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ORIGINAL ARTICLE

Validation of the assessment of folate and vitamin B_{12} intake in women of reproductive age: the method of triads

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Objective: To validate the folate and vitamin B_{12} intakes estimated by a food-frequency questionnaire (FFQ) designed to be used in a case-control study on the association between maternal dietary intake and the risk of having a child with a congenital heart defect.
Design and subjects: The FFQ was filled out by 53 women of reproductive age. Immediately thereafter, blood samples were taken to determine serum folate, red blood cell (RBC) folate and serum vitamin B_{12} concentrations. Subsequently, three dietary 24-h recalls (24HR) were completed during a period of three successive weeks and used as a reference method. The recalls comprised two weekdays and one weekend day. Using the method of triads, validity coefficients were calculated by comparing nutrient intakes derived from the FFQ and 24HR with the corresponding nutritional biomarkers in blood. The validity coefficient is the correlation between the dietary intake reported by the FFQ and the unknown 'true' dietary intake.
Results: The comparison of B-vitamin intakes reported by the FFQ and the mean of the 24HR revealed deattenuated correlation coefficients of 0.98 for folate and 0.66 for vitamin B_{12}. The correlation coefficients between the B-vitamin intakes estimated by the FFQ and concentrations of serum folate, RBC folate and serum vitamin B_{12} were 0.20, 0.28 and 0.21, respectively. The validity coefficients for serum folate, RBC folate and serum vitamin B_{12} were 0.94, 0.75 and 1.00, respectively. The estimated folate and vitamin B_{12} intakes were comparable with the results of the most recent Dutch food consumption survey.
Conclusions: The adapted FFQ is a reliable tool to estimate the dietary intake of energy, macronutrients, folate and vitamin B_{12} in women of reproductive age. Therefore, this FFQ is suitable for the investigation of nutrient-disease associations in future.
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Introduction

Accurate and objective estimates of dietary intake are necessary to assess any effects of nutritional status in epidemiologic studies. In general, validation studies of food-frequency questionnaires (FFQ) are based on comparisons with reference methods, such as multiple food records or dietary recalls. Traditionally, the validity coefficient between dietary questionnaire data and the unknown 'true' habitual intake is assessed by the correlation between the

intakes achieved by the FFQ and the mean value obtained from reference methods. However, the correlation between the reference method and the FFQ may be overestimated, if the sources of errors in these two methods are related. Therefore, the use of biomarkers of nutritional intake is increasingly important in dietary validation studies. Nutritional biomarkers are objective measures of exposure to a certain nutrient and they are not influenced by factors related to misreporting. Therefore, Kaaks (1997) described that at least two additional measurements are necessary to determine the validity coefficient of the FFQ measurements, for instance, nutritional biomarkers and 24-h recalls (24HR). The validity coefficient is the correlation between the dietary intake reported by the FFQ and the unknown 'true' dietary intake (Kaaks, 1997). The method of triads is a triangular approach that uses the correlations between each of the three methods to estimate the validity coefficient. Moreover, this model corrects for bias owing to correlated errors in the repeated measurements from the reference method (Ocke and Kaaks, 1997).

The aim of this study was to validate an FFQ, which was adapted for the estimation of B-vitamin intake in women of childbearing age. We examined the association between the biomarkers and the two dietary assessment methods for the intake of folate and vitamin B_{12}. The method of triads was applied to validate the intake of folate and vitamin B_{12}, estimated by the FFQ and 24HR and the corresponding biomarkers of nutritional intake.

Methods

A subset of women of reproductive age was recruited from an ongoing case–control study designed to investigate determinants in the pathogenesis and prevention of congenital heart defects. Exclusion criteria were pregnancy, breastfeeding, use of vitamin supplements and non-fasting state at the moment of blood sampling, which was approximately 17 months after the index-pregnancy. From October 2004 to January 2005, 53 women fulfilled the study protocol, which included filling out the questionnaires at home, an immediate blood sample during a hospital study visit thereafter, followed by the completing of three 24HR by phone.

