

Is food frequency questionnaire a valid tools to assess intake of folate and vitamin B12 in Azar cohort population?

Sona Azimi

Nutrition Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Elnaz Faramarzi (✉ elnazfaramarzi849@gmail.com)

liver and Gastrointestinal Diseases Research center, Tabriz university of Medical sciences

Parvin Sarbakhsh

Biostatistics, Department of Statistics and Epidemiology, School of Public Health, Tabriz University of Medical Sciences, Tabriz, Iran

Alireza Ostadrahimi

Nutrition Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

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Abstract

Background: Repeated 24-hour recalls and diet diaries are the most dietary methods, which have been used as gold standards in food frequency questionnaire (FFQ) validation studies. But associated random errors between the FFQ and these two dietary assessment methods can result in flawed estimates of validity. Therefore, evaluation biochemical indices have been considered as a reference method in validation studies.

Objective: The aim of this study was to evaluate the validity of the FFQ by comparing the estimated intakes of folate and vitamin B12 with corresponding biochemical markers.

Methods: Participants were 95 healthy adults from Azar Cohort Study. We compared folate and vitamin B12 intakes of food frequency questionnaire with their concentrations in blood specimens. Serum folate and vitamin B12, and of red blood cell folate concentrations, were determined using electrochemiluminescence immunoassay method respectively.

Results: Spearman correlation coefficients between dietary folate and corresponding biomarkers (serum and RBC folate) concentrations were 0.04 (P-value = 0.65), 0.06 (P-value = 0.52) respectively. There was no correlation between dietary vitamin B12 and serum concentrations of this vitamin, whether in crude or energy-adjusted model in the total population studied ($r = -0.134$, $p = 0.19$ in crude model and $r = -0.137$, $p = 0.18$ in energy-adjusted model). According to the findings of this study, 64.51, 60.21 and 54.83 percent of studied population were in the same/adjacent quartiles of dietary folate-serum folate, dietary folate-red blood cell folate and dietary vitamin B12-serum vitamin B12 respectively.

Conclusion: According to our results, it seems that this FFQ may not be a reliable tool to assess intakes of folate and vitamin B12. Therefore, further studies with large sample size are needed to achieve more clear results.

1. Introduction

Folate and vitamin B₁₂ are essential water soluble B vitamins, with shared metabolic pathways. They both participate in single carbon transfer reactions, including acting as a cofactor for the enzyme methionine synthase in the remethylation of homocysteine to methionine [1–6]. Poor folate and vitamin B₁₂ status can lead to impairment in one-carbon metabolism and an increased risk for cardiovascular diseases, through an elevated concentrations of the atherogenic amino acid homocysteine [7, 8]. In addition, according to several clinical studies, there is an inverse association between the development of certain cancers and folate and vitamin B₁₂ status [9–11]. Thus accurate estimate of dietary intake of folate and vitamin B₁₂ is necessary in epidemiological studies to better investigate diet-disease relationships.

The Food Frequency Questionnaire (FFQ) is the preferred method in most epidemiological studies to assess dietary intake of folate and vitamin B₁₂. Mainly due to its low cost and ease of administration [12]

Although the FFQ has these advantages, but like all other dietary assessment methods, random and systematic error can occur when interpreting estimates derived from FFQ data, and limiting its ability to correctly assess dietary intake. Therefore the validity of FFQ in the population of its intended use, is particularly important, as incorrect information may lead to false diet-health associations[13].

Repeated 24-hour recalls and diet diaries are the most dietary methods, which have been used as gold standards in FFQ validation studies. But associated random errors between the FFQ and these two dietary assessment methods can result in flawed estimates of validity. Therefore, biochemical markers measured in the blood have been used as a reference method in validation studies, since they are independent of measurement errors associate measurements from FFQ[14].

The aim of this cross sectional study was to evaluate folate and vitamin B₁₂ intakes of FFQ with their concentrations in blood specimens.

2. Methods

2.1. Study population

The present study is a part of Azar cohort study which is a part of Prospective Epidemiological Research Studies in Iran) [15].

By using simple random method, subsample of 95 healthy adults (35 men, 60 women) who participated in the enrollment phase of Azar cohort included in this study.

The more details about Azar cohort study has been published elsewhere [16, 17]. Eligibility criteria were age (35 to 65 years) and the willingness to participate in the study. Breastfeeding, current pregnancy, vitamin or any other supplement use, smoking, alcoholism, specific diet (e.g., veganism), the utilization of drugs interfering with vitamin B12 and folate metabolism, diseases altering vitamin B12 and folate metabolism, and intestinal or gastric surgeries were applied as the exclusion criteria.

Furthermore, the participants signed informed consent.

2.2. Baseline characteristics information

Demographic information (age, gender), medical history (based on self-report) were collected by questionnaire.

