Association Between Serum 25-Hydroxyvitamin D Level and Upper Respiratory Tract Infection in the Third National Health and Nutrition Examination Survey

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Background: Recent studies suggest a role for vitamin D in innate immunity, including the prevention of respiratory tract infections (RTIs). We hypothesize that serum 25-hydroxyvitamin D (25[OH]D) levels are inversely associated with self-reported recent upper RTI (URTI).

Methods: We performed a secondary analysis of the Third National Health and Nutrition Examination Survey, a probability survey of the US population conducted between 1988 and 1994. We examined the association between 25(OH)D level and recent URTI in 18 883 participants 12 years and older. The analysis adjusted for demographics and clinical factors (season, body mass index, smoking history, asthma, and chronic obstructive pulmonary disease).

Results: The median serum 25(OH)D level was 29 ng/mL (to convert to nanomoles per liter, multiply by 2.496) (interquartile range, 21-37 ng/mL), and 19% (95% confidence interval [CI], 18%-20%) of participants reported a recent URTI. Recent URTI was reported by 24% of participants with 25(OH)D levels less than 10 ng/mL, by 20% with levels of 10 to less than 30 ng/mL, and by 17% with levels of 30 ng/mL or more ($P<.001$). Even after adjusting for demographic and clinical characteristics, lower 25(OH)D levels were independently associated with recent URTI (compared with 25[OH]D levels of ≥30 ng/mL: odds ratio [OR], 1.36; 95% CI, 1.01-1.84 for <10 ng/mL and 1.24; 1.07-1.43 for 10 to <30 ng/mL). The association between 25(OH)D level and URTI seemed to be stronger in individuals with asthma and chronic obstructive pulmonary disease (OR, 5.67 and 2.26, respectively).

Conclusions: Serum 25(OH)D levels are inversely associated with recent URTI. This association may be stronger in those with respiratory tract diseases. Randomized controlled trials are warranted to explore the effects of vitamin D supplementation on RTI.

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UPPER RESPIRATORY TRACT infection (URTI), or the "common cold," is the most widespread infectious disease and the most common reason for US emergency department visits and unscheduled outpatient visits.[1] More than 200 viruses contribute to the clinical syndrome of cough, nasal congestion, nasal discharge, sore throat, and sneezing.[2,3] Most adults in the United States experience 2 to 4 URTIs per year, and most children experience 6 to 10 per year, which carries enormous population morbidity due to the high incidence of disease and disruption caused by symptoms.[4,5]

Because options for curing or preventing URTIs are limited, treatment relies on symptom relief.[6,7] For example, over-the-counter preparations may have modest benefit on symptom duration and severity.[8] For many decades, vitamin C (ascorbic acid) has been marketed and used for the prevention and treatment of URTIs despite the lack of convincing evidence of benefit in community populations.[9] However, prevention of colds/influenza and "immune boosting" remain among the top reasons that Americans take vitamin and herbal supplements.[10]

Although ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) are less commonly used vitamin supplements,[10] the importance of vitamin D for general health has expanded far beyond rickets.[11] Indeed, vitamin D is involved in the regulation of 1000 human genes[12] and, most relevant to this study, seems to have promise in the prevention of infection, including URTI. Because few foods contain ergocalciferol or cholecalciferol, sunlight exposure is the primary determinant of vitamin D status in humans.[11] However, in northern latitudes, be-

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tween November and March, there are insufficient UV-B rays to produce vitamin D. Cannell et al[13] asserted that wintertime vitamin D insufficiency may explain seasonal variation in influenza; this argument may also apply to other RTIs.

The potential mechanism for this observation is suggested by recent evidence that vitamin D plays an important role in innate immunity, particularly through the antimicrobial peptide cathelicidin.[14] Indeed, early epidemiologic studies[15-22] found a strong association between rickets and RTI. Although serum 25-hydroxyvitamin D (25[OH]D) levels of at least 10 ng/mL (to convert to nanomoles per liter, multiply by 2.496) prevent rickets, levels of at least 30 ng/mL are advantageous for general health, with approximately 40 ng/mL considered optimal.[23,24] Recent prospective cohort[25] and case-control[26,27] studies have demonstrated a consistent association between low (including nonrachitic) serum 25 (OH)D levels and RTIs. These preliminary studies, although promising, were based on small, nondiverse cohorts of patients; the association between 25(OH)D level and RTI has not been explored on a population level.

