Mild Vitamin C Deficiency Is Common in the Inpatient Psychiatric Setting

Bilal A. Bari, MD, PhD; Ana Ivkovic, MD; and Bryce A. Wininger, MD

ABSTRACT

Objective: Mild vitamin C deficiency is a psychiatrically relevant nutritional state, with symptoms including apathy, fatigue, and low mood. Although complete vitamin C deficiency has largely been eradicated, mild deficiency remains common in certain populations. Here, we aimed to identify the prevalence of mild vitamin C deficiency in the inpatient psychiatric setting.

Methods: We identified 221 patients with plasma vitamin C levels collected on an inpatient psychiatric unit serving a metropolitan area between January 1, 2015, and March 7, 2022. We identified demographic (age, sex, race, housing status, Area Deprivation Index [an index of neighborhood disadvantage]), substance use (tobacco use, alcohol use), diagnostic (depressive, bipolar, psychotic, anxiety, substance use, catatonia, neurocognitive, autism spectrum), and micronutrient (folate, vitamin B_{12}, vitamin D) risk factors. *DSM-5-TR* was used as the diagnostic system. Bayesian log-normal regressions were constructed to predict vitamin C as a function of these risk factors. We used these same models to predict vitamin C as a function of significant risk factors.

Results: We found that 64% (141 of 221; 95% confidence interval 57%–70%) of patients met criteria for mild vitamin C deficiency. While we did not identify robust demographic, substance use, or diagnostic-based risk factors, we found that folate and vitamin D strongly predicted vitamin C levels. To test the utility of these predictors, we simulated vitamin C as a function of folate and vitamin D and found that predicted deficiency remained high (~50%–55%), even when folate/vitamin D were sufficiently replete.

Conclusions: We find that vitamin C deficiency is highly prevalent in the inpatient psychiatric setting and remains high even when the relevant risk factor profile is favorable.

J Clin Psychiatry 2023;84(4):22m14616

Author affiliations are listed at the end of this article.

Scurvy is among humanity's oldest documented conditions. First reported in the Egyptian Ebers Papyrus in 1550 BC,[1,2] scurvy is characterized by petechiae, perifollicular hemorrhage, ecchymoses, gingival bleeding, and ultimately death due to infection or bleeding.[3] Scurvy is a consequence of profound vitamin C deficiency[4,5] and is reversed with a diet rich in citrus fruits, a discovery credited to the Scottish surgeon James Lind[6] (but see references 7 and 8, as Vasco da Gama may have preempted this discovery by several centuries). With current dietary recommendations[9] and modern diets,[10] the burden of this once commonplace disease has been significantly diminished.

Physical symptoms, however, are not the only consequence of vitamin C deficiency. One of the earliest writings on the psychiatric consequences came from English military surgeon John Woodall, who wrote of a "generall lazinesse" in those with scurvy.[11] Lind, in his treatise, wrote, "...the person eats and drinks heartily, and seems in perfect health; except that his countenance and lazy inactive disposition may portend an approaching scurvy."[6] The British physician Thomas Shapter, best known for his account of cholera, recognized a similar pattern. He wrote of the "phases" of vitamin C deficiency and documented weakness, listlessness, and a lack of motivation as symptoms of the first phase, well before the devastating symptoms of scurvy took hold.[12] Modern experiments have replicated these observations: in healthy volunteers deprived of vitamin C, the symptoms of low mood, weakness, listlessness, and lack of motivation emerge, and recover with repletion.[13,14] We now understand these symptoms as a consequence of mild vitamin C deficiency,[15,16] a psychiatrically relevant state of nutritional deficiency recognized by the World Health Organization and defined by a plasma vitamin C level of < 0.75 mg/dL.[3]

Mild vitamin C deficiency is remarkably common and is seen in a number of geographic contexts[17] (including the United States,[18,19] France,[20–22] the United Kingdom,[23,24] Canada,[25–27] Australia,[28] Brazil,[29,30] Mexico,[31,32] Ecuador,[33] China,[34,35] Thailand,[36] India,[37] Nigeria,[38] and Uganda[39]), medical contexts (medical populations[26,27] and populations with psychiatric illness,[28] inpatient settings,[22,23,25–27] and outpatient settings[18]), and socioeconomic contexts (undomiciled populations[21] and the general population[19]). Risk factors include hospitalization,[16,25] male sex,[19,22] diabetes,[18] poor dietary intake,[19,24] smoking,[19,24] and low socioeconomic status.[19,21]

Vitamin C deficiency is particularly pronounced in the hospital setting, with over half of medical inpatients meeting

Clinical Points

- Although it is well known that mild vitamin C deficiency results in psychiatrically relevant symptoms, the prevalence of vitamin C deficiency in the inpatient psychiatric setting has not previously been reported in the literature.
- Mild vitamin C deficiency is remarkably common in the inpatient psychiatric setting, with 64% of patients meeting criteria.
- We recommend obtaining vitamin C levels as part of admission screening laboratory tests and ensuring that inpatients have access to fruit- and vegetable-rich diets.

criteria for mild vitamin C deficiency.[25–27] However, it is not well understood if vitamin C deficiency is as prevalent in the psychiatric inpatient setting. Here, we sought to identify the prevalence of vitamin C deficiency in psychiatrically hospitalized patients. This is an important and timely question because vitamin C deficiency has known psychiatric consequences yet is not part of the standard screening and workup for psychiatric complaints (eg, thyroid-stimulating hormone, vitamin D, vitamin B_{12}, folate). This is compounded by the logistical challenge of obtaining vitamin C levels, since assays are typically performed at external facilities, which leads to a several-day delay. If we found that vitamin C deficiency was common, then either deficiency could be treated empirically or obtaining vitamin C levels could become a routine part of practice. We found that a substantial fraction of patients met criteria for mild vitamin C deficiency. This condition was common across our patient population and cut across all identifiable patient characteristics, as we did not establish any demographic, substance use, or diagnosis-based risk factors. We found that other markers of micronutrient status (vitamin D and folate, but not vitamin B_{12}) were significantly correlated with vitamin C status. Taken together, we find that mild vitamin C deficiency is remarkably common in an inpatient psychiatric setting, with implications for identification and treatment.