The National Central Committee of Research in Human and the Medical Ethical Committees of all participating hospitals approved the study protocol and written informed consent was obtained of every participant.

Food-frequency questionnaire

The FFQ is developed at the Division of Human Nutrition of the Wageningen University to estimate the dietary intake of energy, fat and fatty acids (Feunekes *et al*., 1993). It is a 104-item questionnaire in which participants report their dietary intake during the previous 4 weeks. Preparation methods, portion sizes and additions can be indicated as well as the frequency of using foods per day, per week, per month or not at all. The FFQ has been updated twice based on data of Dutch national food consumption surveys in 1992 and 1998 (Netherlands Nutrition Centre, 1993, 1998). This FFQ is validated for energy and fat intake and has been adapted to estimate the intake of folate and vitamin B_{12}. Food items rich in these B-vitamins were added when they contributed more than 0.1% to the intake of each of the nutrients of interest according to the food consumption survey of 1998 (Netherlands Nutrition Centre, 1998). In a final step, foods were clustered into food groups and foods were added to guarantee face validity. After all, the FFQ consisted of 121 items and covered the daily intake of each nutrient or food of interest for at least 90% of the population mean intake. The average daily nutrient intake was calculated by multiplying the frequency of consumption of food items by portion size and nutrient content per gram based on the 2001 Dutch food composition table (Netherlands Nutrition Centre, 2001). The existence of underreporting was evaluated by calculating the physical activity level defined by the ratio of reported energy intake (EI) and mean basal metabolic rate (BMR) (Black *et al*., 1991; Goldberg *et al*., 1991). The BMR was estimated according to the Schofield equations (Schofield, 1985).

Twenty four hour recall

After training by a research dietician, a researcher of the Division of Human Nutrition of Wageningen University contacted the participants for a 24HR within 1 week after the hospital visit. The standardized telephone interview took on average 20 min. Women reported the dietary intake from breakfast of the day before till breakfast the next morning. Each subject was contacted three times for a 24HR of 2 days during the week and 1 weekend day covering a period of 3 weeks. Pictures of household measures were used for specific information on portion sizes. The reported foods in the 24HR were coded according to standardized coding procedures. Codes for new foods were added in consultation with a research dietitcian. The dietary intakes were calculated using computer programs Komeet and Orion (BaS Nutrition Software, the Netherlands), which are based on the 2001 electronic version of the Dutch food composition table (Netherlands Nutrition Centre, 2001).

Biomarkers

Venous blood samples were taken after an overnight fast. Blood was collected in an 8.5 ml Vacutainer Serum Separator Tube and in a 4 ml Vacutainer ethylenediaminetetraacetic acid (EDTA) tube (BD Diagnostics, Plymouth, UK) for the determination of serum folate and vitamin B_{12}, and of red blood cell (RBC) folate concentrations, respectively. Directly after blood sampling, the hemolysate was prepared by diluting 0.1 ml full blood in 0.9 ml freshly prepared 1.0% ascorbic acid. Subsequently, the hematocrit of the remaining

EDTA full blood was determined on an ADVIA 120 Hematology Analyzer (Bayer Diagnostics, Leverhusen, Germany). The concentrations of folate and vitamin B_{12} were determined as described before (de Jonge *et al*., 2004). The hemolysate was centrifuged at 1000 *g* for 5 min at 18°C, just before the folate measurement. The hemolysate folate concentration was recalculated into RBC folate concentration using the following formula: (nM hemolysate folate × 10/hematocrit) − (nM serum folate × {1 − hematocrit}/hematocrit) = nM RBC folate. All samples were analyzed within 3 months after collection. Up to the moment of measurement, samples were kept frozen at −80°C.

