Published in final edited form as:
*Am J Clin Nutr*. 2006 April ; 83(4): 905–911.

# Dietary choline and betaine assessed by food-frequency questionnaire in relation to plasma total homocysteine concentration in the Framingham Offspring Study[2]

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## Abstract

**Background:** Epidemiologic studies of choline and betaine intakes have been sparse because a food-composition database was not available until recently. The physiologic relevance of a variation in dietary choline and betaine in the general population and the validity of intake assessed by food-frequency questionnaire (FFQ) have not been evaluated.

**Objective:** This study was conducted to examine the physiologic relevance and validity of choline and betaine intakes measured by an FFQ.

**Design:** We examined the relations between choline and betaine intakes measured by FFQ and plasma total homocysteine (tHcy) concentrations in 1960 participants from the Framingham Offspring Study.

**Results:** Higher intakes of dietary choline and betaine were related to lower tHcy concentrations independent of other determinants, including folate and other B vitamins. For the lowest and highest quintiles of dietary choline plus betaine, the multivariate geometric means for tHcy were 10.9 and 9.9 $\mu$mol/L ($P$ for trend < 0.0001). The inverse association was manifested primarily in participants with low folate intakes ($P$ for interaction < 0.0001). Among participants with folate intakes ≤250 $\mu$g/d, the geometric mean tHcy concentrations in the lowest and highest quintiles of choline plus betaine intakes were 12.4 and 10.2 $\mu$mol/L ($P$ for trend < 0.0001). Except for choline from phosphatidylcholine, individual forms of choline were inversely associated with tHcy concentrations.

**Conclusions:** Our findings provide support for a physiologically important variation in choline and betaine intakes in the general population and for the validity of intake measured by FFQ.

### Keywords

Choline; betaine; phosphocholine; glycerophosphocholine; phosphatidylcholine; lecithin; sphingomyelin; homocysteine; methylation; Framingham Offspring Study

[2]Supported by the Framingham Heart Study of the National Heart, Lung, and Blood Institute of the National Institutes of Health (contract no. N01-HC-25195) and by research grant CA108341 from the National Institutes of Health. SHZ was supported by research grants DK55865 and DK56350 from the National Institutes of Health and the US Department of Agriculture (59-1235-0-0059).

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All authors participated in the design of the study, interpretation of the data, and writing of the manuscript. None of the authors had a personal or financial conflict of interest.

## INTRODUCTION

Choline is an essential human nutrient that serves several biological functions. It is a source of methyl groups, a precursor for the synthesis of phospholipids such as phosphatidylcholine and sphingomyelin, and a precursor for the synthesis of the neurotransmitter acetylcholine (1). Betaine is an osmolyte in addition to its function as a methyl-group donor (2). Homocysteine is converted to methionine by acquiring a methyl group. Folate can donate a methyl group to homocysteine; alternatively, choline is converted to betaine, which can donate a methyl group to homo-cysteine. Extensive epidemiologic research has identified low folate intake as a risk factor for neural tube defects, cardiovascular diseases, and several cancers (3-5). However, epidemio-logic studies on dietary choline and betaine are few because a food-composition database was available only recently (6). In a case-control study, higher choline intake was associated with a reduced risk of neural tube defect independent of folate intake (7). Choline may also be related to other diseases such as neurodegenerative disorders, including Alzheimer disease, through mechanisms unrelated to methyl-group metabolism (8). Higher betaine intake was also related to improvement in atherosclerosis (9) and fatty liver (10).

An elevated plasma concentration of total homocysteine (tHcy) is a risk factor for cardiovascular disease (11-16), dementia (16,17), Alzheimer disease (16,17), some cancers (18-22), and mortality (23,24). Many studies have found that intakes of folate and vitamins B-6 and B-12, nutrients involved in methyl-group metabolism, predict tHcy concentrations (13,25-32). Therefore, it is plausible that intakes of choline and betaine also predict tHcy concentrations. In our study, to assess the physiologic role of choline intake in a free-living population, we examined the relation between intake of choline measured by a food-frequency questionnaire (FFQ) and plasma total tHcy concentrations from participants in the Framingham Offspring Study. Several known determinants of tHcy, including intakes of folate, vitamin B-6, alcohol, and caffeine, predicted tHcy concentrations in this population (28) and were accounted for in the current analyses.

