Vitamin D Supplementation During COVID-19 Infection Is Associated With an Unfavorable Impact of Increased Total Number of Organ Systems Involved

Rachel Quint, MD; Joshua Fogel, PhD; Eric Lam, DO; Sandra Gomez Paz, MD; Sofia Rubinstein, MD

ABSTRACT

Introduction: COVID-19 is a systemic disease that affects multiple organ systems. We investigated the association between vitamin D supplementation and the number of organ systems involved in hospitalized patients with COVID-19.

Methods: This retrospective study included 808 consecutive patients with COVID-19 treated at a tertiary care hospital in the metropolitan New York City area between March 2020 and May 2020. The outcome variable was the total number of involved organ systems, defined as a score reflecting involvement of the respiratory, neurologic, renal, cardiovascular, hepatic, endocrine, musculoskeletal, and hematologic organ systems.

Results: Overall, 249 patients (30.8%) received vitamin D supplementation. The number of organ systems involved was significantly greater among patients who received vitamin D supplementation (mean [SD], 4.7 [1.82]) than among those who did not (mean [SD], 3.5 [1.93]; $P < .001$). Vitamin D supplementation was significantly associated with an increased number of organ systems involved (B,0.30; SE, 0.11; $P = .01$).

Conclusions: Vitamin D supplementation was associated with a greater number of involved organ systems among hospitalized patients with COVID-19. Prospective studies, including randomized clinical trials, are needed to confirm this association.

INTRODUCTION

COVID-19 is a systemic disease that affects multiple organ systems, most commonly the respiratory system, but also the endocrine, musculoskeletal, hematologic,[1] neurologic, renal, cardiovascular, and hepatic systems.[2] COVID-19 symptoms range from asymptomatic to severe illness.[3,4] Increased disease severity and mortality are associated with age older than 70 years, male sex, and the Black and Hispanic race/ethnicities.[5,6] Increased disease severity is also associated with comorbidities, including obesity, diabetes, hypertension, lipid disorders, cardiovascular disease, chronic lung disease, and immunodeficiencies.[7,8]

Vitamin D supplementation has been investigated in patients with COVID-19 across several organ systems. Findings for the respiratory system are mixed. Some studies report that vitamin D supplementation is associated with respiratory improvement, including a decreased need for noninvasive and invasive mechanical ventilation, increased oxygen saturation, decreased respiratory rate, an increased ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2),[9] decreased breathing difficulty, decreased chest congestion, decreased cough,[10] and a lower Pneumonia Severity Index score.[11] However, others report no association between vitamin D supplementation and duration of respiratory support.[12]

Findings for the hematologic system are also mixed. Some studies report that vitamin D supplementation is associated with increased anti-inflammatory cytokines,[13] increased T-helper lymphocytes,[14] decreased fibrinogen,[15] and decreased occurrence of sepsis,[9] suggesting hematologic improvement. However, another

Author affiliations: Department of Medicine, Aurora Health Care, Milwaukee, Wisconsin (Quint); Department of Management, Marketing, and Entrepreneurship, Brooklyn College, Brooklyn, New York (Fogel); Division of Pulmonary and Critical Care Medicine, Department of Medicine, Rutgers New Jersey Medical School, Newark, New Jersey (Lam); Department of Medicine, Nassau University Medical Center, East Meadow, New York (Paz); Division of Nephrology and Hypertension, Department of Medicine, Nassau University Medical Center, East Meadow, New York (Rubinstein).

Corresponding author: Sofia Rubinstein, MD, Nassau University Medical Center, Division of Nephrology and Hypertension, 2201 Hempstead Turnpike, Box 49, East Meadow, NY 11554; email srubinst@numc.edu; ORCID ID 0000-0002-4805-9736

study found no association between vitamin D supplementation and sepsis.[16]

For the renal system, vitamin D supplementation is associated with a lower risk of COVID-19 infection, severe COVID-19 infection, and mortality among patients with advanced chronic kidney disease,[17] as well as decreased blood urea nitrogen levels.[18] For the hepatic system, vitamin D supplementation is associated with lower alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels[9] and decreased alkaline phosphatase (ALP).[19] For the musculoskeletal system, vitamin D supplementation is associated with lower creatine kinase levels, suggesting improved muscle function.[20]

