMI, and season of examination, compared with participants with a serum 25(OH)D concentration of ≥75.0 nmol/L, those with a serum 25(OH)D concentration of <30.0, 30.0–49.9, and 50.0–74.9 nmol/L have ORs of 1.17 (95% CI: 1.01, 1.36), 1.12 (95% CI: 0.99, 1.26), and 1.12 (95% CI: 1.00, 1.25) for head or chest cold (*P*-trend = 0.021), respectively. In the fully adjusted model, using a serum 25(OH)D concentration of ≥75.0 nmol/L as a reference, serum 25(OH)D concentrations of <30.0, 30.0–49.9, and 50.0–74.9 nmol/L were found to be associated with higher odds of a respiratory infection, including influenza, pneumonia, or ear infection (*P*-trend <0.001), with ORs of 1.21 (95% CI: 0.96, 1.53), 1.68 (95% CI: 1.36, 2.07), and 1.84 (95% CI: 1.35, 2.51), respectively.

The stratification analyses showed these associations by age groups, sex, race/ethnicity, season of examination, educational level, family income, smoking status, alcohol intake, and obesity status. As shown in Table 3, a significant interaction between serum 25(OH)D concentrations and obesity status for head or chest cold was observed (*P*-interaction = 0.011). Compared with a serum 25(OH)D concentration of ≥75.0 nmol/L, the lower serum 25(OH)D concentrations were significantly associated with higher odds of a head or chest cold in adults with obesity, but not in nonobese adults. As shown in Table 4, there was a significant association between serum 25(OH)D concentrations and influenza, pneumonia, or ear infection in women but not in men. However, the interaction was not significant (*P*-interaction = 0.081). In addition, participants with a serum 25(OH)D concentration of <30.0 or 30.0–49.9 nmol/L who were examined from November 1 to April 30 had an additional increase in the magnitude of ORs compared with those who were examined from May 1 to October 31. Other stratification analyses showed similar associations in each subgroup (Tables 3 and 4), and no significant interaction was observed between serum 25(OH)D concentrations and other stratifying variables (all *P*-interactions >0.05).

Discussion

In a nationally representative sample of United States adults, low serum 25(OH)D concentrations were associated with high probability of a head or chest cold and a respiratory infection, including influenza, pneumonia, or ear infection, after adjusting for sociodemographic characteristics, dietary and lifestyle factors, BMI, and season of examination.

These findings are in accordance with previous epidemiologic studies showing an inverse association of serum 25(OH)D concentrations with respiratory infections [5–7] and respiratory

Table 2
Associations between serum 25(OH)D concentrations and head or chest colds and infection from influenza, pneumonia, or ear infections among United States adults in NHANES 2001–2014[1]

Respiratory infection	Serum 25(OH)D concentrations				*P*-trend
	≥75.0 nmol/L (Sufficiency)	50.0–74.9 nmol/L (Insufficiency)	30.0–49.9 nmol/L (Moderate deficiency)	<30.0 nmol/L (Severe deficiency)	
Head or chest colds					
n (weighted %)	1250 (14.5%)	2170 (17.4%)	1570 (19.3%)	597 (21.3%)	
Model 1[2]	1.00 (ref.)	1.15 (1.03, 1.28)	1.20 (1.07, 1.34)	1.28 (1.11, 1.48)	<0.001
Model 2[3]	1.00 (ref.)	1.12 (1.01, 1.25)	1.13 (1.01, 1.27)	1.19 (1.02, 1.37)	0.010
Model 3[4]	1.00 (ref.)	1.12 (1.00, 1.25)	1.12 (0.99, 1.26)	1.17 (1.01, 1.36)	0.021
Influenza, pneumonia, or ear infections					
n (weighted %)	254 (2.7%)	484 (3.6%)	426 (5.6%)	171 (6.7%)	
Model 1[2]	1.00 (ref.)	1.30 (1.03, 1.65)	1.94 (1.59, 2.37)	2.27 (1.66, 3.12)	<0.001
Model 2[3]	1.00 (ref.)	1.24 (0.98, 1.57)	1.76 (1.43, 2.16)	1.94 (1.42, 2.66)	<0.001
Model 3[4]	1.00 (ref.)	1.21 (0.96, 1.53)	1.68 (1.36, 2.07)	1.84 (1.35, 2.51)	<0.001

[1] Values are presented as n (prevalence) or odds ratio (95% CI). The sample sizes in cells reflect the participants in this study, the prevalence and ORs in cells are adjusted for NHANES weights to reflect the nationally representative estimates.
[2] Model 1: adjusted for age, sex, race/ethnicity, and season of examination.
[3] Model 2: Model 1+ education, family income status, alcohol intake, smoking, physical activity, total energy intake, and Healthy Eating Index-2010.
[4] Model 3: Model 2+ body mass index.