METHODS

Data Collection

We obtained approval from the Massachusetts General Brigham Institutional Review Board prior to conducting this research. We identified 221 patients with plasma vitamin C levels collected on the Inpatient Psychiatric Service at Massachusetts General Hospital between January 1, 2015, and March 7, 2022. Mild vitamin C deficiency was defined by plasma vitamin C < 0.75 mg/dL following WHO criteria.[3] Frank deficiency, defined by < 0.2 mg/dL, was found in 6% (14 of 221) of subjects. We included data from all subjects that met criteria for mild deficiency. We obtained broadly similar results when we excluded those with frank deficiency (eg, similar conclusions, with slightly different *P* values and Bayes factors). Tobacco use was defined by current smoking status as of the admission. Alcohol use was defined by a score ≥ 4 for males and ≥ 3 for females on the alcohol consumption questions of the Alcohol Use Disorders Identification Test (AUDIT-C).[40] As a proxy for the socioeconomic status, we used the Area Deprivation Index, an index of neighborhood disadvantage.[41,42] The Area Deprivation Index was developed and validated from Census Bureau data to provide an index relevant for health care outcomes.[43,44] Area Deprivation Index spans in percentiles from 1 (lowest level of "disadvantage") to 100 (highest level of "disadvantage"). We used the 2019 data and linked each patient to an Area Deprivation Index using their home ZIP code.

To obtain patient diagnoses, we manually read discharge summaries and categorized admissions into at least 1 of 8 *DSM-5-TR* diagnostic categories,[45] allowing patients multiple diagnoses if appropriate: depressive, bipolar, psychotic, anxiety, substance use, catatonia, neurocognitive, and autism spectrum.

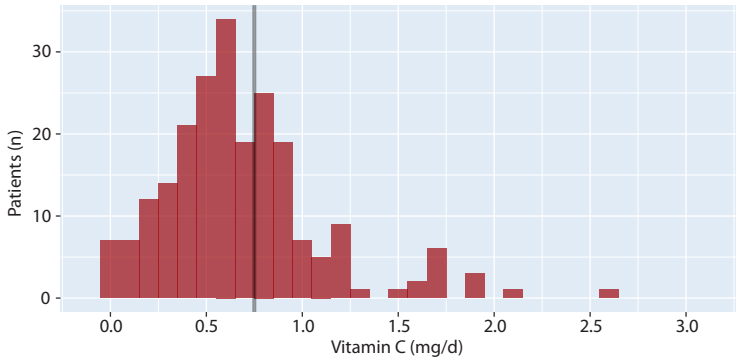
To assess other markers of micronutrient status, we analyzed folate, vitamin B_{12}, and vitamin D, as these are routine admission laboratories. Of the 221 patients with plasma vitamin C levels drawn, folate was checked in 164, vitamin B_{12} was checked in 181, and vitamin D was checked in 186.

Bayesian Log-Normal Regression

We predicted vitamin C as a function of demographic, substance use, diagnostic, or micronutrient data using Bayesian log-normal regression. Bayesian regression is seeing increasing use in medicine as a more intuitive means of statistical analysis with many favorable properties (see Nayak et al[46] for an accessible introduction). We used a log-normal distribution since vitamin C levels are naturally lower bounded at 0 (ie, negative vitamin C levels are not possible) and the empiric distribution has a long right tail (Figure 1). Since Bayesian regressions need to specify prior distributions for parameters, we used weakly informative priors for coefficients and standard deviation parameters. These weakly informative priors posit that large effect sizes are unlikely, shrinking estimates closer to 0. This has the favorable benefit of requiring that effects be more robust before claiming significance. Priors were $N(0, 1)$ for coefficients, including intercept terms, and $\text{Cauchy}^{+}(0, 5)$ for the standard deviation parameter.

We report Bayes factors comparing our models to null intercept-only models. Bayes factors are indices that provide relative evidence for one hypothesis over another. They have the advantage over *P* values of allowing us to make statements about the null hypothesis and to quantify whether an analysis is indeterminate.[47] Under common convention, Bayes factors from 3–10 provide moderate, 10–30 provide strong, 30–100 provide very strong, and > 100 provide extremely strong evidence in favor of the hypothesized model over the null. Bayes factors from 1/3–3 are indeterminate, meaning more data are required to make a conclusion. Bayes factors < 1/3 provide evidence for the null model. These boundaries are not strict, and, like all statistical inference, conclusions should be interpreted in

Figure 1. Plasma Vitamin C Levels[a]



[a]Vitamin C levels were collected on n = 221 patients. The overall mean ± standard deviation level was 0.68 ± 0.41 mg/dL. A total of 141 patients (64%; 95% confidence interval, 57%–70%) met the criterion for mild vitamin C deficiency (< 0.75 mg/dL). The thin black line marks 0.75.

context.[48] Bayes factors in this article can be interpreted as a statement about parsimony. If we compare a model with many parameters (eg, demographic-based predictors) to one with a single parameter (intercept-only null) and find the Bayes factor prefers the null, then this means the null model provides a more parsimonious explanation of the data. We also provide Bayes factors for coefficients within a model, which quantifies how much the data provide evidence for a non-zero coefficient.

Since vitamin C data were left-censored, with the minimum reported as < 0.1 mg/dL, we applied left-censoring techniques in all regressions. For the demographic and substance use regression, continuous variables (here, only Area Deprivation Index) were *z*-scored. For micronutrient regressions (folate, vitamin B_{12}, vitamin D), the input to the model was the *z*-scored log of the relevant micronutrient data. Since some of the folate and vitamin B_{12} data were right-censored, we imputed these values before running the regression. For folate, the maximum level was reported as > 20 ng/mL. To impute these right-censored values, we fit a right-censored log-normal distribution to the data, calculated the mean and standard deviation of this empiric distribution, generated random samples from this empiric distribution, and kept those values > 20 to use as inputs into the vitamin C regression model. For vitamin B_{12}, the reported maximum was > 200 pg/mL, with the details of the imputation procedure otherwise the same.