General and anthropometric information

The general questionnaire provided data on maternal age, educational level and the use of a diet, vitamin supplements or cigarettes. Anthropometry was performed without shoes and jacket, including height (anthropometric rod, SECA, Hamburg, Germany) and weight (weighing scale, SECA, Hamburg, Germany) to the nearest 0.1 cm and 0.5 kg, respectively.

Statistical analysis

The dietary intakes and biomarker concentrations of B-vitamins were log-transformed. The mean dietary nutrient intake was adjusted for total energy intake using the residual method (Willett *et al*., 1997). Differences in intake between the FFQ and 24HR were compared using the paired *t*-test. Pearson correlation coefficients were calculated to evaluate the linear association between the data of the FFQ and the 24HR, and the biomarkers. We deattenuated the crude correlation coefficients by multiplying them with the factor $(1+(\sigma^2_{\text{intra}}/\sigma^2_{\text{inter}})/n)^{1/2}$, where n is the number of repeated 24HR, σ^2_{intra} is the intraindividual variance and σ^2_{inter} is the interindividual variance between the 24HR (Rosner and Willett, 1988). The method of triads was used to calculate the validity coefficient of the FFQ for folate and vitamin B_{12} intake. The validity coefficient is the correlation between the dietary intake reported by the FFQ and the unknown 'true' dietary intake. The estimate is interpreted as the upper limit, whereas the correlation coefficient between the FFQ and biomarker is considered as the lower limit of the true validity coefficient. Confidence intervals were estimated using bootstrap sampling where 1000 samples of equal size ($n = 53$) were obtained by random sampling with replacement (Ocke and Kaaks, 1997). All analyses were performed using SPSS for Windows version 11.0 (SPSS Inc, Chicago, IL, USA).

Results

The study group consisted of 21 case and 32 control mothers aged 24–44 years with a median body mass index of 23.6 kg/m^2. Other general characteristics and the biomarker concentrations are presented in Table 1. All women fulfilled the whole protocol, but 11 women completed the 24HR on 3 weekdays.

Table 1 General characteristics and biomarker concentrations of the 53 women

Variable (unit)	
General characteristics	
Age (years)	32.0 (27.8–36.3)
Weight (kg)	71.0 (66.0–87.2)
Height (m)	1.71 (1.66–1.76)
Body mass index (kg/m^2)	23.6 (21.9–29.3)
Low-energy diet	4 (8)
Vegetarian diet	4 (8)
Current smokers[a]	7 (13)
Low education level[b]	25 (47)
Biomarkers	
Serum folate (nmol/l)	13.5 (11.5–18.3)
RBC folate (nmol/l)	596 (476–745)
Serum vitamin B_{12} (pmol/l)	245 (190–339)

Values are median (interquartile range) or number (percentage).
Abbreviation: RBC, red blood cell.
[a]Defined as ⩾1 cigarette per day.
[b]Primary/lower vocational/intermediate secondary/intermediate vocational education.

The FFQ produced significantly higher estimates of energy and fat intake than the average of the three 24HR (Table 2). The mean difference was 12% for energy intake and 19% for fat intake. The calculated ratio of EI and BMR was 1.45 for the cases and 1.44 for the control group. In general, the dietary intake met the Dutch dietary reference intakes, but folate intake was considerably lower.

The correlation coefficients of the dietary intakes estimated by the FFQ and the average of the three 24HR are shown in Table 3. After energy-adjustment, all correlation coefficients decreased, except for carbohydrates. Correlation coefficients ranged from 0.60 to 0.98 after correction for day-to-day variation, with a lower correlation of 0.41 for carbohydrates. The correlations between the FFQ data and the biomarkers were 0.20 for serum folate, 0.28 for RBC folate and 0.21 for serum vitamin B_{12}, respectively (Table 4).

The validity coefficient of the FFQ was 0.94 for serum folate and 0.75 for RBC folate. The validity coefficient between the FFQ and the 'true' intake was 1.66 for vitamin B_{12} (Table 4).

