HHS Public Access

Author manuscript

Am J Clin Nutr. Author manuscript; available in PMC 2024 July 01.

Published in final edited form as:

Am J Clin Nutr. 2023 July ; 118(1): 241–254. doi:10.1016/j.ajcnut.2023.05.016.

Folate and vitamin B12 usual intake and biomarker status by intake source in United States adults aged ≥19 y: NHANES 2007–2018

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Abstract

Background: Folate and vitamin B12 are important biomarkers of nutritional status of populations.

Objectives: This study aims to estimate folate and vitamin B12 usual intakes among United States adults and examine folate and vitamin B12 biomarker status by intake source.

Methods: We analyzed data for United States adults aged ≥19 y from National Health and Nutrition Examination Survey 2007–2018 (n = 31,128), during which time voluntary corn masa flour (CMF) fortification was started. Usual intake was estimated using the National Cancer Institute method. Folate intake included folate from natural foods and folic acid from 4 sources: enriched cereal grain products (ECGPs), CMF, ready-to-eat cereals (RTEs), and folic acid–containing supplements (SUP). Vitamin B12 intake was mainly from food and supplements.

Results: The median natural food folate intake (222 μg dietary folate equivalents (DFE)/d) was below the estimated average requirement (EAR) of 320 μg DFE/d. The proportions of those who consumed folic acid from ECGP/CMF only, ECGP/CMF + RTE, ECGP/CMF + SUP, and ECGP/CMF + RTE + SUP were 50%, 18%, 22%, and 10%, respectively. Median usual folic acid intakes (μg/d) were 236 (IQR: 152, 439) overall and 134, 313, 496, and 695 in the ECGP/CMF only, ECGP/CMF + RTE, ECGP/CMF + SUP, and ECGP/CMF + RTE + SUP folic acid consumption groups, respectively. Overall, 2.0% (95% CI: 1.7%, 2.3%) of adults, all of whom used folic acid supplements, consumed greater than the tolerable upper intake level (UL) of 1000 μg/d folic acid. The median usual vitamin B12 intake (μg/d) was 5.2 for vitamin B12 supplement nonusers and 21.8 for users. Consumption of RTE and/or supplements with folic

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Author contributions

The authors' responsibilities were as follows – KSC, LFY, and YPQ: initiated the project; YZ: conducted the research, analyzed the data, and wrote the paper; AW: provided support with usual intake calculation and R programming and verified analysis results; KSC, LFY, YPQ, AW, and CMP: contributed to revisions; and all authors: read and approved the final manuscript.

The authors report no conflicts of interest.

acid was associated with higher serum and red blood cell folate concentrations. Vitamin B12 supplement users had significantly higher serum vitamin B12 concentrations.

Conclusions: Folic acid fortification plays a critical role in helping United States adults meet the folate EAR. At current fortification levels, United States adults who do not consume supplements do not have the usual folic acid intake exceeding the UL.

Keywords

NHANES; folic acid; folate; vitamin B12; dietary supplements

Introduction

Vitamins B9 (folate) and B12 (cobalamin) are essential water-soluble vitamins that play a crucial role in DNA synthesis and normal cell growth and function by mediating the transfer of methyl groups in the one-carbon pathway [1]. Major sources of folate are natural food folate and folic acid, which is the synthetic form of folate that is added to foods and contained in supplements. In 1996, the FDA mandated that by 1 January, 1998, all enriched cereal grain products (ECGPs) be fortified with 140 μg folic acid per 100 g product to reduce the risk of having a pregnancy affected by neural tube defects (NTDs) [2]. In 2016, the FDA authorized voluntary folic acid fortification of corn masa flour (CMF) to reduce the risk of NTD-affected pregnancies among Hispanic women of reproductive age [3]. Currently, there are 4 main folic acid sources in the United States: ECGP, CMF, ready-to-eat cereals (RTEs), and folic acid–containing supplements (SUPs). RTEs in the United States are typically fortified to contain 100–400 μg folic acid per serving [4]. Common doses of folic acid in supplements for adults range from 400 to 800 μg [5]. Sources of vitamin B12 include foods of animal origin (e.g., fish, meat, eggs, and dairy products), as well as fortified breakfast cereals, dietary supplements, and prescriptions [6].

Previous studies have estimated the long-term average daily intake, or usual intake, of folic acid and B12 in the United States, although many are using data that are now almost 2 decades old and without assessment of minority populations, such as Asian Americans, or the assessment of the impact of CMF fortification. The median usual intake among United States adults was estimated to be 288 μg/d for folic acid and 8.5 μg/d for vitamin B12, based on data from NHANES 2003–2006 [7]. Self-reported consumption of fortified RTEs and/or supplements with folic acid was associated with higher RBC folate concentrations [7]. Overall, 2.7% of the population, all of whom reported consuming supplements, had folic acid intakes above the tolerable upper intake level (UL) of 1000 μg/d for adults aged ≥19 y [5, 7]. Several studies using more recent NHANES data focused on different subsets of United States populations [8–10] (e.g., women of reproductive age and adults aged >50 y), though none have focused on the overall United States adult population in recent years.

Using recent NHANES data (2007–2018), our analyses examined the usual intake of folate and vitamin B12 among all United States adults aged ≥19 y. During this period, voluntary fortification of CMF with folic acid was started in 2016, and NHANES oversampled Asian Americans (2011–2018). We also examined biomarker concentrations: serum and RBC folate by folic acid sources, and serum vitamin B12 and MMA by vitamin B12 supplement use status. Our findings could help inform decision-making on folic acid fortification and supplementation policies.

Methods

Study population

The NHANES is a series of cross-sectional studies designed to assess the health and nutritional status of adults and children in the United States [11]. NHANES uses a complex, stratified, multistage probability survey design representative of the civilian, noninstitutionalized United States population. Data are collected via household interviews, phone interviews, and physical examinations. Detailed information regarding NHANES is available elsewhere [11]. The survey was reviewed and approved by the NCHS Ethics Review Board, and participants provided written informed consent prior to participation. We selected nonpregnant adults aged ≥19 y from NHANES 2007–2018. Unweighted response rates among adults ranged from 34% (≥80 y) to 87% (16–19 y) depending on the survey cycle and age group [12]. Of the nonpregnant adults aged ≥19 y who attended the medical examination center (MEC) (n = 33,917), we excluded participants whose dietary recall status was not reliable, and participants with missing folic acid source information, leaving 31,128 participants for analyses (Figure 1).

Usual intake

The usual intake of dietary folate included folate from natural foods and folic acid from fortified foods. Total folate usual intake was defined as the sum of dietary folate and folic acid from supplements. We reported total folate intake in µg dietary folate equivalents (DFEs), defined as µg of natural food folate intake plus 1.7 times µg folic acid intake from fortified foods and/or supplements containing folic acid. For this analysis, we combined folic acid from CMF and ECGP into 1 group, as both represent folic acid from fortified staple foods, and USDA food codes used in the NHANES dietary interview data do not allow for sufficient granularity to separate CMF from ECGP. The 4 main folic acid sources (ECGP, CMF, RTE, and SUP) were divided into 4 mutually exclusive consumption groups: *1*) ECGP and CMF consumption only (ECGP/CMF only), *2*) ECGP and CMF plus RTE (ECGP/CMF + RTE), 3) ECGP and CMF plus supplements containing folic acid (ECGP/CMF + SUP), and *4*) folic acid from all available folic acid sources (ECGP/CMF + RTE + SUP). We modeled dietary folate usual intake from 2 24-hour dietary recalls in the NHANES dietary survey using the NCI method [13], accounting for sex, race, age, and weekday/weekend consumption. Dietary intake data for day 1 were collected in person in the MEC, and data for day 2 were obtained by telephone 3–10 d later. Dietary recall weights were computed using NHANES to adjust for differential allocation by day of the week for the dietary intake data collection and additional nonresponse not accounted for by MEC weights [11]. Dietary weights for day 1 of the recall were used for the usual intake calculation. Population distributions (e.g., median and IQR) of dietary usual intake were calculated by generating 300 pseudo people for each participant in the dataset [13].

We calculated the total intake of each nutrient as the sum of the diet (i.e., natural food folate, folic acid in fortified food) and dietary supplement using the "shrink then add" approach to avoid creating data that violate key assumptions of the shrinkage method [14]. The estimated supplement use was based on 30-d supplement use data collected via NHANES household interviews. A participant was classified as a consumer of supplements containing folic acid if he or she reported consuming any supplement with folic acid during the past 30 d. For each participant, the amount of folic acid was summed across all supplements consumed and divided by 30 to yield the average daily amount of supplemental nutrients. Vitamin B12's usual intake was similarly calculated.

The estimated average requirement (EAR) is a daily nutrient intake value that is estimated to meet the requirement of half the healthy individuals in a group [15]. The EAR for folate is 320 μg daily of DFEs for adult men and women (≥ 19 y) [15]. The EAR for vitamin B12 for men and women aged ≥ 19 y is 2 μg daily [15]. The Institute of Medicine established the UL of 1000 μg/d folic acid for adults aged ≥19 y based on evidence that 5000 μg/d was the lowest observed adverse effect level for folic acid, which could mask the anemia of vitamin B12 deficiency and allow neurologic damage to progress when left untreated [15]. We estimated the prevalence of usual folic acid intake above the UL overall and by folic acid consumption groups.