All analyses were performed in R using RStudio. Models were fit using the *brms* package,[49] which is a wrapper for the probabilistic programming language *Stan*.[50] Models were visually inspected with trank plots, which demonstrated adequate chain mixing, suggesting that estimates of the posterior had converged. We computed Bayes factors using the *bayestestR* package.[51,52]

RESULTS

We identified 221 patients with plasma vitamin C levels collected during their inpatient psychiatric admissions. Within this group, 141 patients (64%; 95% confidence interval, 57%–70%) met criteria for mild vitamin C deficiency (< 0.75 mg/dL), a psychiatrically relevant category (Figure 1). To better understand what features may predict mild vitamin C deficiency, we identified demographic, substance use, diagnostic, and other laboratory data for each patient.

Demographic and Substance Use Risk Factors

Among potential demographic and substance use risk factors (Table 1), univariate analysis revealed that deficient patients were more frequently male (63% vs 46%, $P = .022$) and tended to be older, although this latter effect was not significant (49.2 ± 18.2 years vs 44.5 ± 16.7 years, $P = .058$). We found no differences in race (deficient: 60% White, 14% Black, 11% Hispanic, 5% Asian, 10% other; not deficient: 64% White, 6% Black, 10% Hispanic, 6% Asian, 14% other, $P = .44$), current tobacco use (30% vs 38%, $P = .36$), risky alcohol use (AUDIT-C score 1.74 ± 3.33 vs 1.69 ± 3.14, $P = .65$), stable housing (81% vs 76%, $P = .52$), or Area Deprivation Index,[41,42] an index of neighborhood disadvantage relevant for health care outcomes (18.2 ± 13.5 percentile vs 21.3 ± 15.4 percentile, $P = .11$).

We next performed a multivariate analysis of these demographic and substance use factors, since perhaps a combination of factors may better predict vitamin C deficiency. We fit a Bayesian log-normal regression, which predicted vitamin C as a function of demographic and substance use factors. We used Bayes factors to perform model comparison (see Methods for a rationale). Briefly, Bayes factors provide relative evidence for one hypothesis over another, and under usual conventions, Bayes factors > 3 favor the experimental hypothesis and Bayes factors < 1/3 favor the null hypothesis. This model had a Bayes factor of 2.5×10^{-7} compared to a null intercept-only model, demonstrating that the null model was strongly favored as a more parsimonious explanation of the data. To assess whether any single coefficient may be reasonably predictive, we computed Bayes factors on each coefficient—which quantifies whether the evidence supports a non-zero coefficient—and found that no demographic or substance use factor had a Bayes factor > 0.7. We therefore did not identify a single demographic or

Table 1. Demographic and Substance Use, Diagnostic, and Laboratory Data, Split by Vitamin C Status[a]

	Total (N = 221)	Vitamin C status: Not deficient (N = 80)	Vitamin C status: Deficient (N = 141)	*P* value
Demographic and substance use data				
Age, mean (± SD), y	47.5 (± 17.8)	44.5 (± 16.7)	49.2 (± 18.2)	.058
Sex, female	95 (43)	43 (54)	52 (37)	.022
Race				.44
White	136 (62)	51 (64)	85 (60)	
Black	25 (11)	5 (6)	20 (14)	
Hispanic	23 (10)	8 (10)	15 (11)	
Asian	12 (5)	5 (6)	7 (5)	
Other	25 (11)	11 (14)	14 (10)	
Tobacco use	73 (33)	30 (38)	43 (30)	.36
Alcohol (AUDIT-C), mean (± SD)	1.72 (± 3.26)	1.69 (± 3.14)	1.74 (± 3.33)	.65
Housed	175 (79)	61 (76)	114 (81)	.52
Area Deprivation Index, mean (± SD)	19.3 (± 14.3)	21.3 (± 15.4)	18.2 (± 13.5)	.11
Diagnostic data				
Depressive	89 (40)	35 (44)	54 (38)	.51
Bipolar	9 (4)	4 (5)	5 (4)	.86
Psychotic	85 (38)	27 (34)	58 (41)	.35
Anxiety	52 (24)	22 (28)	30 (21)	.38
Substance use	59 (27)	25 (31)	34 (24)	.32
Catatonia	31 (14)	10 (12)	21 (15)	.77
Neurocognitive	37 (17)	11 (14)	26 (18)	.48
Autism spectrum	4 (2)	3 (4)	1 (1)	.27
Laboratory data				
Folate, ng/mL, mean (± SD)	13.9 (± 5.05)	15.3 (± 4.78)	13.2 (± 5.07)	.012
Vitamin B_{12}, pg/mL, mean (± SD)	700 (± 374)	699 (± 365)	700 (± 381)	.98
Vitamin D, ng/mL, mean (± SD)	24.1 (± 14.0)	27.3 (± 13.7)	22.3 (± 13.9)	.0069

[a]Values expressed as n (%) unless otherwise noted.
Abbreviation: AUDIT-C = consumption questions from the Alcohol Use Disorders Identification Test.

substance use predictor that was reasonably predictive of vitamin C levels. To assess this another way, we computed 95% highest density posterior intervals for each coefficient and found that none excluded zero (Figure 2A). In sum, we found no evidence that demographic or substance use data predicted vitamin C levels.

Diagnostic Risk Factors

We next asked whether diagnostic data may predict vitamin C levels. We categorized admissions as related to the following *DSM-5-TR* diagnoses: depressive, bipolar, psychotic, anxiety, substance use, catatonia, neurocognitive, and autism spectrum. Univariate analyses revealed that no diagnostic label was predictive of vitamin C deficiency (Table 1). Like before, we performed a multivariate analysis and found this model had a Bayes factor of 2.6×10^{-6}, strongly disfavoring diagnoses as predictive of vitamin C. We computed Bayes factors on each coefficient and found that no individual diagnosis had a Bayes factor > 0.9 and that none of the 95% highest density posterior intervals excluded 0 (Figure 2B). We therefore found no evidence that diagnoses were predictive of vitamin C levels.

Micronutrient Risk Factors

Finally, we explored other markers of micronutrient status. We chose to look at folate, vitamin D, and vitamin B_{12}, as these were routinely collected on admitted patients. Univariate analysis revealed that folate and vitamin D levels were significantly associated with vitamin C status (Table 1). Patients with mild vitamin C deficiency had lower folate levels (13.2 ± 5.1 ng/mL vs 15.3 ± 4.8 ng/mL, $P = .012$) and vitamin D levels (22.3 ± 13.9 ng/mL vs 27.3 ± 13.7 ng/mL, $P = .0069$), but not vitamin B_{12} levels (700 ± 381 pg/mL vs 699 ± 365 pg/mL, $P = .98$).