In the present study, we examine the association between serum 25(OH)D level and recent URTI in a large cross-sectional sample that represents the entire US population. The primary hypothesis is that serum 25(OH)D level is inversely associated with recent URTI.

METHODS

STUDY DESIGN AND PARTICIPANTS

Between October 18, 1988, and October 15, 1994, the National Center for Health Statistics conducted the Third National Health and Nutrition Examination Survey (NHANES III). We performed a secondary analysis of this nationally representative, cross-sectional sample of the noninstitutionalized US civilian population. We received a waiver from the Partners Human Research Committee and the Colorado Multiple Institutional Review Board as an exempt study.

Full details of the survey methods, including sampling, interview, examination, laboratory measurements, ethics approval, and informed consent, are described elsewhere.[28] Briefly, the survey used a complex, stratified, multistage probability sample design. The NHANES III oversampled certain subgroups of people, including low-income persons, adolescents aged 12 to 17 years, adults 60 years and older, blacks, and Mexican Americans.

Individuals selected for participation were notified by letter approximately 10 days before the home visit for the interview. The NHANES III collected household interview data, including demographic characteristics and data on health and nutrition, for 22 266 of 27 145 invited participants (82.0%) 12 years and older. Most of these participants (19 784 [88.9%]) subsequently underwent physical and laboratory examinations in a mobile examination center or at a home visit. We limited this analysis to the 18 883 participants with reported serum 25(OH)D values, representing 195 million Americans. Because physical and laboratory examinations occurred in mobile examination centers, inclement weather was an issue during data collection. To avoid these issues and improve response, the NHANES III preferentially scheduled data collection in the lower latitudes (further south) during the winter and in the higher latitudes (further north) in the summer.[29]

DATA COLLECTION

From the household interview data, we analyzed information on self-reported age, sex, race/ethnicity, and socioeconomic status, as measured by the poverty to income ratio (the ratio of a family's income to the poverty threshold of a family of the same size). We recorded smoking history (current smoking and pack-years), current asthma, and chronic obstructive pulmonary disease (COPD) diagnosis from self-reported history. We defined COPD based on responses to questions on emphysema or chronic bronchitis. From the examination data, we calculated body mass index as weight in kilograms divided by height in meters squared.

Blood samples collected during the examination were centrifuged, aliquoted, and frozen to –70°C on-site. They were then shipped on dry ice to central laboratories, where they were stored at –70°C until analysis. Serum 25(OH)D levels were measured using a radioimmunoassay kit after extraction with acetonitrile (DiaSorin, Stillwater, Minnesota) by the National Center for Environmental Health (Atlanta, Georgia). We used the date of the physical examination and laboratory data collection to most accurately adjust for the effect of season on serum 25 (OH)D levels.

The primary outcome (recent URTI) was based on the response to the following question: "In the past few days, have you had a cough, cold, or other acute illness?" This question, asked during the physical and laboratory examination visit before spirometric testing, was designed to identify participants with recent URTIs, which could affect spirometry results. Selection of this outcome variable allowed for temporal proximity between 25(OH)D level and recent URTI because serum samples were also obtained during the physical and laboratory examination visit.

STATISTICAL ANALYSIS

We performed statistical analyses using Stata 9.0 (StataCorp LP, College Station, Texas). Using survey commands, we applied the recommended subsample weights for the interview plus examination data to account for unequal probabilities of selection and to accurately represent estimates for the US population. All of the results are presented as weighted values. We calculated variance based on NHANES-provided masked variance units using the Taylor series linearization method. All of the P values are 2-tailed, with $P < .05$ considered statistically significant.

We calculated proportions with 95% confidence intervals (CIs) for demographic factors and those thought to be related to recent URTI (ie, serum 25[OH]D level, season, body mass index, region, current cigarette smoking, smoking history in pack-years, and asthma and COPD diagnoses), overall and in the subset with recent URTI. We categorized serum 25(OH)D levels as less than 10 ng/mL (<25 nmol), 10 to less than 30 ng/mL (25-74.9 nmol/L), and 30 ng/mL or more (≥75 nmol/L).[11,23] To improve interpretability of the analysis, we converted age, poverty to income ratio, body mass index, and smoking pack-year history from continuous to categorical variables. In addition, we dichotomized race to white and nonwhite based on the known effect of melanin on vitamin D synthesis in darker-skinned individuals.[11] We determined univariate associations between risk factors and the outcome of recent URTI using the Pearson χ^2 test for categorical variables and simple ordinal logistic regression for ordinal variables.