Biomarker status

Serum folate was calculated as the sum of individual folate forms, which were measured using microbiologic assays between 2007 and 2010 and by isotope-dilution high-performance liquid chromatography coupled to tandem MS (LC-MS/MS) between 2011 and 2018 [16–22]. Previous studies demonstrated excellent agreement between serum total folate measured using LC-MS/MS and microbiologic assays [23,24]. Whole-blood folate was measured using a microbiologic assay, whereas RBC folate was then calculated after subtracting the contribution of serum folate and normalizing the whole-blood folate data to the hematocrit [16–22]. One previous study showed that serum and RBC folate concentrations in the overall population showed minor fluctuations from 1999 to 2016 [25]. To increase statistical power, we combined data on folate biomarkers for the 6 NHANES cycles included—2007−2018—except that we also compared biomarker concentrations before and after CMF fortification, which started in 2016. Among the 31,128 NHANES participants for this analysis, 3282 and 3169 participants had missing serum folate and RBC folate data, respectively. Serum and RBC folate deficiencies were defined as serum folate <7 nmol/L (~3 ng/mL) and RBC folate <305 nmol/L (~140 ng/mL), respectively [15]. High serum folate concentration thresholds were based on the distribution of this study population: 92 nmol/L (95th percentile), 77 nmol/L (90th percentile), and 60 nmol/L (80th percentile).

Serum vitamin B12 was measured using an electrochemiluminescence immunoassay, and MMA was analyzed using LC-MS/MS [19,20]. MMA is one of the metabolites accumulating in cobalamin (vitamin B12)-deficient cells, and blood concentrations of MMA are functional markers of vitamin B12 status [6]. Vitamin B12 and MMA data were only available for the 2 NHANES cycles included in this analysis—2011–2014. Vitamin B12 deficiency and insufficiency were defined as serum vitamin B12 concentrations <148 pmol/L and <221 pmol/L, respectively [26].

Covariates

We separated age into 3 categories: 19–39, 40–59, and ≥60 y. We divided race/ethnicity based on self-reports into 5 categories: Hispanic, non-Hispanic (NH) White, NH Black, NH Asian, and others. “Hispanic” includes respondents who self-identified as “Mexican American” and self-identified as “Hispanic” ethnicity. NH participants were then categorized based on their self-reported races. Categorization for “NH Asian” became available starting in 2011. Between 2007 and 2010, NH Asians were included in the “other” category, which accounted for 4% of the total study population. Given the change in the definition of “other” during our study period and the small number of participants in this category, we did not report results for “other” separately in the Results. We defined smoking status based on serum cotinine concentrations, measured using an isotope-dilution HPLC. We classified participants with cotinine levels above 10 ng/mL as smokers [27,28] and the rest as nonsmokers. BMI was calculated as weight in kilograms divided by height in meters squared, based on body measurements data collected in the MEC. We used BMI in this analysis as a categorical variable with 4 levels: underweight (<18.5 kg/m^2), normal weight (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), and obese (≥30 kg/m^2).

Statistical analysis

Usual intakes were modeled using SAS, version 9.4 (SAS Institute). All other analyses were conducted in R, version 4.0.2 (R Foundation), and its survey package, version 4.0, to account for the clustered design, probabilistic selection, and nonparticipation. To analyze demographic characteristics and estimate usual intake, we combined day 1 dietary recall weights from the 6 NHANES cycles included (2007–2018), e.g., by dividing the 2-y dietary weights by 6 for folate. For biomarker concentrations, all participants aged ≥1 y who attended the MEC examination were eligible for folate biomarker data before 2017. Starting in 2017, all examined female participants aged 12–49 y were eligible for folate biomarker data, whereas one-half of the other examined participants aged ≥1 y were eligible [22]. Due to this difference in the sampling of folate biomarkers in NHANES 2017–2018, we adjusted day 1 dietary recall weights to account for the probabilistic selection and nonparticipation in the folate subsample in analyses of folate biomarker concentrations by folic acid consumption group. Briefly, all 5092 persons in the folate subsample from NHANES 2017–2018 were stratified into 53 race/ethnicity-age-gender-specific groups. Using the day 1 dietary recall weight as the base weight, a new dietary folate subsample weight was calculated within each adjustment cell to account for selection probability and nonresponse to the laboratory tests [29]. Once poststratification was completed, the weights were raked by day of the week with 2 categories: weekdays defined as Monday to Thursday, and weekends as Friday, Saturday, and Sunday. This new dietary folate subsample weight was then combined with 2-y dietary weights from the other 5 NHANES cycles for analyzing serum and RBC folate biomarker data. For vitamin B12 and MMA, because their concentrations were only available for 2 NHANES cycles (2011–2014), analyses were conducted using a 4-y combined dietary recall weight for these 2 biomarkers. Combined weights were used to calculate adjusted geometric means and prevalence in chi-squared and Wald tests.

Weighted proportions and 95% CIs of United States adults in each of the 4 folic acid consumption groups were estimated in the overall study population and by demographic characteristics (i.e., sex, age category, and race/ethnicity). Differences in proportions were evaluated with the chi-square test. We used natural log transformations on the biomarker concentrations (serum and RBC folate, vitamin B12, and MMA) and estimated the geometric means via multiple linear regression, adjusting for sex, age category, race/ethnicity, current smoking status, and weight status category based on BMI. We assessed statistical differences in the adjusted geometric means across different folic acid consumption groups using the Wald test. Logistic regressions were used to estimate the prevalence of high serum folate, serum folate deficiency, RBC folate deficiency, and serum vitamin B12 deficiency and insufficiency by folic acid consumption group or vitamin B12 supplementation status, accounting for sociodemographic characteristics. Differences in the prevalence across folic acid consumption groups or demographic subgroups were evaluated with the chi-square test. All tests were 2-tailed with a significance level of 0.05.

Results

The proportions of adults who consumed folic acid from ECGP/CMF only, ECGP/CMF + RTE, ECGP/CMF + SUP, and ECGP/CMF + RTE + SUP were 49.8%, 17.6%, 22.4%, and 10.2%, respectively during 2007–2018 (Table 1). A higher percentage of men were in the ECGP/CMF-only group than that of women (52.6% compared with 47.1%; $P < 0.001$), while the percentage of women who consumed supplements containing folic acid (i.e., ECGP/CMF + SUP and ECGP/CMF + RTE + SUP) was higher than that of men (35.3% compared with 29.8%; $P < 0.001$). The percentage of supplement users increased with age—25.4% for 19–39 y were supplement users, compared with 33.2% for 40–59 y ($P < 0.001$) and 42.0% for ≥ 60 y ($P < 0.001$).

Usual intake

Table 2 shows the modeled usual daily intakes of natural food folate, folic acid, and total folate by folic acid consumption group and vitamin B12 intake by vitamin B12 supplementation status in the overall population and by demographic characteristics during 2007–2018. Natural food folate intakes were similar across the 4 folic acid consumption groups and among different demographic subgroups, with a median of 222 μg DFE/d (IQR, 175–276 μg DFE/d), which is below the EAR of 320 μg DFE daily. Among all the subgroups, NH Asian adults in the ECGP/CMF-only group had the highest folate intake from natural foods, with a median of 319 (IQR: 263–382) μg DFE/d. The median usual folic acid intake in the ECGP/CMF-only group was 134 μg/d, equivalent to 228 μg DFE/d, and this was comparable to the natural food intake in this group of 222 μg DFE/d. In the other 3 folic acid consumption groups, folic acid usual intakes were 313 (ECGP/CMF + RTE), 496 (ECGP/CMF + SUP), and 695 μg/d (ECGP/CMF RTE SUP) in the overall study population. Total folate, which is the sum of natural food folate and folic acid from fortified foods and supplements, increased with increasing folic acid intake sources or supplements containing folic acid among all demographic groups (i.e., ECGP/CMF only < ECGP/CMF + RTE < ECGP/CMF SUP < ECGP/CMF RTE SUP group). In the overall study population, 5.9% (95% CI: 5.7, 6.1) had a total folate intake below the EAR.

After voluntary CMF fortification, the median folic acid usual intake (μg/d) in the overall population was slightly lower (229 [IQR: 149, 403] during 2017–2018 compared with 237 [IQR: 152, 446] during 2007–2016), although it was slightly higher among Hispanic adults (211 [IQR: 148, 321] during 2017–2018 compared with 207 [IQR: 147, 304] during 2007–2016) (data not shown). After CMF fortification, the percentage of Hispanic adults with total folate intake below EAR remained steady at 5.5%, although it was slightly higher in the overall population at 6.1% (95% CI: 5.8, 6.5).

Folic acid and vitamin B12 supplement use were highly correlated. Among folic acid supplement nonusers, 95% did not take vitamin B12 supplements (95% CI: 94.6%, 95.7%). Among folic acid supplement users, 98% (95% CI: 97.5%, 98.5%) also took vitamin B12 supplements. The median usual vitamin B12 intake was 5.2 (IQR: 4.0, 6.7) μg/d among vitamin B12 supplement nonusers and 21.8 (IQR: 10.8, 53.8) μg/d among users (Table 2). The 25th percentiles of vitamin B12 intake for all demographic subgroups (ranging from 3.1 μg/d for NH Asian vitamin B12 supplement nonusers to 13.5 μg/d for age 60+ y vitamin B12 supplement users) were above the EAR of 2 μg daily.