We fit Bayesian log-normal regressions to predict vitamin C as a function of folate, vitamin B_{12}, or vitamin D. Here, we found moderate evidence that folate (Bayes factor 9.6), no evidence that vitamin B_{12} (Bayes factor 0.3), and very strong evidence that vitamin D (Bayes factor 950) predicted vitamin C. The 95% highest density posterior intervals supported this view, with intervals for folate and vitamin D excluding 0 (Figure 2C).

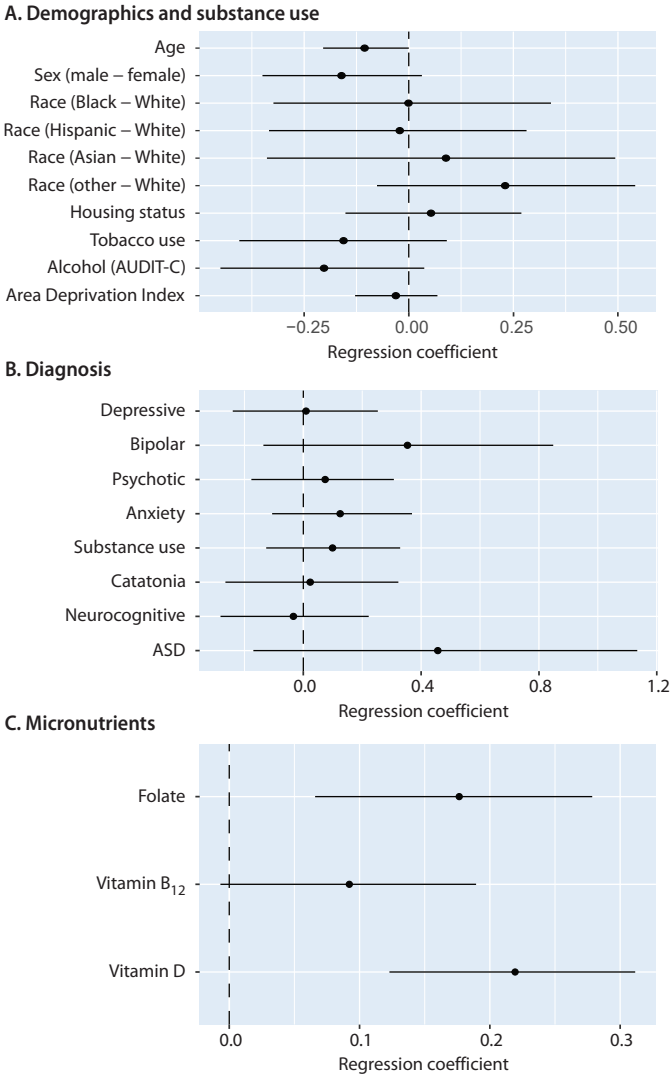
The positive correlation between multiple micronutrients and vitamin C suggests that these deficiencies are most likely a function of relative malnutrition. However, prior work has demonstrated there may be a specific sensitivity to vitamin C deficiency.[29] We therefore sought to address whether the prevalence of vitamin C deficiency would remain high even when folate/vitamin D were sufficiently replete (Figure 3). For each model, we simulated vitamin C levels as a function of folate or vitamin D, across a range of reasonable clinically relevant values (for the folate model, 2.0 ng/mL to 20.0 ng/mL; for the vitamin D model, 5.0 ng/mL to 50.0 ng/mL). When folate or vitamin D levels were frankly deficient (folate = 2.0 ng/mL, vitamin D = 5.0 ng/mL), predicted vitamin C deficiency was high, at ~90%. However, when folate or vitamin D levels were replete (folate = 20.0 ng/mL, vitamin D = 50.0 ng/mL), predicted vitamin C deficiency remained reasonably high (~50%–55% even with high levels of folate and vitamin D). Therefore, predicted vitamin C deficiency remained high, even when other micronutrient markers were sufficiently replete.

DISCUSSION

Mild vitamin C deficiency is associated with a number of psychiatrically relevant symptoms, including fatigue, dysthymia, and apathy. Despite its relevance to psychiatry, vitamin C has received comparatively little attention in the literature. Here we find that the prevalence of mild vitamin C deficiency in the inpatient psychiatric setting is remarkably high, at 64% (95% confidence interval 57%–70%).

What accounts for this high prevalence? For one, it is remarkably easy to become vitamin C deficient, as the body stores last about 2–3 months.[53] Maintaining this store requires a diet containing fresh produce, since vitamin C is quickly lost when food is cooked.[54] Approximately 20% of US adults consume less than 60 mg of vitamin C daily, less than the recommended 75–90 mg/d[9,55,56]

Figure 2. Multivariate Regression Coefficients[a]

