Homocysteine, cardiovascular disease risk factors, and habitual diet in the French Supplementation with Antioxidant Vitamins and Minerals Study[1–3]

Louise I Mennen, Geneviève Potier de Courcy, Jean-Claude Guilland, Véronique Ducros, Sandrine Bertrais, Jean-Pierre Nicolas, Michèle Maurel, Marjorie Zarebska, Alain Favier, Claire Franchisseur, Serge Hercberg, and Pilar Galan

ABSTRACT

Background: An elevated plasma total homocysteine (tHcy) concentration seems to increase the risk of cardiovascular disease.

Objective: We evaluated the determinants of tHcy in healthy French adults.

Design: tHcy was measured by HPLC and fluorometric detection in 1139 women and 931 men aged 35–60 y. Subjects were participants of the Supplementation with Antioxidant Vitamins and Minerals Study, which investigates the effects of antioxidant supplementation on chronic diseases. Red blood cell folate (RBCF), plasma vitamins B-6 and B-12, and cardiovascular disease risk factors were also measured. The habitual diet was assessed in 616 subjects. Cross-sectional analyses were adjusted for age, smoking, energy intake, and concentration or intake of folate and vitamin B-6, where appropriate.

Results: The mean (± SD) tHcy concentration was 8.74 ± 2.71 μmol/L in women and 10.82 ± 3.49 μmol/L in men. In women, tHcy was positively related to age ($P = 0.001$), apolipoprotein B ($P < 0.01$), serum triacylglycerol ($P < 0.01$), fasting glucose ($P = 0.02$), and coffee and alcohol consumption (both $P < 0.01$) and inversely related to RBCF ($P = 0.11$) and plasma vitamin B-12 ($P = 0.08$) and vitamin B-6 ($P = 0.01$) intakes. In men, tHcy was positively associated with body mass index ($P = 0.03$), blood pressure ($P < 0.02$), serum triacylglycerol ($P < 0.01$), fasting glucose ($P = 0.01$), and energy intake ($P < 0.01$) and inversely associated with physical activity ($P = 0.04$), RCBF ($P = 0.02$), plasma vitamin B-12 ($P = 0.09$), and dietary fiber ($P < 0.01$), folate ($P = 0.03$), and vitamin B-6 ($P = 0.09$) intakes.

Conclusion: To control tHcy, decreasing coffee and alcohol consumption may be important in women, whereas increasing physical activity, dietary fiber, and folate intake may be important in men. *Am J Clin Nutr* 2002;76:1279–89.

KEY WORDS Homocysteine, habitual diet, folate, cardiovascular disease risk, men, women, coffee, Supplementation with Antioxident Vitamins and Minerals Study, France

INTRODUCTION

Many epidemiologic studies have shown that an elevated concentration of plasma total homocysteine (tHcy) is an independent risk factor for coronary ischemic disease, stroke, peripheral vascular disease, and venous thrombosis (1, 2). The concentrations of tHcy are partly determined by the common 677C→T methylenetetrahydrofolate reductase (EC 1.7.99.5) polymorphism; carriers of the *T* allele have higher tHcy concentrations than do noncarriers (3). Age and sex are 2 other important determinants of tHcy; it is known that tHcy increases steadily with age and that tHcy is higher in men than in women (4–9). Major lifestyle determinants of tHcy in apparently healthy subjects are dietary and plasma folate, vitamin B-6 and B-12, smoking, coffee consumption, and physical activity (4–10). Evidence also exists that tHcy is related to classic cardiovascular disease risk factors such as blood pressure, body mass index, and blood lipids (4, 7, 10, 11). The determinants of tHcy, however, likely are to vary among cultures and countries. Previous studies on lifestyle determinants of tHcy have taken place in Anglo-Saxon countries (United States, Canada, and northern Europe), and one has been performed in Southeast Asia. No information is available on the relation of tHcy and cardiovascular disease and lifestyle factors in middle and southern Europe, where lifestyle habits and cardiovascular disease morbidity are quite different from those in Anglo-Saxon countries.

Although the incidence of cardiovascular disease is lower in France than in northern Europe, it remains the major cause of morbidity and mortality. For effective prevention of this disease,

[1] From the UMR INSERM unit 557/INRA unit 1125, Institut Scientifique et Technique de la Nutrition et de l'Alimentation, ISTNA (LIM, GPdC, SB, MM, MZ, CF, SH, and PG) and Unité de Surveillance et d'Epidémiologie Nutritionnelle, InVS (LIM and SH), Conservatoire National des Arts et Metiers, Paris; the Laboratoire de Physiologie, Faculté de Médecine, Dijon, France (J-CG); the Laboratoire de Laboratoire de Biologie du Stress Oxydant, Faculté de Pharmacie, Grenoble, France (VD and AF); and the Laboratoire de Biochimie Médicale et Pédiatrique, INSERM unit 308, Faculté de Médecine, Vandoeuvre-lès-Nancy, France (J-PN).

[2] Supported in part by a grant from Kellogg's Produit Alimentaire, Rosny sous Bois, France. Bio-Rad, Vitry sur Seine, France, and Carlo Erba, Val de Reuil, France, provided materials for analyzing blood samples.

[3] Address reprint requests to LI Mennen, ISTNA/CNAM, 5 rue du Vertbois, 75003 Paris, France. E-mail: s_mennen@vcnam.cnam.fr.

Received July 25, 2001.

Accepted for publication February 7, 2002.

it is important to know which are the modifiable determinants of the cardiovascular disease risk factors, including tHcy. In the present study, therefore, we evaluated tHcy in a large French population of healthy men and women between 35 and 60 y of age.

SUBJECTS AND METHODS

Subjects

The subjects were participants in the Supplementation with Antioxidant Vitamins and Minerals Study, an ongoing randomized, double-blind, placebo-controlled, primary-prevention trial designed to evaluate the effect of daily antioxidant supplementation (vitamin C, vitamin E, β-carotene, selenium, and zinc) at nutritional doses on the incidence of cancer and ischemic heart disease. The cohort consists of women aged 35–60 y ($\bar{x}$ ± SD: 46.4 ± 6.7 y) and men aged 45–60 y (51.1 ± 4.7 y), and none of them use vitamin supplements. Subjects were invited to participate by a multimedia campaign in the whole of France. Potential subjects received detailed information on the study and performed a self-test of acceptability of the daily supplement. A total of 12 735 subjects were included at baseline in 1994 and are being followed up for 8 y. Details on recruitment and study design were described earlier (12). For the present analyses, only those subjects were included for whom homocysteine concentrations were measured (n = 2070), which was a random sample of the total population, with a sex ratio of 50%. For 616 subjects in this group, detailed information on the habitual diet was also available.

The Supplementation with Antioxidant Vitamins and Minerals Study was approved by the ethical committee for studies on human subjects (CCPPRB no. 706) of Paris-Cochin Hospital and the Comité National Informatique et Liberté (CNIL no. 334641), which advocates that all medical information is confidential and anonymous.