The vitamin D endocrine system creates an active form of vitamin D, which acts on multiple systems, including the endocrine,[21,22] neurologic,[23,24] and cardiovascular systems.[25] Because vitamin D deficiency is associated with increased COVID-19 disease severity,[26] several review articles have suggested that vitamin D supplementation may improve COVID-19-related health concerns involving the endocrine,[27] neurologic,[28] and cardiovascular[29] systems. However, studies examining vitamin D supplementation in patients with COVID-19, regardless of baseline vitamin D status, and its association with endocrine, neurologic, and cardiovascular system involvement have not been reported. Furthermore, we are unaware of any studies evaluating the association between vitamin D supplementation and multisystem organ involvement in hospitalized patients with COVID-19. Therefore, we examined the association between vitamin D supplementation and the number of organ systems, including the respiratory, neurologic, renal, cardiovascular, hepatic, endocrine, musculoskeletal, and hematologic systems.

METHODS

Setting

This retrospective study included 808 consecutive patients with COVID-19 treated at a public tertiary care hospital in the metropolitan New York City area. All patients were admitted from March through May 2020. Ethical approval was obtained from the hospital institutional review board. A waiver for informed consent was granted because of the retrospective study design.

Variables

Demographic variables included age (years), sex (male/female), and race/ethnicity (White, African American, Hispanic, East Asian, Southeast Asian [eg, India, Pakistan], and Other). Comorbidities included obesity (body mass index >30 kg/m^2) and the Charlson Comorbidity Index (CCI), which is based on the presence of multiple comorbidities.[30]

Disease severity variables included the quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) score[31] (range, 0-3; 1 point each for respiratory rate >22 breaths/min, systolic blood pressure <100 mmHg, and Glasgow Coma Scale <15[32]), intensive care unit (ICU) admission at any point during hospitalization, invasive mechanical ventilation at admission, and oxygen requirements during hospitalization (none, low FiO_2 [≤55%], high FiO_2 [>55%], and invasive mechanical ventilation).

Treatment management variables included the use of vasopressors (phenylephrine, dobutamine, norepinephrine, epinephrine, or dopamine) and other treatments (defined as receipt of 1 or more of the following: therapeutic anticoagulation, glucocorticoids, or antibiotics at admission; remdesivir; interleukin-6 inhibitors; and convalescent plasma).

We investigated the involvement of 8 organ systems: respiratory, cardiovascular, endocrine, hematologic, hepatic, musculoskeletal, neurologic, and renal. Respiratory involvement was defined as a new requirement for supplemental oxygen or nadir oxygen satura-

Table 1. Sample Characteristics of Vitamin D Supplementation and Patients With COVID-19 (N = 808)

Variables	No Vitamin D Mean [SD] or Frequency (%) (n = 559)	Vitamin D Mean [SD] or Frequency (%) (n = 249)	*P* value
Demographics			
Age (years), mean	59.3 [17.13]	61.1 [15.06]	.16
Female sex	250 (44.7)	77 (30.9)	<.001
Race/ethnicity			.01
White	130 (23.3)	74 (29.7)	
African American	137 (24.5)	55 (22.1)	
Hispanic	259 (46.3)	95 (38.2)	
East Asian	18 (3.2)	8 (3.2)	
Southeast Asian	9 (1.6)	7 (2.8)	
Other	6 (1.1)	10 (4.0)	
Comorbidities			
Obesity	215 (38.5)	86 (34.5)	.29
CCI, mean	2.7 [2.46]	3.1 [2.46]	.02
Disease severity			
qSOFA, mean	1.5 [0.63]	1.5 [0.61]	.78
Intensive care unit admission	222 (39.7)	164 (65.9)	<.001
Invasive mechanical ventilation admission	23 (4.1)	21 (8.4)	.01
Oxygen requirement hospitalization			<.001
None	117 (20.9)	20 (8.0)	
Low FiO_2 (≤55%)	217 (38.8)	72 (28.9)	
High FiO_2 (>55%)	135 (24.2)	59 (23.7)	
Invasive mechanical ventilation	90 (16.1)	98 (39.4)	
Treatment management			
Vasopressor	56 (10.0)	68 (27.3)	<.001
All other treatments	521 (93.2)	244 (98.0)	.01
Organ system involvement			
No. of organ systems involved, mean	3.5 [1.93]	4.7 [1.82]	<.001

Abbreviations: CCI, Charlson Comorbidity Index; qSOFA, quick Sequential/Sepsis-related Organ Failure Assessment.