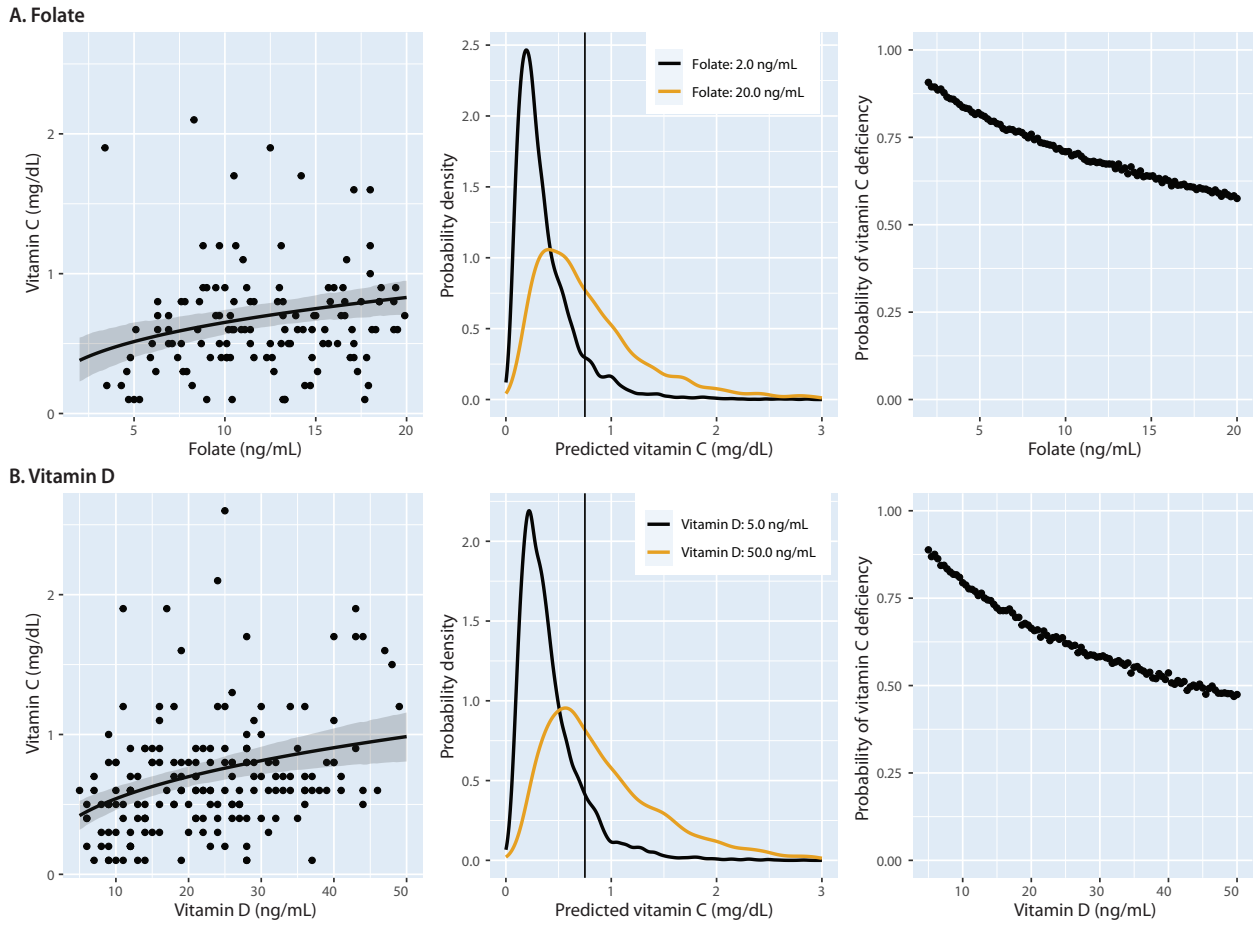


[a]We fit Bayesian log-normal regressions predicting plasma vitamin C as a function of demographic and substance use, diagnostic, or micronutrient factors. We computed the 95% highest density posterior interval for each coefficient (or difference in coefficients, if more interpretable). (A) For the demographic and substance use regression, none of the intervals excluded 0. (B) For the diagnostic regression, none of the intervals excluded 0. (C) For the micronutrient regression, the intervals for folate and vitamin D excluded 0. Mean [95% interval]: folate, 0.18 [0.07–0.28]; vitamin B_{12}, 0.09 [−0.01–0.19]; vitamin D, 0.22 [0.12–0.31].
Abbreviations: ASD = autism spectrum disorder, AUDIT-C = consumption questions from the Alcohol Use Disorders Identification Test.

Psychiatrically ill patients are known to have poor diets low in fruits and vegetables[57] and those with psychiatric disorders tend to be socioeconomically disadvantaged.[58] We also know the disease processes themselves contribute. For example, one of the criteria of major depressive disorder is a decrease in appetite, which would certainly contribute to deficiency.[45] We note that the high prevalence of vitamin C deficiency is not unique to populations with psychiatric illness. Hospitalized medical patients show similar rates of deficiency (56%–85%), which likely speaks to the multifactorial nature of deficiency.[25–27,30] Because vitamin C levels were collected at the beginning of hospitalization, deficiency reflects pre-hospitalization practices, and not differences between the practice patterns of psychiatric vs medical inpatient units.

Our analysis relating vitamin C to folate/vitamin D revealed that the probability of vitamin C deficiency remained high, even when folate/vitamin D levels were sufficiently high. This highlights the importance of independently assessing vitamin C levels, rather than extrapolating vitamin C status from the levels of other micronutrients. One should keep in mind that our analysis relating vitamin C to other micronutrients is a simulation only, which we pursued since our relatively small sample size limited our ability to query vitamin C levels at the extremes of other micronutrient levels. One observation that increases confidence in our

Figure 3. Predicted Vitamin C as a Function of Folate or Vitamin D[a]



[a]We fit Bayesian log-normal regressions predicting vitamin C as a function of folate or vitamin D. We then simulated data by providing fictive folate or vitamin D levels as inputs to this model to predict vitamin C distributions. For each model, we ran across a range of clinically relevant values.

Left panels: Vitamin C as a function of (A) folate or (B) vitamin D, with a best-fit line ± 95% highest density posterior interval for the mean (in gray shade). Note that the line for the mean is shifted slightly toward the tail (here, upward) because this is a log-normal distribution, and the mean is closer to the tail than the median.

Middle panels: Predicted vitamin C distribution as a function of low and high levels of (A) folate or (B) vitamin D. Low and high values for folate are 2.0 ng/mL and 20.0 ng/mL, respectively; low and high values for vitamin D are 5.0 ng/mL and 50.0 ng/mL, respectively. The black line marks 0.75 mg/dL, a criterion for mild vitamin C deficiency.

Right panels: Predicted probability of vitamin C deficiency (percent of distribution below 0.75 mg/dL) across a range of (A) folate or (B) vitamin D values.

analysis is that a sizeable fraction of patients with high levels of folate and vitamin D have vitamin C levels below 0.75 mg/dL (Figure 3).