To evaluate the independent association between serum 25 (OH)D level and recent URTI, we created multivariable models by progressively adding covariates that might confound or alter the 25(OH)D-URTI association. Factors known to be associated with serum 25(OH)D levels[30] but not directly related to URTI, such as milk intake, vitamin D supplementation, and

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Table 1. Characteristics of the Study Population, Overall and in the Subset With Recent URTI

Variable	Observations, No.[a]	US Population Estimate (95% CI), in Millions[a,b]	Recent URTI (95% CI), %	*P* Value[c]
Total	18 883	195	19 (18-20)	
Serum 25(OH)D, ng/mL				
<10	684	4 (3-4)	24 (20-29)	<.001
10 to <30	12 302	104 (99-108)	20 (19-22)	
≥30	5897	87 (78-97)	17 (15-19)	
Season				
Winter, Dec-Feb	4342	33 (22-45)	26 (23-29)	<.001
Spring, Mar-May	5246	39 (27-51)	18 (16-21)	
Summer, June-Aug	4504	66 (44-87)	13 (11-15)	
Fall, Sept-Nov	4646	56 (37-74)	21 (19-24)	
Age, y				
12-19	2955	26 (24-29)	22 (19-24)	.11
20-39	6496	78 (72-84)	18 (17-20)	
40-59	4262	53 (49-58)	18 (16-20)	
≥60	5163	37 (33-41)	19 (17-21)	
Sex				
Male	8840	94 (87-96)	18 (16-19)	.04
Female	10 043	101 (99-102)	20 (18-22)	
Race				
White	7428	146 (141-151)	19 (17-20)	.26
Nonwhite	11 455	48 (44-52)	20 (18-22)	
Poverty to income ratio				
≤1	4387	25 (22-28)	22 (18-25)	.046
>1	12 744	157 (154-160)	18 (17-20)	
BMI				
<20	1900	21 (19-23)	21 (18-24)	.55
20-24.9	6542	75 (68-81)	19 (17-21)	
25-29.9	6028	59 (54-63)	17 (15-20)	
≥30	4336	40 (36-44)	20 (18-22)	
Region				
Northeast	2510	40 (35-44)	17 (15-18)	<.001
Midwest	3672	47 (42-51)	16 (14-18)	
South	8245	67 (59-75)	24 (22-26)	
West	4456	41 (26-56)	17 (14-20)	
Current cigarette smoking				
Yes	4249	50 (46-54)	27 (25-30)	<.001
No	14 634	145 (142-148)	16 (15-17)	
Cigarette pack-years				
0	10 918	103 (100-106)	17 (16-18)	<.001
1-9	3893	42 (39-46)	21 (19-24)	
10-19	1372	17 (16-19)	21 (18-25)	
≥20	2700	32 (29-35)	21 (19-23)	
Current diagnosis of asthma				
Yes	939	11 (9-12)	26 (22-29)	<.001
No	17 944	184 (183-185)	18 (17-20)	
Current diagnosis of COPD				
Yes	1159	13 (12-15)	33 (29-38)	<.001
No	17 724	181 (180-183)	18 (17-19)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; COPD, chronic obstructive pulmonary disease; 25(OH)D, 25-hydroxyvitamin D; URTI, upper respiratory tract infection.

SI conversion factor: To convert 25(OH)D to nanomoles per liter, multiply by 2.496.

[a] Some variables do not sum to the total because of missing data.

[b] Estimates are based on weighted data from the Third National Health and Nutrition Examination Survey.

[c] The *P* values are based on the Pearson χ^2 test for categorical variables and on simple ordinal logistic regression for ordinal variables, with 2-tailed $P < .05$ considered statistically significant.

sunlight exposure, were not included in the models owing to collinearity. Because season may affect serum 25(OH)D levels and recent URTI, we evaluated this important variable separately and with other covariates. We reported odds ratios (ORs) with 95% CIs for variables in the model. In addition, we evaluated interaction terms for asthma and COPD, conditions that we hypothesized might have clinically important effect modification on the 25(OH)D-URTI association.