Dietary assessment

The subjects kept a 24-h dietary record randomly every 2 mo, for a total of 6 records/y (2 weekend days and 4 weekdays), so that each day of the week and all seasons were covered for the mean intake of all participants. Information was collected with the use of the Minitel Telematic Network. The Minitel is a small terminal widely used in France as an adjunct to the telephone. At the beginning of the study, participants received free of charge a tiny central processing unit specifically developed for the study and loaded with specialized software that allows subjects to fill out the computerized dietary record off-line and to transmit data during brief telephone connections. The software allowed the subjects to have an interactive discussion with the coordinating center and ask questions, which were answered within a day by one of the investigators. These capabilities and an instruction manual for codification of foods guided the participants during the completion of the records. The manual contains photographs showing portions in 3 sizes, and along with the 2 intermediate and 2 extreme positions, 7 choices are available to indicate the consumed portion. Photos of portion sizes were previously validated with the use of 780 subjects in a pilot study (13). Data on variables such as cooking methods, seasoning, types of foods (fresh, frozen, canned, etc), and place and time of consumption were also collected.

TABLE 1
General characteristics of the study population

	Women (n = 1139)	Men (n = 931)
Age (y)	46.8 ± 6.5[1]	51.4 ± 4.8
Current smokers (n [%])	160 [14]	162 [17]
Menopause (n [%])	376 [33]	—
BMI (kg/m^2)	23.5 ± 4.1	25.5 ± 3.3
Waist-hip ratio	0.77 ± 0.07	0.92 ± 0.06
Systolic blood pressure (mm Hg)	121.5 ± 13.6	130.3 ± 13.9
Diastolic blood pressure (mm Hg)	77.9 ± 8.7	83.8 ± 8.4
Total cholesterol (mmol/L)	5.70 ± 0.95	5.89 ± 0.92
Serum triacylglycerol (mmol/L)	0.95 ± 1.22	1.38 ± 0.93
Apolipoprotein A-I (g/L)	1.70 ± 0.25	1.55 ± 0.23
Apolipoprotein B (g/L)	1.02 ± 0.23	1.17 ± 0.25
Fasting glucose (mmol/L)	5.44 ± 0.80	5.92 ± 0.97
Homocysteine (μmol/L)	8.74 ± 2.71	10.82 ± 3.49
Red blood cell folate (nmol/L)	606.1 ± 208.8	635.9 ± 199.1
Pyridoxal 5′-phosphate (nmol/L)	59.0 ± 62.8	54.7 ± 26.7
Plasma vitamin B-12 (pmol/L)[2]	367.0 ± 112.6	332.6 ± 95.5

[1] $\bar{x}$ ± SD.
[2] n = 176 women, 133 men.

Measurements of risk indicators

All measurements were performed at the end of the second study year. Weight and height and waist and hip circumferences were measured while the subjects were wearing underwear, and body mass index was calculated by dividing weight by the square of height (kg/m^2). Blood pressure was measured one time at each arm with a standard mercury sphygmomanometer in subjects who had been lying down for 10 min. The mean of these 2 measurements was taken for analyses. Information about smoking habits was obtained by means of a questionnaire. Blood samples were obtained in Vacutainer tubes (Becton Dickinson, Le pont de Claix, France) from subjects who had

TABLE 2
Habitual daily dietary intakes in a subsample of the study population[1]

	Women (n = 310)	Men (n = 306)
Energy (kJ)	7189.6 ± 2034.4	9541.7 ± 2244.2
Carbohydrate (g)	178.7 ± 58.9	229.8 ± 62.3
Total fat (g)	76.4 ± 26.1	93.6 ± 27.4
Protein (g)	74.3 ± 19.3	95.0 ± 21.6
Animal	53.0 ± 15.5	66.9 ± 17.8
Vegetable	21.3 ± 7.3	28.1 ± 9.7
Dietary fiber (g)	11.0 ± 4.2	12.8 ± 5.6
Soluble	2.5 ± 1.0	2.8 ± 1.2
Nonsoluble	8.5 ± 3.4	10.1 ± 4.6
Vitamin B-6 (mg)	1.6 ± 0.5	2.0 ± 0.5
Vitamin B-12 (μg)	6.3 ± 4.5	7.5 ± 5.0
Folate (μg)	268.2 ± 91.5	306.4 ± 88.4
Fruit (g)	173.4 ± 114.8	200.6 ± 141.8
Vegetables (g)	154.3 ± 75.7	155.5 ± 75.6
Coffee (mL)	240.5 ± 268.0	206.2 ± 200.0
Tea (mL)	178.8 ± 252.4	75.6 ± 169.8
Alcohol (g)	9.6 ± 11.2	24.8 ± 21.4

[1] $\bar{x}$ ± SD.

TABLE 3
Adjusted mean (95% CI) total plasma homocysteine (tHcy) concentrations by risk factors for cardiovascular disease and B vitamins in women