We found that folate and vitamin D, but not vitamin B_{12}, were associated with vitamin C deficiency. Prior work has demonstrated that not all micronutrients are correlated with vitamin C. One study found that malnourished patients were deficient in vitamin C, but not vitamin A, vitamin E, or vitamin B_2, suggesting a particular sensitivity to vitamin C.[29] In our study, the relationship between folate and vitamin C is likely because the two are found in similar sources, and dietary deficiency would similarly deplete both. The relationship for vitamin B_{12} and vitamin D is less clear, as natural and fortified versions are both found in similar food sources (predominantly meat and dairy). Perhaps because vitamin D deficiency is more common than vitamin B_{12} deficiency, there is a natural floor effect with vitamin B_{12}.[59,60] More likely, we were simply underpowered to detect a difference with vitamin B_{12}, since a Bayes factor of 0.3 is not definitively in favor of the null hypothesis. In this case, malnutrition would be the most straightforward explanation.

Prior literature has demonstrated that male sex, smoking, and low socioeconomic status are commonly found risk factors for vitamin C deficiency.[19] We only found age as a risk factor on univariate analysis, which disappeared with multivariate analysis. We believe this is because vitamin C deficiency is particularly prevalent in our population, minimizing or negating the effect of additional risk factors that may be relevant for the general population. We refer the interested reader to Carr and Rowe[61] for a thoughtful contemporary review of the risk factors underlying vitamin C deficiency.

Our study has a number of limitations. Unlike other micronutrients (vitamin B_{12}, vitamin D, and folate) that were routinely collected, vitamin C levels were collected in only a subset of patients. In general, vitamin C was collected if

there was a concern for a produce-limited diet, if patients were unable to provide a reliable history (eg, psychosis), or based on clinical judgment (as part of a diagnostic workup, physical examination findings concerning for scurvy, etc). This bias in sampling might explain, in part, the high rates of vitamin C deficiency we observed—equivalent to rates observed in medically hospitalized patients. Because the psychiatric symptoms of vitamin C deficiency are relatively mild and since our study was performed in the inpatient setting, where symptoms tend to be more extreme, we found that symptomatology had limited utility in determining who was vitamin C deficient. For example, essentially all patients with depression who require inpatient hospitalization will report dysthymia, fatigue, or apathy, regardless of whether they are vitamin C deficient. Consistent with this, exploratory data analysis revealed no enrichment of symptoms in those with low vitamin C levels. Additionally, if symptomatology were the primary factor driving bias in sampling, one may expect a lower rate of vitamin C deficiency in patients unable to provide a clear history (eg, psychosis or catatonia), as this patient population will not necessarily be enriched for symptoms of vitamin C deficiency. As we show in Figure 2B, diagnostic factors were not predictive of plasma vitamin C. We cannot rule out that this inference is limited by small sample size, since most Bayes factors for individual diagnostic categories were indeterminate, suggesting the need for more data. We hypothesize that the relationship between vitamin C and symptomatology will be more pronounced in the outpatient setting, where milder psychiatric symptoms are more prevalent.

Our study has a number of other limitations. We used records from 1 inpatient psychiatric unit in an academic hospital serving a large metropolitan area. Unique practices within our hospital system likely affected data collection practices—for example, there is a greater consideration for the psychoactive impact of nutrition than is standard for the field of psychiatry. Other limitations include using ZIP code, a fairly crude measure, as a proxy for socioeconomic status, as there can be tremendous variability in socioeconomic status within a single ZIP code. Finally, we likely had limited power in identifying various risk factors, a number of which are firmly established in the literature (eg, male sex, cigarette smoking). Overall, these limitations make it clear that a prospective study, in which vitamin C is collected in a more unbiased manner, is a necessary next step to better understand the prevalence of vitamin C deficiency and associated risk factors in the inpatient psychiatric setting.

There is a physiological basis for why mild vitamin C deficiency may predispose to psychiatric symptoms. The cerebrospinal fluid vitamin C concentration is 3- to 5-fold higher than plasma concentrations, suggesting higher metabolism by the nervous system.[62] Vitamin C is involved in norepinephrine synthesis, modulation of neurotransmission by dopamine and glutamate, and the regulation of catecholamine and acetylcholine release from synapses.[16] It is also a powerful antioxidant, protecting against excitotoxicity from glutamate.[16] Vitamin C deficiency additionally disrupts cortico-basal-ganglia processing, which may predispose to apathy and difficulty enacting willed motor movements.[63]

The psychiatric consequences of vitamin C deficiency generally correct with adequate repletion. Notably, repletion improves mild mood symptoms across a range of settings,[26,27,64] including healthy individuals.[65] In contrast, there seems to be no such improvement in major depressive disorder based on a recent systematic review.[66] Notably, however, this review did not assess vitamin C status in depressed patients prior to supplementation, which is a frequent limitation of nutrition intervention studies that often yield negative findings. While it remains unlikely (yet unclear) that vitamin C deficiency contributes to profound neurovegetative depression, it can likely limit recovery from acute psychiatric crises. Given the high prevalence of vitamin C deficiency in the inpatient setting combined with the difficulty of identifying deficient patients based on risk factors, we make the following suggestions for changing clinical practice: we suggest routinely collecting vitamin C levels to allow for patient-specific recommendations, and we recommend that psychiatric treatment units ensure patient diets contain daily fresh fruits and vegetables (and to initiate such diets after the plasma level is drawn). For patients with limited oral intake or with differing dietary preferences, oral repletion (500 mg bid or renal-attenuated dosing) is a cheap and well-tolerated alternative.

Nutrition remains an important and often overlooked aspect of psychiatric illness. The field is in need of well-designed studies that identify patients with specific deficiencies and measure clinical outcomes pre- and post-repletion. Such work is a key foundation of precision psychiatry and will allow us to treat patients in a targeted manner.

Article Information

Published Online: June 14, 2023. https://doi.org/10.4088/JCP.22m14616

Submitted: August 3, 2022; accepted January 31, 2023.

To Cite: Bari BA, Ivkovic A, Wininger BA. Mild vitamin C deficiency is common in the inpatient psychiatric setting. *J Clin Psychiatry*. 2023;84(4):22m14616.

Author Affiliation: Department of Psychiatry, Massachusetts General Hospital, Boston.

Corresponding Author: Bilal A. Bari, MD, PhD, 15 Parkman St, WACC 812, Boston, MA 02114 (bbari@partners.org).

Relevant Financial Relationships: None.

Funding/Support: This work was supported by grant R25MH094612 from the National Institute of Mental Health, Bethesda, MD (Bari).