2.3. Dietary Assessment

Dietary intake was assessed using a semi-quantitative FFQ during the previous year which was composed of 111-food items. Items were categorized into 10 major food groups: bread and cereals, beans, meat and its products, milk and dairy products, vegetables, fruits, oils, oil seeds and butter, sweets and miscellaneous. The frequency of consumption of each food group was asked in 5 levels: times per day, times per week, times per month, times per year and months per year. To obtain more accurate results, standard serving sizes and colorful food album were provided to aid participants to estimate the

portion size. Average daily consumption of any food item was calculated by multiplying the frequency of consumption of food items by the corresponding portion size. The daily intake of total energy, folate and vitamin B₁₂ were analyzed by using the Nutritionist IV food composition database.

2.4. Biomarkers

Subsequent to 12–14 hours of overnight fast, we took venous blood samples. Based on the electrochemiluminescence immunoassay technique (German Siemens folate and vitamin B12 dual kit, Immulite 2000 systems analyzers), vacutainer serum separator and ethylenediaminetetraacetic acid (EDTA) tubes were employed to collect blood in order to determine serum vitamin B12 and folate and to measure the folate concentration of red blood cells (RBCs). Immediately after blood samples were taken, 1 cc of full blood was diluted within the same amount of distiller water to prepare hemolysate. A NIHON KOHDEN cell counter (Japanese Celltac model) was employed to perform a complete blood count (CBC).

2.5. Anthropometric measurement

A mounted tape was employed to measure the height at the beginning of the research. During this time, the arms of the participant were freely hanging by the sides. The recording was performed to the closest 0.5 cm. Once light clothing and barefoot participants had been ensured, a Seca scale was employed to carry out the weight recording of the participants to the closest 0.1 kg. The weight (kg) was divided by the squared height (m) to calculate the body mass index (BMI).

2.6. Statistical Analyses

The Kolmogorov-Smirnov test was applied to examine the normality of the data. The normally-distributed data were described using “mean \pm standard deviation. Moreover, data of non-normal distribution were described by the median(IQ). Through the Mann-Whitney U-test Student’s t-test for continuous variables of normal and non-normal distributions, respectively, the male and female participants underwent comparisons in terms of the mean biochemical measurement, mean FFQ derived estimate, and mean demographic characteristics. On account of variable non-normality, FFQ validity was examined using the Spearman correlation coefficient and the comparison of energy-adjusted and crude intakes from the FFQ and the corresponding nutrient vitamin B12 and folate plasma contents. The classification of the vitamin B12 and folate intakes into four equal categories was performed so that the average vitamin B12 and folate content trends of the categories would be studied. Furthermore, the consistency of the FFQ intakes and the respective biomarkers was measured as the ratio of participants categorized into the same, same/adjacent, and extreme distribution quartiles for a specific nutrient intake. Moreover, data were analyzed in SPSS V. 11. The significance level was chosen to be p-values smaller than 0.05.

3. Results

The participant characteristics and the corresponding mean intakes of nutrients from FFQ as well as the concentrations of biomarkers are reported in Table 1. The participants were calculated to have an average age of 48.09 ± 7.79 years. The median(IQ) of vitamin B12 was found to be 176(106) pg/ml, while

the median(IQ) of folate was measured to be 6.76(5.73) ng/ml. The male and female participants showed no significant serum folate differences (p-value = 0.26). The male and female participants, however, exhibited a significant serum vitamin B12 difference (p-value = 0.002). The total participants, female participants, and male participants were found to have the average total energy intakes of 3910.57 ± 1182.63 , 3725.47 ± 1059.93 , and 4227.47 ± 1324.05 kcal/d, respectively. The Mann-Whitney u-test was applied to compare the median(IQ) vitamin B12 and folate intakes, where the male and female participants did not exhibit any significant differences.

Table 1

Summary of demographic characteristics, FFQ – derived estimates and nutritional biomarkers of participants

Variable(unit)	All(n = 95)	Male(n = 35)	Female(n = 60)	P-value
Age (yr)	48.09 \pm 7.79*	49.97 \pm 7.47	47 \pm 7.83	0.07
Height (cm)	162.79 \pm 9.75	171.86 \pm 7.37	157.51 \pm 6.56	< 0.001
Weight (kg)	73.85 \pm 11.45	76.90 \pm 10.89	72.07 \pm 11.48	0.04
Body Mass Index (kg/m ²)	27.91 \pm 4.30	25.91 \pm 2.93	29.07 \pm 4.55	< 0.001
Serum folate (ng/ml)	6.76(5.73)**	6.71(5.50)	7.08(5.81)	0.26
Serum vitamin B ₁₂ (pg/ml)	176(106)	152(39)	189(132)	0.002
RBC ¹ folate (ng/ml)	190.70 \pm 101.34	183.41 \pm 87.25	194.95 \pm 109.21	0.83
Energy (Kcal/day)	3910.57 \pm 1182.63	4227.47 \pm 1324.05	3725.47 \pm 1059.93	0.041
Folate (μ g/day)	547.5714(260.43)	578.5714(356.86)	542.5714(227.25)	0.721
Vitamin B ₁₂ (μ g/day)	4.3714(3.42)	4.4886(2.88)	3.9707(3.16)	0.420
*Normally distributed variables have been described as Mean \pm SD and compared using independent t test between male and female				
**Non normally distributed variables have been described as Median(IQ) and compared using Mann Whitney u test between male and female				
¹ red blood cell folate				

