Influence of reporting error on the relation between blood folate concentrations and reported folic acid–containing dietary supplement use among reproductive-aged women in the United States[1,2]

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ABSTRACT

Background: Folic acid intake is the most important predictor of blood folate concentrations among nonpregnant women, but the reporting of folic acid–containing supplement use is subject to error.

Objective: We assessed the effect of reporting error of supplement use on blood folate concentrations.

Design: Data from the third National Health and Nutrition Examination Survey were analyzed. Respondents to that survey were asked twice about supplement use: ie, during the household interview, to recall use in the previous month, and during the physical examination, to recall use in the previous 24 h. To examine the effect of error reporting, we classified women (aged 15–44 y) into 5 groups according to supplement use in the previous month (nonusers, those ingesting < 400 μg/d, and those ingesting ≥ 400 μg/d) and in the 24 h before the physical examination (yes or no). We expected nonappreciable differences in red blood cell (RBC) folate concentration by status of 24-h recall within the same category of previous-month use because RBC folate reflects long-term average consumption. We calculated covariate-adjusted means of serum and RBC folate concentrations.

Results: Among women who reported average daily use of ≥ 400 μg folic acid in the previous month, the adjusted mean RBC folate was 436.5 nmol/L (95% CI: 406.7, 466.3 nmol/L) in those who did not take the supplement in the previous 24 h and 519.7 nmol/L (95% CI: 496.2, 543.2 nmol/L) in those who did do so ($P < 0.01$). This significant difference indicates apparently erroneous reporting of supplement use in the previous month by some participants.

Conclusion: The effect of reporting error on blood folate concentrations is important in interpreting survey results, evaluating health education campaigns, and identifying populations needing special education programs. *Am J Clin Nutr* 2003;77:196–203.

KEY WORDS Folic acid, blood folate concentration, misclassification, third National Health and Nutrition Examination Survey, NHANES III

INTRODUCTION

Rates of neural tube defects (NTDs) can be lowered by increased consumption of folic acid before and during early pregnancy (1–4). To assist in increasing consumption, the fortification of enriched grain products with folic acid became mandatory in the United States in 1998 (5). For the same purpose, several organizations promote increased use of folic acid–containing dietary supplements by reproductive-aged women (6, 7).

Several surveys have been conducted to monitor reported folic acid intake, as well as serum and red blood cell (RBC) folate concentrations among women of reproductive age in an effort to evaluate the impact of public health efforts to increase the consumption of folic acid to prevent NTDs (3, 8–13). The findings of those surveys show that synthetic folic acid (ie, folic acid supplements or food-fortifying folic acid) is the most effective means of increasing blood folate concentration in women. These surveys are most likely to be continued to evaluate the impact of folic acid on NTD rates and on other health outcomes, such as birth defects other than NTDs, reproductive health, and cardiovascular diseases (14–19). However, reported folic acid intake is subject to error. For example, the regular use of folic acid–containing supplements may mean strict daily use in the same amount for some women. This variation in reported intake may translate into different blood folate concentrations for different type of regular users, which might be important to consider in interpretation of survey results, evaluation of health education campaigns, and identification of populations in need of special education programs.

The third National Health and Nutrition Examination Survey (NHANES III) was a nationally representative survey of households in the United States (20). The survey collected interview data and blood samples to determine folic acid intake and blood folate concentrations. In the present study, we examined the effect of reporting error of folic acid–containing supplement use on the blood folate concentrations among the reproductive-aged women. We expected that RBC folate concentrations would not differ significantly between the 2 groups of women reporting regular daily use of folic acid supplements—those who reported taking and those who reported not taking such supplements in the previous 24 h—if the 2 groups were otherwise similar. However, if those who reported regular use but not in the previous 24 h were more subject to reporting error or were generally less compliant, then RBC folate concentration might reflect that distinction. We also determined whether women in these 2 groups differed in a number of characteristics.

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SUBJECTS AND METHODS

NHANES III used a stratified multistage probability design to obtain a sample of the civilian, noninstitutionalized US population aged ≥2 mo (20). A household interview and a physical examination were conducted for each survey participant. We selected all nonpregnant, reproductive-aged (15–44 y) women who participated in NHANES III during 1988–1994 and who gave a blood sample during the physical examination. All samples were collected before the mandated fortification of cereal grains with folic acid was initiated.