UL of folic acid

Overall, 2.0% (95% CI: 1.7%, 2.3%) of adults consumed folic acid above UL during 2007–2018. Figure 2 shows the cumulative distribution of usual intake for United States adults by folic acid source. For United States adults who did not consume supplements containing folic acid (i.e., in ECGP/CMF only and ECGP/CMF + RTE groups), 0% exceeded the UL. For supplement users, 3.9% exceeded the UL (95% CI: 3.4%, 4.5%) in ECGP/CMF + SUP group, and 10.9% exceeded the UL (95% CI: 9.2%, 12.7%) in ECGP/CMF + RTE + SUP group. Among people with usual intake above UL, ~69% were women, 80% were NH White; 36% were aged ≥60 y. After voluntary CMF fortification (from 2017 to 2018), the percentage of participants who consumed folic acid above the UL remained consistent (2.1% [95% CI: 1.6%, 2.5%] compared with 2.0% [95% CI: 1.7%, 2.3%] from 2007 to 2016). Among Hispanic adults, the percentage of participants who consumed folic acid above the UL remained the same at 1.3% before and after CMF fortification.

Biomarker status

Higher serum and RBC folate concentrations were associated with the consumption of additional folic acid sources or supplements containing folic acid ($P < 0.05$) in the overall population and all demographic groups. For example, participants consuming RTE and/or supplements with folic acid had significantly higher RBC folate concentrations (nmol/L) (ECGP/CMF only: 976 [95% CI: 963, 989], ECGP/CMF + RTE: 1130 [95% CI: 1110, 1150], ECGP/CMF + SUP: 1307 [95% CI: 1283, 1332], ECGP/CMF + RTE + SUP: 1467 [95% CI: 1439, 1495]; Table 3). Among the different race and ethnicity groups, NH White adults had the highest serum and RBC folate concentrations, whereas NH Black adults had the lowest concentrations, followed by Hispanic adults. After voluntary CMF fortification starting in 2016, RBC folate concentration (nmol/L) in Hispanic adults was higher (1042 (95% CI: 1004, 1083) during 2017–2018 compared with 995 [95% CI: 978, 1012] during 2007–2016) whereas serum folate concentration (nmol/L) was slightly lower (32.6 [95% CI: 30.8, 34.4] during 2017–2018 compared with 34.4 [95% CI: 33.7, 35.1] during 2007–2016) (data not shown). In comparison, RBC folate concentrations (nmol/L) in the overall study population remained consistent (1117 [95% CI: 1079, 1157] during 2017–2018 compared with 1115 [95% CI: 1098, 1132] during 2007–2016) and serum folate concentration (nmol/L) was slightly lower (35.0 [95% CI: 33.0, 37.1] during 2017–2018 compared with 38.0 [95% CI: 37.3, 38.6] during 2007–2016) (data not shown).

Serum vitamin B12 concentrations (pmol/L) were significantly higher among vitamin B12 supplement users (482, 95% CI: 468, 496) than nonusers (347, 95% CI: 341, 353), which is consistent across age, sex, and race/ethnicity groups (Table 4). Among vitamin B12 supplement users, serum vitamin B12 concentration increased with age, though among nonusers, the youngest age group (19–39 y) had the highest vitamin B12 concentration. Correspondingly, MMA concentrations were lower among vitamin B12 supplement users than nonusers in the overall study population and all demographic groups (Table 4; not statistically significant for adults aged 19–39 y, NH Asian adults). In addition, MMA concentrations increased significantly with age in the overall study population as well as across vitamin B12 supplement use strata.

Prevalence of high serum folate and deficiencies in folate and vitamin B12

Percentages of adults with high serum folate increased in the order of ECGP/CMF only, ECGP/CMF + RTE, ECGP/CMF + SUP, and ECGP/CMF + RTE + ECGP consumption groups, regardless of thresholds used (Table 5). Chi-square tests showed that these percentage differences across folic acid consumption groups were statistically significant. Supplement users (in the ECGP/CMF + SUP and ECGP/CMF + RTE + SUP groups) had higher percentages of high serum folate than nonusers. This increase in percentages of adults with high serum folate between supplement users and nonusers remained true across demographic groups (i.e., by sex, age category, and race/ethnicity). In the overall study population, there was a significantly higher proportion of females than males with high serum folate, and the proportion with high serum folate increased with age. Folate deficiency was rare in the study population—mean serum folate deficiency was ≤0.7% and mean RBC folate deficiency was ≤ 1.2% in the 4 folic acid groups (Table 5). For the overall population, there was no difference between males and females in the proportion of serum or RBC folate deficiency, though proportions differed significantly for different age groups and race and ethnicity groups. For the overall population, folic acid consumption groups did not have a significant association with the proportion of RBC folate deficiency but had a significant association with the proportion of serum folate deficiency.

The mean vitamin B12 deficiency was 3.6% in the overall population and 4.4% and 2.3% between vitamin B12 supplement nonusers and users, respectively (Table 6). Except for those aged 40–59 y and NH Black adults, vitamin B12 supplement users had a significantly lower proportion with vitamin B12 deficiency than nonusers in the overall study population as well as across demographic groups. Likewise, vitamin B12 supplement users had a significantly lower percentage of vitamin B12 insufficiency (4.5 to 8.2% among vitamin B12 supplement users across demographic groups compared with 12.4 to 18.5% among nonusers).

Discussion

This analysis showed that during 2007–2018, 2.0% (95% CI: 1.7%, 2.3%) of adults exceeded the UL for folic acid. At the current fortification levels, United States adults who did not consume supplements containing folic acid (nearly 70%) did not have the usual folic acid intake exceeding the UL. Folate deficiency was low in the United States population. However, consuming folate from natural foods alone did not meet the EAR in the overall study population and all subgroups. When additional folic acid was added through fortification, median total folate intakes in the ECGP/CMF-only group were above the EAR for all the demographic groups. Consumption of RTE and/or supplements with folic acid further increased usual folate intake, with all the demographic groups having their 25th percentiles above the EAR. Intake of vitamin B12 among most United States adults met the EAR, with vitamin B12 supplement users having as high as 6 times the intake of nonusers. Serum vitamin B12 deficiency was 3.6% in the overall population, though a few subgroups had more than 5% of adults with vitamin B12 deficiency. Serum vitamin B12 insufficiency was on average 16.3% among vitamin B12 supplement nonusers and 5.9% among users. Over 95% of folic acid supplement users also consumed vitamin B12 supplements.

Findings from our study are generally consistent with earlier studies and current knowledge on folate, vitamin B12, and health. Yang et al. [7] found that 2.7% of adults, all of whom were supplement users, consumed more than the UL of folic acid between 2003 and 2006. Likewise, a study on the characteristics of United States adults with a usual daily folic acid intake above the UL found that consumption of supplements containing folic acid is the main factor associated with a usual intake exceeding the UL [30]. Our study shows that the percentage of people with folic acid intake above UL was even lower at 2% between 2007 and 2018, all of whom consumed supplements containing folic acid. Between 2007 and 2018, 33% of adults consumed supplements containing folic acid, which was lower than the 40% observed between 2003 and 2006 [7]. Another study using NHANES data (2007–2014) with a focus on United States adults aged ≥51 y found that consistent multivitamin use increased the prevalence of exceeding the UL for folic acid, with 8%–10% multivitamin users (consistent and sporadic use) exceeding the UL [10]. Our results showed that for supplement users among all adults (≥19 y), 3.9% exceeded the UL in the ECGP/CMF + SUP group, and 10.9% exceeded the UL in the ECGP/CMF + RTE + SUP group. Our usual intake estimates in each of the 4 folic acid consumption groups are comparable with those reported earlier by Yang et al. [7], though we used the NCI method to estimate usual intake although Yang et al. [7] used Software for Intake Distribution Estimation (PC-SIDE). The different methods used for estimating usual intake could have contributed to the small difference we observed in folate usual intake, in addition to the difference in time periods (2007–2018 compared with 2003–2006). After the voluntary fortification of CMF (2017–2018), folic acid usual intake, the percentage of participants with usual intake exceeding the UL, serum, and RBC folate concentrations for the overall population did not increase from before the voluntary fortification (2007–2016), suggesting a very limited impact of CMF on the overall population. Among Hispanic adults, RBC folate concentration was higher after CMF fortification, although detailed subgroup analysis on this topic and additional assessment when more data after CMF fortification become available may be warranted.

To our knowledge, this is the first time NH Asians could be separated from the "other" group for folate and vitamin B12 usual intake analysis using NHANES. We found some distinctive dietary patterns. For example, among all the demographic subgroups and folic acid consumption groups, NH Asian adults in the ECGP/CMF-only group had the highest natural food folate intake with a median of 319 (IQR: 263–382) μg DFE/d. In most of the other demographic subgroups, adults in ECGP/CMF had the lowest natural food folate intake. In addition, only 9.4% of NH Asian adults were in the ECGP/CMF + RTE group versus 16.9 to 19.3% in the other 3 race/ethnicity groups.

Deficiencies in folate and vitamin B12 are known to cause developmental defects, impair cognitive function, or block normal blood production [1]. Several biomarkers of folate status are available in NHANES. Serum folate is an indicator of short-term folate intake, whereas RBC folate is an indicator of long-term status. We found that adults with ECGP/CMF as their only source of folic acid had lower usual daily total folic acid intake and lower RBC folate concentrations than adults consuming additional folic acid from diet and/or supplements. This is similar to the findings by Crider et al. [8] using NHANES data from 2007 to 2012 among women of reproductive age (12–49 y). In addition, Wang et al. [9] found that the RBC folate concentrations for lesser acculturated Hispanic women of reproductive age, who were born outside the United States and residing in the United States for <15 y, increased significantly from 894 nmol/L (95% CI: 844–946) in 2011–2016 to 1018 nmol/L (95% CI: 982–1162) in 2017–2018, after the FDA authorized voluntary folic acid fortification of CMF in 2016 [9]. The geometric mean RBC folate concentration in our study among all Hispanic adults increased from 995 nmol/L [95% CI: 978, 1012] in 2007–2016 to 1042 nmol/L (95% CI: 1004, 1083) in 2017–2018.

