## Original Article

# Association of Vitamin B12 and Folate Deficiency with Vasovagal Syncope: A Case-Control Study

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## Highlights

- Vitamin B12 and folate status were evaluated in adults with vasovagal syncope.
- No association was found between vitamin deficiency and vasovagal syncope overall.
- Lower vitamin B12 levels were observed in patients with frequent syncope.

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## ABSTRACT

**Background:** Clinical evidence suggests an association between vitamin B12 deficiency and vasovagal syncope (VVS) in pediatric patients. This study investigated the association of vitamin B12 and folate deficiency with VVS in adults.

**Methods:** In this case-control study, adult patients with VVS who presented to the tertiary syncope unit for head-up tilt table testing comprised the case group. Age- and sex-matched individuals without syncope history from the population-based Tehran Cohort Study served as the control group. Exclusion criteria included but were not limited to the use of vitamin B supplements, carbamazepine, or phenobarbital, and sleeve gastrectomy. Serum vitamin B12, folate, and homocysteine levels were measured and compared.

**Results:** From February 2020 through February 2021, 44 patients comprised the case group, matched with 44 controls (mean age, 37.9 years; 23 [52.3%] females in each group). No statistically significant difference existed between the groups in vitamin B12 or folate deficiency or serum levels. Serum vitamin B12 levels were significantly lower in patients with frequent VVS (≥3 lifetime episodes) than in patients with infrequent VVS (<3 lifetime episodes) (233.8 [80.7] vs 305.2 [118.1] pg/mL; P=0.042), and the association remained significant after adjustment for confounders (P=0.026).

**Conclusion:** No association existed between vitamin B12 or folate deficiency or serum levels and VVS. Frequent VVS was associated with lower serum vitamin B12 levels than infrequent VVS.

**Keywords:** Syncope; Vasovagal; Folic Acid; Folic Acid Deficiency; Vitamin B12; Vitamin B12 Deficiency; Homocysteine

## Introduction

Vasovagal syncope (VVS) is a common and potentially debilitating condition with limited treatment strategies, particularly for frequent VVS.[1,2] VVS, the most common type of syncope,[1,2] accounts for 0.8% to 3.0% of emergency room visits and 1% of hospital admissions.[3-6] VVS can be a life-disrupting condition,[7] and quality of life for patients with recurrent VVS can be as impaired as that for patients with chronic diseases, such as rheumatoid arthritis[8,9] and chronic low back pain.[9] Furthermore, 33% of patients with VVS incur injuries due to episodes, with greater fragility among older patients.[10] In addition to lost productivity and other indirect costs, VVS imposes $2.4 billion annually on the US health system for hospitalization of patients with VVS.[11,8] Despite this substantial psychosocial and financial burden of VVS, treatment options are scarce, especially for patients with frequent VVS.[12] Improved knowledge about VVS pathophysiology is critical for developing novel preventive and therapeutic strategies to reduce its burden.[1,2] Investigation of possible mechanisms is thus encouraged as the basis for future interventions to treat VVS or at least a subgroup of these patients.[12,13] Increased serum catecholamine levels may play a role in VVS pathophysiology,[14-19] and vitamin B12 deficiency may increase catecholamines through biochemically plausible mechanisms.[20,21] Evidence suggests an association between vitamin B12 deficiency and VVS in pediatric patients.[22,23] Nonetheless, no methodologically rigorous study has investigated this association in adult or elderly patients with VVS.[24] Concurrent evaluation of vitamin B12 and folate, two vitamins with interwoven biochemical pathways, is encouraged.[22]

In this case-control study, we aimed to investigate the possible association of vitamin B12 and folate deficiency with VVS in adults from the syncope unit of a tertiary referral hospital and a population-based cohort.

## Methods

### Data Sources

Patients with VVS who presented to the syncope unit[25,12,13] of Tehran Heart Center,[26] Tehran, Iran, for head-up tilt table testing (HUTT) from February 2020 through February 2021 comprised the case group. The control group was selected from the population-based Tehran Cohort Study (TeCS) of adult inhabitants of Tehran.[27] Demographic and baseline data were retrieved from the syncope registry of Tehran Heart Center[25] for the case group and from the TeCS database[27] for the control group. The study protocol followed the Declaration of Helsinki (2013) and was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1397.856). Informed consent was obtained from all participants after discussion of the study protocol and before inclusion.