During the physical examination, blood was collected by venipuncture from all persons aged ≥4 y. The analysts in the NHANES Central Laboratory measured serum and RBC folate. For phase 2 (1991–1994) of NHANES III, a simultaneous folate-vitamin B-12 radioassay (Quanta Phase II Kit; Bio-Rad Laboratories, Hercules, CA) was used. The Quanta Phase I kit assay (folate alone) had been used for phase 1 of NHANES III (1988–1991). Subsequent analyses determined that the folate concentrations obtained with the Phase I kit were ≈30% higher than those obtained with the Phase II kit; therefore, an adjustment factor was calculated and applied to the NHANES III serum and RBC values obtained with the Phase I kit. After the adjustment, the folate values obtained in phase 1 of the survey were ≈32% lower (9). A detailed discussion of the methods used to measure folate concentrations in NHANES III was published by Raiten and Fisher (21).

Factors affecting blood folate concentration

During the household interview, participants were asked about the use of dietary supplements during the previous month (including single vitamins, multivitamins, minerals, herbs, and other similar nutritional substances) and the frequency of any such use. For each supplement reported, the interviewer recorded the name of the product and the manufacturer. After the survey, the NHANES staff constructed a database of the nutrients and ingredients for these reported products. We calculated the daily folate intake for each supplement on the basis of the folate content in one dose of the product, the daily intake reported, and the frequency of use reported for the previous month. The daily intake of each product was then totaled for all products reported to ascertain the average daily folate intake from all supplements for each respondent. This intake became the average daily dose of folic acid consumed. The overwhelming majority of reproductive-aged women (93.1%; 95% CI: 91.1, 95.2) reported using only one brand of folic acid–containing supplement during the previous 30 d.

To examine the association between reported use of folic acid–containing dietary supplements and blood folate concentrations, we classified all respondents into 3 groups on the basis of their report during the household interview: nonusers; those who ingested <400 μg folic acid daily; and those who ingested ≥400 μg folic acid daily. Those who ingested <400 μg folic acid daily included those who reported taking amounts such as a single 200-μg folic acid–containing supplement daily in the previous 30 d and those who reported taking a single 400-μg folic acid–containing supplement for <30 d of the previous 30 d. Similarly, those who ingested ≥400 μg folic acid daily included those who reported taking a single 400-μg folic acid–containing supplement daily in the previous 30 d and those who reported taking 800 μg folic acid–containing supplement for >15 d in the previous 30 d.

During the physical examination (typically done within 3 wk after the household interview), the respondents were asked if they took any supplements, regardless of whether they contained folic acid, in the previous 24 h (yes or no; no information on type of supplement was obtained). To assess the effects of potential misreporting of the use of folic acid–containing dietary supplements on blood folate concentrations, we further classified the supplement users on the basis of 24-h and previous-month recall: those who ingested <400 μg folic acid daily, but not in the previous 24 h [<400 μg/d (no) group]; those who ingested <400 μg folic acid daily, including the previous 24 h [<400 μg/d (yes) group]; those who ingested ≥400 μg folic acid daily, but not in the previous 24 h [≥400 μg/d (no) group]; and those who ingested ≥400 μg folic acid daily, including the previous 24 h [≥400 μg/d (yes) group]. We hypothesized that both RBC and serum folate concentrations are related to long-term use of dietary supplements but that the use of a supplement during the previous 24 h should not measurably change a person's RBC folate concentration, although the serum folate concentration could change.

For the estimation of folate intake from foods, participants were interviewed by a trained dietary interviewer and questioned about all foods and beverages (except plain drinking water) consumed in the previous 24 h. The NHANES staff used the US Department of Agriculture survey nutrient database to assign nutrient values to the dietary recalls (22). The estimated total food folate intake includes the naturally occurring folates in the foods, as well as the folic acid from fortified cereals and ready-to-eat meals at the time of survey, 1988–1994 (ie, folic acid from foods fortified before the general fortification mandate of 1998).

We included several other factors in our models that could affect blood folate concentration, such as age, education level, ethnicity, smoking status, total weeks of exposure to folic acid–containing supplements, body mass index (BMI; in kg/m^2), poverty income ratio, contraceptive use, and fasting status.