Data on serum vitamin B12 in NHANES directly reflect the range of circulating vitamin B12 concentrations in individuals. We found serum vitamin B12 deficiency and insufficiency were both significantly lower among vitamin B12 supplement users than nonusers. Also, as expected, vitamin B12 supplement users had significantly higher serum vitamin B12 concentrations and lower MMA concentrations than nonusers. Similar to previous studies using NHANES data [31,32], we found that MMA concentration increased with age for both vitamin B12 supplement users and nonusers. No homocysteine concentration data were available in NHANES during our study period.

Although low intake of both folate and vitamin B12 is known to be associated with serious health outcomes, there has been a long-standing concern about the possible ill effects of high folic acid intake, especially in the context of low vitamin B12 [33]. This current manuscript is not designed to directly address this concern. Reassuringly, we found a low prevalence of high folic acid intake, and it is limited to voluntary consumers of folic acid supplements. However, we did find a small percentage of vitamin B12 supplement users with persistent insufficiency and deficiency (2.3% with vitamin B12 deficiency and 5.9% with insufficiency). This finding is consistent with other analyses, and Samson et al. [34] suggested that insufficient vitamin B12 status among individuals using supplements containing vitamin B12 may indicate that they were unable to adequately absorb vitamin B12. Wang et al. [35] also found that both RBC and serum folate concentrations increased with declining kidney function without differences in folic acid intake. Together, these findings suggest caution should be taken in interpreting the association of high blood folate concentrations with adverse outcomes, as they may reflect artifacts of a disease status (e.g., issues of excretion) and not high folic acid intake. Awareness of this potential artifact is critical for the evaluation of the existing literature, as similar analyses can produce different results depending on the adjustment of disease status. When, after consideration of spurious findings due to other causes (e.g., malabsorption of vitamin B12 and kidney disease), high folate and low vitamin B12 persist to be associated with adverse outcomes, a careful evaluation of intakes and outcomes should be conducted. Randomization of exposure through trials, or more easily, Mendelian randomization, will be critical for causal inference.

Strengths

Our study has several strengths. First, we used available data between 2007 and 2018 from a large nationally representative sample of United States adults, with oversampling of certain population subgroups by age and race/ethnicity. As a result, we had a large sample size of over 30,000 participants, which in most scenarios provided stable estimates in subgroups that account for only a small percentage of the population. For example, we reported data for NH Asian adults as its own category, which became available in NHANES starting in 2011. Second, folate and vitamin B12 biomarkers were used to evaluate dose-response across folic acid consumption groups or vitamin B12 supplement use status. Third, we applied the updated NCI method to estimate the usual daily intake of folate and vitamin B12. The NCI method allows the estimation of usual intake distributions of daily and episodically consumed components for populations and sub-populations and the prediction of individual intakes, which allows for the incorporation of individual and time-dependent covariates [13]. Nutrient usual intakes from natural and fortified foods and supplements were combined to estimate total usual intakes using the preferred “shrink then add” method.

Limitations

Potential limitations include the inability to examine temporal associations due to the cross-sectional design of the survey. Dietary data were self-reported and collected at the time of the medical examination or shortly thereafter. Supplement data were collected during household interviews, in which participants were asked about their use of dietary supplements during the past 30 d. Thus, to estimate the total intake, we combined data obtained from 2 different instruments. We did not analyze the usual folic acid intake from CMF alone, as USDA food codes used in the NHANES dietary interview data did not allow for the separation of CMF from ECGP.

Conclusions

Folate deficiency was low in the United States population. Overall, 2% of adults consumed folic acid >UL. At current fortification levels, United States adults who did not consume supplements did not have the usual folic acid intake exceeding the UL. Folate from natural foods alone did not meet the EAR of folate. When folic acid from fortified foods was included, the median total folate intake for all demographic groups was above the EAR. Folic acid fortification plays a critical role in helping the general population meet the nutritional requirement for folate. Most United States adults in all demographic subgroups had vitamin B12 intakes above the EAR. However, even among vitamin B12 supplement users, there were 2% with vitamin B12 deficiency and 6% with insufficiency, suggesting the need to explore alternative routes of vitamin B12 administration and the need for further research.

Acknowledgments

We would like to thank Kevin Dodd, Regan Bailey, and Janet Tooze for their help in using the NCI method for the usual intake calculation.

Funding

The authors reported no funding received for this study.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of CDC.

Data availability

Publicly available datasets were analyzed in this study. The data can be found at https://wwwn.cdc.gov/nchs/nhanes/default.aspx (accessed November 22, 2022).

Abbreviations:

CMF	corn masa flour
DFE	dietary folate equivalent
EAR	estimated average requirement
ECGP	enriched cereal grain product
LC-MS/MS	liquid chromatography coupled to tandem MS
MEC	medical examination center
NH	non-Hispanic
NTD	neural tube defect
RTE	ready-to-eat cereal
SUP	folic acid–containing supplement
UL	tolerable upper intake level

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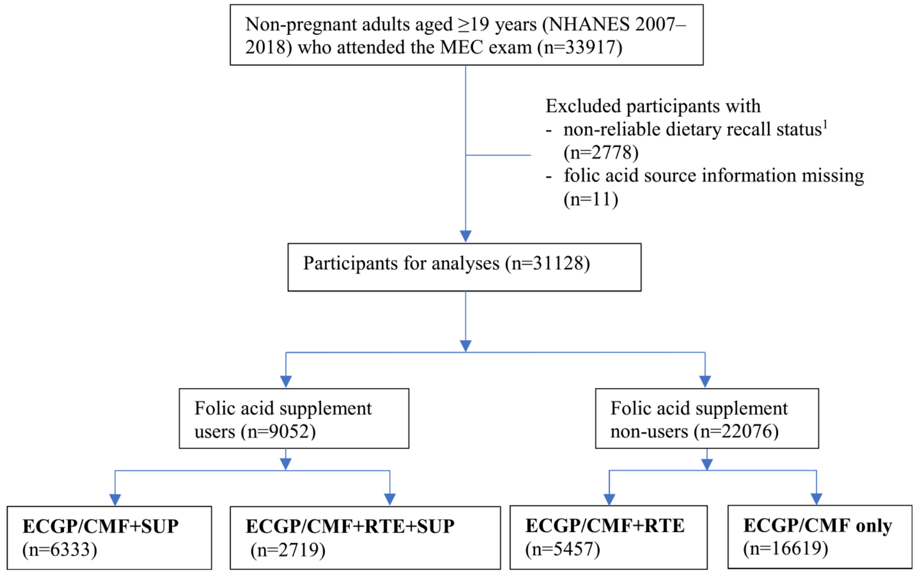
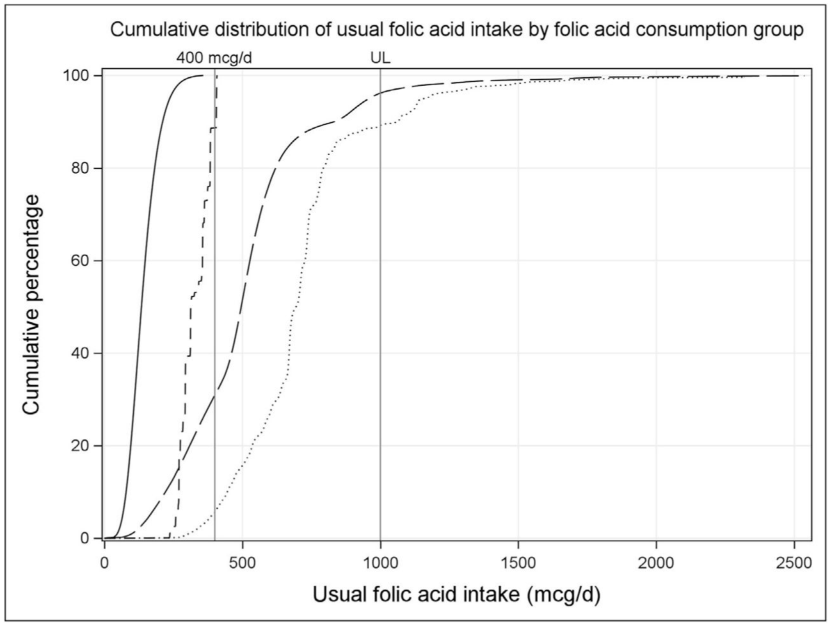


FIGURE 1.

Study population by supplement use status and folic acid consumption group. CMF, corn masa flour; ECGP, enriched cereal grain product; MEC, medical examination center; RTE, ready-to-eat cereal; SUP, folic acid–containing supplement.

[1]Dietary status was nonreliable when the DR1DRSTZ variable in NHANES was coded as "not reliable," "not done," or "missing" or when the DR2DRSTZ variable was coded as "not reliable."



ECGP/CMF only
ECGP/CMF + RTE
ECGP/CMF + SUP
ECGP/CMF + RTE + SUP.

FIGURE 2.

Cumulative distribution of usual folic acid intake by folic acid consumption group, NHANES, 2007–2018. Folic acid consumption group: CMF, corn masa flour; ECGP, enriched cereal grain product; RTE, ready-to-eat cereal; SUP, supplements containing folic acid; UL, tolerable upper intake level.