	tHcy[1]	*P* for trend	tHcy[2]	*P* for trend
	μmol/L		*μmol/L*	
Age				
35–40 y (*n* = 232)	8.05 (7.70, 8.40)		7.99 (7.64, 8.34)	
40–45 y (*n* = 302)	8.62 (8.33, 8.91)		8.63 (8.32, 8.94)	
45–50 y (*n* = 290)	8.75 (8.44, 9.06)		8.81 (8.48, 9.14)	
50–55 y (*n* = 213)	9.31 (8.96, 9.66)		9.39 (9.02, 9.76)	
55–60 y (*n* = 146)	9.18 (8.73, 9.63)	0.0001	9.19 (8.76, 9.64)	0.0001
Smoker				
Never (*n* = 712)	8.68 (8.48, 8.88)		8.70 (8.50, 8.90)	
Former (*n* = 309)	8.81 (8.52, 9.10)		8.89 (8.80, 9.18)	
Current (*n* = 162)	8.83 (8.42, 9.24)	0.54	8.82 (8.41, 9.23)	0.61
Physical activity				
None (*n* = 429)	8.85 (8.60, 9.00)		8.83 (8.58, 9.08)	
<1 h walking/d (*n* = 336)	8.73 (8.44, 9.02)		8.73 (8.46, 9.00)	
>1 h walking/d (*n* = 418)	8.62 (8.37, 8.87)	0.21	8.59 (8.34, 884)	0.18
Menopause				
No	8.67 (8.47, 8.87)		8.67 (8.47, 8.87)	
Yes	8.79 (8.44, 9.14)	0.59	8.75 (8.40, 9.10)	0.72
BMI (kg/m^2)				
<20.7 (*n* = 233)	8.96 (8.61, 9.31)		8.87 (8.52, 9.22)	
20.7–22.4 (*n* = 234)	8.48 (8.13, 8.93)		8.46 (8.11, 8.81)	
22.5–25.2 (*n* = 234)	8.67 (8.32, 9.02)		8.71 (8.36, 9.06)	
25.3 (*n* = 134)	8.80 (8.45, 9.15)	0.73	8.78 (8.43, 9.13)	0.98
Waist-to-hip ratio				
<0.724 (*n* = 237)	8.67 (8.32, 9.02)		8.66 (8.31, 9.01)	
0.724–0.760 (*n* = 231)	8.63 (8.28, 8.98)		8.67 (8.32, 9.02)	
0.761–0.800 (*n* = 234)	8.66 (8.31, 9.01)		8.56 (8.21, 8.91)	
0.801 (*n* = 232)	8.95 (8.58, 9.32)	0.28	8.94 (8.59, 9.29)	0.38
Systolic blood pressure (mm Hg)				
<115 (*n* = 298)	8.87 (8.56, 9.18)		8.32 (8.03, 8.61)	
115–124 (*n* = 300)	8.52 (8.23, 8.81)		8.48 (8.19, 8.77)	
125–129 (*n* = 78)	8.05 (7.44, 8.66)		8.02 (7.41, 8.63)	
130 (*n* = 297)	8.89 (8.58, 9.20)	0.59	8.91 (8.62, 9.20)	0.77
Diastolic blood pressure (mm Hg)				
<75 (*n* = 322)	8.70 (8.41, 8.99)		8.65 (8.36, 8.94)	
75–79 (*n* = 94)	8.81 (8.26, 9.36)		8.79 (8.26, 9.32)	
80–84 (*n* = 340)	8.56 (8.27, 8.85)		8.54 (8.27, 8.61)	
85 (*n* = 217)	8.90 (8.55, 9.25)	0.64	8.93 (8.58, 9.28)	0.45
Total cholesterol (mmol/L)				
<5.04 (*n* = 293)	8.42 (8.11, 8.73)		8.44 (8.13, 8.75)	
5.05–5.71 (*n* = 296)	8.72 (8.41, 9.03)		8.73 (8.42, 9.04)	
5.72–6.28 (*n* = 298)	8.92 (8.61, 9.23)		8.94 (8.65, 9.23)	
6.29 (*n* = 293)	8.84 (8.53, 9.15)	0.05	8.73 (8.42, 9.04)	0.13
Serum triacylglycerol (mmol/L)				
<0.60 (*n* = 273)	8.49 (8.16, 8.82)		8.47 (8.16, 8.78)	
0.60–0.79 (*n* = 286)	8.63 (8.32, 8.94)		8.60 (8.29, 8.91)	
0.80–1.08 (*n* = 276)	8.69 (8.38, 9.00)		8.69 (8.38, 9.00)	
1.09 (*n* = 284)	9.11 (8.80, 9.42)	0.009	9.09 (8.78, 9.40)	0.007
Apolipoprotein A-I (g/L)				
<1.54 (*n* = 285)	8.71 (8.40, 9.02)		8.65 (8.34, 8.96)	
1.54–1.68 (*n* = 273)	8.64 (8.33, 8.95)		8.67 (8.36, 8.98)	
1.69–1.85 (*n* = 279)	8.75 (8.44, 9.06)		8.69 (8.38, 9.00)	
1.86 (*n* = 281)	8.82 (8.51, 8.13)	0.55	8.85 (8.54, 9.16)	0.39
Apolipoprotein B (g/L)				
<0.87 (*n* = 275)	8.28 (7.95, 8.63)		8.30 (7.99, 8.61)	
0.87–1.00 (*n* = 288)	8.57 (8.26, 8.88)		8.55 (8.24, 8.86)	
1.01–1.16 (*n* = 278)	9.08 (8.77, 9.39)		9.07 (8.76, 9.38)	
1.17 (*n* = 277)	9.01 (8.69, 9.33)	0.0004	8.95 (8.64, 9.26)	0.001

(Continued)

TABLE 3 (*Continued*)

	tHcy[1]	*P* for trend	tHcy[2]	*P* for trend
	µmol/L		*µmol/L*	
Fasting glucose (mmol/L)				
<5.11 (*n* = 315)	8.44 (8.15, 8.73)		8.40 (8.09, 8.71)	
5.11–5.38 (*n* = 271)	8.73 (8.42, 9.04)		8.67 (8.36, 8.98)	
5.39–5.71 (*n* = 308)	8.90 (8.91, 9.19)		8.91 (8.62, 9.20)	
5.72 (*n* = 286)	8.85 (8.54, 9.16)	0.05	8.88 (8.57, 8.19)	0.02
Red blood cell folate (µmol/L)				
<454.0 (*n* = 291)	9.56 (9.27, 9.85)		9.14 (8.41, 9.87)	
454.0–580.6 (*n* = 292)	8.94 (8.65, 9.23)		9.35 (8.66, 10.04)	
580.7–721.7 (*n* = 292)	8.42 (8.13, 8.71)		8.78 (8.04, 9.52)	
721.8 (*n* = 291)	7.95 (7.64, 7.26)	0.0001	8.40 (7.64, 9.16)	0.11
Pyridoxal 5′-phosphate (nmol/L)				
<32.0 (*n* = 293)	8.71 (8.40, 9.02)		8.98 (8.06, 9.90)	
32.0–45.7 (*n* = 289)	8.80 (8.49, 9.11)		8.66 (7.97, 9.35)	
45.8–63.7 (*n* = 294)	8.83 (8.52, 9.14)		8.89 (8.18, 9.60)	
63.8 (*n* = 292)	8.59 (8.28, 8.90)	0.64	9.15 (8.50, 9.80)	0.68
Plasma vitamin B-12 (pmol/L)				
<284 (*n* = 44)	9.66 (8.95, 10.37)		9.54 (8.81, 10.27)	
284–341 (*n* = 44)	9.11 (8.40, 9.82)		9.05 (8.32, 9.78)	
342–430 (*n* = 45)	8.26 (7.35, 8.97)		8.25 (7.56, 8.96)	
431 (*n* = 44)	8.74 (8.03, 9.45)	0.03	8.83 (8.10, 9.56)	0.08

[1] Adjusted for age (except for age).

[2] Adjusted for age (except for age), smoking (except for smoking), pyridoxal 5′-phosphate (except for pyridoxal 5′-phosphate), and red blood cell folate (except for red blood cell folate).

been fasting for 12 h. Fasting glucose, total cholesterol, and serum triacylglycerol were all measured by an enzymatic method (Technicon DAX, Eragny sur Oise, France). Apolipoprotein (apo) A-I and apo B were measured by using a nephelemetric assay (BNA; Behring, Paris la Défence, France) and lipoprotein(a) with an immunonephelimetric assay (Array Beckman, Roissy Charles de Gaulle, France). Blood samples for measurement of plasma tHcy were collected in EDTA-containing tubes, which were centrifuged within the hour after the blood sampling at room temperature for 10 min at 3000 × *g*. The plasma fraction was then transferred to cryotubes, which were kept at −20° C until measurement 6 mo later. tHcy was measured as described earlier (14) by HPLC and fluorometric detection with a Bio-Rad kit (Hercule SA, Vitry sur Seine, France). The concentration of red blood cell folate was estimated by microbiological assay, pyridoxal 5′-phosphate (PLP) by HPLC and fluorometric detection, and vitamin B-12 (*n* = 309) by an automated chemiluminescence method (Chiron Diagnostics, East Walpole, MA). Laboratory quality assurance included analysis of serum from standard pools with each run and, if available, international standards.