Statistical analysis

We used sample weights in the analysis to account for unequal probability of selection and nonresponse to produce estimates of means and percentiles that represented the civilian, noninstitutionalized US population. We used SUDAAN statistical software, version 7.0 (Research Triangle Institute, Research Triangle Park, NC) to account for the complex survey design in variance estimates (23).

We used Pearson's chi-square statistic to test the differences in proportions of selected categorical covariates and the pairwise *t* test for continuous covariates by supplement-user groups. We used a nonparametric median scores method to test the differences in median blood folate concentration by different supplement-user groups. The statistical tests were conducted among the supplement users according to 24-h recall status, ie, we compared the <400 μg/d (yes) group with the <400 μg/d (no) group and the ≥400 μg/d (yes) group with the ≥400 μg/d (no) group.

Using linear regression, we estimated the effects of the selected covariates on blood folate concentrations. We applied stepwise regression techniques to assist in the selection of variables for the final multivariate model ($\alpha = 0.15$). We also estimated least-square means (covariate adjusted means) of blood folate concentration in the 5 supplement-use groups, with control for age, food folate intake, ethnicity, educational attainment, smoking status, BMI, poverty income ratio, total weeks of exposure to folic acid–containing supplements, and fasting status. We used logistic regression to compare the characteristics of women who reported not taking folic acid–containing supplements in the previous 24 h (= 1) with the characteristics of those who reported taking supplements in the previous 24 h (= 0). As in the linear regression analysis, we applied stepwise regression techniques to select variables for the final logistic regression models. Because the distributions of serum and RBC folate as well as of food folate intake were skewed, a logarithmic transformation was applied to the data in analysis.

TABLE 1
Selected characteristics of nonpregnant women aged 15–44 y by estimated daily folic acid intake from folic acid–containing dietary supplements, third National Health and Nutrition Examination Survey, 1988–1994[1]

	Folic acid intake from folic acid–containing dietary supplements				
		<400 μg/d		≥400 μg/d	
Characteristics	Nonusers	Not taken in the previous 24 h	Taken in the previous 24 h	Not taken in the previous 24 h	Taken in the previous 24 h
Number of respondents[2]	3731	217	108	376	373
Age (y)[3]	29.8 ± 0.34	30.0 ± 0.78	31.8 ± 1.06	31.3 ± 0.65	32.7 ± 0.53[4]
Food folate intake[5]	173.5 ± 2.75	199.8 ± 14.4	198.6 ± 16.0	201.0 ± 10.2	226.6 ± 11.2
Total exposure to folic acid–containing supplements (wk)[6]	—	20.6 (3.4, 101.6)	45.9 (5.6, 157.3)[4]	47.1 (10.7, 101.1)	50.1 (18.4, 222.4)
Race or ethnicity (%)					
White	67.5	84.9	79.6	75.1	82.6
Non-Hispanic black	15.0	9.3	8.7	10.8	9.7
Mexican American	7.0	3.8	3.0	4.0	3.6
Other	10.5	1.9	8.7	10.1	4.1[4]
Education level (%)					
<12 y	29.6	13.5	8.7	16.9	14.4
12–15 y	56.2	58.1	54.6	55.2	54.3
≥16 y	14.2	28.5	36.7	27.9	31.3
Poverty income ratio (%)					
<1	24.6	12.5	5.8	15.7	9.6[4]
≥1	75.4	87.5	94.2	84.3	90.4
Smoking status (%)					
Nonsmoker	55.1	58.3	57.7	55.2	62.5
Former smoker	12.7	12.2	19.0	18.4	16.8
Current smoker	32.2	29.4	23.4	26.4	20.7
Contraceptive pill use (%)					
Nonuser	26.2	17.7	24.7	16.6	16.5
<6 mo	51.4	47.8	47.1	60.8	60.9
≥6 mo	22.5	34.5	28.3	22.6	22.6
BMI (%)					
≥27.3 (kg/m^2)	30.0	21.4	26.5	27.6	21.2
<27.3 (kg/m^2)	70.0	78.6	73.5	72.4	78.8
Fasting status (%)					
<9 h	39.4	39.2	47.7	35.5	45.7
≥9 h	60.7	60.8	52.3	64.5	54.3

[1] No statistical comparisons were made between the categories on the basis of reported use in the past month.
[2] Values for food folate intake were missing for 102 respondents [70 respondents in nonuser group, 6 in <400 μg/d (no) group, 17 in ≥400 μg/d (no) group, and 9 in ≥400 μg/d (yes) group].
[3] $\bar{x}$ ± SEM.
[4] Significantly different from those who had not taken a supplement in the previous 24 h, $P < 0.05$.
[5] Geometric $\bar{x}$ ± SEM.
[6] Median; 25th and 75th percentiles in parentheses.