TABLE 1

Proportion of United States adults aged ≥19 y by folic acid consumption group and demographic characteristics: NHANES 2007–2018

Characteristic	Folic acid consumption group									
	All participants		ECGP/CMF only		ECGP/CMF + RTE		ECGP/CMF + SUP		ECGP/CMF + RTE + SUP	
	n[1]	Percentage (95% CI)	n	Percentage (95% CI)	n	Percentage (95% CI)	n	Percentage (95% CI)	n	Percentage (95% CI)
Total										
Total	31,128	100	16,619	49.8 (48.6, 51.0)	5457	17.6 (17.0, 18.2)	6333	22.4 (21.6, 23.2)	2719	10.2 (9.5, 10.9)
Sex										
F	15,796	51.3 (50.6, 51.9)	7979	47.1 (45.7, 48.6)	2832	17.6 (16.8, 18.4)	3516	24.4 (23.4, 25.4)	1469	10.9 (10.0, 11.8)
M	15,332	48.7 (48.1, 49.4)	8640	52.6 (51.2, 54.0)	2625	17.6 (16.8, 18.4)	2817	20.3 (19.2, 21.4)	1250	9.5 (8.7, 10.3)
Age										
19–39 y	10,712	37.1 (35.7, 38.5)	6274	56.0 (54.5, 57.4)	2055	18.6 (17.6, 19.6)	1710	18.3 (17.1, 19.4)	673	7.1 (6.4, 7.9)
40–59 y	10,070	36.7 (35.8, 37.7)	5548	50.3 (48.6, 52.1)	1583	16.5 (15.3, 17.7)	2170	23.6 (22.1, 25.0)	769	9.6 (8.5, 10.8)
≥60 y	10,346	26.2 (25.1, 27.2)	4797	40.3 (38.5, 42.0)	1819	17.7 (16.7, 18.8)	2453	26.5 (25.0, 28.0)	1277	15.5 (14.1, 16.8)
Race/Ethnicity										
NH White	12,891	66.1 (63.3, 68.9)	5837	45.1 (43.6, 46.6)	2479	18.0 (17.2, 18.8)	2926	24.4 (23.3, 25.5)	1649	12.5 (11.5, 13.4)
NH Black	6725	11.4 (9.9, 12.9)	4007	59.7 (58.2, 61.2)	1095	16.9 (15.7, 18.1)	1235	17.7 (16.5, 19.0)	388	5.7 (5.1, 6.3)
Hispanic	7966	14.5 (12.6, 16.5)	4761	59.6 (57.9, 61.3)	1474	19.3 (17.9, 20.7)	1290	15.9 (14.8, 17.1)	441	5.1 (4.5, 5.8)
NH Asian[2]	2291	5.5 (4.5, 6.5)	1311	57.6 (53.8, 61.5)	235	9.4 (7.8, 11.0)	600	26.2 (23.8, 28.7)	145	6.8 (5.1, 8.4)

Abbreviations: CMF, corn masa flour; ECGP, enriched cereal grain product; NH, non-Hispanic; RTE, ready-to-eat cereal: SUP, folic acid–containing supplement.

[1] n is unweighted. All percentages and CIs are weighted and took into account the complex sampling design.

[2] NH Asian estimates are for 2011–2018.

TABLE 2

Usual daily intakes of natural food folate, folic acid, total folate, and vitamin B12 by folic acid consumption group and demographic characteristics in United States adults aged ≥19 y: NHANES 2007–2018

Characteristics	Folic acid consumption group				
	All participants	ECGP + CMF only	ECGP + CMF + RTE	ECGP + CMF + SUP	ECGP + CMF + RTE + SUP
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Total					
Total					
Natural food folate intake (µg DFE/d)	222 (175, 276)	216 (171, 266)	219 (174, 270)	235 (183, 294)	229 (181, 283)
Folic acid intake (µg/d)	236 (152, 439)	134 (102, 172)	313 (285, 374)	496 (350, 590)	695 (585, 777)
Total folate intake (µg DFE/d)	644 (475, 967)	447 (369, 533)	737 (682, 895)	1070 (833, 1262)	1400 (1228, 1567)
Vitamin B12 intake (all) (µg/d)	6.6 (4.6, 11.9)	—	—	—	—
Vitamin B12 intake (B12 supp nonusers) (µg/d)	5.2 (4.0, 6.7)	—	—	—	—
Vitamin B12 intake (B12 supp users) (µg/d)	21.8 (10.8, 53.8)	—	—	—	—
Sex					
F					
Natural food folate intake (µg DFE/d)	196 (155, 241)	188 (149, 231)	189 (152, 231)	211 (170, 257)	203 (163, 249)
Folic acid intake (µg/d)	208 (131, 452)	110 (84, 143)	273 (265, 284)	489 (344, 579)	660 (586, 730)
Total folate intake (µg DFE/d)	565 (418, 947)	379 (315, 449)	662 (626, 695)	1041 (798, 1209)	1340 (1173, 1499)
Vitamin B12 intake (all) (µg/d)	5.5 (3.9, 11.2)	—	—	—	—
Vitamin B12 intake (B12 supp nonusers) (µg/d)	4.2 (3.3, 5.3)	—	—	—	—
Vitamin B12 intake (B12 supp users) (µg/d)	17.1 (9.7, 54.7)	—	—	—	—
M					
Natural food folate intake (µg DFE/d)	251 (198, 310)	242 (194, 296)	252 (204, 304)	266 (203, 337)	261 (210, 319)
Folic acid intake (µg/d)	262 (176, 435)	158 (124, 197)	391 (358, 405)	506 (357, 599)	754 (590, 790)
Total folate intake (µg DFE/d)	714 (538, 1004)	512 (430, 602)	908 (858, 953)	1114 (875, 1311)	1509 (1276, 1625)
Vitamin B12 intake (all) (µg/d)	7.7 (5.4, 12.9)	—	—	—	—
Vitamin B12 intake (B12 supp nonusers) (µg/d)	6.3 (4.8, 8.0)	—	—	—	—
Vitamin B12 intake (B12 supp users) (µg/d)	24.5 (12.8, 47.6)	—	—	—	—
Age					
19–39 y					

Characteristics	Folic acid consumption group				
	All participants	ECGP + CMF only	ECGP + CMF + RTE	ECGP + CMF + SUP	ECGP + CMF + RTE + SUP
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Natural food folate intake (μg DFE/d)	225 (178, 278)	218 (174, 267)	222 (174, 277)	248 (198, 306)	229 (178, 287)
Folic acid intake (μg/d)	241 (167, 365)	152 (118, 192)	335 (325, 422)	469 (307, 592)	699 (539, 825)
Total folate intake (μg DFE/d)	649 (496, 873)	477 (394, 568)	823 (735, 956)	1031 (766, 1271)	1420 (1160, 1674)
Vitamin B12 intake (all) (μg/d)	6.5 (4.8, 9.4)	—	—	—	—
Vitamin B12 intake (B12 supp nonusers) (μg/d)	5.6 (4.3, 7.1)	—	—	—	—
Vitamin B12 intake (B12 supp users) (μg/d)	13.5 (9.5, 27.5)	—	—	—	—
40–59 y					
Natural food folate intake (μg DFE/d)	229 (180, 284)	221 (174, 274)	228 (187, 274)	239 (185, 299)	244 (193, 303)
Folic acid intake (μg/d)	228 (145, 432)	128 (98, 165)	288 (278, 375)	494 (349, 584)	699 (559, 768)
Total folate intake (μg DFE/d)	640 (470, 962)	442 (362, 530)	725 (682, 891)	1070 (834, 1256)	1400 (1190, 1581)
Vitamin B12 intake (all) (μg/d)	6.6 (4.5, 12.0)	—	—	—	—
Vitamin B12 intake (B12 supp nonusers) (μg/d)	5.1 (3.8, 6.6)	—	—	—	—
Vitamin B12 intake (B12 supp users) (μg/d)	21.2 (10.8, 53.2)	—	—	—	—
≥60 y					
Natural food folate intake (μg DFE/d)	208 (163, 260)	204 (163, 250)	201 (158, 250)	215 (164, 275)	214 (172, 262)
Folic acid intake (μg/d)	253 (142, 534)	111 (83, 144)	284 (255, 327)	505 (439, 590)	656 (645, 737)
Total folate intake (μg DFE/d)	663 (453, 1118)	396 (327, 471)	659 (617, 795)	1080 (925, 1252)	1351 (1282, 1499)
Vitamin B12 intake (all) (μg/d)	7.7 (4.6, 28.7)	—	—	—	—
Vitamin B12 intake (B12 supp nonusers) (μg/d)	4.8 (3.5, 6.3)	—	—	—	—
Vitamin B12 intake (B12 supp users) (μg/d)	29.5 (13.5, 105.2)	—	—	—	—
Race/Ethnicity					
NH White					
Natural food folate intake (μg DFE/d)	222 (174, 276)	215 (171, 265)	217 (172, 267)	236 (183, 296)	228 (181, 282)
Folic acid intake (μg/d)	256 (157, 492)	130 (99, 167)	311 (291, 378)	500 (367, 596)	704 (604, 785)
Total folate intake (μg DFE/d)	678 (489, 1047)	439 (364, 521)	764 (692, 897)	1082 (861, 1273)	1408 (1234, 1596)
Vitamin B12 intake (all) (μg/d)	7.2 (4.9, 14.6)	—	—	—	—
Vitamin B12 intake (B12 supp nonusers) (μg/d)	5.4 (4.2, 7.0)	—	—	—	—
Vitamin B12 intake (B12 supp users) (μg/d)	23.3 (11.2, 55.1)	—	—	—	—
NH Black					