The energy-adjusted and crude correlation between serum vitamin B12 and serum folate and between FFQ estimates and RBC folate contents are reported in Table 2 for both the male and female participants. In general, the biomarkers and FFQ estimates did not exhibit any significant correlations. Energy-adjustment Models I and II enhanced the serum folate-dietary folate correlations for both the male and

female participants. The crude model and Energy-adjusted Models I and II yielded better correlations for the male participants as compared to the female ones.

Table 2
Correlations between FFQ-derived estimates and biomarkers

FFQ-estimates daily dietary intakes	Biomarkers	Men			Women		
		Crude	Energy- adjusted I	Energy- adjusted II*	Crude	Energy- adjusted I	Energy- adjusted II
Folate(µg/d)	Serum Folate(ng/ml)	0.09	0.18	0.17	0.04	0.07	0.10
Folate(µg/d)	RBC Folate(ng/ml)	0.07	0.06	0.06	0.07	-0.11	0.02
Vitamin B ₁₂ (µg/d)	Serum B ₁₂ (pg/ml)	0.05	0.15	0.02	-0.15	-0.19	-0.25
*correlations were adjusted for age, gender and BMI							

The cross-classification into quartiles between the FFQ estimates and biomarkers is shown in Table 3. As can be seen, 30%, 64.51%, 60.21%, and 54.83% of the participants fell in the same/adjacent quartiles of FFQ estimates and serum folate, vitamin B12, and RBC folate content, respectively. The participants in the same quarantine had the minimum percentages (below 30%). No significant rises occurred in the RBC folate, vitamin B12, and serum folate concentrations due to FFQ-estimated daily diary intake enhancement (p-value < 0.05), as shown in Table 4.

Table 3
Cross-classification into quartiles between FFQ-derived estimates and biomarkers

FFQ-estimates daily dietary intakes	Biomarkers	All(n = 95)		
		Same(%)	Same/adjacent(%)	Extreme(%)
Folate(µg/d)	Serum Folate(ng/ml)	21.5	64.51	35.48
Folate(µg/d)	RBC Folate(ng/ml)	27.95	60.21	39.78
Vitamin B ₁₂ (µg/d)	Serum B ₁₂ (pg/ml)	20.21	54.83	45.74

Table 4
Concentrations of biomarkers by quartile of FFQ-derived estimates

Folate intake($\mu\text{g}/\text{d}$)	n	Serum folate(ng/ml)		RBC folate(ng/ml)	
		Mean \pm SD	P*	Mean \pm SD	P
< 454.28	24	6.39 \pm 1.025		185.63 \pm 25.26	
454.28-547.57	23	8.32 \pm 1.021		185.44 \pm 25.18	
547.57-714.71	25	7.27 \pm 0.91		172.72 \pm 22.58	
> 714.71	23	8.69 \pm 1.021	0.401	211.35 \pm 25.16	0.634
Serum vitaminB ₁₂ (pg/ml)					
Vitamin B ₁₂ intake($\mu\text{g}/\text{d}$)		Mean \pm SD	*p		
< 2.634	24	223.74 \pm 48.25			
2.634–4.371	24	231.01 \pm 37.87			
4.371–6.055	23	215.81 \pm 40.04			
> 6.055	24	268.90 \pm 39.24	0.767		
* P : One way ANOVA test					

4. Discussion

The aim of this study was to validate the FFQ used in national cohort study to assess the dietary intakes of folate and vitamin B₁₂ against serum folate, vitamin B₁₂ and red blood cell folate in healthy adults. In this study, the correlation (crude, adjusted I, adjusted II) between dietary intakes of folate and vitamin B₁₂ and their corresponding biomarkers was weak. Similar findings were cited in other studies too. Vioque et al(2013)[18], Signorello et al (2010)[19], Hagoort et al (2007)[20] and Yen et al (2003)[21] showed weak correlations between dietary intakes of folate and serum folate concentrations (0.06, 0.19, 0.2, 0.2 respectively)[18–21]. Also, in the study conducted by Van de rest et al(2007)[22] to validate the FFQ in elderly people, the weak correlation was found between dietary intakes of folate and corresponding biomarkers(r = 0.14 for serum folate and r = 0.05 for RBC folate). The weak correlations also were found

in studies by Jackson et al(2011) [23] and Bacardi-Gascon et al(2003)[24] between dietary intakes of folate and corresponding biomarkers($r = 0.11$, $r =$ not stated respectively). Also, in the study conducted by Vioque et al(2013) [18]among pregnant women, non-significant correlation was found for vitamin B₁₂($r = 0.12$).