Table 3
Stratification analyses of associations between serum 25(OH)D concentrations and head or chest colds among United States adults in NHANES 2001–2014[1,2]

Subgroups	Serum 25(OH)D concentrations				*P*-interaction
	≥75.0 nmol/L (Sufficiency)	50.0–74.9 nmol/L (Insufficiency)	30.0–49.9 nmol/L (Moderate deficiency)	<30.0 nmol/L (Severe deficiency)	
Age groups					0.398
20–59 y	1.00 (ref.)	1.09 (0.95, 1.25)	1.10 (0.95, 1.27)	1.18 (0.99, 1.41)	
≥60 y	1.00 (ref.)	1.19 (1.02, 1.39)	1.20 (0.99, 1.47)	1.15 (0.87, 1.53)	
Sex					0.081
Men	1.00 (ref.)	1.19 (1.02, 1.39)	1.08 (0.89, 1.30)	1.23 (0.97, 1.55)	
Women	1.00 (ref.)	1.05 (0.92, 1.21)	1.17 (1.02, 1.34)	1.14 (0.93, 1.40)	
Race/ethnicity					0.736
Non-Hispanic White	1.00 (ref.)	1.09 (0.96, 1.24)	1.10 (0.95, 1.27)	1.16 (0.88, 1.52)	
Others	1.00 (ref.)	1.30 (1.10, 1.54)	1.30 (1.09, 1.54)	1.38 (1.16, 1.63)	
Season of examination					0.266
1 November–30 April	1.00 (ref.)	1.05 (0.91, 1.21)	1.09 (0.93, 1.28)	1.08 (0.91, 1.30)	
1 May–31 October	1.00 (ref.)	1.18 (1.02, 1.36)	1.14 (0.98, 1.32)	1.34 (1.06, 1.68)	
Education					0.344
High school or less	1.00 (ref.)	1.18 (1.02, 1.36)	1.07 (0.91, 1.26)	1.12 (0.91, 1.38)	
College or higher	1.00 (ref.)	1.08 (0.93, 1.26)	1.18 (1.00, 1.39)	1.24 (0.96, 1.60)	
Family income to poverty ratio					0.188
<2	1.00 (ref.)	1.26 (1.09, 1.45)	1.14 (0.97, 1.33)	1.30 (1.07, 1.58)	
≥2	1.00 (ref.)	1.06 (0.91, 1.24)	1.11 (0.95, 1.30)	1.02 (0.79, 1.31)	
Cigarette smoking					0.345
Nonsmoker	1.00 (ref.)	1.06 (0.95, 1.19)	1.08 (0.95, 1.23)	1.12 (0.93, 1.35)	
Current smoker	1.00 (ref.)	1.31 (1.06, 1.60)	1.22 (0.97, 1.54)	1.28 (0.97, 1.68)	
Alcohol drinking					0.454
Nondrinker	1.00 (ref.)	1.14 (1.01, 1.28)	1.15 (1.01, 1.30)	1.14 (0.96, 1.35)	
Current drinker	1.00 (ref.)	1.12 (0.90, 1.39)	1.06 (0.84, 1.33)	1.26 (0.91, 1.74)	
Obesity status					0.011
Obesity	1.00 (ref.)	1.41 (1.19, 1.67)	1.41 (1.16, 1.71)	1.47 (1.15, 1.88)	
Non-obesity	1.00 (ref.)	1.02 (0.89, 1.17)	1.01 (0.87,1.17)	1.04 (0.84, 1.29)	

[1] Values are presented as OR (95% CI), and are adjusted for NHANES weights to reflect the nationally representative estimates.
[2] Models were adjusted for age, sex, race/ethnicity, season of examination, educational level, family income status, smoking status, alcohol intake, physical activity, total energy intake, Healthy Eating Index-2010, and body mass index by excluding the corresponding stratified variables.