RESULTS

Characteristics of the weighted NHANES III sample, stratified by recent URTI status, are given in **Table 1**. The participants had a median age of 38 years; 52% were female and 75% were white. Overall, the median serum 25 (OH)D level was 29 ng/mL (interquartile range, 21-37

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Table 2. Associations Between Serum 25(OH)D Level and Recent URTI in Unadjusted and Multivariable Models

	OR (95% CI)[a]		
	Model 1	Model 2	Model 3
Serum 25(OH)D, ng/mL			
<10	1.55 (1.18-2.05)[b]	1.37 (1.06-1.76)[b]	1.36 (1.01-1.84)[b]
10 to <30	1.27 (1.11-1.47)[b]	1.20 (1.05-1.38)[b]	1.24 (1.07-1.43)[b]
≥30	1 [Reference]	1 [Reference]	1 [Reference]
Season			
Winter, Dec-Feb		1.54 (1.25-1.89)[b]	1.48 (1.12-1.96)[b]
Spring, Mar-May		1 [Reference]	1 [Reference]
Summer, June-Aug		0.69 (0.56-0.85)[b]	0.66 (0.52-0.84)[b]
Fall, Sep-Nov		1.22 (1.00-1.50)[b]	1.25 (0.99-1.57)
Age, per ↑10 y			0.95 (0.91-0.98)[b]
Female sex			1.13 (0.97-1.32)
White race			1.11 (0.94-1.32)
Poverty to income ratio			0.98 (0.94-1.01)
BMI			1.00 (0.99-1.01)
Region			
Northeast			1 [Reference]
Midwest			1.26 (0.95-1.68)
South			1.17 (0.92-1.49)
West			1.21 (0.90-1.61)
Current cigarette smoking			1.81 (1.55-2.12)[b]
Smoking history, per ↑10 pack-years			1.01 (0.98-1.04)
Asthma			1.24 (1.00-1.53)[b]
COPD			1.87 (1.47-2.38)[b]

Abbreviations: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio; URTI, upper respiratory tract infection.

SI conversion factor: To convert 25(OH)D to nanomoles per liter, multiply by 2.496.

[a] Based on multivariable logistic regression models for the outcome of recent URTI. Model 1 includes serum 25(OH)D alone; model 2, serum 25(OH)D plus season; and model 3, serum 25(OH)D plus all covariates.

[b] $P<.05$ for the association between the predictor variable and the outcome of recent URTI adjusted for all other variables in the model.

ng/mL). Serum 25(OH)D levels of less than 10 ng/mL were present in 2% (95% CI, 2%-2%) of the population and of 10 to less than 30 ng/mL in 53% (95% CI, 51%-55%). The proportion of participants who reported recent URTI was 19% (95% CI, 18%-20%).

The proportions of participants with recent URTI, stratified by characteristics, are also given in Table 1. The median serum 25(OH)D level was slightly lower in participants reporting URTI (28 ng/mL) compared with those without URTI (29 ng/mL) ($P<.001$). Other characteristics associated with recent URTI included winter and fall seasons, age 12 to 19 years compared with age 20 years and older, female sex, low socioeconomic status (poverty to income ratio, ≤1), South region, current cigarette smoking, more than 0 cigarette pack-years, asthma, and COPD ($P<.05$ for all).

Compared with individuals with serum 25(OH)D levels of 30 ng/mL or more, those with levels less than 10 ng/mL or 10 to less than 30 ng/mL had 55% and 27% higher odds of recent URTI, respectively (**Table 2**, model 1). In further stratification of the group with 25(OH)D levels of 30 ng/mL or more, those with levels of 30 to less than 40 ng/mL had similar odds of recent URTI compared with those with levels of 40 ng/mL or more (OR, 0.99; 95% CI, 0.81-1.21). After adjusting for season, lower serum 25 (OH)D levels were still associated with a significantly higher URTI (Table 2, model 2). Indeed, the 25(OH)D-URTI association was consistent across all seasons (**Figure**). Changing the months included for each season did not materially alter the results (data not shown). When all the covariates were added to the model, serum 25(OH)D level retained its significant inverse relationship with URTI (Table 2, model 3). Winter season, younger age, current cigarette smoking, asthma, and COPD also were associated with significantly higher odds of URTI.