### Study Population

The case group consisted of adult patients with VVS aged 18 to 70 years. These patients received the diagnosis after comprehensive history taking, physical examination, and guideline-indicated diagnostic workups,[1,2] including electrocardiography, echocardiography, Holter monitoring, and laboratory data in the syncope unit.[25] The control group comprised age- and sex-matched individuals without syncope history from TeCS.

Exclusion criteria were as follows: use of midodrine or fludrocortisone; use of oral or parenteral vitamin B supplements, including but not limited to folic acid, vitamin B12, vitamin B complex, or hair supplements in the last 6 months; gastric, intestinal, or bariatric surgery; alcohol use disorder; use of antiepileptic medications interfering with vitamin B12 or folate metabolism, including phenytoin, phenobarbital, or carbamazepine; use of methotrexate or isoniazid; history of malabsorption, including celiac disease, Crohn disease, or ulcerative colitis; and history of malignancy.

### Study Exposures

The hypothesis was greater vitamin B12 or folate deficiency in patients with VVS than in controls. Serum vitamin B12, folate, and homocysteine levels were measured. Homocysteine, a metabolite whose elevation

indicates functional vitamin B12 or folate deficiency, was included. Blood samples were obtained from the case group after intravenous line insertion for routine HUTT preparation and before testing. Control group blood samples were obtained during TeCS standard procedures. Participants fasted for at least 8 hours before blood sampling. All samples were handled in dark containers for light-sensitive biochemicals, centrifuged within a few hours of sampling, and stored at −80 °C. Analyses used Abbott diagnostic chemiluminescence kits.
Vitamin B12 deficiency was defined as serum vitamin B12 less than 187 pg/mL, and folate deficiency as serum folate less than 3.1 ng/mL. Elevated homocysteine levels may indicate a functional deficiency of either vitamin B12 or folate.[20] Vitamin B12 or folate deficiency was thus defined as serum homocysteine greater than 16.2 µmol/L in males or greater than 13.6 µmol/L in females, vitamin B12 deficiency, or folate deficiency.

## Study Covariates

Baseline demographic characteristics, past medical history, drug history, family history, and syncopal history were obtained from the databases mentioned above. In addition to demographic characteristics and past medical history, study covariates that may interfere with serum vitamin B12 or folate levels were selected to minimize confounding effects. History of hypo- or hyperthyroidism and use of proton pump inhibitors, $H_2$ receptor blockers, metformin, and oral contraceptive pills were specifically recorded. Family history of syncope, seizure, or sudden death was also investigated. Evidence of lower serum thyroid-stimulating hormone (TSH) levels in pediatric patients with VVS and positive HUTT than in those with negative HUTT [23] prompted measurement of serum TSH as a potential confounder. TSH was measured using the Abbott diagnostic chemiluminescence kit and protocol described above. In the case group, the number of syncopal episodes in the last year and lifetime was recorded. Patients were categorized by lifetime syncopal episodes as frequent VVS (≥3 episodes) or infrequent VVS (<3 episodes). All case group patients underwent HUTT according to the Italian protocol. [28] Hemodynamic response in positive HUTT was categorized according to the modified VASIS classification [29] as follows: Type 1, mixed; Type 2A, cardioinhibition without asystole; Type 2B, cardioinhibition with asystole; and Type 3, vasodepressor.

## Sample Size Calculation

The present study is the first to compare serum vitamin B12 levels between patients with VVS and healthy controls in adults. Sample size was calculated from a similar study of adolescents in which 47.2% of patients with VVS had vitamin B12 deficiency compared with 18.0% of controls. [22] To achieve 80% power, we needed 39 patients per group to reach statistical significance at the 0.05 level.