Characteristics	Folic acid consumption group				
	All participants	ECGP + CMF only	ECGP + CMF + RTE	ECGP + CMF + SUP	ECGP + CMF + RTE + SUP
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Natural food folate intake (μg DFE/d)	192 (153, 236)	190 (152, 234)	183 (148, 222)	203 (162, 248)	199 (159, 245)
Folic acid intake (μg/d)	192 (136, 295)	125 (97, 158)	286 (276, 370)	475 (304, 551)	677 (511, 722)
Total folate intake (μg DFE/d)	533 (414, 720)	403 (330, 485)	655 (648, 847)	992 (718, 1157)	1336 (1090, 1452)
Vitamin B12 intake (all) (μg/d)	5.5 (4.1, 8.2)	—	—	—	—
Vitamin B12 intake (B12 supp nonusers) (μg/d)	4.8 (3.7, 6.0)	—	—	—	—
Vitamin B12 intake (B12 supp users) (μg/d)	16.3 (9.7, 38.3)	—	—	—	—
Hispanic					
Natural food folate intake (μg DFE/d)	235 (187, 290)	232 (186, 285)	242 (193, 298)	238 (189, 294)	231 (178, 293)
Folic acid intake (μg/d)	208 (147, 306)	144 (110, 184)	316 (282, 368)	479 (305, 581)	680 (499, 722)
Total folate intake (μg DFE/d)	601 (464, 797)	476 (391, 571)	785 (684, 901)	1032 (757, 1249)	1353 (1077, 1558)
Vitamin B12 intake (all) (μg/d)	5.8 (4.2, 8.5)	—	—	—	—
Vitamin B12 intake (B12 supp nonusers) (μg/d)	5.1 (3.9, 6.5)	—	—	—	—
Vitamin B12 intake (B12 supp users) (μg/d)	17.5 (9.7, 52.0)	—	—	—	—
NH Asian[1]					
Natural food folate intake (μg DFE/d)	254 (197, 319)	319 (263, 382)	254 (207, 307)	294 (238, 355)	132 (96, 176)
Folic acid intake (μg/d)	222 (142, 393)	147 (111, 190)	292 (257, 327)	496 (341, 591)	669 (469, 780)
Total folate intake (μg DFE/d)	650 (487, 932)	745 (624, 876)	638 (615, 751)	1172 (927, 1387)	1185 (906, 1392)
Vitamin B12 intake (all) (μg/d)	5.7 (3.8, 10.5)	—	—	—	—
Vitamin B12 intake (B12 supp nonusers) (μg/d)	4.3 (3.1, 5.7)	—	—	—	—
Vitamin B12 intake (B12 supp users) (μg/d)	16.6 (9.6, 37.5)	—	—	—	—

Abbreviations: CMF, corn masa flour; DFE, dietary folate equivalents; ECGP, enriched cereal grain product; NH, non-Hispanic; RTE, ready-to-eat cereal: SUP, folic acid–containing supplement; B12 supp, vitamin B12 supplement.

[1]NH Asian estimates are based on 24-h dietary recalls during 2011–2018.

TABLE 3

Serum folate and RBC folate concentrations by folic acid consumption group and demographic characteristics among United States adults aged ≥19 y: NHANES 2007–2018

Folic acid consumption group	Adjusted serum folate concentration[1] (nmol/L)		Adjusted RBC folate concentration[1] (nmol/L)	
	Unweighted n	Geometric mean (95% CI)	Unweighted n	Geometric mean (95% CI)
Total				
Total				
Total	27,837	37.4 (36.7, 38.1)	27,950	1114 (1099, 1130)
ECGP/CMF only	14,751	30.2 (29.6, 30.8)	14,830	976 (963, 989)
ECGP/CMF + RTE	4945	38.6 (37.8, 39.5)	4962	1130 (1110, 1150)
ECGP/CMF + SUP	5657	48.0 (47.0, 49.1)	5672	1307 (1283, 1332)
ECGP/CMF + RTE + SUP	2484	57.3 (56.1, 58.5)	2486	1467 (1439, 1495)
P value[2]	—	<0.001	—	<0.001
Sex				
F				
Total	14,385	39.2 (38.3, 40.1)	14,442	1127 (1108, 1147)
ECGP/CMF only	7221	31.6 (30.9, 32.4)	7257	983 (967, 1000)
ECGP/CMF + RTE	2613	40.2 (39.1, 41.3)	2623	1133 (1108, 1159)
ECGP/CMF + SUP	3187	50.4 (49.0, 51.8)	3202	1327 (1297, 1357)
ECGP/CMF + RTE + SUP	1364	60.7 (58.8, 62.6)	1360	1500 (1461, 1540)
P value	—	<0.001	—	<0.001
M				
Total	13,452	35.6 (35.0, 36.2)	13,508	1103 (1086, 1120)
ECGP/CMF only	7530	28.7 (28.1, 29.4)	7573	968 (952, 985)
ECGP/CMF + RTE	2332	37.2 (36.1, 38.4)	2339	1126 (1102, 1152)
ECGP/CMF + SUP	2470	45.5 (44.2, 46.8)	2470	1285 (1256, 1316)
ECGP/CMF + RTE + SUP	1120	53.9 (52.3, 55.5)	1126	1432 (1394, 1470)
P value	—	<0.001	—	<0.001
Age				
19–39 y				
Total	9784	33.4 (32.8, 34.0)	9819	1019 (1003, 1035)

Folic acid consumption group	Adjusted serum folate concentration[1] (nmol/L)		Adjusted RBC folate concentration[1] (nmol/L)	
	Unweighted n	Geometric mean (95% CI)	Unweighted n	Geometric mean (95% CI)
ECGP/CMF only	5690	28.5 (28.0, 29.1)	5717	911 (897, 925)
ECGP/CMF + RTE	1889	35.7 (34.7, 36.7)	1894	1041 (1018, 1065)
ECGP/CMF + SUP	1578	39.8 (38.6, 41.2)	1584	1126 (1099, 1153)
ECGP/CMF + RTE + SUP	627	48.6 (46.4, 51.0)	624	1235 (1194, 1277)
P value		<0.001		<0.001
40–59 y				
Total	9072	36.5 (35.7, 37.4)	9109	1118 (1098, 1138)
ECGP/CMF only	4956	29.7 (29.0, 30.5)	4978	982 (965, 1000)
ECGP/CMF + RTE	1441	37.8 (36.3, 39.3)	1444	1136 (1100, 1172)
ECGP/CMF + SUP	1965	45.4 (43.9, 46.9)	1974	1300 (1267, 1335)
ECGP/CMF + RTE + SUP	710	52.5 (50.2, 54.9)	713	1450 (1399, 1503)
P value	—	<0.001	—	<0.001
≥60 y				
Total	8981	45.4 (44.3, 46.5)	9022	1264 (1240, 1289)
ECGP/CMF only	4105	32.7 (31.6, 33.9)	4135	1050 (1024, 1077)
ECGP/CMF + RTE	1615	44.5 (42.8, 46.3)	1624	1257 (1222, 1293)
ECGP/CMF + SUP	2114	64.5 (62.2, 67.0)	2114	1589 (1542, 1637)
ECGP/CMF + RTE + SUP	1147	75.1 (72.9, 77.5)	1149	1779 (1729, 1830)
P value	—	<0.001	—	<0.001
Race/Ethnicity				
NH White				
Total	11,769	39.3 (38.4, 40.1)	11,781	1183 (1163, 1204)
ECGP/CMF only	5302	30.9 (30.1, 31.7)	5314	1023 (1006, 1042)
ECGP/CMF + RTE	2285	40.2 (39.0, 41.4)	2293	1186 (1158, 1214)
ECGP/CMF + SUP	2649	51.0 (49.5, 52.5)	2644	1392 (1358, 1426)
ECGP/CMF + RTE + SUP	1533	60.2 (58.8, 61.7)	1530	1552 (1519, 1586)
P value	—	<0.001	—	<0.001
NH Black				
Total	5749	30.9 (30.3, 31.6)	5806	914 (899, 929)
ECGP/CMF only	3423	25.3 (24.7, 26.0)	3459	803 (790, 817)

Folic acid consumption group	Adjusted serum folate concentration[1] (nmol/L)		Adjusted RBC folate concentration[1] (nmol/L)	
	Unweighted n	Geometric mean (95% CI)	Unweighted n	Geometric mean (95% CI)
ECGP/CMF + RTE	933	33.1 (32.0, 34.3)	940	982 (945, 1021)
ECGP/CMF + SUP	1058	37.3 (35.9, 38.7)	1069	1039 (1007, 1072)
ECGP/CMF + RTE + SUP	335	46.2 (43.0, 49.7)	338	1248 (1184, 1315)
P value	—	<0.001	—	<0.001
Hispanic				
Total	7270	35.1 (34.4, 35.8)	7285	1016 (1000, 1033)
ECGP/CMF only	4312	30.1 (29.4, 30.9)	4325	928 (911, 946)
ECGP/CMF + RTE	1361	36.9 (35.5, 38.4)	1360	1046 (1014, 1080)
ECGP/CMF + SUP	1186	42.6 (40.9, 44.3)	1191	1177 (1146, 1210)
ECGP/CMF + RTE + SUP	411	51.0 (48.4, 53.8)	409	1300 (1244, 1359)
P value	—	<0.001	—	<0.001
NH Asian[3]				
Total	1930	36.7 (35.5, 38.0)	1957	1054 (1029, 1079)
ECGP/CMF only	1093	32.0 (31.0, 33.0)	1110	923 (899, 947)
ECGP/CMF + RTE	204	39.5 (37.3, 41.9)	205	1030 (991, 1071)
ECGP/CMF + SUP	512	50.7 (48.6, 53.0)	517	1270 (1225, 1316)
ECGP/CMF + RTE + SUP	121	59.1 (54.5, 64.1)	125	1358 (1268, 1454)
P value	—	<0.001	—	<0.001

Abbreviations: CMF, corn masa flour; ECGP, enriched cereal grain product; NH, non-Hispanic; RTE, ready-to-eat cereal: SUP, folic acid–containing supplement.