## SUBJECTS AND METHODS

### Subjects

Participants in this analysis were members of the Framingham Offspring Study, who were offspring and their spouses of the participants in the Framingham Heart Study, an epidemiologic study of heart disease. The Framingham Heart Study was established in Framingham, MA, between 1948 and 1950 with a cohort of 5209 men and women aged 30-59 y (33). By 1971, the original cohort included 1644 husband-wife pairs and 1921 single individuals. The offspring of the original cohort and the offsprings' spouses were invited to participate in the Framing-ham Offspring Study in 1971. Overall, 5135 of the 6838 eligible individuals participated in the first examination (34,35); 82% of the participants lived in Massachusetts. The age range of participants was between 12 and 58 y, but most were between 20 and 52 y at the first round of examinations, which was begun in 1971 and completed in 1975. The Offspring cohort undergoes repeat examination approximately every 3–4 y. Nearly all participants are whites. Of the 3799 individuals who attended the fifth examination cycle of the study between 1991 and 1994, 1960 (920 men and 1040 women) had valid FFQs; had complete data on plasma tHcy, vitamin, and creatinine concentrations; were free of diagnosed cardiovascular disease; and were not taking medications that might alter tHcy concentrations (28). These men and women were included in the current analyses. The mean age of the participants was 54 y for both men and women, with a range of 28-82 y. The procedures and protocols of the study were approved by the Institutional Review Board for Human Research at Boston Medical Center.

### Measurements

Usual dietary intake was assessed with a semiquantitative FFQ covering ≈130 food items (36). Before the fifth examination of the cohort, the FFQ was mailed to participants, who were asked to complete the form and bring it to their appointments. The questionnaire also included items about the use of vitamin supplements and the type of breakfast cereal most frequently consumed.

The choline and betaine composition of individual foods was added to the FFQ's nutrient database (Harvard University Food Composition Database) with the use of values published by Zeisel et al (6) and from the US Department of Agriculture's choline database (37). Total choline intake was calculated as the sum of intake from free choline, phosphocholine, glycerophosphocholine, phosphatidylcholine (lecithin), and sphingomyelin. We used the regression-residual method to adjust nutrient intakes for a total energy intake of 1803 kcal/d (median energy intake in this population) (38).

As part of the fifth cohort examination, fasting (>10 h) blood samples were obtained for measurement of tHcy (28). Plasma tHcy was measured by HPLC with fluorometric detection (39). The CV for the assay was 8%.

### Statistical analyses

To determine the main food sources of choline and betaine in this population, we calculated the contribution of each food in the FFQ by summing the amount consumed by all participants and dividing this by the total intake from all foods for all participants (40). We used logarithmically transformed tHcy concentrations to improve normality of the distribution and exponentiated the values to provide geometric means and 95% CIs. We assessed the age- and sex-adjusted and multivariate-adjusted geometric mean tHcy concentrations and 95% CIs within quintiles of dietary choline and betaine by using SAS PROC GLM (version 8.2; SAS Institute, Cary, NC). Multivariate-adjusted models included age, sex, smoking, alcohol intake, caffeine intake, hypertensive medication use, serum creatinine concentrations, and intakes of fo-late, vitamin B-6, and vitamin B-12; all of these were predictors of tHcy concentrations in this population or other populations (27,28). Tests for trend were conducted by using the median value for each category of intake as a continuous variable. Tests for interaction were conducted by introducing an interaction term (choline plus betaine × the factor of interest) in a multivariate model.

## RESULTS

Mean intakes and correlations of energy-adjusted choline and betaine in the Framingham Offspring Study are presented in Table 1. The energy-adjusted mean (±SD) choline intake was 313 ± 61 mg/d. The mean values were 314 mg/d for women and 312 mg/d for men. Approximately half of choline intake came from phosphatidylcholine. The energy-adjusted mean for betaine intake was 208 ± 90 mg/d. The mean values were 216 mg/d for women and 200 mg/d for men. The correlation between choline and betaine was low, because food sources were quite different. The correlations between the choline and betaine and the B vitamins which are related to methyl-group metabolism (folate and vitamins B-6 and B-12) are of interest because these nutrients share food sources. However, the correlations between betaine and these vitamins were low (0.27 for folate, 0.20 for vitamin B-6, and 0.10 for vitamin B-12). The correlations between choline and these vitamins were modest also (0.21 for folate, 0.32 for vitamin B-6, and 0.34 for vitamin B-12).