Data analyses

Intakes of energy, protein (animal and vegetable), carbohydrate, total fat, fiber (soluble and nonsoluble), and alcohol were calculated from food consumption with the use of the French computerized food-composition table CIQUAL (15). We used data from those subjects who completed 6 records in the year before the blood sample for homocysteine measurement was taken.

Associations between homocysteine concentrations and cardiovascular disease risk factors and dietary factors were evaluated by using analyses of covariance adjusted for age, smoking, and folate and PLP concentrations or folate and vitamin B-6 intakes, where appropriate. Independent continuous variables were divided in quartiles, which were created separately for men and women. Fasting glucose and serum triacylglycerol were log transformed to obtain a normal distribution.

RESULTS

General characteristics of the subjects are shown in **Table 1**, and dietary intakes are presented in **Table 2**. The intake of folate was strongly positively associated with red blood cell folate concentration and vitamin B-6 with PLP in both men and women, but no relation was observed between vitamin B-12 consumption and vitamin B-12 plasma concentrations. The intake of these vitamins was also associated with the intake of total energy and with the intake of macronutrients.

In women, tHcy was strongly positively associated with age, even after adjustment for smoking, red blood cell folate, and PLP (**Table 3**). Furthermore, tHcy was positively related to serum triacylglycerol, apo B, and fasting glucose. The positive relation with total cholesterol diminished after adjustment for age, smoking, PLP, and red blood cell folate. Plasma vitamin B-12 and red blood cell folate were both inversely related to tHcy in women, although these relations were not statistically significant at a 5% level when these variables were joined in one model. No relation was observed between tHcy and smoking, body mass index, waist-hip ratio, blood pressure, apo A-I, menopause, or PLP.

In men, no relation was observed between tHcy and age or smoking (**Table 4**). Physical activity was inversely related to tHcy, even after adjustment for age, smoking, PLP, and red

TABLE 4
Adjusted mean (95% CI) total plasma homocysteine (tHcy) concentrations by risk factors for cardiovascular disease and B vitamins in men

	tHcy[1]	*P* for trend	tHcy[2]	*P* for trend
	μmol/L		*μmol/L*	
Age				
45–50 y (*n* = 343)	10.37 (10.00, 10.74)		10.34 (9.97, 10.71)	
50–55 y (*n* = 290)	11.12 (10.71, 11.53)		11.08 (10.67, 11.49)	
55–60 y (*n* = 281)	11.11 (10.70, 11.52)	0.79	11.12 (10.71, 11.43)	0.45
Smoker				
Never (*n* = 369)	10.81 (10.44, 11.16)		10.88 (10.51, 11.25)	
Former (*n* = 427)	10.82 (10.49, 11.11)		10.80 (10.45, 11.15)	
Current (*n* = 167)	10.97 (10.42, 11.52)	0.64	10.75 (10.20, 11.30)	0.69
Physical activity				
None (*n* = 300)	11.29 (10.88, 11.70)		11.20 (10.81, 11.59)	
<1 h walking/d (*n* = 189)	10.67 (10.16, 11.18)		10.77 (9.28, 11.26)	
>1 h walking/d (*n* = 474)	10.62 (10.31, 10.93)	0.01	10.67 (10.36, 10.98)	0.04
BMI (kg/m^2)				
<23.3 (*n* = 199)	10.71 (10.20, 11.22)		10.63 (10.14, 11.12)	
23.3–25.0 (*n* = 201)	10.39 (9.88, 10.90)		10.34 (9.85, 10.83)	
25.1–27.2 (*n* = 201)	11.23 (10.72, 11.74)		11.28 (10.79, 11.77)	
27.3 (*n* = 199)	10.99 (10.48, 11.50)	0.14	11.13 (10.64, 11.62)	0.03
Waist-to-hip ratio				
<0.881 (*n* = 202)	10.53 (10.02, 11.04)		10.36 (9.87, 10.85)	
0.881–0.920 (*n* = 196)	11.18 (10.67, 11.69)		11.14 (10.65, 11.63)	
0.921–0.962 (*n* = 201)	10.76 (10.25, 11.27)		10.86 (10.37, 11.35)	
0.963 (*n* = 199)	10.88 (10.37, 11.39)	0.59	11.06 (10.57, 11.55)	0.11
Systolic blood pressure (mm Hg)				
<125 (*n* = 283)	10.48 (10.07, 10.89)		10.50 (10.09, 10.91)	
125–129 (*n* = 72)	10.97 (10.12, 11.82)		10.49 (9.68, 11.30)	
130–139 (*n* = 229)	11.20 (10.73, 11.67)		11.17 (10.72, 11.62)	
140 (*n* = 253)	11.03 (10.58, 11.48)	0.09	11.12 (10.69, 11.55)	0.02
Diastolic blood pressure (mm Hg)				
<80 (*n* = 141)	10.27 (9.66, 10.88)		10.11 (9.52, 10.70)	
80–84 (*n* = 288)	10.69 (10.26, 11.12)		10.71 (10.30, 11.12)	
85–89 (*n* = 78)	10.84 (10.07, 11.61)		10.87 (10.14, 11.60)	
90 (*n* = 321)	11.34 (10.95, 11.73)	0.005	11.34 (10.95, 11.73)	0.0008
Total cholesterol (mmol/L)				
<5.28 (*n* = 244)	10.66 (10.11, 11.11)		10.57 (10.14, 11.00)	
5.28–5.87 (*n* = 239)	10.62 (10.17, 11.07)		10.77 (10.32, 11.22)	
5.88–6.44 (*n* = 241)	10.95 (10.50, 11.40)		10.99 (10.56, 11.42)	
6.45 (*n* = 239)	11.13 (10.68, 11.58)	0.09	11.01 (10.58, 11.44)	0.13
Serum triacylglycerol (mmol/L)				
<0.82 (*n* = 233)	10.43 (9.98, 10.88)		10.40 (9.95, 10.85)	
0.82–0.14 (*n* = 233)	10.92 (10.47, 11.37)		10.89 (10.46, 11.32)	
0.15–1.66 (*n* = 235)	10.81 (10.36, 11.26)		10.76 (10.33, 11.19)	
1.67 (*n* = 235)	11.32 (10.87, 11.77)	0.01	11.42 (10.97, 11.87)	0.004
Apolipoprotein A-I (g/L)				
<1.39 (*n* = 237)	11.27 (10.82, 11.72)		11.10 (10.67, 11.53)	
1.39–1.52 (*n* = 222)	10.78 (10.31, 11.25)		10.78 (10.33, 11.23)	
1.53–1.67 (*n* = 236)	10.74 (10.29, 10.17)		10.79 (10.34, 11.24)	
1.68 (*n* = 241)	10.68 (10.12, 11.13)	0.09	10.78 (10.35, 11.21)	0.35
Apolipoprotein B (g/L)				
<1.01 (*n* = 226)	10.58 (10.11, 11.05)		10.65 (10.20, 11.10)	
1.01–1.16 (*n* = 242)	10.69 (10.24, 11.14)		10.74 (10.31, 11.17)	
1.17–1.33 (*n* = 231)	11.33 (10.86, 11.80)		11.22 (10.67, 11.57)	
1.34 (*n* = 237)	10.89 (10.44, 11.34)	0.14	10.86 (10.41, 11.31)	0.28
Fasting glucose (mmol/L)				
<5.44 (*n* = 239)	10.44 (9.99, 10.89)		10.40 (9.95, 11.85)	
5.44–5.77 (*n* = 226)	10.78 (10.31, 11.25)		10.81 (10.36, 11.26)	
5.78–6.21 (*n* = 265)	10.91 (10.48, 11.34)		10.90 (10.47, 11.33)	
6.22 (*n* = 233)	11.22 (10.77, 11.67)	0.02	11.21(10.76, 11.66)	0.01