Note: Fisher exact test comparisons performed for race/ethnicity due to expected cell size less than 5.

tion <95%. Cardiovascular involvement was defined as a new elevation in troponin I (>0.04 ng/mL), new supraventricular tachycardia, new or worsening atrial fibrillation, new atrioventricular block, new ventricular tachycardia, new-onset or acute-on-chronic heart failure, or new use of inotropes or vasopressors. Endocrine involvement was defined as a new or increased baseline insulin requirement or blood glucose level < 60 mg/dL or >140 mg/dL. Hematologic involvement was defined as an absolute neutrophil count <1.8 × 109/L or >7 × 109/L, hemoglobin < 9.2 g/dL, platelet count <110×109/L, or a white blood cell count (WBC) < 4 × 109/L or >11 × 109/L. Hepatic involvement was defined as a total serum bilirubin level >1.1 mg/dL or an ALT level greater than 1.5 times the upper limit of normal limit (> 60 IU/L). Musculoskeletal involvement was defined as a creatine kinase (CK) level >1000 U/L. Neurologic involvement was defined as a change in baseline mental status, a new decrease in Glasgow Coma Scale score,[32] or new-onset cerebrovascular accident, transient ischemic attack, or seizure. Renal involvement was defined as a 1.5-fold increase in serum creatinine from baseline according to Acute Kidney Injury Network criteria[33] or an absolute increase in serum creatinine > 0.3 mg/dL.

Organ system involvement was summarized as a score ranging from 0 (no organ systems involved) to 8 (all 8 organ systems involved).

Statistical Analysis

Continuous variables were summarized using means and standard deviations. Categorical variables were summarized using frequencies and percentages. Analysis of variance was used to compare patients who did and did not receive vitamin D supplementation with respect to potential continuous covariates. The chi-square test or Fisher exact test was used to compare vitamin D supplementation status with potential categorical covariates.

Any variable that was statistically significant in the univariable analyses was included in the multivariable linear regression analysis for the outcome variable of number of organ systems involved.

Four additional sensitivity analyses were conducted. The first added qSOFA as a continuous predictor to the multivariable model. The second added qSOFA as a categorical predictor (not high risk, scores of 0-1; high risk, scores of 2-3). This cut-off was based on previous literature indicating that qSOFA scores of 2 and 3 are associated with a high risk of organ dysfunction.[34] The third analysis consisted of a stratified analysis of patients with non-high-risk qSOFA scores. The fourth consisted of a stratified analysis of patients with high-risk qSOFA scores.

Forest plots are presented for the multivariable regression analyses shown in the Tables. All *P* values were 2-sided, and statistical significance was set at $P < .05$. IBM SPSS Statistics, Version 29 (IBM Corporation) was used for the statistical analyses. Stata/SE Version 17 (StataCorp LLC) was used to generate the forest plots.

Table 2. Multivariate Linear Regression Analysis for Number of Organ Systems Involved

Variables	Vitamin D B (SE)	95% CI	*P* value
Vitamin D supplementation	0.30 (0.11)	0.10 to 0.52	.01
Female sex	-0.29 (0.10)	-0.48 to -0.10	.003
Race/ethnicity			
White	ref	ref	
African American	0.04 (0.13)	-0.22 to 0.30	.77
Hispanic	-0.32 (0.12)	-0.56 to 0.08	.01
East Asian	-0.34 (0.28)	-0.88 to 0.20	.22
Southeast Asian	0.11 (0.34)	-0.54 to 0.81	.76
Other	-0.43 (0.34)	-1.13 to 0.23	.21
CCI	0.12 (0.02)	0.08 to 0.16	<.001
Intensive care unit admission	0.56 (0.24)	0.07 to 1.02	.02
Invasive mechanical ventilation admission	0.03 (0.03)	-0.03 to 0.10	.08
Oxygen requirement hospitalization			
None	ref	ref	
Low FiO_2 (≤55%)	0.71 (0.14)	0.40 to 0.96	<.001
High FiO_2 (>55%)	1.48 (0.27)	0.88 to 1.97	<.001
Invasive mechanical ventilation	2.28 (0.30)	1.69 to 2.89	<.001
Vasopressor	1.09 (0.18)	0.75 to 1.45	<.001
All other treatments	0.30 (0.22)	-0.14 to 0.72	.17
Constant	1.80 (0.24)	1.33 to 2.27	<.001

Abbreviations: B, unstandardized beta; SE, standard error; CCI, Charlson Comorbidity Index; ref, reference.