The main dietary sources of choline and betaine in this cohort are listed in Table 2; these figures were calculated from the composition of a given food and its frequency of consumption (40).

Animal-based foods, including red meat, poultry, milk, and eggs, were the main sources of choline. Grain products and vegetables such as spinach and beets were the main sources of betaine. Ten main sources of these nutrients accounted for 65% of choline intake and 81% of betaine intake.

Higher intakes of choline and betaine were each related to lower plasma tHcy concentrations (Table 3). The associations were consistent in age- and sex-adjusted analyses and in multivariate analyses that adjusted for other predictors of tHcy concentrations, including intakes of folate and B vitamins. Because choline is irreversibly converted to betaine when it donates a methyl group to tHcy, we also combined the intakes of choline and betaine; the combined values also predicted tHcy concentrations. For the lowest and highest quintiles of combined dietary choline and betaine, the multivariate geometric mean tHcy concentrations were 10.9 and 9.9 $\mu$mol/L, respectively ($P$ for trend < 0.0001), after adjusting for multiple predictors of tHcy concentrations. The intakes of all of the individual choline compounds predicted tHcy concentrations except phosphatidylcholine (Table 4).

Because either folate or choline (through betaine) can donate a methyl group to tHcy, it is plausible that the pathway mediated by choline and betaine becomes more important when folate intake is low. To evaluate this hypothesis, we stratified the association between intake of choline plus betaine and tHcy concentrations by 3 levels of folate intake (≤250, >250 to ≤400, and >400 $\mu$g/d; Table 5). Consistent with our hypothesis, choline plus betaine predicted tHcy only when folate intake was low (≤250 $\mu$g/d; $P$ for interaction < 0.0001). For increasing quintiles of dietary choline plus betaine, the corresponding mean tHcy concentrations were 12.4, 11.2, 10.7, 10.8, and 10.2 $\mu$mol/L ($P$ for trend < 0.0001).

Alcohol is a folate antagonist and reduces bioavailable folate concentrations (41,42). Choline plus betaine predicted tHcy concentrations only among alcohol drinkers ($P$ for interaction = 0.03) (Table 5).

We also examined the association between dietary choline plus betaine and tHcy concentrations by age (≤50, 51–60, and >60 y) and sex (male and female) (Table 5). The associations did not differ by age groups ($P$ for interaction = 0.29) but differed by sex; men showed a stronger association than did women ($P$ for interaction = 0.004).

## DISCUSSION

In our study, intakes of choline and betaine predicted plasma tHcy concentrations independent of other important predictors, including intakes of folate and B vitamins. The inverse association between choline plus betaine and tHcy concentrations was manifested among participants with low folate intake and participants consuming alcohol.

Choline has several biological functions. Along with folate, it is a source of methyl groups. Choline is oxidized to betaine, which can donate a methyl group to homocysteine to form methionine. Choline is involved in lipid transport as a precursor for phospholipids such as phosphatidylcholine and sphingomyelin, which are incorporated into cellular membrane and are involved in signal transduction (1). Choline affects nerve signaling as a precursor for the neurotransmitter acetylcholine and is essential in brain development and normal memory function (43-47). Perturbation of phospholipid metabolism and neurotransmitter production may underlie development of degenerative diseases such as Alzheimer disease. Animal studies have found that prolonged depletion of choline promotes fatty liver, DNA hypomethylation, and tumor development in the liver even in the absence of any additional carcinogens (48-50). Betaine is an osmolyte; protects cells, proteins, and enzymes from environmental stress (2); and shows a beneficial effect for atherosclerosis (9) and fatty liver (10). Until recently, dietary choline and betaine have not been extensively investigated in epidemiologic

studies because of lack of food-composition databases. Whether choline and betaine intakes would be measured accurately by using an FFQ and whether the variation of intake in the general population is physiologically important have not been examined. Our findings provide strong evidence that choline and betaine intakes measured by FFQs are valid and support the contention that variation in intake among free-living populations is physiologically meaningful.

Although choline is synthesized in the body, humans still need choline from diet. The recommended daily intake was set in 1998 at 550 mg/d for men and 425 mg/d for women (51). Our data show that mean intake in this population is lower than the recommended daily intake. A study measured the choline content of ad libitum diets by healthy adult volunteers housed in a clinical research center and compared these with intake from 3-d food records assessed immediately before study enrollment (52). Male and female subjects consumed 631 and 443 mg choline/d when observed, but the intakes estimated from the food records were significantly lower. This difference between observed and reported intakes was not apparent when data were normalized for energy intake, which suggests that the choline composition of the diet was reported accurately but that energy intake was underre-ported on the food records (52).