RESULTS

Of the 5579 reproductive-aged women who were interviewed and examined, 774 were excluded (351 because they were pregnant, 294 because data about blood folate concentrations were unavailable, 124 because data about supplement taking in the previous 24 h were not available, and 5 because they did not answer the question of dietary supplement use in the previous month). Of the remaining 4805 nonpregnant women who participated, 325 (9.2%; 95% CI: 7.8, 10.5) reported average daily use of supplements that provided <400 μg folic acid, and 749 (19.9%; 95% CI: 18, 21.9) reported a mean daily ingestion of ≥400 μg folic acid. Among the 325 women, 95.4% (95% CI: 92.9, 97.9) reported taking one brand of folic acid–containing supplement and 14.4% (95% CI: 8.1, 20.8) reported taking the supplement daily in the previous 30 d. Among the 749 women, 92.1% (95% CI: 89.3, 94.9) reported taking one brand of folic acid–containing supplement, and 98.4% (95% CI: 97.3%, 99.5%) reported taking the supplement daily in the previous 30 d. The use of any folic acid–containing supplements in last month was associated with white race, higher educational level, greater amount of food folate intake, nonsmoking status, and poverty income ratio > 1 (results not shown).

Among those who reported average daily use of supplements with <400 μg folic acid, 65.6% (95% CI: 57.5, 73.7) also reported not taking supplements during the 24 h preceding the physical examination. Among those who reported average daily use of supplements with ≥400 μg folic acid, 50.1% (95% CI: 43.5, 56.7) reported not taking supplements in the previous 24 h.

Table 1 shows the selected characteristics of the respondents included in the study by the 5 categories of folic acid–containing dietary supplement use. Statistical tests for significance were made between those within the same average daily supplement-consumption categories who reported taking and not taking supplements in the previous 24 h. No statistical comparisons

TABLE 2
Serum and red blood cell (RBC) folate concentrations among nonpregnant women aged 15–44 y by selected covariates, third National Health and Nutrition Examination Survey, 1988–1994[1]

	Serum folate			RBC folate		
Selected predictors	β coefficients	SE	*P* value	β coefficients	SE	*P* value
Age at interview (y)	0.003	0.002	0.152	0.005	0.001	<0.001
Vitamin use						
≥400 μg/d	0.52	0.050	<0.001	0.36	0.020	<0.001
<400 μg/d	0.25	0.035	<0.001	0.17	0.033	<0.001
Vitamin nonusers	Referent	—	—	Referent	—	—
Total exposure to folic acid–containing supplements (wk)	0.004	0.001	0.004	0.002	0.001	0.013
Food folate intake (μg)						
High (>251 μg)	0.28	0.032	<0.001	0.20	0.023	<0.001
Medium (139–251 μg)	0.10	0.035	0.009	0.09	0.022	<0.001
Low (<139 μg)	Referent	—	—	Referent	—	—
Race or ethnicity						
Other	0.021	0.053	0.696	0.02	0.037	0.558
Mexican American	−0.06	0.033	0.079	−0.04	0.026	0.143
Non-Hispanic black	−0.11	0.029	<0.001	−0.24	0.024	<0.001
White	Referent	—	—	Referent	—	—
Smoking status						
Current smoker	−0.17	0.029	<0.001	−0.16	0.019	<0.001
Former smoker	0.01	0.042	0.891	0.01	0.032	0.670
Nonsmoker	Referent	—	—	Referent	—	—
BMI (kg/m^2)						
>27.3	−0.17	0.032	<0.001	0.013	0.023	0.562
≤27.3	Referent	—	—	Referent	—	—
Poverty income ratio						
<1	−0.07	0.028	0.026	−0.01	0.023	0.561
≥1	Referent	—	—	Referent	—	—

[1] Regression coefficients of logarithms; n = 4703; 102 respondents were excluded from the multivariate analysis because of missing covariates.

were made between categories on the basis of reported use in the previous month, ie, the nonusers, those who ingest <400 μg/d, and those who ingest ≥400 μg/d.