[1] Adjusted for sex, age category, race/ethnicity, current smoking status, and BMI.

[2] *P* value for testing differences in concentrations across different folic acid consumption groups based on the Wald test.

[3] NH Asian estimates are for 2011–2018.

TABLE 4

Vitamin B-12 and MMA concentrations by vitamin B12 supplement use status and sociodemographic characteristics among United States adults aged ≥19 y: NHANES 2007–2018

Vitamin B12 supplement use	Adjusted serum vitamin B12 concentration[1] (pmol/L)		Adjusted MMA concentration[1] (nmol/L)	
	Unweighted n	Geometric mean (95% CI)	Unweighted n	Geometric mean (95% CI)
Total				
Total				
Total	9297	390 (384, 396)	9298	150 (147, 153)
B12 supp user	2960	482 (468, 496)	2958	140 (136, 144)
B12 supp nonuser	6337	347 (341, 353)	6340	156 (153, 160)
P value[2]	—	<0.001	—	<0.001
Sex				
F				
Total	4707	397 (391, 403)	4709	149 (145, 153)
B12 supp user	1634	493 (475, 511)	1634	141 (137, 147)
B12 supp nonuser	3073	349 (342, 357)	3075	155 (149, 161)
P value	—	<0.001	—	<0.001
M				
Total	4590	383 (374, 393)	4589	152 (148, 156)
B12 supp user	1326	470 (453, 488)	1324	139 (134, 144)
B12 supp nonuser	3264	344 (335, 352)	3265	158 (154, 161)
P value	—	<0.001	—	<0.001
Age				
19–39 y				
Total	3302	375 (368, 383)	3301	132 (129, 135)
B12 supp user	832	443 (430, 455)	830	128 (124, 132)
B12 supp nonuser	2470	357 (349, 364)	2471	131 (128, 135)
P value	—	<0.001	—	0.19
40–59 y				
Total	3129	385 (376, 395)	3128	152 (148, 156)
B12 supp user	1009	473 (450, 497)	1008	139 (134, 145)

Vitamin B12 supplement use	Adjusted serum vitamin B12 concentration[1] (pmol/L)		Adjusted MMA concentration[1] (nmol/L)	
	Unweighted n	Geometric mean (95% CI)	Unweighted n	Geometric mean (95% CI)
B12 supp nonuser	2120	338 (330, 347)	2120	160 (155, 165)
P value	—	<0.001	—	<0.001
≥60 y				
Total	2866	419 (405, 433)	2869	178 (173, 184)
B12 supp user	1119	535 (511, 560)	1120	166 (160, 172)
B12 supp nonuser	1747	341 (329, 352)	1749	195 (187, 204)
P value	—	<0.001	—	<0.001
Race/Ethnicity				
NH White				
Total	3908	382 (375, 389)	3906	159 (155, 162)
B12 supp user	1512	467 (450, 484)	1510	150 (146, 154)
B12 supp nonuser	2396	335 (329, 342)	2396	169 (164, 174)
P value	—	<0.001	—	<0.001
NH Black				
Total	2069	426 (414, 438)	2068	130 (126, 133)
B12 supp user	556	542 (513, 572)	556	119 (115, 124)
B12 supp nonuser	1513	383 (372, 395)	1512	130 (126, 135)
P value	—	<0.001	—	<0.001
Hispanic				
Total	1985	402 (387, 417)	1988	134 (130, 138)
B12 supp user	454	504 (454, 560)	454	122 (116, 129)
B12 supp nonuser	1531	369 (353, 386)	1534	130 (126, 134)
P value	—	<0.001	—	0.044
NH Asian[3]				
Total	1054	389 (371, 408)	1055	140 (133, 147)
B12 supp user	352	496 (460, 535)	352	131 (122, 141)
B12 supp nonuser	702	358 (343, 374)	703	141 (133, 150)
P value	—	<0.001	—	0.082

Abbreviations: B12 supp, vitamin B12 supplement; NH, non-Hispanic.

[1]Adjusted for sex, age category, race/ethnicity, current smoking status, and BMI.

[2]*P* value for testing differences in concentrations between vitamin B12 supplement users and nonusers based on the Wald test.

[3]NH Asian estimates are for 2011–2018.

TABLE 5

Adjusted prevalence (95% CI) of high serum folate, serum folate deficiency, and RBC folate deficiency by folic acid consumption group and sociodemographic characteristics among United States adults aged ≥19 y: NHANES 2007–2018

Characteristics	Folic acid consumption group					
	All participants	**ECGP/CMF only**	**ECGP/CMF + RTE**	**ECGP/CMF + SUP**	**ECGP/CMF + RTE + SUP**	***P* value**[1]
	Percentage (95% CI)	**Percentage (95% CI)**	**Percentage (95% CI)**	**Percentage (95% CI)**	**Percentage (95% CI)**	
High serum folate >92 nmol/L (95th percentile)						
Total	5.0 (4.5, 5.5)	1.4 (1.1, 1.7)	2.8 (2.1, 3.5)	8.4 (7.4, 9.4)	11.8 (10.3, 13.3)	<0.001
Sex[2]						
F	6.5 (5.8, 7.2)	1.9 (1.4, 2.4)	3.6 (2.5, 4.8)	11.5 (9.9, 13.0)	16.4 (14.1, 18.7)	<0.001
M	3.3 (2.8, 3.8)	1.0 (0.6, 1.3)	1.9 (1.1, 2.7)	5.1 (4.1, 6.1)	6.9 (5.2, 8.5)	<0.001
Age[2]						
19–39 y	1.6 (1.2, 2.0)	0.4 (0.1, 0.7)	1.1 (0.5, 1.6)	2.3 (1.2, 3.5)	5.9 (3.7, 8.1)	<0.001
40–59 y	2.8 (2.2, 3.5)	0.8 (0.5, 1.2)	1.9 (0.6, 3.2)	5.1 (3.7, 6.5)	6.2 (3.6, 8.8)	<0.001
≥60 y	11.7 (10.6, 12.7)	3.7 (2.9, 4.6)	6.5 (4.7, 8.3)	21.4 (19.0, 23.7)	28.2 (24.6, 31.7)	<0.001
Race/Ethnicity[2]						
NH White	5.8 (5.2, 6.4)	1.8 (1.3, 2.2)	3.6 (2.5, 4.6)	10.3 (8.9, 11.7)	14.0 (12.0, 16.0)	<0.001
NH Black	2.4 (1.8, 3.0)	1.0 (0.6, 1.4)	0.4 (0.1, 0.8)	3.7 (2.6, 4.7)	6.4 (2.8, 10.0)	<0.001
Hispanic	2.3 (1.9, 2.7)	0.5 (0.3, 0.6)	1.7 (1.0, 2.5)	3.2 (2.2, 4.2)	7.1 (4.5, 9.7)	<0.001
NH Asian[3]	4.4 (3.3, 5.5)	1.6 (0.8, 2.4)	2.2 (0.3, 4.0)	9.3 (6.8, 11.8)	12.2 (7.0, 17.5)	<0.001
High serum folate >77 nmol/L (90th percentile)						
Total	9.8 (9.1, 10.4)	3.0 (2.5, 3.5)	6.7 (5.5, 7.9)	16.7 (15.3, 18.1)	23.0 (21.2, 24.8)	<0.001
Sex[2]						
F	12.4 (11.5, 13.4)	4.2 (3.4, 4.9)	8.9 (7.0, 10.7)	21.8 (19.9, 23.8)	29.3 (26.4, 32.3)	<0.001
M	6.8 (6.2, 7.4)	1.8 (1.3, 2.3)	4.4 (3.1, 5.8)	11.3 (9.6, 12.9)	16.1 (13.6, 18.7)	<0.001
Age[2]						
19–39 y	3.8 (3.2, 4.4)	1.0 (0.7, 1.4)	3.2 (1.9, 4.5)	6.7 (4.9, 8.5)	12.5 (9.5, 15.5)	<0.001
40–59 y	7.1 (6.1, 8.1)	2.5 (1.8, 3.2)	5.3 (3.0, 7.6)	12.1 (10.0, 14.2)	16.0 (12.2, 19.8)	<0.001
≥60 y	20.4 (19.0, 21.8)	6.4 (4.9, 7.9)	13.5 (10.6, 16.4)	36.9 (34.1, 39.7)	47.2 (43.2, 51.2)	<0.001
Race/Ethnicity[2]						