(Continued)

TABLE 4 (*Continued*)

	tHcy[1]	*P* for trend	tHcy[2]	*P* for trend
	μmol/L		*μmol/L*	
Red blood cell folate (μmol/L)				
<501.7 (*n* = 236)	12.39 (11.96, 82)		13.04 (11.88, 14.20)	
501.7–610.4 (*n* = 238)	11.01 (10.56, 11.44)		10.95 (9.75, 12.15)	
610.5–748.2 (*n* = 238)	9.98 (9.55, 10.41)		10.06 (8.73, 11.39)	
748.2 (*n* = 237)	9.99 (9.56, 10.42)	0.0001	10.78 (9.06, 12.50)	0.02
Pyridoxal 5′-phosphate (nmol/L)				
<36.3 (*n* = 293)	10.93 (10.48, 11.38)		10.96 (9.35, 12.57)	
32.3–48.7 (*n* = 239)	10.67 (10.22, 11.12)		10.96 (9.47, 12.45)	
48.8–66.2 (*n* = 239)	11.06 (10.61, 11.51)		12.08 (10.94, 13.22)	
66.3 (*n* = 238)	10.70 (10.25, 11.15)	0.78	10.82 (9.68, 11.96)	0.82
Plasma vitamin B-12 (pmol/L)				
<267 (*n* = 33)	12.56 (11.25, 13.87)		12.28 (10.95, 13.61)	
267–309 (*n* = 33)	11.31 (10.00, 12.62)		10.81 (9.50, 12.12)	
310–386 (*n* = 35)	11.26 (9.99, 12.53)		11.37 (10.10, 12.64)	
387 (*n* = 33)	10.66 (9.3511.97)	0.06	10.37 (9.04, 11.70)	0.09

[1] Adjusted for age (except for age).

[2] Adjusted for age (except for age), smoking (except for smoking), pyridoxal 5′-phosphate (except for pyridoxal 5′-phosphate), and red blood cell folate (except for red blood cell folate).

blood cell folate. Furthermore, after adjustment, tHcy was positively associated to body mass index, systolic and diastolic blood pressure, serum triacylglycerol, and fasting glucose. The positive trend with total cholesterol was not statistically significant at a 5% level. Both red blood cell folate and plasma vitamin B-12 were inversely associated with tHcy, but the latter was not statistically significant at a 5% level. No association was observed between tHcy and apo A-I, apo B, or PLP. The differences in the associations of tHcy and cardiovascular disease risk factors between men and women were tested in a linear regression model where an interaction term for sex and the risk factor was included. The coefficients for interaction between sex and systolic and diastolic blood pressure and body mass index were statistically significant ($P < 0.05$).

Total fat, carbohydrate, and total energy intake were not associated with tHcy in women (**Table 5**). Intake of animal protein, soluble and nonsoluble fiber, dietary folate, riboflavin, and vegetables were inversely associated with tHcy, but these relations lost statistical significance at a 5% level after adjustment for age, smoking, total energy intake, dietary folate, and vitamin B-6. Intake of vitamin B-6 was inversely associated with tHcy, but intake of vitamin B-12 was not. Coffee and alcohol consumption were strongly positively associated with tHcy. There was no association between tHcy and fruit or tea consumption.

Energy intake was inversely associated with tHcy in men, but no association was found with any of the macronutrients (**Table 6**). Both nonsoluble and soluble dietary fiber were inversely related to tHcy, even after adjustment for age, energy intake, smoking, and dietary folate and vitamin B-6 intakes, although nonsoluble fiber was not statistically significant at a 5% level. Of the B vitamins, dietary folate and vitamin B-6 remained associated with tHcy after multiple adjustment; the latter was not statistically significant at a 5% level. tHcy and fruit and vegetable consumption were no longer related after adjustment for age, smoking, total energy intake, and folate and vitamin B-6 intake. There was no clear association of tHcy with coffee, tea, or alcohol consumption in men.

DISCUSSION

The results of the present study suggest that the determinants of tHcy are not the same for women and men. Although serum triacylglycerol, fasting glucose, and plasma vitamin B-12 seemed to be important determinants of tHcy in both women and men, most classic cardiovascular disease risk factors were associated with tHcy in men but not in women. Furthermore, none of the lifestyle determinants were the same in women and men.

The present data used a cross-sectional design, which implies that no conclusions can be drawn on the causal effect of the determinants of tHcy. It may be that tHcy is a indicator of ongoing cardiovascular disease, which could explain the relation with other risk factors for cardiovascular disease (16). Dietary habits, however, were estimated in the year before tHcy was measured. It is, therefore, more likely that diet may have a causal effect on tHcy. This is especially the case for dietary folate and vitamin B-12 intake, because it is known from intervention studies that they decrease tHcy (17).

The dietary data were only available in a subsample of the total population in which tHcy was measured. This could have biased the relation between tHcy and dietary factors. However, the general characteristics were similar in the subsample to those in the total population (data not shown), which indicates that the subsample was not a distinct group. It has to be noted, however, that our subjects were not representative of the total French population. They were rather healthy, and not many subjects with very high levels of the cardiovascular disease risk factors were included, which may have underestimated the observed associations.

The difference between men and women in the relation of tHcy with age was probably caused by the fact that the age range in the women was much larger than in the men. Even

TABLE 5
Adjusted mean (95% CI) total plasma homocysteine (tHcy) concentrations by daily nutrient and food intakes in women