When the potential effects of selected covariates are accounted for, the results of the stepwise regression suggest that folic acid–containing dietary supplement use, food folate intake, smoking status, ethnicity, BMI, and poverty income ratio were independently associated with blood folate concentrations. Folic acid–containing dietary supplement use was the most important predictor of blood folate concentrations among selected covariates (**Table 2**).

The covariate-adjusted mean serum folate concentration among women who reported no use of supplements was 9.7 nmol/L (95% CI: 9.2, 10.2 nmol/L), whereas that among women who reported average daily use of <400 μg folic acid was 12.6 nmol/L (95% CI: 11.6, 13.6 nmol/L) and that among women who reported average daily use of ≥400 μg folic acid was 16.3 nmol/L (95% CI: 15.3, 17.4 nmol/L). Of the women who reported daily use of <400 μg folic acid, the adjusted mean serum folate was 54.1% higher in those who reported taking supplements in the previous 24 h than it was among those who reported no use of supplements in the previous 24 h ($P < 0.01$). Among women who reported average daily use of ≥ 400 μg folic acid, it is 55.1% higher for the corresponding comparison ($P < 0.01$) (**Table 3**).

The covariate-adjusted mean RBC folate concentration among women who reported no use of supplements was 331.7 nmol/L (95% CI: 321.9, 341.9 nmol/L), whereas that among women who reported average daily use of <400 μg folic acid was 392.4 nmol/L (95% CI: 370.7, 415.4 nmol/L) and that among women who reported average daily use of ≥400 μg folic acid was 473.6 nmol/L (95% CI: 455.9, 491.8 nmol/L). Of women who reported average daily use of <400 μg folic acid, the adjusted mean RBC folate was 17.8% higher in those who reported taking supplements in the previous 24 h than it was among those who reported no use of supplements in the previous 24 h ($P < 0.01$). Among women who reported average daily use of ≥400 μg folic acid, the same comparison represented a 19.1% higher RBC folate concentration ($P < 0.01$). When we further restricted our analysis to women who reported using a 400-μg folic acid–containing supplement daily for ≥8 wk, the differences in serum and RBC folate concentrations between those who reported taking and not taking the supplement 24 h before physical examination remained unchanged (Table 3).

The percentile distribution of serum and RBC folate concentrations by folic acid–containing supplement-use groups is shown in **Figures 1** and **2**. Similar to that of covariate adjusted means, the median serum folate was 77.0% (20.0 compared with 11.3 nmol/L) and 90.0% (24.7 compared with 13.0 nmol/L) higher among women in the <400 and ≥400 μg/d (yes) groups, respectively, than it was among women in the <400 and ≥400 μg/d (no) groups. The corresponding comparisons for RBC folate were 26.7% (489.8 compared with 386.6 nmol/L) and 30.7% (572.4 compared with 437.9 nmol/L) higher, respectively.

Among women who reported average daily use of <400 μg folic acid, those of races or ethnicities other than white, black, and Mexican American were more likely to take supplements in the previous 24 h than were those of other ancestries [odds ratio (OR): 0.12; 95% CI: 0.02, 0.60). Women who had less long-term exposure to folic acid–containing supplements were more likely to report not taking supplements in the previous 24 h. The OR for

TABLE 3
Serum and red blood cell (RBC) folate concentrations among nonpregnant women aged 15–44 y by estimated daily folic acid intake from folic acid–containing dietary supplements, third National Health and Nutrition Examination Survey, 1988–1994[1]

	Folic acid intake from folic acid–containing dietary supplements						
		<400 μg/d		≥400 μg/d		Single 400 μg/d supplement for >8 wk[2]	
	Nonusers (n = 3661)	Not taken in the previous 24 h (n = 211)	Taken in the previous 24 h (n = 108)	Not taken in the previous 24 h (n = 359)	Taken in the previous 24 h (n = 364)	Not taken in the previous 24 h (n = 266)	Taken in the previous 24 h (n = 262)
Serum folate (nmol/L)	9.7 ± 0.24	10.9 ± 0.63	16.8 ± 0.82[3]	13.2 ± 0.61	21.0 ± 0.80[3]	13.7 ± 0.89	20.9 ± 0.83[3]
RBC folate (nmol/L)	331.1 ± 5.07	371.0 ± 14.3	436.9 ± 15.6[3]	436.5 ± 15.2	519.7 ± 12.0[3]	454.4 ± 16.2	535.4 ± 14.7[3]