## Statistical Analysis

Data were described as mean (SD) or No. (%) for continuous and categorical variables, respectively. The student *t* test and the $\chi^2$ or Fisher exact test compared continuous and categorical variables between groups, respectively. Binary logistic regression modeled odds ratios (ORs) and 95% confidence intervals (CIs). In the case group, linear regression predicted serum vitamin B12 levels, with age, sex, TSH, and lifetime syncopal episode frequency (≥3 vs <3 episodes) as independent variables. All analyses used R version 4.0.3 (2020-10-10). The significance level was 0.05 with two-sided tests for all hypotheses.

# Results

## Baseline Characteristics

Of 157 patients with definite VVS referred for HUTT to the Syncope Unit of Tehran Heart Center from February 2020 through February 2021, 44 were included in the case group after exclusions. Exclusions comprised 107 patients due to vitamin B supplement use, 2 due to carbamazepine use, 2 due to phenobarbital use, 1 due to sleeve gastrectomy history, and 1 due to malignancy history. Case group patients were aged 37.9 (14.7) years; 23 (52.3%) were females. The control group comprised 44 age- and sex-matched individuals without syncope history from TeCS, aged 37.9 (13.9) years; 23 (52.3%) were females. Baseline characteristics are presented in Table 1. No significant differences existed between groups in characteristics potentially confounding serum

vitamin B12 or folate levels, including smoking, alcohol consumption, related medication use, and past medical history (Table 1). In the case group, 13 (29.5%) and 21 (47.7%) patients had more than three syncopal episodes in the last year and lifetime, respectively. Based on the study definition, 28 (63.4%) patients had frequent VVS, and 16 (36.4%) had infrequent VVS. Of 17 (38.6%) patients with positive HUTT, vasodepressor response was most common (7 [41.2%]), followed by mixed response (5 [29.4%]) (Table 1).

## Association of Vitamin B12/Folate and VVS

Serum vitamin B12, folate, homocysteine, and TSH levels and vitamin B12 and folate deficiency prevalence are compared between groups in (Table 2). No statistically significant differences existed between patients and controls for these parameters (Table 2). Although vitamin B12 deficiency prevalence did not differ significantly between patients with frequent and infrequent VVS (8/28 [28.6%] vs 2/16 [12.5%]; P=0.283), the difference may be clinically important and reach statistical significance with larger samples (OR=2.80, 95% CI, 0.52 to 15.23; P=0.233) (Table 2).

Serum vitamin B12 levels were lower in patients with frequent VVS than in patients with infrequent VVS (233.8 [80.7] vs 305.2 [118.1] pg/mL; P=0.042). This difference remained significant after adjustment for age, sex, and TSH (Table 3). Linear regression showed that frequent VVS was associated with lower serum vitamin B12 levels than infrequent VVS (coefficient=−73.97, 95% CI, −138.54 to −9.40; P=0.026) (Table 3) (Figure 1).