disease-related mortality [9, 10]. Data from NHANES III [5] and NHANES 2001–2006 [6] also showed an inverse association between serum 25(OH)D concentrations and respiratory disease. Another cross-sectional study including 5011 adults aged 45–69 y revealed that low serum 25(OH)D concentrations were associated with high ORs of asthma, bronchitis, wheezing, and chest tightness [7]. One prospective study of 9554 Germans found that participants with a serum 25(OH)D concentration >50 nmol/L have a 150% high risk of respiratory disease-related mortality during a median follow-up period of 9.5 y than those with a serum 25(OH)D concentration <30 nmol/L [29]. Another cohort study including 3292 community-dwelling Japanese aged 40 y and over revealed that using quartile 1 as reference, serum 25(OH)D concentration in quartile 4 was associated with an increased risk of respiratory infection-related mortality by 153% [9].

In addition, the significant association between serum 25(OH)D concentrations and respiratory infection based on observational studies was consistent with the results of interventional studies. A meta-analysis of 46 interventional studies found that vitamin D supplementation reduced the risk of acute respiratory infections [11]. Further, subgroup analyses revealed that protective effects were observed in participants receiving standard doses (400–1000 IU/d) and aged 1–15 y [11]. However, the significant protective effect of vitamin D supplementation against acute respiratory infections was not observed in participants with a baseline serum 25(OH)D concentration of <25.0 nmol/L. Evidence from these clinical trials did not support the notion that vitamin D supplementation could prevent respiratory infections among adults with vitamin D deficiency. Thus, further studies should be conducted to validate the findings in the future.

The associations between serum 25(OH)D concentrations and respiratory infection could be influenced by potential confounders to some extent. Our results showed that the ORs of influenza, pneumonia, or ear infection significantly decreased in the final model. Previous population-based studies reported that age, sex, season of examination, physical inactivity, smoking status, obesity, and dietary factors correlated with serum 25(OH) D concentrations [30–34]. Similarly, sociodemographic characteristics, lifestyle factors, and BMI may be associated with the risk of respiratory infection [35–37]. For example, obesity was inversely related to serum 25(OH)D concentrations [32, 33] and was associated with increased risks of pneumonia and influenza [35, 36]. Therefore, residuals from these confounders should be controlled and eliminated when focusing on the association between serum 25(OH)D concentrations and respiratory infection. Furthermore, these findings emphasized the potential benefits of adherence to healthy lifestyle activities and maintaining a normal BMI on vitamin D status and respiratory health.

The mechanisms by which vitamin D reduces the incidence of respiratory infections include cellular natural immunity and adaptive immunity [38]. Moreover, 1,25-dihydroxyvitamin D, a biologically active vitamin D metabolite, is a steroid hormone.

Table 4
Stratification analyses of associations between serum 25(OH)D concentrations and infection from influenza, pneumonia, or ear infections among United States adults in NHANES 2001–2014[1,2]