[1] $\bar{x}$ ± SEM. Means adjusted by age, food folate intake, race or ethnicity, education, smoking status, BMI, poverty income ratio, total weeks of exposure to folic acid–containing supplements, and fasting status.
[2] Analysis restricted to women who reported taking a single 400-μg folic acid–containing supplement daily for the past 30 d and who took it for ≥8 wk.
[3] Significantly different from those who had not taken a supplement in the previous 24 h, $P < 0.05$. No statistical comparisons were made between the categories on the basis of reported use in the past month.

not taking supplements in the previous 24 h is also elevated among women who had a poverty income ratio <1 (OR: 1.87; 95% CI: 0.86, 4.06). Among women who reported average daily use of ≥400 μg folic acid, women who had not taken folic acid in the previous 24 h were of races or ethnicities other than white, black, and Mexican American; had lower food folate intake; and had a shorter long-term exposure to folic acid–containing supplements than did the women who had taken the supplement in the previous 24 h (**Table 4**). Elevated ORs, although not significantly elevated, were also observed among smokers, those who had a BMI of ≥27.3, and those who fasted longer.

DISCUSSION

Before cereal grain products began to be fortified with folic acid, the daily consumption of folic acid–containing supplements was the single most important predictor of blood folate concentration among nonpregnant women aged 15–44 y in the United States. Blood folate concentrations among women who took supplements were substantially higher than those among women who did not take supplements. Synthetic folic acid is the most effective means of optimizing blood folate concentrations in women. Given the high correlations between folic acid intake and blood folate concentrations, an accurate measure of reported folic acid–containing supplement use is needed to effectively prevent NTDs and, possibly, other adverse health conditions (14, 16–19, 24–28).

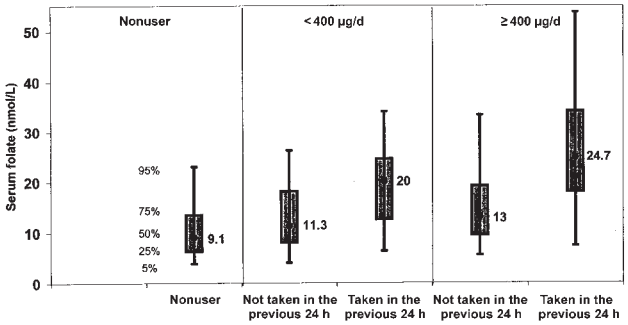

FIGURE 1. Percentile distribution of serum folate (nmol/L) among nonpregnant women aged 15–44 y by mean estimated daily folic acid intake from dietary supplements, third National Health and Nutrition Examination Survey, 1988–1994 (n = 4805).

Our results suggest that women who reported taking supplements in the previous 24 h were more likely to accurately recall supplement use in the previous month than were women who reported not doing so, and the frequency of folic acid–containing supplement use in both of these groups [< 400 μg/d and ≥ 400 μg/d (yes) groups] was likely to be higher than that among those who reported not taking supplements in the previous 24 h. Because more than half (55.2%) of the women who reported supplement use in the previous month did not take supplements in the previous 24 h, we must take into account the influence of reporting error when we examine the relation between folic acid–containing supplement use and blood folate concentrations with the use of NHANES III data. The substantially higher mean RBC folate concentration in our study among women who reported taking folic acid–containing supplements in the previous 24 h but who had the same estimated daily average of supplement use in the previous month as women who did not report taking a supplement in the previous 24 h indicates apparently erroneous reporting of supplement use in the previous month by some participants. The impact of apparently erroneous reporting of supplement use was profound in NHANES III, and the effect of the daily ingestion of 400 μg of folic acid–containing supplement on RBC folate concentration was therefore probably underestimated by ≈20%.