**Table 1.** Baseline characteristics of the study participants

| Characteristic | Case (No.=44) | Control (No.=44) | P |
|---|---|---|---|
| Demographics | | | |
| Age, y | 37.9 (14.7) | 37.9 (13.9) | 0.994 |
| Female sex | 23 (52.3%) | 23 (52.3%) | 1.000 |
| Smoking | 7 (15.9%) | 6 (13.6%) | 0.764 |
| Alcohol consumption | 1 (2.3%) | 1 (2.3%) | 1.000* |
| Body mass index, kg/m² | 27.0 (8.7) | 25.3 (3.6) | 0.251 |
| Past medical history | | | |
| Diabetes mellitus | 0 (0%) | 0 (0%) | – |
| Hypertension | 7 (15.9%) | 5 (11.4%) | 0.534 |
| Dyslipidemia | 6 (13.6%) | 9 (20.5%) | 0.395 |
| Coronary artery disease | 1 (2.3%) | 0 (0%) | 1.000* |
| Hypothyroidism | 4 (9.1%) | 1 (2.3%) | 0.360 |
| Hyperthyroidism | 1 (2.3%) | 0 (0%) | 1.000* |
| Medication History | | | |
| Proton pump inhibitors | 4 (9.1%) | 2 (4.5%) | 0.676* |
| $H_2$ receptor blockers | 1 (2.3%) | 1 (2.3%) | 1.000* |
| Metformin | 1 (2.3%) | 1 (2.3%) | 1.000* |
| Oral contraceptive pills | 1 (2.3%) | 0 (0%) | 1.000* |
| Family history | | | |
| Syncope | 3 (6.8%) | 0 (0%) | 0.241* |
| Seizure | 3 (6.8%) | 1 (2.3%) | 0.616* |
| Sudden death | 2 (4.5%) | 1 (2.3%) | 1.000* |
| Syncopal History (cases only) | | | |
| Previous Year's Episodes | | | |
| 1 episode | 14 (31.8%) | – | – |
| 2 episodes | 8 (18.2%) | – | – |
| 3 episodes | 3 (6.8%) | – | – |
| >3 episodes | 13 (29.5%) | – | – |
| Lifetime Episodes | | | |
| 1 episode | 7 (15.9%) | – | – |
| 2 episodes | 9 (20.5%) | – | – |
| 3 episodes | 7 (15.9%) | – | – |
| >3 episodes | 21 (47.7%) | – | – |
| Positive HUTT | 17 (38.6%) | – | – |
| HUTT Response | | | |
| Mixed | 5 (29.4%) | – | – |
| Cardioinhibition without asystole | 1 (5.9%) | – | – |
| Cardioinhibition with asystole | 4 (23.5%) | – | – |
| Vasodepressor | 7 (41.2%) | – | – |

Data are presented as mean (SD) or number (%).
HUTT: head-up tilt table test
* Fisher exact test was done for comparison.

**Table 2.** Comparison of laboratory data and prevalence of vitamin B12/folate deficiency between patients and controls, and between patients with recurrent VVS and patients with infrequent VVS

| Characteristic | Case (No.=44) | Control (No.=44) | P | Frequent VVS (No.=28) | Infrequent VVS (No.=16) | P |
|---|---|---|---|---|---|---|
| Vitamin B12, pg/mL | 259.7 (100.8) | 238.0 (82.7) | 0.271 | 233.8 (80.7) | 305.2 (118.1) | 0.042 |
| Folate, ng/mL | 7.8 (3.7) | 7.4 (3.0) | 0.526 | 8.1 (4.1) | 7.4 (2.9) | 0.530 |
| Homocysteine, µmol/L | 15.6 (10.0) | 13.5 (5.1) | 0.234 | 14.6 (7.1) | 17.2 (13.8) | 0.505 |
| Vitamin B12 deficiency | 10 (22.7%) | 15 (34.1%) | 0.237 | 8 (28.6%) | 2 (12.5%) | 0.283* |
| Folate deficiency | 2 (4.5%) | 0 (0%) | 0.494* | 1 (3.6%) | 1 (6.3%) | 1.000* |
| Vitamin B12/folate deficiency | 18 (40.9%) | 22 (50.0%) | 0.392 | 13 (46.4%) | 5 (31.3%) | 0.325 |
| TSH, U/mL | 2.3 (1.4) | 2.3 (1.7) | 0.947 | 2.1 (1.2) | 2.6 (1.7) | 0.254 |

Data are presented as mean (SD) or number (%).
TSH: thyroid-stimulating hormone
* Fisher exact test was done for comparison.

**Table 3.** Linear regression model for predicting serum vitamin B12 based on syncopal history

| Characteristic | Coefficient | 95% CI | P |
|---|---|---|---|
| Age, y | 0.18 | –1.91 to 2.28 | 0.862 |
| Sex | | | |
| Male | Reference | | |
| Female | 36.83 | –25.10 to 98.75 | 0.236 |
| TSH, U/mL | 2.89 | –19.90 to 25.69 | 0.799 |
| Lifetime Syncopal Episodes | | | |
| Infrequent (<3 episodes) | Reference | | |
| Frequent (≥3 episodes) | –73.97 | –138.54 to –9.40 | 0.026 |