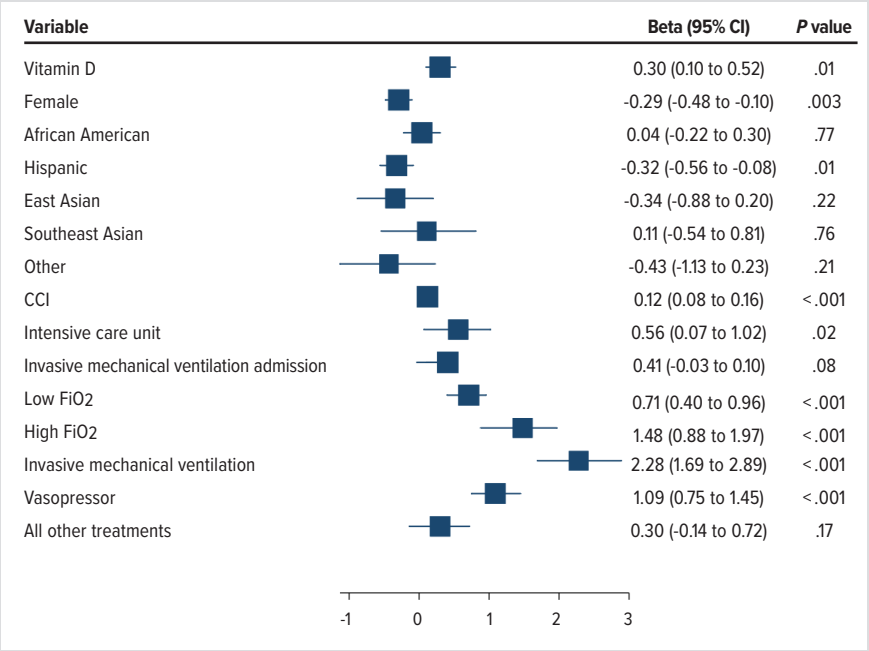
Note: adjusted R square = 0.56.

RESULTS

The sample included 249 patients (30.8%) who received vitamin D supplementation and 559 (69.2%) who did not. Table 1 compares patients who did and did not receive vitamin D supplementation. Patients who received vitamin D supplementation had a lower percentage of females and Hispanic individuals than those who did not receive vitamin D supplementation. Patients who received vitamin D supplementation had a higher mean CCI than those who did not receive vitamin D supplementation. They also had a higher frequency of ICU admission, invasive mechanical ventilation at admission, and invasive mechanical ventilation during hospitalization. In addition, patients who received vitamin D supplementation had a higher frequency of vasopressor use and receipt of other treatments than those who did not receive vitamin D supplementation.

Table 2 shows the multivariable linear regression analysis for the number of organ systems involved. Vitamin D supplementation was significantly associated with an increased number of organ systems involved. Female sex and Hispanic race/ethnicity were significantly associated with a decreased number of organ systems involved. Higher CCI, ICU admission, and all levels of oxygen support during hospitalization were significantly associated with an increased number of organ systems involved. Vasopressor use was also significantly associated with an increased number of

Figure. Forest Plot for Predictor Variables in the Multivariate Linear Regression Analysis for Number of Organ Systems Involved



Abbreviation: CCI, Charlson Comorbidity Index.