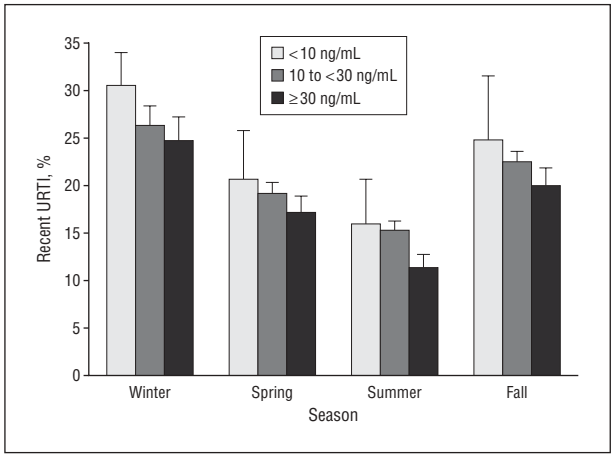

Figure. Participants with recent upper respiratory tract infection (URTI) stratified by serum 25-hydroxyvitamin D level (to convert to nanomoles per liter, multiply by 2.496) and season. Error bars represent standard errors of estimates.

Compared with participants without asthma, a similar proportion of participants with asthma had serum 25

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(OH)D levels less than 10 ng/mL (both groups, 2%; $P=.87$). Participants with vs without COPD were more likely to have serum 25(OH)D levels less than 10 ng/mL (3% vs 2%, $P=.04$), but this association was not significant after adjusting for demographics, season, and smoking status ($P=.12$). Among asthmatic participants, those with 25 (OH)D levels less than 10 ng/mL had a higher reported rate of recent URTI than did those with levels of 30 ng/mL or more (59% vs 22%, $P<.001$). A similar association observed in COPD participants was also observed by 25 (OH)D strata (45% vs 31%, respectively), although the association was not statistically significant ($P=.20$).

While controlling for all other covariates, serum 25 (OH)D levels less than 10 ng/mL were associated with 5.67 higher odds of recent URTI in participants with asthma compared with levels of 30 ng/mL or more and 2.26 higher odds in participants with COPD. In comparison, serum 25(OH)D levels less than 10 ng/mL were associated with only 1.24 higher odds of URTI in participants without asthma and 1.27 higher odds in those without COPD. When individually adding interaction terms to the final multivariable model, the interaction term for COPD was not significant (P for interaction = .30) but was significant for asthma (P for interaction = .007).

COMMENT

To our knowledge, this is the first population-based study to evaluate and demonstrate an association between serum 25(OH)D level and URTI. The association seems to be robust, with a clinically and statistically significant association present in all seasons and when controlling for potential confounders. The dose-response association between lower levels of vitamin D and recent URTI provides further credibility to the findings.

Although early clinical studies[14-22] supported an association between rickets found with serum 25(OH)D levels less than 10 ng/mL and RTI, more recent studies[25-27] have found an effect of low (including nonrachitic) serum 25(OH)D levels. For example, Laaksi et al[25] found that young male Finnish soldiers with serum 25(OH)D levels of less than 16 ng/mL at baseline had a 63% increased risk of absence from duty due to RTI than did soldiers with serum 25(OH)D levels 16 ng/mL or more during the following 6 months. In addition, case-control studies from India[26] and Turkey[27] reported an association between serum 25(OH)D levels of less than 20 ng/mL and acute lower RTI in children and neonates, respectively.

In this study, we also found that individuals with respiratory tract diseases (ie, asthma and COPD) are of particular interest. Effect modification by asthma, and possibly COPD, on the association between serum 25(OH)D level and recent URTI indicates that the role of vitamin D may be of greater importance for individuals with these common conditions. Potential explanations may be that those with respiratory tract diseases are more susceptible to RTI[31,32] and have increased frequency of lower respiratory tract symptoms of higher severity and longer duration.[33,34] These findings are particularly important given the high morbidity from asthma and COPD exacerbation and merit further investigation.

Preliminary studies on vitamin D supplementation and RTI also have been promising. Two interventional cohort studies with 600 to 700 IU daily of vitamin D from cod liver oil and multivitamin supplementation[35] and 60 000 IU weekly from a vitamin D or calcium supplement[36] found a decrease in RTIs in children receiving supplementation. One randomized controlled trial[37] of bone loss in postmenopausal black women found that 7.7% of women randomized to receive 800 to 2000 IU of vitamin D daily reported respiratory tract symptoms during 3-year follow-up compared with 25.0% in the control group. Another substudy[38] of a randomized controlled trial for fracture prevention found a nonsignificant 10% reduced odds of wintertime infection in participants randomized to receive 800 IU of vitamin D daily ($P=.23$). However, these studies were post hoc analyses of adverse events reported in studies of skeletal health, and dedicated trials are warranted.