TSH: thyroid-stimulating hormone

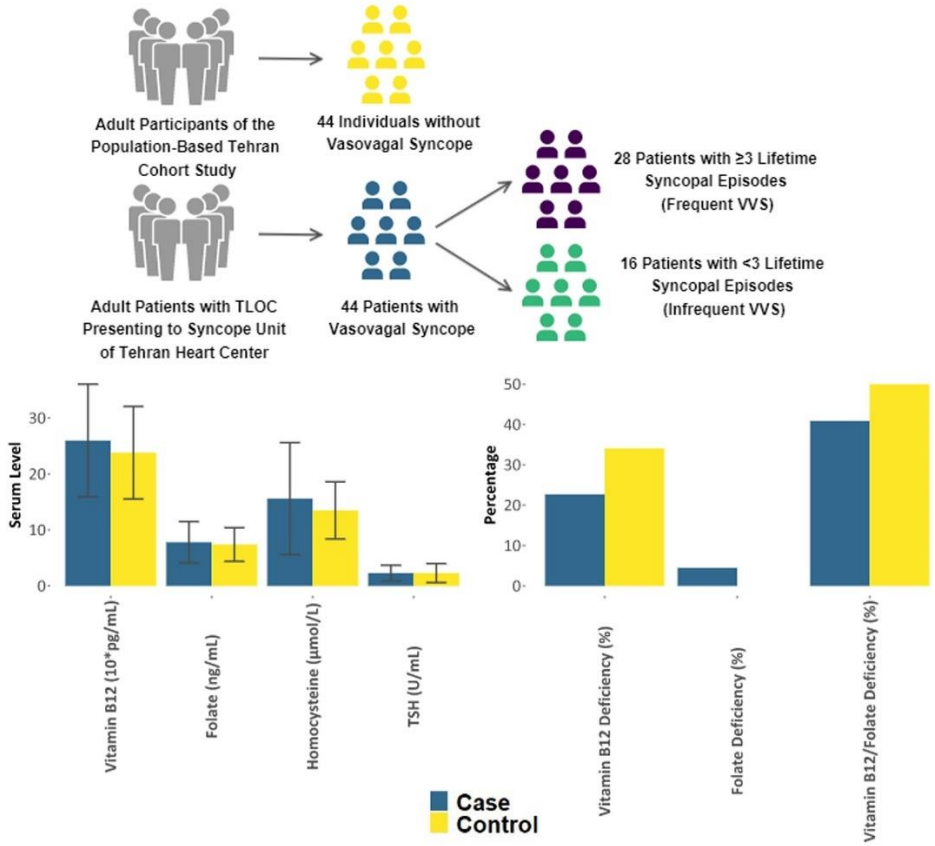


**Figure 1**. Comparison of laboratory data and prevalence of vitamin B12/folate deficiency between patients and controls.

## Discussion

The current case-control study from a tertiary referral hospital and population-based cohort found no significant difference in vitamin B12 or folate deficiency or serum levels between adult patients with VVS and controls. Patients with frequent VVS had lower serum vitamin B12 levels than patients with infrequent VVS. Vitamin B12 deficiency prevalence may be higher in patients with frequent VVS than in those with infrequent VVS, albeit not statistically significant, and may be clinically important.

## Biochemical Mechanism of VVS in Vitamin B12/Folate Deficiency

VVS pathophysiology is poorly understood, prompting efforts to develop novel treatment strategies for this potentially debilitating condition.[30] One hypothesis states that VVS involves parasympathetic overactivation in response to exaggerated sympathetic activation, indicated by increased serum catecholamine levels.[14-17, 31,18,19] Patients with VVS have normal resting serum catecholamine levels but elevated levels in response to head-up tilting, similar to actual syncopal episodes.[14-19] Ineffective metabolism of released catecholamines contributes to elevated levels.[21] Catecholamine metabolism occurs via catechol-*O*-methyltransferase (COMT)– and monoamine oxidase (MAO)–dependent pathways. The COMT pathway requires *S*-adenosyl methionine (SAM), which depends on sufficient vitamin B12 and folate levels.[20] Vitamin B12 and folate serve as cofactors for catecholamine degradation. Vitamin B12 or folate deficiency thus decreases SAM, impairs COMT-dependent catecholamine degradation, elevates serum catecholamine levels in response to VVS triggers, and precipitates syncope.