According to the previous studies, an advantage of using biomarkers in validation studies, is that the measurement errors are not correlated with errors of the FFQ intakes. However, biomarkers are affected by several physiologic, environmental, and genetic and lifestyle factors, that results in weak or modest correlations between intake and biomarkers[25].

Although, statistical adjustment was used to moderate the effects of these factors, the weak correlations observed between biomarkers and the FFQ-estimated data would be related to their effect[25].

Within-person variation of serum and RBC concentrations over time, might also have an important effect on the correlations. Repeated measurements of blood parameters over a specified period of time can be a solution to overcome this. However, in the study conducted by Van de rest et al(2007),[22] duplicate measurements of blood parameters, did not improve correlations [20].

The weak correlations observed in this study can be due to the homogeneity of the studied population with regard to strict exclusion criteria such as any use of vitamins or other supplements, most studies in which the good correlations were observed between dietary intakes and corresponding biomarkers, the use of supplements as exclusion criteria was not considered. 0.29, 0.36 and 0.53 were the crude correlations between serum folate concentrations and folate intake estimated by a FFQ in Chiu, Shuibi and Vioque studies respectively [18, 26, 27]. In another study conducted by Baric in vegetarians, good correlations were observed for serum and RBC folate concentrations($r = 0.41$ and $r = 0.36$ respectively) [28]. Moreover, good correlations were observed between serum vitamin B₁₂ concentrations and vitamin B₁₂ intake estimated by a FFQ in previous studies with considering the use of supplement ($r = 0.21$, 0.22 and 0.40) [22, 26, 27].

In our study, the correlations between dietary intakes of FFQ and their respective plasma concentrations of the nutrients folate and vitamin B₁₂, were assessed in crude, energy-adjusted I and energy-adjusted II models in both men and women. Our results showed that Energy-adjustment (both models) led to an increase of correlation between dietary folate and serum folate concentrations ($r = 0.14$, $p = 0.16$ in model I and $r = 0.13$, $p = 0.19$ in model II), which is in consistent with previous studies[18, 19, 23, 26].

Also in our study the correlation in all three models were better in men than women, which was in consistent with studies conducted by Van De Rest et al (2007)[22]and Signorella et al (2009)[19].

Like many other validation studies, we also investigate the ability of the FFQ to correctly classify subjects in quartiles of dietary intakes based on corresponding biomarkers. According to the results of this study, mean concentrations of serum folate, vitamin B₁₂ and RBC folate in quartiles of dietary intakes showed

no significant increase (P-value = 0.05). these results are in consistent with the results obtained from the previous studies [19, 22, 23].

The main strength of this study is the use of biochemical markers measured in the blood level to validate the FFQ used in national cohort study to assess dietary intakes of folate and vitamin B₁₂. Also the measurement of red blood cell folate along with serum folate, which allows us a better interpretation of body folate status [29] is the other strength of this validation study.

Limitations of the present study are the lack of analysis of other variables such as methylmalonic acid(MMA) and total homocysteine(tHcy) that are better predictors of folate and vitamin B₁₂ status. Also the effect of combined genetic polymorphisms on folate metabolism was not consider in this study. Further the small sample size which wouldn't be generalized to broader adults population in the country, is one of the other limitations of this study.

In conclusion, these findings indicate that the FFQ used in this study may not be a valid tool to investigate dietary intakes of folate and vitamin B₁₂. But further studies with more participants are needed.

Abbreviations

-Food Frequency Questionnaire: FFQ

- Non Communicable Disease: NCD

-Body Mass Index: BMI

-Ethylene di amine tetra acetic acid: EDTA

-Red Blood Cell: RBC

Declarations

Ethics approval and consent to participate

This study was approved by the ethic committee of Tabriz University of medical sciences (TBZMED.REC.1394.116). In this study, all methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all individual participants included in the study.

Availability of data and materials

The data that support the findings of this study are available from [Vice Chancellor for Research] but restrictions apply to the availability of these data, which were used under license for the current study,

and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [Vice Chancellor for Research]

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

-The conception or design of the work: EF, ARO

-The acquisition, analysis: PS, SA

OR interpretation of data: EF, PS, SA

Drafted the work or substantively revised: EF, SA

All authors have read and approved the manuscript

Consent for publication

Not Applicable

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Authors' Note

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