Characteristics	Folic acid consumption group					
	All participants	ECGP/CMF only	ECGP/CMF + RTE	ECGP/CMF + SUP	ECGP/CMF + RTE + SUP	*P* value[1]
	Percentage (95% CI)	Percentage (95% CI)	Percentage (95% CI)	Percentage (95% CI)	Percentage (95% CI)	
NH White	11.4 (10.6, 12.3)	3.7 (2.9, 4.5)	8.3 (6.6, 9.9)	20.1 (18.1, 22.0)	26.8 (24.6, 29.1)	<0.001
NH Black	4.8 (4.0, 5.6)	1.6 (1.1, 2.1)	2.4 (1.2, 3.5)	7.9 (6.4, 9.4)	13.6 (8.3, 19.0)	<0.001
Hispanic	5.3 (4.6, 5.9)	1.5 (1.1, 2.0)	4.4 (3.1, 5.8)	8.0 (6.2, 9.7)	13.2 (9.3, 17.2)	<0.001
NH Asian	8.7 (7.0, 10.3)	3.6 (2.3, 4.8)	3.8 (1.4, 6.3)	17.8 (14.0, 21.5)	20.6 (12.8, 28.5)	<0.001
High serum folate >60 nmol/L (80th percentile)						
Total	19.8 (18.8, 20.8)	7.1 (6.3, 7.8)	17.8 (16.0, 19.5)	33.2 (31.3, 35.1)	45.1 (42.3, 47.9)	<0.001
Sex[2]						
F	23.5 (22.1, 24.8)	9.3 (8.1, 10.4)	21.4 (18.8, 24.0)	38.8 (36.4, 41.3)	53.2 (49.5, 57.0)	<0.001
M	15.9 (14.9, 16.8)	4.8 (4.0, 5.6)	14.2 (12.1, 16.3)	27.1 (24.6, 29.7)	36.6 (32.9, 40.2)	<0.001
Age[2]						
19–39 y	11.0 (9.9, 12.1)	3.8 (3.0, 4.5)	12.2 (10.1, 14.2)	18.4 (15.7, 21.2)	30.7 (26.4, 34.9)	<0.001
40–59 y	17.5 (16.1, 18.9)	6.3 (5.2, 7.3)	16.6 (13.3, 19.9)	28.7 (25.6, 31.8)	38.1 (32.6, 43.6)	<0.001
≥60 y	34.2 (32.1, 36.2)	12.5 (10.7, 14.4)	27.1 (23.8, 30.4)	59.1 (55.9, 62.4)	72.5 (68.5, 76.5)	<0.001
Race/Ethnicity[2]						
NH White	22.5 (21.3, 23.7)	8.0 (6.9, 9.1)	20.3 (18.1, 22.6)	37.8 (35.1, 40.4)	50.1 (46.8, 53.4)	<0.001
NH Black	10.9 (9.6, 12.2)	3.6 (2.8, 4.4)	8.2 (6.0, 10.4)	19.0 (16.5, 21.5)	29.9 (22.8, 36.9)	<0.001
Hispanic	14.2 (12.9, 15.4)	5.4 (4.4, 6.4)	13.8 (11.1, 16.4)	23.3 (20.4, 26.3)	35.6 (29.1, 42.1)	<0.001
NH Asian	19.4 (17.1, 21.6)	9.9 (7.9, 12.0)	15.8 (10.2, 21.4)	36.8 (32.1, 41.6)	51.2 (41.4, 61.0)	<0.001
Serum folate deficiency (<7 nmol/L)[4]						
Total	0.6 (0.4, 0.7)	0.6 (0.4, 0.8)	0.7 (0.3, 1.1)	0.5 (0.3, 0.7)	0.4 (0.2, 0.7)	0.012
Sex						
F	0.5 (0.4, 0.6)	—	—	—	—	—
M	0.6 (0.5, 0.8)	—	—	—	—	—
Age[2]						
19–39 y	0.5 (0.3, 0.7)	—	—	—	—	—
40–59 y	0.6 (0.4, 0.9)	—	—	—	—	—
≥60 y	0.6 (0.4, 0.8)	—	—	—	—	—
Race/Ethnicity[2]						

Characteristics	Folic acid consumption group					
	All participants	**ECGP/CMF only**	**ECGP/CMF + RTE**	**ECGP/CMF + SUP**	**ECGP/CMF + RTE + SUP**	***P* value**[1]
	Percentage (95% CI)	**Percentage (95% CI)**	**Percentage (95% CI)**	**Percentage (95% CI)**	**Percentage (95% CI)**	
NH White	0.5 (0.4, 0.7)	—	—	—	—	—
NH Black	0.9 (0.5, 1.3)	—	—	—	—	—
Hispanic	0.6 (0.3, 0.9)	—	—	—	—	—
NH Asian	0.7 (0.2, 1.2)	—	—	—	—	—
RBC folate deficiency (<305 nmol/L)[4]						
Total	1.0 (0.7, 1.3)	1.0 (0.7, 1.3)	0.9 (0.4, 1.5)	1.2 (0.7, 1.7)	1.0 (0.5, 1.5)	0.247
Sex						
F	1.2 (0.8, 1.5)	—	—	—	—	—
M	0.9 (0.5, 1.3)	—	—	—	—	—
Age[2]						
19–39 y	0.7 (0.4, 0.9)	—	—	—	—	—
40–59 y	0.9 (0.6, 1.3)	—	—	—	—	
≥60 y	1.7 (1.0, 2.3)	—	—	—	—	—
Race/Ethnicity[2]						
NH White	1.0 (0.7, 1.4)	—	—	—	—	—
NH Black	1.2 (0.7, 1.7)	—	—	—	—	—
Hispanic	1.1 (0.6, 1.5)	—	—	—	—	—
NH Asian	0.6 (0.2, 1.0)	—	—	—	—	—

Abbreviations: CMF, corn masa flour; ECGP, enriched cereal grain product; NH, non-Hispanic; RTE, ready-to-eat cereal: SUP, folic acid–containing supplement.

[1] *P* values for testing differences in prevalence across different folic acid consumption groups using a chi-square test.

[2] *P* values were <0.05 for testing difference in prevalence across different demographic subgroups using a chi-square test, e.g., female compared with male.

[3] All NH Asian estimates are for 2011–2018.

[4] Estimates by folic acid consumption group and demographic characteristics were suppressed due to small sample size and unreliable estimates, i.e., degree of freedom <8.

TABLE 6

Adjusted prevalence (95% CI) of serum vitamin B12 deficiency and insufficiency by vitamin B12 supplement use status and sociodemographic characteristics among United States adults aged ≥19 y: NHANES 2007–2018

Characteristics	Vitamin B12 supplement use status			
	All participants	Vitamin B12 nonuser	Vitamin B12 user	*P* value[1]
	Percentage (95% CI)	Percentage (95% CI)	Percentage (95% CI)	
Serum Vitamin B12 deficiency (<148 pmol/L)				
Total	3.6 (2.9, 4.4)	4.4 (3.6, 5.1)	2.3 (1.3, 3.3)	<0.001
Sex				
F	3.7 (3.1, 4.3)	4.2 (3.5, 5.0)	2.9 (1.5, 4.2)	0.042
M	3.6 (2.4, 4.7)	4.4 (3.1, 5.8)	1.7 (0.7, 2.8)	<0.001
Age				
19–39 y	4.4 (3.3, 5.5)	5.2 (4.2, 6.2)	3.1 (0.9, 5.2)	0.034
40–59 y	2.7 (1.9, 3.5)	3.0 (1.9, 4.1)	2.1 (0.8, 3.4)	0.222
≥60 y	3.7 (2.2, 5.3)	5.3 (3.4, 7.1)	1.8 (0.4, 3.2)	<0.001
Race/Ethnicity				
NH White	3.4 (2.6, 4.3)	4.3 (3.4, 5.3)	2.1 (0.9, 3.3)	<0.001
NH Black	4.7 (2.5, 7.0)	4.4 (2.7, 6.1)	5.4 (0.7, 10.0)[4]	0.607
Hispanic	3.4 (2.3, 4.4)	3.9 (2.8, 4.9)	1.6 (0.4, 2.7)[4]	0.002
NH Asian[2]	4.1 (2.5, 5.7)	5.7 (3.8, 7.6)	2.8 (0.5, 5.1)[4]	0.038
Serum Vitamin B12 insufficiency (<221 pmol/L)				
Total	12.5 (11.3, 13.8)	16.3 (14.9, 17.8)	5.9 (4.4, 7.3)	<0.001
Sex				
F	13.1 (12.0, 14.3)	17.0 (15.6, 18.5)	6.7 (5.0, 8.4)	<0.001
M	11.9 (9.8, 14.0)	15.5 (13.0, 18.0)	5.0 (3.3, 6.7)	<0.001
Age				
19–39 y	13.5 (11.7, 15.3)	15.6 (13.9, 17.2)	7.7 (4.9, 10.4)	<0.001
40–59 y	11.8 (9.7, 13.9)	15.7 (12.4, 18.9)	5.8 (4.0, 7.5)	<0.001
≥60 y	12.3 (10.5, 14.1)	18.5 (15.8, 21.1)	4.5 (2.9, 6.0)	<0.001
Race/Ethnicity[3]				

Characteristics	Vitamin B12 supplement use status			
	All participants	Vitamin B12 nonuser	Vitamin B12 user	*P* value[1]
	Percentage (95% CI)	Percentage (95% CI)	Percentage (95% CI)	
NH White	12.9 (11.2, 14.6)	17.7 (15.7, 19.7)	5.7 (3.8, 7.6)	<0.001
NH Black	10.8 (8.3, 13.4)	12.4 (9.9, 14.9)	8.2 (4.2, 12.2)	0.030
Hispanic	11.5 (10.0, 12.9)	13.2 (11.5, 14.8)	6.2 (3.9, 8.6)	<0.001
NH Asian	14.1 (11.4, 16.8)	16.5 (13.3, 19.7)	7.3 (4.1, 10.5)	<0.001

Abbreviation: NH, non-Hispanic.

[1] *P* values for testing differences in prevalence across different vitamin B12 supplement use groups using a chi-square test.

[2] All NH Asian estimates are for 2011–2018.

[3] *P* values were < 0.05 for testing differences in prevalence across different demographic subgroups using a chi-square test.

[4] Degree of freedom <8.