	tHcy[1]	*P* for trend	tHcy[2]	*P* for trend
	μmol/L		*μmol/L*	
Energy (kJ)				
<6065 (*n* = 77)	9.33 (8.68, 9.94)		8.73 (8.02, 9.44)	
6065–7064 (*n* = 78)	8.67 (8.04, 9.30)		8.52 (7.91, 9.13)	
7065–8164 (*n* = 78)	8.64 (8.03, 9.25)		8.86 (8.25, 9.47)	
8165 (*n* = 77)	8.85 (8.22, 9.48)	0.30	9.37 (8.58, 10.16)	0.20
Total fat (g)				
<61.7 (*n* = 77)	9.21 (8.40, 10.02)		9.03 (8.22, 9.84)	
61.7–74.0 (*n* = 78)	8.46 (7.85, 9.07)		8.44 (7.81, 9.07)	
74.1–88.7 (*n* = 77)	8.80 (8.15, 9.45)		8.88 (8.25, 9.75)	
88.8 (*n* = 78)	9.01 (8.22, 9.80)	0.99	9.14 (8.67, 9.93)	0.73
Carbohydrate (g)				
<141.6 (*n* = 77)	9.05 (8.24, 9.86)		8.91 (8.10, 9.72)	
141.6–172.6 (*n* = 78)	8.67 (8.02, 9.32)		8.59 (7.94, 9.24)	
172.7–207.5 (*n* = 78)	9.14 (8.49, 9.79)		9.25 (8.62, 9.88)	
207.6 (*n* = 77)	8.63 (7.82, 9.44)	0.73	8.74 (7.91, 9.57)	0.96
Vegetable protein (g)				
<16.6 (*n* = 78)	9.13 (8.32, 9.84)		8.92 (8.19, 9.65)	
16.6–20.4 (*n* = 77)	9.26 (8.65, 9.87)		9.19 (8.56, 9.82)	
20.5–24.3 (*n* = 78)	8.59 (7.98, 9.20)		8.67 (8.04, 9.30)	
24.4 (*n* = 77)	8.51 (7.78, 9.24)	0.17	8.71 (7.98, 9.44)	0.56
Animal protein (g)				
<42.6 (*n* = 77)	9.77 (9.08, 10.46)		9.53 (8.82, 10.24)	
42.6–51.5 (*n* = 78)	8.66 (8.03, 9.29)		8.57 (7.96, 9.18)	
51.6–60.7 (*n* = 78)	8.61 (8.00, 9.22)		8.55 (7.94, 9.16)	
60.8 (*n* = 77)	8.46 (7.81, 9.11)	0.02	8.85 (8.12, 9.58)	0.27
Nonsoluble fiber (g)				
<6.12 (*n* = 77)	9.56 (8.91, 10.21)		9.25 (8.56, 9.94)	
6.12–7.86 (*n* = 78)	9.11 (8.48, 9.74)		8.92 (8.29, 9.55)	
7.87–10.44 (*n* = 78)	8.37 (7.76, 8.98)		8.47 (7.86, 9.10)	
10.45 (*n* = 77)	8.46 (7.83, 9.09)	0.009	8.85 (8.14, 9.56)	0.35
Soluble fiber (g)				
<1.70 (*n* = 77)	9.45 (8.80, 10.10)		9.14 (8.43, 9.85)	
1.70–2.39 (*n* = 78)	9.10 (8.49, 9.71)		9.00 (8.39, 9.61)	
2.40–3.01 (*n* = 78)	8.46 (8.85, 9.07)		8.53 (7.92, 9.14)	
3.01 (*n* = 77)	8.48 (7.85, 9.11)	0.02	8.81 (8.14, 9.48)	0.39
Folate (μg)				
<209 (*n* = 78)	9.46 (8.79, 10.13)		9.16 (8.43, 9.89)	
209–261 (*n* = 77)	8.86 (8.25, 9.47)		8.87 (8.22, 9.52)	
262–313 (*n* = 78)	9.16 (8.55, 9.77)		9.19 (8.54, 9.84)	
314 (*n* = 77)	8.00 (7.33, 8.67)	0.01	8.29 (7.56, 9.02)	0.22
Vitamin B-6 (mg)				
<1.30 (*n* = 77)	9.77 (9.08, 9.46)		9.59 (8.81, 10.37)	
1.30–1.53 (*n* = 77)	9.35 (8.66, 9.96)		9.26 (8.61, 9.81)	
1.54–1.87 (*n* = 79)	8.30 (7.69, 8.91)		8.38 (7.77, 9.01)	
1.88 (*n* = 77)	8.09 (7.42, 8.76)	0.0004	8.27 (7.52, 9.02)	0.01
Vitamin B-12 (g)				
<3.64 (*n* = 77)	9.19 (8.54, 9.84)		8.86 (8.19, 9.53)	
3.64–4.74 (*n* = 78)	8.86 (8.23, 9.49)		8.88 (8.25, 9.51)	
4.75–7.48 (*n* = 77)	8.63 (8.00, 9.26)		8.69 (8.06, 9.32)	
7.49 (*n* = 78)	8.80 (8.15, 9.45)	0.36	9.07 (8.42, 9.72)	0.77
Riboflavin (mg)				
<1.23 (*n* = 77)	9.53 (8.84, 10.22)		9.14 (8.39, 9.89)	
1.23–1.50 (*n* = 78)	9.30 (8.69, 9.91)		9.11 (8.46, 9.76)	
1.51–1.84 (*n* = 78)	8.48 (7.83, 9.13)		8.60 (7.95, 9.25)	
1.85 (*n* = 77)	8.18 (7.51, 8.85)	0.005	8.63 (7.88, 9.18)	0.32

(Continued)

TABLE 5 (*Continued*)

	tHcy[1]	*P* for trend	tHcy[2]	*P* for trend
	μmol/L		*μmol/L*	
Vegetables (g)				
<104.3 (*n* = 77)	9.22 (8.59, 9.84)		8.91 (8.22, 9.60)	
104.3–148.7 (*n* = 78)	9.38 (8.77, 9.99)		8.36 (7.75, 8.97)	
148.8–197.4 (*n* = 78)	9.03 (8.41, 9.72)		9.05 (8.42, 9.68)	
197.5 (*n* = 77)	7.86 (7.25, 8.47)	0.002	8.16 (7.49, 8.83)	0.13
Fruit (g)				
<97.0 (*n* = 77)	9.18 (8.45, 10.81)		8.98 (8.33, 9.63)	
97.0–150.6 (*n* = 78)	8.34 (7.71, 8.63)		8.35 (7.74, 8.96)	
150.7–234.7 (*n* = 78)	9.11 (8.48, 9.74)		9.07 (8.46, 9.68)	
234.8 (*n* = 77)	8.86 (8.23, 8.49)	0.91	9.09 (8.44, 9.74)	0.50
Coffee (mL)				
<74 (*n* = 78)	8.33 (7.68, 8.94)		8.39 (7.78, 9.00)	
74–183 (*n* = 77)	8.78 (8.15, 9.41)		8.67 (8.06, 9.28)	
184–327 (*n* = 78)	8.81 (8.18, 9.44)		8.81 (8.20, 9.42)	
328 (*n* = 77)	9.57 (8.96, 10.18)	0.008	9.62 (9.01, 10.23)	0.006
Tea (mL)				
0 (*n* = 120)	9.28 (8.69, 9.77)		9.28 (7.77, 9.77)	
1–59 (*n* = 35)	8.57 (7.64, 9.50)		8.50 (7.57, 9.43)	
60–301 (*n* = 78)	8.41 (7.80, 9.02)		8.33 (7.72, 8.94)	
302 (*n* = 77)	8.85 (8.24, 9.46)	0.28	8.94 (8.33, 9.57)	0.38
Alcohol (g)				
<1.2 (*n* = 77)	8.55 (7.92, 9.187)		8.42 (7.79, 9.05)	
1.3–5.0 (*n* = 78)	8.29 (7.68, 8.90)		8.31 (7.71, 8.91)	
5.1–15.0 (*n* = 78)	9.19 (8.57, 9.81)		9.23 (8.63, 9.83)	
15.1 (*n* = 77)	9.47 (8.85, 10.09)	0.01	9.53 (8.90, 10.16)	0.001

[1] Adjusted for age.