Subgroups	Serum 25(OH)D concentrations				*P*-interaction
	≥75.0 nmol/L (Sufficiency)	50.0–74.9 nmol/L (Insufficiency)	30.0–49.9 nmol/L (Moderate deficiency)	<30.0 nmol/L (Severe deficiency)	
Age groups					0.386
20–59 y	1.00 (ref.)	1.22 (0.94, 1.60)	1.78 (1.37, 2.31)	1.83 (1.31, 2.57)	
≥60 y	1.00 (ref.)	1.06 (0.77, 1.45)	1.23 (0.85, 1.77)	2.02 (1.17, 3.49)	
Sex					0.081
Men	1.00 (ref.)	1.05 (0.78, 1.41)	1.31 (0.94, 1.82)	1.20 (0.77, 1.86)	
Women	1.00 (ref.)	1.35 (0.99, 1.82)	2.03 (1.47, 2.80)	2.32 (1.55, 3.48)	
Race/ethnicity					0.129
Non-Hispanic White	1.00 (ref.)	1.16 (0.87, 1.55)	1.78 (1.35, 2.35)	2.24 (1.36, 3.68)	
Others	1.00 (ref.)	1.38 (1.04, 1.83)	1.54 (1.17, 2.01)	1.56 (1.15, 2.12)	
Season of examination					0.587
1 November–30 April	1.00 (ref.)	1.33 (0.93, 1.91)	1.90 (1.38, 2.62)	2.13 (1.40, 3.24)	
1 May–31 October	1.00 (ref.)	1.12 (0.85, 1.48)	1.45 (1.08, 1.93)	1.44 (0.90, 2.31)	
Education					0.259
High school or less	1.00 (ref.)	1.29 (0.91, 1.83)	1.60 (1.12, 2.28)	1.57 (1.02, 2.40)	
College or higher	1.00 (ref.)	1.17 (0.86, 1.59)	1.75 (1.29, 2.39)	2.14 (1.35, 3.40)	
Family income to poverty ratio					0.125
<2	1.00 (ref.)	1.19 (0.86, 1.64)	1.49 (1.11, 2.01)	2.02 (1.37, 3.00)	
≥2	1.00 (ref.)	1.29 (0.96, 1.75)	1.94 (1.46, 2.58)	1.58 (0.97, 2.58)	
Cigarette smoking					0.612
Nonsmoker	1.00 (ref.)	1.29 (0.98, 1.70)	1.72 (1.35, 2.18)	1.97 (1.32, 2.93)	
Current smoker	1.00 (ref.)	1.04 (0.73, 1.47)	1.60 (1.11, 2.30)	1.56 (0.95, 2.56)	
Alcohol drinking					0.183
Nondrinker	1.00 (ref.)	1.29 (1.01, 1.65)	1.59 (1.27, 1.98)	1.97 (1.40, 2.77)	
Current drinker	1.00 (ref.)	1.04 (0.65, 1.68)	2.00 (1.18, 3.37)	1.48 (0.76, 2.89)	
Obesity status					0.905
Obesity	1.00 (ref.)	1.34 (0.92,1.96)	1.78 (1.26, 2.53)	2.09 (1.32, 3.31)	
Nonobese	1.00 (ref.)	1.13 (0.85, 1.50)	1.59 (1.21, 2.09)	1.64 (1.10, 2.42)	

[1] Values are presented as odds ratio (95% CI), and are adjusted for NHANES weights to reflect the nationally representative estimates.
[2] Models were adjusted for age, sex, race/ethnicity, season of examination, educational level, family income status, smoking status, alcohol intake, physical activity, total energy intake, overall diet quality indicated by Healthy Eating Index-2010, and BMI by excluding the corresponding stratified variables.

Antimicrobial peptides induced by vitamin D, including cathelicidin, LL-37, and defensins, have different antiviral effects against respiratory viruses, such as rhinovirus [39] and influenza [40]. Several studies have shown that vitamin D could inhibit viral reproduction directly [39, 40]. Furthermore, substantial evidence revealed that vitamin D could reduce proinflammatory cytokines, which may cause cytokine storms and lead to death in patients with lower respiratory tract infections [4, 38]. That is, it suppresses responses mediated by type 1 helper T cells. Meanwhile, it promotes cytokine production by type 2 helper T cells and significantly improves the induction of regulatory T cells, thereby inhibiting inflammatory processes [41].

The current study may have major public health implications. Vitamin D deficiency is commonly observed among individuals in the United States and other countries worldwide. The role of vitamin D in preventing respiratory infections may be beneficial for public health. The decreased incidence of respiratory infections not only reduces the disease burden on the health care system but also indirectly provides more medical resources for other diseases.

The current study had several strengths. The nationally representative data from NHANES, which can help generalize our findings to a broader population. In addition, the availability of numerous variables, including comprehensive information on demographic and socioeconomic characteristics, anthropometric measures, and dietary and lifestyle factors, can provide an opportunity to adjust for a variety of potential confounders. However, this research also had some limitations. First, this was an observational study; therefore, a causal relationship between serum 25(OH)D concentrations and respiratory infections could not be established. In addition, large-scale randomized controlled trials should be conducted to determine causality. Second, respiratory infection was based on self-reported information within the last 30 d. Hence, prospective studies on confirmed respiratory infections might improve the accuracy of risk estimation. Third, although several potential confounders were adjusted, residual confounding by unmeasured factors might still exist.

In conclusion, A low serum 25(OH)D concentration was associated with increased risks of respiratory infection. Further studies on laboratory-confirmed infections are needed to confirm our findings.

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Disclosures

The authors report no conflicts of interest.

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Data Availability

Data from the National Health and Nutrition Examination Survey (NHANES) are publicly available and can be accessed directly at https://wwwn.cdc.gov/Nchs/Nhanes.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjnut.2022.10.006.

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