Role of the Funders/Sponsor: The funding agencies did not play a role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

ORCID: Bilal Bari: https://orcid.org/0000-0002-8381-3802

REFERENCES

1. Georg E. *Stern Ludwig. Papyros Ebers: das Hermetische Buch u¨ber die Arzneimittel der alten A¨gypter in hieratischer Schrift*. Engelmann; 1875.
2. Ebbell B. *The Papyrus Ebers: The Greatest Egyptian Medical Document*. Levin & Munksgaard; 1937.
3. World Health Organization. *Scurvy and Its Prevention and Control in Major Emergencies Tech Rep*. World Health Organization; 1999.
4. Hodges RE, Hood J, Canham JE, et al. Clinical manifestations of ascorbic acid deficiency in man. *Am J Clin Nutr*. 1971;24(4):432–443.

5. Combs GF, McClung JP. *Vitamin C in The Vitamins: Fundamental Aspects in Nutrition and Health*. 5th ed. Elsevier; 2017:267–295.
6. Lind J. *A Treatise on the Scurvy*. Sands, Murray, and Cochran; 1757.
7. Martini E. How did Vasco da Gama sail for 16 weeks without developing scurvy? *Lancet*. 2003;361(9367):1480.
8. Ravenstein Ernst Georg. *A Journal of the First Voyage of Vasco da Gama, 1497–1499*. Hakluyt Society; 2017.
9. Institute of Medicine. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. The National Academies Press; 2000.
10. Magiorkinis E, Beloukas A, Diamantis A. Scurvy: past, present and future. *Eur J Intern Med*. 2011;22(2):147–152.
11. John W. *The Surgions Mate. The First Compendium on Naval Medicine, Surgery and Drug Therapy (London 1617)*. Birkhauser; 1617.
12. Shapter T. On the recent occurrence of scurvy in Exeter and the neighbourhood. *Prov Med Surg J*. 1847;11(11):281–285.
13. Kinsman RA, Hood J. Some behavioral effects of ascorbic acid deficiency. *Am J Clin Nutr*. 1971;24(4):455–464.
14. Levine M, Conry-Cantilena C, Wang Y, et al. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. *Proc Natl Acad Sci U S A*. 1996;93(8):3704–3709.
15. Buzina R, Suboticanec K. Vitamin C and physical working capacity. *Int J Vitam Nutr Res suppl*. 1985;27:157–166.
16. Plevin D, Galletly C. The neuropsychiatric effects of vitamin C deficiency: a systematic review. *BMC Psychiatry*. 2020;20(1):315.
17. Rowe S, Carr AC. Global vitamin C status and prevalence of deficiency: a cause for concern? *Nutrients*. 2020;12(7):1–20.
18. Johnston CS, Thompson LL. Vitamin C status of an outpatient population. *J Am Coll Nutr*. 1998;17(4):366–370.
19. Schleicher RL, Carroll MD, Ford ES, et al. Serum vitamin C and the prevalence of vitamin C deficiency in the United States: 2003–2004 National Health and Nutrition Examination Survey (NHANES). *Am J Clin Nutr*. 2009;90(5):1252–1263.
20. Hercberg S, Preziosi P, Galan P, et al. Vitamin status of a healthy French population: dietary intakes and biochemical markers. *Int J Vitam Nutr Res*. 1994;64(3):220–232.
21. Malmauret L, Leblanc J, Cuvelier I, et al. Dietary intakes and vitamin status of a sample of homeless people in Paris. *Eur J Clin Nutr*. 2002;56(4):313–320.
22. Fain O, Pariés J, Jacquart B, et al. Hypovitaminosis C in hospitalized patients. *Eur J Intern Med*. 2003;14(7):419–425.
23. Gariballa S, Forster S. Effects of acute-phase response on nutritional status and clinical outcome of hospitalized patients. *Nutrition*. 2006;22(7-8):750–757.
24. Mosdøl A, Erens B, Brunner EJ. Estimated prevalence and predictors of vitamin C deficiency within UK's low-income population. *J Public Health (Oxf)*. 2008;30(4):456–460.
25. Gan R, Eintracht S, Hoffer LJ. Vitamin C deficiency in a university teaching hospital. *J Am Coll Nutr*. 2008;27(3):428–433.
26. Evans-Olders R, Eintracht S, Hoffer LJ. Metabolic origin of hypovitaminosis C in acutely hospitalized patients. *Nutrition*. 2010;26(11-12):1070–1074.
27. Zhang M, Robitaille L, Eintracht S, et al. Vitamin C provision improves mood in acutely hospitalized patients. *Nutrition*. 2011;27(5):530–533.
28. Gabb G, Gabb B. Scurvy not rare. *Aust Fam Physician*. 2015;44(7):438–440.
29. Da Cunha DF, Cunha SF, Unamuno MR, et al. Serum levels assessment of vitamin A, E, C, B2 and carotenoids in malnourished and non-malnourished hospitalized elderly patients. *Clin Nutr*. 2001;20(2):167–170.
30. Avelino DD, Maltos AL, Portari GV, et al. Vitamin C status in hospitalized adults according to subjective global assessment method. *JPEN J Parenter Enteral Nutr*. 2019;43(6):789–793.
31. García OP, Ronquillo D, del Carmen Caamaño M, et al. Zinc, vitamin A, and vitamin C status are associated with leptin concentrations and obesity in Mexican women: results from a cross-sectional study. *Nutr Metab (Lond)*. 2012;9(1):59.
32. Villalpando S, Montalvo-Velarde I, Zambrano N, et al. Vitamins A, and C and folate status in Mexican children under 12 years and women 12-49 years: a probabilistic national survey. *Salud Publica Mex*. 2003;45(suppl 4):S508–S519.
33. Hamer DH, Sempértegui F, Estrella B, et al. Micronutrient deficiencies are associated with impaired immune response and higher burden of respiratory infections in elderly Ecuadorians. *J Nutr*. 2009;139(1):113–119.
34. Lam TK, Freedman ND, Fan J-H, et al. Prediagnostic plasma vitamin C and risk of gastric adenocarcinoma and esophageal squamous cell carcinoma in a Chinese population. *Am J Clin Nutr*. 2013;98(5):1289–1297.