[2] Adjusted for age, smoking, energy intake (except for energy intake), dietary folate (except for folate), and vitamin B-6 (except for vitamin B-6).

though no statistically significant relation was found in the men, tHcy was highest in the oldest category, and the truncated distribution may have been too small to show an association. The differences between men and women in the associations of tHcy with systolic and diastolic blood pressure and body mass index are more difficult to explain. Although Morris et al (18) showed that differences in tHcy concentrations may be explained by the differences in estrogen status, we did not observe a difference in tHcy between pre- and postmenopausal women. Nygard et al (4) observed statistically significant associations between tHcy and blood pressure, total cholesterol, and serum triacylglycerol in both men and women. However, they did not divide the variables in quartiles but used fixed limits to create categories of cardiovascular disease risk factors. It was not possible to follow the same strategy in our population because too few subjects had elevated risk factors. Curiously, de Bree et al (11), who also used quartiles in their statistical analyses, observed an association between tHcy and total and HDL cholesterol in women but not in men. They did not find an effect of blood pressure. Jacques et al (8) showed positive relations between body mass index in quartiles and tHcy, but they did not separate their analyses between women and men, which means it is possible that their observed relation was caused by a strong relation in men only, as we observed in our study.

Differences in the use of categories for the explaining variable may also be an explanation for the contradictory results on the association of tHcy with physical activity. Again, Nygard et al (4) used a 4-category variable, from no exercise to heavy training, to describe physical activity and found lower tHcy concentrations in those with the highest physical activity. We used a separation in 3 classes and observed only an effect in men, whereas Saw et al (9) distinguished only between having or not having weekly exercise, and found no effect on tHcy. This indicates that to show a relation of tHcy with physical activity, these habits should be questioned in detail, so that accurate separations can be made between different categories.

Many studies observed higher concentrations of tHcy in smokers than in nonsmokers (4, 6, 7–10), although Rasmussen et al (7) could not confirm this in elderly women and Lussier-Cacan et al (5) did not find any association at all. It is known, however, that smokers eat less fruit and vegetables and may thus have a lower intake of folate and vitamin B-6 (19). Indeed, we observed lower concentrations of folate and PLP in smokers than in nonsmokers (data not shown). It seems therefore logical that the positive trend between smoking and tHcy in men in our study disappeared after adjustment for folate and PLP concentrations. This phenomenon was also found in the study by Saw et al (9), indicating that the effects of smoking may thus be biased by concomitant dietary factors.

The relations between dietary habits and tHcy were investigated previously. Stolzenberg-Solomon et al (20) found an inverse relation between tHcy and dietary protein intake in 260 male and female retired schoolteachers. Jacques et al (8) observed inverse associations between tHcy and intakes of

TABLE 6
Adjusted mean (95% CI) total plasma homocysteine (tHcy) concentrations by daily nutrient and food intakes in men

	tHcy[1]	*P* for trend	tHcy[2]	*P* for trend
	μmol/L		*μmol/L*	
Energy (kJ)				
<7980 (*n* = 76)	10.36 (9.49, 11.23)		9.47 (8.50, 10.44)	
7980–9372 (*n* = 77)	11.11 (10.24, 11.98)		10.84 (9.99, 11.69)	
9373–9472 (*n* = 77)	10.42 (9.57, 11.25)		10.68 (9.83, 11.53)	
9473 (*n* = 76)	11.77 (10.90, 12.64)	0.07	12.67 (11.70, 13.64)	0.0001
Total fat (g)				
<74.0 (*n* = 76)	11.40 (10.29, 12.51)		11.31 (10.18, 12.44)	
74.0–91.5 (*n* = 77)	11.22 (10.35, 12.09)		11.04 (10.17, 11.91)	
91.6–109.9 (*n* = 77)	10.67 (9.78, 11.56)		10.72 (9.83, 10.61)	
110.0 (*n* = 76)	10.36 (9.25, 11.47)	0.23	10.58 (9.47, 11.69)	0.41
Carbohydrate (g)				
<186.6 (*n* = 76)	10.92 (9.91, 11.93)		10.77 (9.74, 11.80)	
186.6–223.2 (*n* = 77)	11.25 (10.38, 12.12)		11.15 (10.28, 12.02)	
223.3–272.2 (*n* = 77)	11.32 (10.45, 12.19)		11.35 (10.50, 12.20)	
272.3 (*n* = 76)	10.15 (9.28, 11.02)	0.38	10.38 (9.37, 11.39)	0.71
Vegetable protein (g)				
<22.7 (*n* = 76)	11.45 (10.42, 12.48)		11.13 (10.08, 12.18)	
22.7–26.5 (*n* = 77)	11.12 (10.27, 11.97)		11.16 (10.21, 12.01)	
26.6–32.2 (*n* = 77)	10.75 (9.86, 11.54)		10.75 (9.88, 11.72)	
32.3 (*n* = 76)	10.31 (9.34, 11.28)	0.14	10.60 (9.59, 11.61)	0.45
Animal protein (g)				
<54.6 (*n* = 76)	11.08 (10.25, 11.91)		10.62 (9.61, 11.63)	
54.6–65.0 (*n* = 77)	11.31 (10.46, 12.16)		11.29 (10.44, 12.14)	
65.1–76.9 (*n* = 77)	11.38 (10.51, 12.25)		11.42 (10.57, 12.27)	
77.0 (*n* = 76)	9.86 (8.95, 10.76)	0.11	10.31 (9.28, 11.34)	0.76
Nonsoluble fiber (g)				
<6.83 (*n* = 76)	12.48 (11.53, 13.33)		12.09 (11.18, 13.00)	
6.83–9.13 (*n* = 77)	10.93 (10.10, 11.76)		10.85 (10.02, 11.68)	
9.14–12.6 (*n* = 77)	9.65 (8.82, 10.48)		9.69 (8.88, 10.50)	
12.7 (*n* = 76)	10.60 (9.85, 11.45)	0.0005	11.04 (10.17, 11.91)	0.07
Soluble fiber (g)				
<1.94 (*n* = 76)	12.53 (11.70, 13.36)		12.40 (11.49, 13.31)	
1.94–2.57 (*n* = 77)	11.29 (10.46, 12.12)		11.33 (10.48, 12.18)	
2.58–3.40 (*n* = 77)	9.85 (9.02, 10.68)		9.86 (9.05, 10.67)	
3.41 (*n* = 76)	9.97 (9.10, 10.85)	0.0001	10.05 (9.06, 11.04)	0.0005
Folate (μg)				
<247 (*n* = 76)	12.01 (11.10, 12.92)		11.88 (10.93, 11.83)	
247–293 (*n* = 77)	10.94 (10.09, 11.79)		10.60 (9.75, 11.45)	
294–365 (*n* = 77)	11.30 (10.45, 12.15)		11.30 (10.45, 12.15)	
366 (*n* = 76)	9.39 (8.48, 10.28)	0.0006	9.87 (8.92, 10.82)	0.03
Vitamin B-6 (mg)				
<1.63 (*n* = 77)	11.37 (10.42, 11.32)		10.93 (9.90, 11.96)	
1.63–1.90 (*n* = 76)	11.97 (11.12, 12.82)		11.89 (11.04, 12.74)	
1.91–2.22 (*n* = 77)	11.04 (10.79, 11.89)		11.13 10.28, 11.98)	
2.23 (*n* = 76)	9.25 (8.32, 10.18)	0.002	9.69 (9.68, 10.70)	0.09
Vitamin B-12 (g)				
<4.66 (*n* = 76)	10.93 (10.04, 11.82)		10.80 (9.93, 11.67)	
4.66–5.98 (*n* = 77)	11.35 (10.48, 12.22)		11.34 (10.49, 12.19)	
5.99–9.05 (*n* = 77)	11.25 (10.38, 12.12)		11.13 (10.28, 11.98)	
9.06 (*n* = 76)	10.11 (9.24, 10.98)	0.22	10.38 (9.51, 11.25)	0.49
Riboflavin (mg)				
<1.23 (*n* = 76)	11.95 (11.12, 12.78)		11.46 (10.45, 11.47)	
1.23–1.50 (*n* = 77)	11.06 (10.21, 11.91)		10.91 (10.06, 11.76)	
1.51–1.84 (*n* = 77)	10.86 (10.01, 11.71)		11.06 (10.21, 11.91)	
1.85 (*n* = 76)	9.80 (8.91, 9.69)	0.003	10.23 (9.24, 11.22)	0.17