Discussion

The aim of this study was to validate the adapted FFQ for the assessment of folate and vitamin B_{12} intake in women of reproductive age. Therefore, we collected intake data by two dietary assessment methods, determined concentrations of nutritional biomarkers and applied the method of triads.

The differences between the FFQ and 24HR for estimation of energy and fat intake are shown by others as well

Table 2 The daily intakes estimated by the FFQ and the repeated 24-h recalls and the dietary reference intakes

Nutrients	*Units/day*	*FFQ*	*24HR*	*DRI*[a]
Energy	MJ[b]	9.1 (7.7–10.8)[c]	8.6 (7.1–10.0)	9.7–10.2
Total fat	g	87.2 (68.7–112.3)[c]	73.8 (61.6–97.1)	
	en%	36.8 (32.7–39.2)[c]	35.6 (31.2–38.2)	20–40
Total protein	g	77.6 (67.7–90.5)	81.1 (64.1–87.7)	50–52
	en%	14.6 (13.1–15.6)[c]	14.9 (13.3–17.1)	9–25
Total carbohydrates	g	262 (210–299)	247 (209–281)	
	en%	47.6 (43.2–50.8)	48.4 (43.5–51.4)	40
Folate[d]	μg	177 (138–222)	169 (148–199)	300
Vitamin B_{12}[d]	μg	3.9 (2.7–4.7)	3.4 (2.6–4.3)	2.8
Vitamin B_6[d]	mg	1.7 (1.5–1.9)	1.6 (1.3–1.9)	1.5

Values are median (interquartile range).
Abbreviations: DRI, dietary reference intakes; en%, percentage of total energy intake; FFQ, food-frequency questionnaire; 24HR, 24-h recall.
[a]Dutch dietary reference intakes for non-pregnant women between 19 and 50 years of age indicate the estimated average requirement for energy, adequate intake for fat, recommended dietary allowance (RDA) with the upper level for proteins, and RDA for carbohydrates and B-vitamins (Health Council of the Netherlands, 2001, 2003).
[b]1 kcal = 4.184 kJ.
[c]Comparison of the estimates of the FFQ and 24HR by the paired *t*-test, $P<0.05$.
[d]Data are log-transformed for statistical analysis.

Table 3 Correlations between the estimates of the dietary intake by the FFQ and the 24HR

Nutrient	*Pearson correlation coefficient*		
	Crude	*Energy adjusted*[a]	*Deattenuated*[b]
Energy (MJ)	0.45[c]	—	0.60
Fat (g)	0.53[c]	0.35[c]	0.82
Protein (g)	0.55[c]	0.40[c]	0.81
Carbohydrates (g)	0.31[c]	0.36[c]	0.41
Folate (μg)[d]	0.40[c]	0.36[c]	0.98
Vitamin B_{12} (μg)[d]	0.49[c]	0.39[c]	0.66

[a]Adjusted for energy by the residual method (Willett *et al.*, 1997).
[b]Deattenuation implies correction for day-to-day variation of the repeated 24-h recalls (Rosner and Willett, 1988).
[c]$P<0.05$.
[d]Data are log-transformed.

Table 4 Correlation coefficients between each of the dietary assessment methods and the validity coefficient calculated by the method of triads

	Correlation coefficients			*Validity coefficient*[a]		
	r_{QM}	r_{RM}	r_{QR}	ρ_{QT}	*95% CI*	*Range*[b]
Serum folate	0.20	0.22	0.98	0.94	0.36–1.00	0.20–0.94
RBC folate	0.28	0.49	0.98	0.75	0.30–1.00	0.28–0.75
Serum vitamin B_{12}	0.21	0.05	0.66	1.00	0.30–1.00	0.21–1.00

Abbreviations: FFQ, food-frequency questionnaire; r_{QM}, correlation between FFQ and biomarker; r_{RM}, correlation between 24-h recall and biomarker; r_{QR}, correlation between FFQ and 24-h recall; ρ_{QT}, validity coefficient of the questionnaire; 95% CI, 95% confidence interval; RBC, red blood cell.
[a]Validity coefficients and confidence interval limits above 1 were set to 1.00.
[b]The lower limit is r_{QM} and the upper limit is calculated with the method of triads (Ocke and Kaaks, 1997).