The emerging role of vitamin D in innate immunity provides a plausible mechanism for the inverse association between serum 25(OH)D level and URTI.[14] The only known human cathelicidin, hCAP-18 (LL-37), enhances microbial killing in phagocytic vacuoles, acts as a chemoattractant for neutrophils and monocytes, and has a defined vitamin D–dependent mechanism.[39,40] Pathogenic antigens interact with toll-like receptors on macrophages to upregulate the expression of genes that code for the vitamin D receptor and for the 1α-hydroxylase enzyme that converts 25(OH)D to the biologically active 1,25-dihydroxyvitamin D.[41,42] In turn, 1,25-dihydroxyvitamin D interacts with the promoter of the gene for cathelicidin,[43] which enhances the production of hCAP-18.[44,45]

The presence of sufficient levels of 25(OH)D, the major circulating form of vitamin D, is necessary to activate hCAP-18 expression and to enhance macrophage function and innate immunity.[45] In studies of *Mycobacterium tuberculosis,* Liu et al[42] found a direct association of serum 25(OH)D levels with cathelicidin expression and killing of intracellular *M tuberculosis*. Furthermore, black individuals, known to have increased susceptibility to tuberculosis infection, had low serum 25(OH)D levels and inefficient cathelicidin messenger RNA induction, but supplementation of 25(OH)D to the reference range restored induction of cathelicidin messenger RNA.[42]

The results from our article provide additional evidence from a large, diverse population of the inverse association between serum 25(OH)D level and RTI. Although serum 25(OH)D levels of less than 10 ng/mL were associated with the highest rate of recent URTI, serum 25(OH)D levels of 10 to less than 30 ng/mL also were associated with higher adjusted odds of URTI compared with levels of 30 ng/mL or more. Although individuals with serum 25(OH)D levels of less than 10 ng/mL have the least efficient cathelicidin expression, serum 25 (OH)D levels of 30 ng/mL or more may be necessary for the optimal induction of cathelicidin messenger RNA.[42] Although comparison of groups with 25(OH)D levels of 30 to less than 40 ng/mL and 40 ng/mL or more suggested a possible plateau of effect after approximately 30 ng/mL, this analysis was underpowered to evaluate whether higher 25(OH)D levels (ie, 40 ng/mL) provide additional benefit.

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Current recommendations for vitamin D supplementation (200-600 IU/d) are unlikely to achieve optimal serum 25(OH)D levels (ie, approximately 30-40 ng/mL) in most of the US population.[46] Randomized controlled trials of higher-dose vitamin D supplementation (≥1000 IU/d), particularly in the winter season, at higher latitudes, and for individuals with respiratory tract diseases, will help clarify the role of vitamin D supplementation in the reduction of RTI.

This study has some potential limitations. We could not control for all potential confounders, but we selected covariates most likely to be associated with serum 25(OH)D level and recent URTI. Unmeasured confounders may have an effect on the association between 25(OH)D level and URTI. Thus, causal inference is not possible, and we cannot exclude that the results are merely an epiphenomenon; randomized controlled trials are valuable for determining the causal nature of an observed association. Reverse causation (ie, lower serum 25[OH]D levels due to recent URTI and, thus, decreased outdoor activity) seems unlikely because the half-life of serum 25 (OH)D is 2 to 3 weeks[11] and URTIs last only 3 to 4 days,[3] but it may affect the enhanced vitamin D–URTI association in participants with asthma and COPD owing to longer symptom duration in those individuals.

The primary outcome (recent URTI) is a relatively crude and self-reported measure that may include other non-RTIs; however, limitations on the accuracy of this outcome would be expected to reduce the magnitude of associations. Serum samples were collected at only 1 point in time and were preferentially collected in northern states in the summer and in southern states in the winter. As a result, serum 25(OH)D levels are likely higher than would be expected by random sampling across all seasons. Although the overall serum 25(OH)D level and the recent URTI rate may be affected, it is unlikely that their association would be materially different. Nevertheless, we encourage efforts to replicate these findings in independent samples.

In conclusion, serum 25(OH)D levels have an independent, inverse association with recent URTI. Although 25(OH)D levels less than 30 ng/mL and URTI were higher in the winter season, the inverse association was present throughout the year. Individuals with respiratory tract diseases, such as asthma, who have low serum 25(OH)D levels may be even more susceptible to RTI. Vitamin D supplementation may reduce the incidence of URTI and exacerbations of respiratory tract diseases. Randomized controlled trials are warranted to explore the direct effect of vitamin D supplementation and to establish optimal levels of serum 25(OH)D in the prevention of RTI.

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