35. Frankenfeld CL, Lampe JW, Shannon J, et al. Fruit and vegetable intakes in relation to plasma nutrient concentrations in women in Shanghai, China. *Public Health Nutr*. 2012;15(1):167–175.
36. Viroonudomphol D, Mahaisiriyodom A, Mingkhawn R, et al. Relationship between serum antioxidant vitamins A, E, and C and lipid profiles in priest subjects at the Priest Hospital. *Southeast Asian J Trop Med Public Health*. 2005;36(suppl 4):246–253.
37. Ravindran RD, Vashist P, Gupta SK, et al. Prevalence and risk factors for vitamin C deficiency in north and south India: a two centre population based study in people aged 60 years and over. *PLoS One*. 2011;6(12):e28588.
38. Nwagha UI, Iyare EE, Ejezie FE, et al. Parity related changes in obesity and some antioxidant vitamins in non-pregnant women of South-Eastern Nigeria. *Niger J Clin Pract*. 2012;15(4):380–384.
39. Kiondo P, Tumwesigye NM, Wandabwa J, et al. Plasma vitamin C assay in women of reproductive age in Kampala, Uganda, using a colorimetric method. *Trop Med Int Health*. 2012;17(2):191–196.
40. Bush K, Kivlahan DR, McDonell MB, et al. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med*. 1998;158(16):1789–1795.
41. Kind AJH, Buckingham WR. Making neighborhood-disadvantage metrics accessible—the neighborhood atlas. *N Engl J Med*. 2018;378(26):2456–2458.
42. University of Wisconsin School of Medicine and Public Health. Area Deprivation Index. Version 3.0. 2019. Accessed March 11, 2022. https://www.neighborhoodatlas.medicine.wisc.edu/
43. Singh GK. Area deprivation and widening inequalities in US mortality, 1969-1998. *Am J Public Health*. 2003;93(7):1137–1143.
44. Kind AJH, Jencks S, Brock J, et al. Neighborhood socioeconomic disadvantage and 30-day rehospitalization: a retrospective cohort study. *Ann Intern Med*. 2014;161(11):765–774.
45. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders DSM-5-TR*. Fifth Edition, Text Revision. American Psychiatric Association. 2022.
46. Nayak SM, Bari BA, Yaden DB, et al. A Bayesian reanalysis of a trial of psilocybin versus escitalopram for depression. *Psychedelic Med*. 2022;1(1):18–26. >
47. Keysers C, Gazzola V, Wagenmakers EJ. Using Bayes factor hypothesis testing in neuroscience to establish evidence of absence. *Nat Neurosci*. 2020;23(7):788–799.
48. Quintana DS, Williams DR. Bayesian alternatives for common null-hypothesis significance tests in psychiatry: a non-technical guide using JASP. *BMC Psychiatry*. 2018;18(1):178.
49. Bürkner P-C. Advanced Bayesian multilevel modeling with the R Package brms. *R J*. 2018;10(1):395–411.
50. Stan Development Team. Stan Modeling Language Users Guide and Reference Manual. Version 2.30. 2022. https://github.com/stan-dev/stan/releases
51. Makowski D, Ben-Shachar MS, Chen SHA, et al. Indices of effect existence and significance in the Bayesian framework. *Front Psychol*. 2019;10:2767.
52. Dominique M, Ben-Shachar MS, Daniel L. bayestestR: describing effects and their uncertainty, existence and significance within the Bayesian framework. *J Open Source Softw*. 2019;4:1–18.
53. Hodges RE, Baker EM, Hood J, et al. Experimental scurvy in man. *Am J Clin Nutr*. 1969;22(5):535–548.
54. Ashor AW, Siervo M, Mathers JC. *Vitamin C, Antioxidant Status, and Cardiovascular Aging in Molecular Basis of Nutrition and Aging*. Elsevier; 2016:609–619.
55. Adrianne B. *Vitamin C Safety in Humans in Vitamin C in Health and Disease*. In: Packer L, Fuchs J, eds. Marcel Dekker; 1997:367–379.
56. Frei B, Trabe MG. The new US Dietary Reference Intakes for vitamins C and E. *Redox Rep*. 2001;6(1):5–9.
57. Dipasquale S, Pariante CM, Dazzan P, et al. The dietary pattern of patients with schizophrenia: a systematic review. *J Psychiatr Res*. 2013;47(2):197–207.
58. Dohrenwend BP. Socioeconomic status (SES) and psychiatric disorders: are the issues still compelling? *Soc Psychiatry Psychiatr Epidemiol*. 1990;25(1):41–47.
59. Allen LH. How common is vitamin B-12 deficiency? *Am J Clin Nutr*. 2009;89(2):693S–696S.
60. Cashman KD. Vitamin D deficiency: defining, prevalence, causes, and strategies of addressing. *Calcif Tissue Int*. 2020;106(1):14–29.
61. Carr AC, Rowe S. Factors affecting vitamin C status and prevalence of deficiency: a global health perspective. *Nutrients*. 2020;12(7):1963.
62. Ridge BD, Fairhurst E, Chadwick D, et al. Ascorbic acid concentrations in human plasma and cerebrospinal fluid [proceedings]. *Proc Nutr Soc*. 1976;35(2):57A–58A.
63. Brown TM. Neuropsychiatric scurvy. *Psychosomatics*. 2015;56(1):12–20.
64. Mazloom Z, Ekramzadeh M, Hejazi N. Efficacy of supplementary

vitamins C and E on anxiety, depression and stress in type 2 diabetic patients: a randomized, single-blind, placebo-controlled trial. *Pak J Biol Sci*. 2013;16(22):1597–1600.
65. Brody S. High-dose ascorbic acid increases intercourse frequency and improves mood: a randomized controlled clinical trial. *Biol Psychiatry*. 2002;52(4):371–374.
66. Yosaee S, Keshtkaran Z, Abdollahi S, et al. The effect of vitamin C supplementation on mood status in adults: a systematic review and meta-analysis of randomized controlled clinical trials. *Gen Hosp Psychiatry*. 2021;71:36–42.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Early Career Psychiatrists section. Please contact Joseph F. Goldberg, MD, at jgoldberg@psychiatrist.com.