Although choline is widely available in food, our data show that most choline intake in the general population comes from only a few food sources. Humans can obtain betaine either from diet or from endogenous synthesis from choline. Most betaine intake in our population also came from limited food sources.

Methylation of homocysteine by choline and betaine is confined to the liver and kidney, but methylation of homocysteine by folate exists in all body cells (53). Methylation pathways mediated by choline and betaine and folate are interrelated; disruption of one pathway may affect the others. Studies among animals and humans support this possibility. Animals with a choline-deficient diet had lower hepatic folate concentrations (54), and animals with folate deficiency had depletion of hepatic choline concentrations (55). Folate supplementation raised plasma betaine concentrations in a clinical trial (56). Depletion and subsequent repletion of folate intake affected plasma choline concentrations (57). An inverse association between plasma betaine and tHcy concentrations was most pronounced at low serum folate concentrations (58). Our data also show that choline and betaine intakes affect tHcy concentrations and, presumably, methyl-group metabolism, especially when folate intake is low. In other words, even if folate intake is low, methyl-group metabolism may function properly if choline and betaine intakes are adequate. This may help explain some discrepancies in the findings of previous epidemiologic studies that examined folate intake and chronic diseases (59). In a case-control study, higher maternal periconceptional choline and betaine intakes were associated with a reduced risk of neural tube defects, a disease related to one-carbon metabolism (7); the multivariate odds ratio for the highest compared with lowest quartile of choline intake was 0.51 (95% CI: 0.25, 1.07), independent of folate intake.

Depletion of choline intake in humans raised plasma tHcy concentrations after a methionine load (60), and betaine supplementation reduced the elevation of plasma tHcy concentration after a methionine load (61). Supplementation of betaine (1.5–6 g/d or higher) was used to lower tHcy concentrations among people with hyperhomocysteinemia (53) and lowered fasting tHcy concentrations in the general population up to 20% (61). High-dose supplementation of choline as phosphatidylcholine (2.6 g choline/d) lowered fasting as well as postmethionine-loaded concentrations of tHcy in healthy men (62). The doses used in those studies are not easily achieved by typical diet. Our study adds further evidence that intakes of <1 g choline or betaine/d can reduce tHcy concentrations in a free-living population.

Among the choline-containing compounds, phosphatidylcholine was not related to plasma tHcy concentrations, even though it was the largest component of total choline intake. Because phosphatidylcholine and sphingomyelin are lipid soluble, whereas other choline compounds are water soluble (6), the former are absorbed through different pathways and may have different bioavailabilities and fates. Phosphatidylcholine supplementation did lower plasma tHcy concentrations, although the dose was much higher than that normally available from diet alone (62).

We found that the association between choline plus betaine intakes and tHcy concentrations was stronger among men than among women. This may be partly due to higher folate concentrations in women than in men in this population (63). Women may also have higher de novo synthesis of choline (48,62) and lower tHcy concentrations than men (27). A preliminary analysis of choline intake and tHcy concentrations in women did not find an association (64).

In conclusion, we found that intakes of choline and betaine predicted plasma tHcy concentrations, especially when folate intakes were low. Our data support the validity of intake measured by FFQs and indicate the physiologic importance of these nutrients within the range consumed by a general population. Future epidemiologic studies examining methyl-group availability and chronic diseases should account for these nutrients in addition to folate.

**Acknowledgements**

We thank Laura Sampson for construction of the choline intake database and Eileen Hibert and Gail Rogers for computer support.