Table 3. Multivariable Linear Regression Analysis for Number of Organ Systems Involved From the Subset of Patients With Non-High-Risk Quick Sequential/Sepsis-Related Organ Failure Assessment Scores

Variables	Vitamin D B (SE)	95% CI	*P* value
Vitamin D supplementation	0.32 (0.14)	0.04 to 0.60	.03
Age (years)	0.02 (0.01)	0.004 to 0.03	.01
Female sex	-0.44 (0.12)	-0.68 to -0.20	.003
Race/ethnicity			
White	ref	ref	
African American	0.15 (0.18)	-0.20 to 0.49	.41
Hispanic	-0.24 (0.16)	-0.54 to 0.07	.13
East Asian	-0.06 (0.52)	-1.08 to 0.96	.91
Southeast Asian	0.27 (0.52)	-0.75 to 1.29	.61
Other	-0.51 (0.73)	-1.95 to 0.92	.48
CCI	0.01 (0.04)	-0.07 to 0.08	.82
Intensive care unit	0.74 (0.34)	0.07 to 1.02	0.03
Oxygen requirement hospitalization			
None	ref	ref	
Low FiO_2 (≤55%)	0.56 (0.16)	0.25 to 0.88	<.001
High FiO_2 (>55%)	1.08 (0.37)	0.37 to 1.80	.003
Invasive mechanical ventilation	2.22 (0.40)	1.44 to 3.00	<.001
Vasopressor	1.01 (0.25)	0.52 to 1.49	<.001
All other treatments	0.51 (0.25)	0.02 to 1.00	.04
Constant	0.99 (0.37)	0.26 to 1.72	.01

Abbreviations: B, unstandardized beta; SE, standard error; CCI, Charlson Comorbidity Index; ref, reference.

Note: adjusted R square = 0.60.

organ systems involved. The Figure shows the corresponding forest plot.

Sensitivity analyses were conducted with qSOFA included as a predictor variable (data not shown). In the analysis that included qSOFA as a continuous variable, vitamin D supplementation (B, 0.33; SE, 0.11; 95% CI, 0.12-0.53, $P = .002$) and qSOFA (B, 0.29; SE, 0.08; 95% CI; 0.14-0.45, $P < .001$) were each significantly associated with an increased number of organ systems involved. In the analysis that included qSOFA as a categorical variable, vitamin D supplementation (B, 0.32, SE, 0.11; 95% CI, 0.11-0.53; $P = .003$) and a high-risk qSOFA score (B, 0.33; SE, 0.10; 95% CI, 0.14-0.52; $P < .001$) were each significantly associated with an increased number of organ systems involved.

Supplemental Table 1 shows comparisons between patients who did and did not receive vitamin D supplementation among those with non-high-risk qSOFA scores. The pattern of significant findings was similar to that of the overall sample, except that age was significantly different, with a higher mean age among patients who received vitamin D supplementation, and invasive mechanical ventilation at admission no longer differed significantly between groups. Supplemental Table 2 shows comparisons between patients who did and did not receive vitamin D supplementation among those with high-risk qSOFA scores. The pattern of significant findings was similar to that of the overall sample, except that race/ethnicity, CCI, and receipt of other treatments did not differ significantly between groups.

Additional sensitivity analyses were conducted separately among patients with non-high-risk and high-risk qSOFA scores. Table 3 shows the multivariable linear regression analysis for the number of organ systems involved among patients with non-high-risk qSOFA scores. Vitamin D supplementation was significantly associated with an increased number of organ systems involved. Table 4 shows the multivariable linear regression analysis among patients with high-risk qSOFA scores. Vitamin D supplementation was again significantly associated with an increased number of organ systems involved. Supplemental Figures 1 and 2 show the corresponding forest plots.

DISCUSSION

In this study, vitamin D supplementation was significantly associated with a greater number of organ systems involved. Female sex and Hispanic race/ethnicity were significantly associated with a lower number of organ systems involved. CCI, ICU admission, oxygen requirements (low FiO_2 ≤55%, high FiO_2 >55%,

invasive mechanical ventilation), and vasopressor use were significantly associated with a greater number of organ systems involved.

Previous studies have reported either no association[12] or a favorable association between vitamin D supplementation and reduced COVID-19 disease severity when examining individual organ systems.[9-11,13,35] Our findings differ from this pattern. The COVID-19 virus enters the body by binding to the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed on endothelial and epithelial cells throughout the body.[36,37] The ACE2 receptor is involved in the breakdown of angiotensin II.[38,39] Angiotensin II helps maintain blood pressure through vasoconstriction and may contribute to fibrosis, inflammation, and cellular hypertrophy.[39-42] Elevated angiotensin II levels are associated with more severe COVID-19 symptoms.[43,44] Binding of the virus to ACE2 results in decreased ACE2 expression and a subsequent increase in angiotensin II levels.[45-47] Vitamin D upregulates ACE2 receptor expression, resulting in increased breakdown of angiotensin II.[48,49] Because SARS-CoV-2 binds to ACE2 receptors, it is possible that increased ACE2 expression associated with vitamin D supplementation could facilitate viral spread to additional organs and contribute to more extensive disease involvement.[50] A greater number of involved organ systems has been associated with worse prognosis in patients with COVID-19.[51] Thus, this hypothesis may help explain our finding that vitamin D supplementation was associated with a greater number of organ systems involved.