(Feunekes *et al.*, 1993; Sevak *et al.*, 2004) and can be explained by underreporting in the 24HR (Goris *et al.*, 2000; Harrison *et al.*, 2000; Johansson *et al.*, 2002). The correlation coefficients between the FFQ and 24HR for energy and fat were lower (Feunekes *et al.*, 1993) or comparable with other studies (Johansson *et al.*, 2002; Sevak *et al.*, 2004). The correlation coefficient for carbohydrates was higher (Johansson *et al.*, 2002; Messerer *et al.*, 2004; Sevak *et al.*, 2004) and the coefficient for proteins was similar to (Sevak *et al.*, 2004) or even higher than the coefficients reported by others (Johansson *et al.*, 2002; Messerer *et al.*, 2004). The macronutrient intakes estimated by both methods were in line with the Dutch dietary reference intakes for women between 19 and 50 years of age (Health Council of the Netherlands, 2001, 2003) and the data of the Dutch national food consumption survey of 2003 (Hulshof *et al.*, 2004) and, therefore, we conclude that the FFQ is a valid method to estimate macronutrient intakes.

The correlation coefficients between the FFQ and 24HR for folate were comparable with other studies (0.40 versus 0.37 and 0.49, respectively) (Bacardi-Gascon *et al.*, 2003; Sevak *et al.*, 2004) or even higher (0.29) (Messerer *et al.*, 2004) and the correlation coefficient for vitamin B_{12} was slightly lower, that is, 0.49 versus 0.58 (Sevak *et al.*, 2004). In the latter study, more than three 24HR have been applied through which the overall day-to-day variation of B-vitamin intake is minimized, resulting in a higher correlation coefficient. Despite the high day-to-day variation of these B-vitamin intakes that is demonstrated by the increased correlation coefficients after correction for day-to-day variation in the

24HR, the correlation coefficients between the FFQ and 24HR were significant. Moreover, these B-vitamin intakes were similar to the Dutch dietary reference intakes with the exception of folate (Health Council of the Netherlands, 2001, 2003), which is known to be low in the Dutch diet (Konings *et al*., 2001; Groenen *et al*., 2004; van Rooij *et al*., 2004).

The correlation between the FFQ and the biomarkers is slightly higher for RBC folate than reported by others (0.28 versus 0.08 and 0.25, respectively) (Green *et al*., 1998; Pufulete *et al*., 2002). Higher correlation coefficients of 0.38 and 0.39 were reported for serum folate (Green *et al*., 1998; Pufulete *et al*., 2002). These differences can be explained by the better reflection of the recent dietary intake by serum folate, whereas the RBC folate concentration is a measure of the long-term folate status in particular (Bailey, 1990; Bates and Thurnham, 1995; Willett, 1998). Our FFQ covers the intake of a reasonably long period of 4 weeks and may, therefore, demonstrate a higher correlation with RBC folate than with serum folate. For vitamin B_{12}, the correlation was comparable with the report (0.19) of Green *et al*. (1998).

To our knowledge, this FFQ validation study is the first to assess the validity of the folate and vitamin B_{12} intake using the method of triads. The validation coefficients are rather high, suggesting that the adapted FFQ is valid for both the assessment of folate and vitamin B_{12} intakes. Nevertheless, we emphasize that small differences in low sample correlations may result in rather large differences in the estimated validity coefficients (Ocke and Kaaks, 1997). Furthermore, we cannot rule out the presence of a positive correlation between the random errors of the questionnaire and 24HR measurements. Thus, the validity coefficients might be overestimated. Therefore, the estimates must be interpreted as the upper limits of the unknown 'true' validity coefficients (Ocke and Kaaks, 1997). However, the FFQ adequately assesses the intake of folate and vitamin B_{12} according to the Dutch national food consumption survey of 2003 (Hulshof *et al*., 2004).