## Clinical Evidence of VVS and Vitamin B12/Folate Deficiency

Clinical evidence links vitamin B12 deficiency and VVS in pediatric patients;[23,22] evidence is scarce and weak in adults and older adults.[24] In one case-control study, pediatric patients with VVS (n=125) had higher vitamin B12 deficiency prevalence (47.2% vs 18.0%; P<0.001) and lower serum vitamin B12 levels (352.8 vs 411.3 pg/mL; P<0.001) than healthy controls (n=50), but similar folate levels.[22] In another study, pediatric patients with VVS and positive HUTT (n=80) had higher vitamin B12 deficiency prevalence (80.0% vs 52.5%; P=0.001) and lower serum vitamin B12 levels (282 vs 358 pg/mL; P=0.01) than those with negative HUTT (n=80).[23]

Despite this evidence in pediatric patients younger than 18 years, there are only descriptive studies in other age groups.[24,32,33] These studies showed that the prevalence of vitamin B12 deficiency might be as high as 70% in adult[24] or 23% in elderly[33] patients with VVS and a positive HUTT; nevertheless, no comparison was made with a control group. Notably, supplementation with intramuscular vitamin B12 in patients with deficiency reduced HUTT-induced syncope by 50% to 60% during a 6-month follow-up. [24] Although these findings may imply an association between vitamin B12 and VVS in adults, the lack of an appropriate control group limits their generalizability. Moreover, our results do not support this association, at least in a general population of patients with VVS referred to our syncope unit. This finding contrasts with the current evidence in pediatric patients. This discrepancy may be attributed to physiologic differences in dietary needs and growth between adults and adolescents, as most pediatric patients included in the abovementioned studies were older than 10 years.[22,23]

## Implications for Practice and Research

Our findings may support measuring serum vitamin B12 in adult patients with frequent VVS and treating existing deficiencies, particularly when other class I–recommended strategies, such as increased salt and fluid intake, are not effective.[1,2] The possible association between refractory or recurrent VVS and vitamin B12 deficiency,[24,32] the potential clinical benefit of treatment, and the safety of assessment and administration encourage this approach in clinical practice. Still, future research is warranted to define the role of vitamin B12 deficiency in VVS clearly. The current evidence and our findings call for studies to investigate this association in adult patients with frequent VVS. Furthermore, future randomized controlled trials will determine the effectiveness of vitamin B12 supplementation in these patients. The current evidence for this

intervention lacks an appropriate control group,[24,32] which limits its validity and generalizability.

## Limitations

The present study has several limitations. First, its observational case-control design is subject to inherent bias, although selecting controls from a population-based cohort helped reduce this risk. Second, more than two-thirds of screened patients were excluded because of recent vitamin B supplementation, and a similar pattern was seen in the control group; this high supplement use was likely related to the COVID-19 pandemic, during which vitamin intake increased substantially.[34,35] Third, the sample size was modest, partly because non–COVID-19 health care utilization dropped during the pandemic, limiting eligible participants.[36] Finally, although homocysteine was measured, we did not assess methylmalonic acid, a more sensitive marker of vitamin B12 deficiency.[37] Dietary patterns (eg, vegetarian or low-meat diets, reduced dairy intake) were not assessed and may influence individual vitamin B12 levels, although no difference in vitamin B12 was observed between cases and controls.

## Conclusion

In this study from a tertiary referral hospital and a population-based cohort, we found no difference in vitamin B12 or folate deficiency, or their serum levels between adult patients with VVS and controls; nevertheless, frequent VVS was associated with a lower serum vitamin B12 compared to infrequent VVS. Future studies are warranted to investigate the role of vitamin B12 deficiency in frequent VVS and the efficacy of supplementation with vitamin B12 in these patients.

## Declarations:

## Ethical Approval

The study was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1397.856) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

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## Conflict of Interest

The authors declare no potential conflicts of interest.

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