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**TABLE 1**

Mean intakes and correlations of energy-adjusted choline compounds and betaine in the Framingham Offspring Study of 920 men and 1040 women

| | | Correlations | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Intake | Total choline | Free choline | Choline from glycerophosphocholine | Choline from phosphocholine | Choline from phosphatidylcholine | Choline from sphingomyelin | Betaine |
| | *mg/d* | | | | | | | |
| Total choline | 313 ± 61[1] | 1.00 | 0.57 | 0.50 | 0.57 | 0.72 | 0.67 | 0.14 |
| Free choline | 77 ± 19 | | 1.00 | 0.50 | 0.39 | 0.08 | 0.06 | 0.28 |
| Choline from glycerophosphocholine | 54 ± 21 | | | 1.00 | 0.54 | −0.08 | 0.11 | 0.11 |
| Choline from phosphocholine | 14 ± 5 | | | | 1.00 | 0.22 | 0.43 | 0.17 |
| Choline from phosphatidylcholine | 150 ± 43 | | | | | 1.00 | 0.73 | 0.05 |
| Choline from sphingomyelin | 18 ± 6 | | | | | | 1.00 | −0.05 |
| Betaine | 208 ± 90 | | | | | | | 1.00 |

[1] $\bar{x}$ ± SD (all such values).

**TABLE 2**

Food sources of choline and betaine in the Framingham Offspring Study of 920 men and 1040 women

| | Choline | | | Betaine | | |
|---|---|---|---|---|---|---|
| Rank | Food | Percentage | Cumulative percentage | Food | Percentage | Cumulative percentage |
| | | % | % | | % | % |
| 1 | Red meat | 14.26 | 14.26 | Spinach | 25.14 | 25.14 |
| 2 | Poultry | 12.98 | 27.24 | Pasta | 11.84 | 36.98 |
| 3 | Milk | 9.52 | 36.76 | White bread | 9.35 | 46.33 |
| 4 | Eggs | 7.57 | 44.33 | Cold breakfast cereal | 8.05 | 54.38 |
| 5 | Fish | 5.22 | 49.55 | English muffins, bagels, or rolls | 7.07 | 61.45 |
| 6 | Coffee | 4.00 | 53.55 | Dark bread | 5.95 | 67.40 |
| 7 | Beer | 3.29 | 56.84 | Beer | 3.97 | 71.37 |
| 8 | Potatoes | 4.03 | 60.87 | Pizza | 3.39 | 74.76 |
| 9 | Oranges and orange juice | 2.27 | 63.14 | Beets | 2.91 | 77.67 |
| 10 | Broccoli | 1.88 | 65.02 | Red meat | 2.83 | 80.50 |

## TABLE 3

Geometric mean (95% CI) total plasma homocysteine concentrations by quintile (Q) of energy-adjusted choline and betaine intakes in the Framingham Offspring Study of 920 men and 1040 women

| Mean intake (mg/d) | Age and sex adjusted | Multivariate adjusted 1[1] | Multivariate adjusted 2[2] |
|---|---|---|---|
| Choline + betaine | *μmol/L* | *μmol/L* | *μmol/L* |
| Q1, 383 | 10.5 (10.2, 10.9) | 11.3 (10.9, 11.8) | 10.9 (10.5, 11.3) |
| Q2, 462 | 9.6 (9.3, 9.9) | 10.3 (9.9, 10.7) | 10.0 (9.7, 10.4) |
| Q3, 511 | 9.3 (9.0, 9.6) | 10.0 (9.6, 10.4) | 9.8 (9.5, 10.2) |
| Q4, 564 | 9.2 (8.9, 9.5) | 9.8 (9.5, 10.2) | 9.8 (9.4, 10.2) |
| Q5, 689 | 9.0 (8.7, 9.3) | 9.7 (9.3, 10.0) | 9.9 (9.6, 10.3) |
| *P* for trend[3] | <0.0001 | <0.0001 | <0.0001 |
| Choline | | | |
| Q1, 234 | 10.1 (9.8, 10.4) | 11.0 (10.5, 11.4) | 10.6 (10.2, 11.0) |
| Q2, 283 | 9.9 (9.6, 10.2) | 10.7 (10.3, 11.1) | 10.4 (10.0, 10.8) |
| Q3, 311 | 9.5 (9.2, 9.8) | 10.3 (9.9, 10.7) | 10.1 (9.7, 10.5) |
| Q4, 339 | 9.0 (8.7, 9.3) | 9.7 (9.4, 10.1) | 9.7 (9.3, 10.1) |
| Q5, 401 | 9.0 (8.8, 9.3) | 9.7 (9.3, 10.1) | 9.8 (9.5, 10.2) |
| *P* for trend[3] | <0.0001 | <0.0001 | <0.0001 |
| Betaine | | | |
| Q1, 112 | 10.0 (9.7, 10.3) | 10.7 (10.3, 11.2) | 10.4 (10.1, 10.8) |
| Q2, 159 | 9.7 (9.4, 10.0) | 10.5 (10.1, 11.0) | 10.3 (9.9, 10.7) |
| Q3, 196 | 9.4 (9.1, 9.7) | 10.1 (9.7, 10.5) | 9.9 (9.6, 10.3) |
| Q4, 235 | 9.1 (8.9, 9.4) | 9.9 (9.5, 10.3) | 9.8 (9.4, 10.1) |
| Q5, 340 | 9.2 (8.9, 9.5) | 9.9 (9.6, 10.3) | 10.1 (9.8, 10.5) |
| *P* for trend[3] | <0.0001 | <0.0001 | 0.05 |