The validity coefficient for vitamin B_{12} is greater than 1, which is known as a Heywood case. A Heywood case occurs if the product of two correlation coefficients is much larger than the third correlation. For vitamin $B_{12,}$ the correlation coefficient between the biomarker and 24HR was much lower than the other two correlation coefficients. An explanation for this finding is that vitamin B_{12} is mainly bound to the metabolically inert protein haptocorrin. Only about 20% of vitamin B_{12} is bound to transcobalamin, which represents the biologically active fraction that can be delivered to all tissues of the body. Moreover, it has a rapid turnover with a half-life of 1–2 h (Chanarin, 1990). As blood sampling was done in the morning after an overnight fast, this may explain the lower correlation between the 24HR and the vitamin B_{12} concentration as well. The differences in correlation coefficients, however, can still be due to random sampling fluctuation between measurements of both 24HR and biomarkers.

Despite the demonstrated validity of the adapted FFQ, we have to consider the strengths and limitations of our study. The size of the study population is comparable with other validation studies (53 versus 34 and 36, respectively) (Pufulete *et al*., 2002; Bacardi-Gascon *et al*., 2003). However, validation studies were performed in 100 up to 200 subjects, but in those studies the method of triads was not applied (Messerer *et al*., 2004; Sevak *et al*., 2004). The sample size was relatively small with wide confidence intervals of the validity coefficients as a consequence. Validity studies with several hundreds of subjects, more accurate biomarkers or both are, therefore, needed to estimate validity coefficients with a higher precision. It should be kept in mind, however, that Heywood cases can still occur as a result of relatively small sampling fluctuations if the validity coefficient of 1 of the measurements is close to either 1 or 0 (Ocke and Kaaks, 1997).

The 24HR estimate the intake of a few days and might, therefore, give an inappropriate assessment of the habitual diet. On the other hand, the 24HR were performed during a period of 3 weeks, which is quite comparable with the reference period of the FFQ. Moreover, the 24HR and FFQ estimates may contain correlated errors. The advantage of the triangular approach of the method of triads is that random errors in biomarker assessment are independent of those in both FFQ and 24HR measurements (Ocke and Kaaks, 1997).

Dietary assessment methods are known to have a bias towards underestimation of habitual energy intake. Therefore, we investigated the overall underreporting bias. Compared with the cutoff value of 1.55 that allows measurement imprecision arising from day-to-day variability, some underreporting may have been present (Black *et al*., 1991; Goldberg *et al*., 1991). However, the FFQ covered a 4-week period and therefore, the day-to-day variability of food intake was minimized. Moreover, the FFQ is representative of long-term habitual intake according to the cutoff value of 1.35 (Black *et al*., 1991; Goldberg *et al*., 1991).

The B-vitamin concentrations may be influenced by general characteristics like smoking or the use of a vegetarian diet (Bates and Thurnham, 1995; Willett, 1998). In our study, some women were smoking or used a vegetarian diet, but their biomarker concentrations were within the normal ranges (Sauberlich, 1999; Cikot *et al*., 2001). The biochemical concentrations reflect the individual vitamin status that is determined not only by the metabolism and genes but also by parameters affecting the food intake, such as seasonal variation and pregnancy. These effects on dietary intake are minimized because the study was performed in 53 non-pregnant women between October 2004 and January 2005.

In conclusion, these findings indicate that the FFQ adapted for folate and vitamin B_{12} intake is a valid method to estimate the dietary intake of energy, macronutrients and these B-vitamins in women of reproductive age. Moreover, the relative validity of the FFQ for folate and vitamin B_{12} intake is comparable with the validity in other studies.

Therefore, this FFQ is suitable for the investigation of associations between nutrition and disease in Dutch women in future.

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