Female sex was associated with a lower number of organ systems involved compared with male sex. Previous research shows that COVID-19 severity and mortality are increased in males compared with females.[52,53] Our findings regarding the number of organ systems involved are consistent with this pattern and may reflect lower disease severity among females.

Hispanic patients had a lower number of involved organ systems than White patients. Individuals older than 65 years are at increased risk for severe COVID-19 infection.[54] In our sample, Hispanic patients had a mean age of 54.2 (SD, 14.47) years compared with 65.6 (SD, 18.07) years among White patients. Because Hispanic patients in our sample were substantially younger, age may partially explain their lower number of involved organ systems.

Higher CCI, ICU admission, oxygen requirements, and vasopressor use were each associated with a greater number of involved organ systems. These measures are markers of greater COVID-19 severity.[8,55-57] Accordingly, the observed association with a higher number of organ systems involved is consistent with this pattern. These findings may also reflect confounding by indication, whereby patients with more severe illness experience greater multisystem involvement.

Strengths, Limitations, and Future Research

This study has several strengths. To our knowledge, it is the first study to report an association between vitamin D supplementation and a greater number of involved organ systems among hospitalized patients with COVID-19. A second strength is the use of the novel outcome measure of number of organ systems involved.

The study also has several limitations. First, the dose of vitamin D dose supplementation was not recorded. Second, we did not determine whether vitamin D supplementation was initiated during hospitalization or represented continuation of prehospital supplementation. However, the primary research question was whether vitamin D supplementation during hospitalization was associated with improvement, no change, or worsening of physiologic manifestations of COVID-19 during acute illness. Third, baseline vitamin D levels were unavailable; therefore, vitamin D deficiency status could not be determined. Fourth, as an observational study, the findings cannot establish causality. Future randomized clinical trials are needed to evaluate causal relationships. Fifth, because the study was conducted at a single tertiary care hospital, generalizability may be limited. Sixth, although the outcome measure is novel, it is not a standardized clinical endpoint such as mortality. Finally, although sensitivity analyses were conducted to address potential unmeasured confounders of disease severity, other unmeasured confounders may exist that could introduce potential bias.

Table 4. Multivariable Linear Regression Analysis for Number of Organ Systems Involved From the Subset of Patients With High-Risk Quick Sequential/Sepsis-Related Organ Failure Assessment Scores

Variables	Vitamin D B (SE)	95% CI	*P* value
Vitamin D supplementation	0.39 (0.16)	0.06 to 0.71	.02
Female sex	0.09 (0.15)	-0.21 to 0.39	0.55
Intensive care unit	0.39 (0.35)	0.31 to 1.08	0.27
Invasive mechanical ventilation admission	0.54 (0.30)	-0.04 to 1.12	0.07
Oxygen requirement hospitalization			
None	ref	ref	
Low FiO_2 (≤55%)	0.63 (0.29)	0.06 to 1.19	.03
High FiO_2 (>55%)	1.60 (0.43)	0.76 to 2.44	<.001
Invasive mechanical ventilation	2.21 (0.47)	1.28 to 3.13	<.001
Vasopressor	1.10 (0.27)	0.57 to 1.62	<.001
Constant	2.37 (0.27)	1.85 to 2.90	<.001

Abbreviations: B, unstandardized beta; SE, standard error; CCI, Charlson Comorbidity Index; ref, reference.

Note: adjusted R square = 0.44.

CONCLUSIONS

Vitamin D supplementation was associated with a greater number of organ systems involved among hospitalized patients with COVID-19. Prospective studies, including randomized clinical trials, are needed to determine whether this association is causal and to confirm these findings.

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Appendices: Supplemental Tables and Figures are available at www.wmjonline.org

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