[1] Adjusted for age, sex, smoking, alcohol intake, caffeine intake, hypertensive medication use, and serum creatinine concentration.

[2] Adjusted for the variables in multivariate 1 plus intakes of folate, vitamin B-6, and vitamin B-12.

[3] Calculated with median intake in each quintile as a continuous variable.

## TABLE 4

Age- and sex-adjusted and multivariate-adjusted geometric mean (95% CI) total plasma homocysteine concentrations by quintile (Q) of energy-adjusted choline intakes (5 main food sources) in the Framingham Offspring Study of 920 men and 1040 women

| Mean intake (mg/d) | Age and sex adjusted | Multivariate adjusted[1] |
|---|---|---|
| Free choline (coffee, potato, beer, milk, and chicken) | *μmol/L* | *μmol/L* |
| Q1, 55 | 10.0 (9.7, 10.3) | 10.6 (10.2, 11.0) |
| Q2, 68 | 9.4 (9.1, 9.7) | 10.0 (9.6, 10.4) |
| Q3, 75 | 9.5 (9.2, 9.7) | 10.1 (9.8, 10.5) |
| Q4, 84 | 9.3 (9.0, 9.6) | 9.9 (9.6, 10.3) |
| Q5, 105 | 9.4 (9.1, 9.7) | 9.9 (9.6, 10.3) |
| *P* for trend[2] | 0.006 | 0.01 |
| Choline from glycerophosphocholine (milk, fish, beer, coffee, and yogurt) | | |
| Q1, 30 | 10.2 (9.9, 10.5) | 10.7 (10.3, 11.1) |
| Q2, 41 | 9.9 (9.6, 10.2) | 10.6 (10.2, 11.0) |
| Q3, 50 | 9.4 (9.1, 9.7) | 10.0 (9.7, 10.4) |
| Q4, 61 | 9.2 (8.9, 9.5) | 9.9 (9.5, 10.2) |
| Q5, 87 | 8.8 (8.5, 9.1) | 9.5 (9.1, 9.8) |
| *P* for trend[2] | <0.0001 | <0.0001 |
| Choline from phosphocholine (milk, chicken, broccoli, potato, and tomato) | | |
| Q1, 8 | 10.6 (10.2, 10.9) | 10.7 (10.4, 11.1) |
| Q2, 11 | 9.6 (9.4, 9.9) | 10.1 (9.7, 10.5) |
| Q3, 13 | 9.3 (9.0, 9.6) | 9.8 (9.5, 10.2) |
| Q4, 16 | 9.1 (8.9, 9.4) | 10.0 (9.6, 10.4) |
| Q5, 21 | 8.9 (8.6, 9.1) | 9.8 (9.5, 10.2) |
| *P* for trend[2] | <0.0001 | 0.0003 |
| Choline from phosphatidylcholine (red meat, chicken, eggs, fish, and shellfish) | | |
| Q1, 99 | 10.0 (9.6, 10.3) | 10.4 (10.0, 10.8) |
| Q2, 127 | 9.4 (9.1, 9.7) | 10.0 (9.6, 10.4) |
| Q3, 147 | 9.4 (9.1, 9.7) | 10.2 (9.8, 10.6) |
| Q4, 168 | 9.4 (9.1, 9.7) | 10.1 (9.7, 10.5) |
| Q5, 211 | 9.3 (9.0, 9.6) | 10.0 (9.7, 10.4) |
| *P* for trend[2] | 0.005 | 0.12 |
| Choline from sphingomyelin (chicken, red meat, milk, eggs, and fish) | | |
| Q1, 11 | 9.9 (9.6, 10.2) | 10.5 (10.1, 10.8) |
| Q2, 15 | 9.8 (9.5, 10.2) | 10.4 (10.1, 10.8) |
| Q3, 18 | 9.3 (9.0, 9.6) | 9.9 (9.6, 10.3) |
| Q4, 20 | 9.5 (9.2, 9.8) | 10.1 (9.8, 10.5) |
| Q5, 27 | 9.0 (8.8, 9.3) | 9.7 (9.4, 10.1) |
| *P* for trend[2] | <0.0001 | 0.0002 |

[1] Adjusted for age, sex, smoking, hypertension medication use, serum creatinine, and intakes of alcohol, caffeine, folate, vitamin B-6, and vitamin B-12.