We have conducted a series of multiple regression analyses to examine the predictability of serum and RBC folate concentrations by the different classification variables of folic acid–containing supplement use (recall of previous 24-h use, self-reported use in the previous month, and both). For each multiple regression model, we kept other covariates unchanged as presented in Table 2 and changed only the supplement-use classification variables from "taken 24 h before" (yes or no) to "vitamin use status calculated from the previous month" (nonuser, < 400 μg group, and ≥ 400 μg group), and to a combined variable with 5 categories [nonusers, < 400 μg/d (no) group, < 400 μg/d (yes) group, ≥ 400 μg/d (no) group, and ≥ 400 μg/d (yes) group]. Using the variable of 24-h recall of supplement use represented a slight improvement in prediction over the use of the variable of supplement use over the past month for serum folate concentration (adjusted R^2 of 0.271 and 0.266, respectively). For predicting RBC folate concentration, supplement use over the past month had a considerably better predictive power than did the variable of last 24-h recall of supplement use (adjusted R^2 of 0.280 and 0.247, respectively). The prediction of both serum and RBC folate

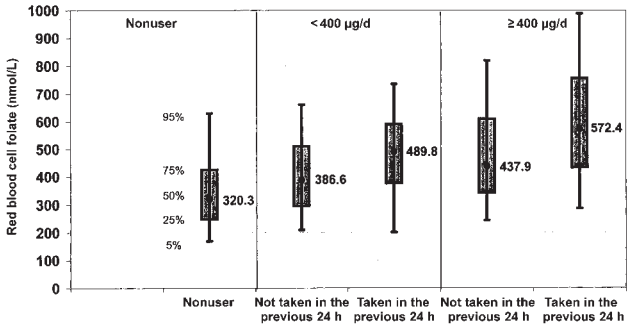

FIGURE 2. Percentile distribution of red blood cell folate (nmol/L) among nonpregnant women aged 15–44 y by mean estimated daily folic acid intake from dietary supplements, third National Health and Nutrition Examination Survey, 1988–1994 (n = 4805).

concentrations are improved when we considered the use over the past month and use within the past 24 h simultaneously, as indicated by an adjusted R^2 of 0.306 for serum and 0.293 for RBC folate concentrations. Our results suggest that the 24-h recall of supplement use is a reasonable predictor of serum folate concentration but a poor predictor of RBC folate concentration. The true effect of synthetic folic acid on the RBC folate concentration is better represented by the women who reported in NHANES III that they had ingested ≥400 μg folic acid daily over the past month and taken the supplements in the previous 24 h. To study the relation between blood folate concentrations and reported folic acid–containing dietary supplement use with NHANES III data, investigators should use information on both the last 24-h recall and self-reported supplement use over the past month. Investigators should also be cautious of the possible influence of reporting error when studying the relation between folic acid–containing supplement use and other folate blood concentration-related measurements such as homocysteine concentration by the use of NHANES III data.

NHANES III results provided a prefortification baseline assessment of blood folate concentrations. In assessing the effects of dietary supplement use on blood folate concentration, few investigators have focused on the impact of potential errors in reporting supplement use (11, 29). These studies probably underestimated the effects of folic acid–containing supplements on blood folate concentrations. In addition, one of the national health objectives for 2010, called the Healthy People 2010 goals (29), is to

TABLE 4
Selected characteristics among women who reported not taking folic acid–containing supplements for 24 h before examination and women who took them in the 24 h before examination by dietary supplement use categories, third National Health and Nutrition Examination Survey, 1988–1994