[2] Calculated with median intake in each quintile as a continuous variable.

**TABLE 5**

Multivariate-adjusted geometric mean (95% CI) total plasma homocysteine concentrations by quintile (Q) of energy-adjusted choline plus betaine and categories of other factors in the Framingham Offspring Study of 920 men and 1040 women[1]

| | Quintile of choline plus betaine | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | *P* for trend[2] | *P* for interaction |
| Folate intake | | | *μmol/L* | | | | |
| ≤250 μg/d (*n* = 525) | 12.4 (11.6, 13.2) | 11.2 (10.5, 11.9) | 10.7 (9.9, 11.6) | 10.8 (9.9, 11.8) | 10.2 (9.1, 11.4) | <0.0001 | |
| >250 to ≤400 μg/d (*n* = 793) | 10.9 (10.2, 11.6) | 10.3 (9.8, 10.9) | 10.6 (10.0, 11.2) | 10.3 (9.8, 10.9) | 10.6 (10.0, 11.1) | 0.51 | |
| >400 μg/d (*n* = 642) | 8.8 (8.3, 9.5) | 8.7 (8.1, 9.4) | 8.4 (7.9, 9.0) | 8.5 (8.0, 9.1) | 8.7 (8.2, 9.3) | 0.86 | <0.0001 |
| Alcohol intake | | | | | | | |
| 0 g/d (*n* = 484) | 10.9 (10.2, 11.6) | 9.6 (8.9, 10.4) | 9.8 (9.0, 10.6) | 9.9 (9.1, 10.7) | 10.3 (9.5, 11.2) | 0.23 | |
| >0 to ≤15 g/d (*n* = 1029) | 10.5 (9.9, 11.0) | 9.8 (9.4, 10.4) | 9.7 (9.2, 10.2) | 9.7 (9.2, 10.2) | 9.6 (9.1, 10.1) | 0.007 | |
| >15 g/d (*n* = 447) | 12.1 (11.1, 13.1) | 11.2 (10.3, 12.1) | 10.4 (9.6, 11.3) | 10.1 (9.3, 10.9) | 10.3 (9.6, 11.2) | 0.0004 | 0.03 |
| Age | | | | | | | |
| ≤50 y (*n* = 752) | 10.4 (9.7, 11.0) | 9.5 (8.9, 10.1) | 8.9 (8.4, 9.6) | 8.9 (8.3, 9.5) | 9.5 (8.8, 10.1) | | |
| 51 to ≤60 y (*n* = 654) | 11.4 (10.7, 12.1) | 10.1 (9.5, 10.8) | 10.3 (9.6, 11.0) | 10.3 (9.6, 10.9) | 10.4 (9.8, 11.0) | | |
| >60 y (*n* = 554) | 11.4 (10.6, 12.3) | 11.1 (10.3, 12.0) | 10.9 (10.2, 11.8) | 10.7 (10.0, 11.6) | 10.4 (9.6, 11.2) | | 0.29 |
| Sex | | | | | | | |
| Male (*n* = 920) | 11.6 (11.0, 12.2) | 10.8 (10.2, 11.4) | 10.6 (10.1, 11.2) | 10.3 (9.8, 10.9) | 10.1 (9.6, 10.7) | <0.0001 | |
| Female (*n* = 1040) | 10.2 (9.8, 10.7) | 9.3 (8.8, 9.8) | 9.2 (8.7, 9.6) | 9.3 (8.8, 9.8) | 9.6 (9.1, 10.1) | 0.07 | 0.004 |

[1] Values were adjusted for age, sex, smoking, hypertension medication use, serum creatinine, and intakes of alcohol, caffeine, folate, vitamin B-6, and vitamin B-12.

[2] Calculated with median intake in each quintile as a continuous variable.