	Dietary supplement use category[1]			
	<400 μg/d (n = 319)		≥400 μg/d (n = 723)	
Characteristic	Odds ratio	95% CI	Odds ratio	95% CI
Age group				
≥35 y	0.84	0.34, 2.07	0.90	0.49, 1.65
25–34 y	0.82	0.35, 1.94	1.11	0.58, 2.12
<25 y	Referent	—	Referent	—
Food folate intake				
High (>251 μg)	2.04	0.79, 5.28	0.58	0.35, 0.95
Medium (139–251 μg)	1.97	0.96, 4.04	0.76	0.43, 1.35
Low (<139 μg)	Referent	—	Referent	—
Total exposure to folic acid–containing supplements (wk)	0.998	0.996, 1.00	0.998	0.997, 1.00
Race or ethnicity				
Other	0.12	0.02, 0.60	2.67	0.98, 7.27
Mexican American	0.70	0.34, 1.46	1.07	0.58, 1.98
Non-Hispanic black	0.87	0.44, 1.75	0.92	0.58, 1.47
White	Referent	—	Referent	—
Education				
≥16 y	0.40	0.09, 1.78	1.53	0.54, 4.34
12–15 y	0.63	0.14, 2.75	1.16	0.54, 2.47
<12 y	Referent	—	Referent	—
Poverty income ratio				
<1	1.87	0.86, 4.06	1.35	0.70, 2.62
≥1	Referent	—	Referent	—
Smoking status				
Current smoker	0.89	0.35, 2.29	1.55	0.79, 3.02
Former smoker	0.69	0.26, 1.83	1.52	0.81, 2.86
Nonsmoker	Referent	—	Referent	—
BMI (kg/m^2)				
≥27.3	0.69	0.29, 1.64	1.45	0.92, 2.29
<27.3	Referent	—	Referent	—
Fasting status				
≥9 h	1.12	0.51, 2.43	1.38	0.94, 2.00
<9 h	Referent	—	Referent	—

[1] Results of comparing subjects who had not taken a supplement in the previous 24 h with those who had.

increase the proportion of pregnancies begun with an adequate folic acid concentration among nonpregnant women aged 15–44 y to reduce NTD rates. These goals were based on blood folate concentrations as measured among women aged 15–44 y who reported using folic acid–containing supplements and who participated in NHANES III. Our findings may be important to consider in evaluating progress toward meeting the Healthy People 2010 goals.

We adjusted for age, ethnicity, educational attainment, food folate intake, smoking status, poverty income ratio, BMI, total number of weeks of exposure to folic acid–containing supplements, and fasting status. The variations in blood folate concentration could result from other factors, such as inherent interindividual variations in folate absorption and metabolism, eg, a mutation in methylenetetrahydrofolate reductase gene (30), or, though unlikely, laboratory analytic variations. Little reason exists to believe that the distribution of these factors should be significantly different by 24-h recall of the use of folic acid–containing supplements.

Our estimate of those who averaged ≥400 μg folic acid daily use included those who reported taking a single 400-μg dose of folic acid supplement daily in the past month and those who reported taking larger amounts, eg, 800 μg folic acid for 15 d in the past month (higher dose for fewer days). If we assume that the higher-dose-for-fewer-days treatment is unlikely to produce a biological response as good as that of regular use (a greater percentage of the higher dose could be excreted as unaltered folic acid in the urine), an alternative explanation for our findings could be that the ingestion of folic acid in the previous 24 h identified those who ingested ≥400 μg folic acid daily for the past month as distinct from those who reported taking the less effective treatment (higher dose for fewer days) in the previous month. This alternative explanation is unlikely to be true in our study. Among women who reported average daily intake of folic acid ≥400 μg, only 1.2% (95% CI: 0.2, 2.2) were in the higher-dose-for-fewer-days treatment category. The proportion of those taking the higher dose for fewer days was significantly greater ($P < 0.05$) among those who reported not taking folic acid (1.5%; 95% CI: 0.1, 3.0) than it was among those who reported having taken folic acid in the previous 24 h (0.9%; 95% CI: 0.4, 2.1). The differences in serum and RBC folate concentration between those who did and did not take folic acid–containing supplements in the previous 24 h remained unchanged after the exclusion of those women who were in the higher-dose-for-fewer-days category (results not shown). The most likely reason for this was erroneous reporting of daily supplement use.

When interpreting or comparing the absolute values of serum and RBC folate concentration derived from NHANES III with the values from other studies, readers should keep in mind that the serum and RBC folate concentrations collected from phase 1 of the survey (1988–1991) were adjusted downward by about 32% after the discovery that the values produced with the Phase I kit were too high (21). However, the main findings of the present study with respect to relative differences in serum and RBC folate concentrations within and between the categories of folic acid–containing supplement use should not be affected by the adjustment in folate values.

Our results suggest that the profound effect of reporting error of supplement use on blood folate concentrations is important to consider in the interpretation of survey results, the evaluation of health education campaigns aimed to increase awareness and consumption of folic acid among women of childbearing ages, and the identification of populations in need of special education programs.

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