(Continued)

TABLE 6 (*Continued*)

	tHcy[1]	*P* for trend	tHcy[2]	*P* for trend
	μmol/L		*μmol/L*	
Vegetables (g)				
<100.5 (*n* = 76)	11.09 (10.22, 11.87)		10.79 (9.90, 11.68)	
100.5–144.2 (*n* = 77)	11.69 (10.84, 12.53)		11.53 (10.68, 12.38)	
144.3–200.3 (*n* = 77)	10.78 (9.93, 11.63)		10.83 (9.98, 11.68)	
200.4 (*n* = 76)	10.08 (9.19, 10.97)	0.05	10.50 (9.57, 11.43)	0.48
Fruit (g)				
<103.4 (*n* = 76)	11.46 (10.39, 12.27)		11.00 (10.07, 11.93)	
103.4–169.7 (*n* = 77)	11.01 (10.16, 11.86)		10.89 (10.02, 11.67)	
169.8–273.2 (*n* = 77)	10.94 (10.07, 11.81)		11.06 (10.21, 11.91)	
273.3 (*n* = 76)	10.24 (9.37, 11.11)	0.06	10.70 (9.75, 11.65)	0.76
Coffee (mL)				
<77 (*n* = 76)	10.57 (9.70, 11.44)		10.64 (9.79, 11.49)	
77–161 (*n* = 77)	11.34 (10.49, 12.19)		11.23 (9.40, 12.06)	
162–284 (*n* = 77)	10.29 (9.44, 11.14)		10.29 (9.46, 11.12)	
285 (*n* = 76)	11.46 (10.59, 12.33)	0.41	11.49 (10.44, 12.34)	0.40
Tea (mL)				
0 (*n* = 201)	10.97 (10.44, 11.50)		10.91 (10.40, 11.42)	
1–54 (*n* = 29)	10.93 (9.48, 12.38)		11.20 (9.79, 12.61)	
55 (*n* = 76)	10.75 (9.92, 11.58)	0.67	10.80 (9.95, 11.65)	0.83
Alcohol (g)				
<9.1 (*n* = 76)	10.44 (9.58, 11.30)		10.31 (9.43, 11.19)	
9.2–20.4 (*n* = 77)	10.96 (10.11, 11.81)		10.99 (10.13, 11.85)	
20.5–35.4 (*n* = 77)	10.89 (10.04, 11.74)		10.79 (9.92, 11.66)	
35.5 (*n* = 76)	11.35 (10.49, 12.21)	0.17	11.57 (10.68, 12.46)	0.08

[1] Adjusted for age.

[2] Adjusted for age, smoking, energy intake (except for energy intake), dietary folate (except for folate), and vitamin B-6 (except for vitamin B-6).

folate, vitamin B-6, and riboflavin, but they did not separate their analyses for men and women. In the study by Rasmussen et al (7), subjects with a high folate intake had a lower tHcy concentration, but this was stronger in younger than in older women. Neither of these 2 studies presented information on intake of fruit and vegetables or dietary fiber. Oshaug et al (21) evaluated tHcy in relation to diet in 310 healthy male offshore workers. Vegetable intake but not fruit intake was inversely associated with tHcy, as was the consumption of skimmed milk and bread. No adjustment was made for intake of folate, vitamin B-6, or vitamin B-12. In the present study the inverse relation between fruit and vegetable intake and tHcy disappeared after adjustment for folate intake, indicating that the folate content of fruit and vegetables determines the relation with tHcy. This, however, was not the case for dietary fiber, indicating that dietary fiber may have a separate effect on tHcy in men, independent of folate intake. Residual confounding may be another explanation for this, as men may have had more difficulties in correct recording of food intake than do women. Confounding by folate intake may also be important for the relation with total energy intake, as we observed in men; folate intake is positively associated with total energy intake and inversely with tHcy and may thus diminish a positive relation between total energy intake and tHcy. This explains why the relation between these factors becomes stronger after adjustment for folate intake. Although vitamin B-6 intake was strongly related to tHcy, no relation of tHcy with PLP was observed. PLP is the bioactive form of vitamin B-6, and when enough vitamin B-6 is ingested, as in an apparently healthy adult population, the concentration of PLP will reach a plateau. At this concentration PLP will not reflect vitamin B-6 intake, because PLP is produced in response to biological needs. Furthermore, intervention studies showed that adding vitamin B-6 supplementation to folic acid supplementation did not further lower blood homocysteine (17). Indeed, the strength of the relation between tHcy and vitamin B-6 intake diminished after adjustment for folate intake, and it is possible that residual confounding is the explanation of the observed relation. The lack of association between vitamin B-12 intake and tHcy in both men and women confirms the result of Jacques et al (8). In contrast, the relation between riboflavin or folate (in women) and tHcy was no longer significant after multiple adjustment. This may be because of the lower number of subjects in the present study for which dietary data were available.

Many studies observed a higher tHcy with a higher coffee consumption and to a lesser extent with a lower tea consumption (7–9, 20, 22). A recent intervention study showed that consumption of a high dose of chlorogenic acid, a major polyphenol in coffee, or consumption of black tea increases tHcy 4–5 h after intake (23). The present study could confirm this only for coffee consumption in women. However, none of the aforementioned studies separated their analyses for women and men. The fact that no relation between tHcy and tea was seen can be ascribed to the low tea consumption in our study, which is typical for a French population.

In conclusion, the determinants of tHcy are not the same for women as for men. To prevent cardiovascular disease, a decrease in coffee and alcohol consumption seems to be important in women, whereas an increase in physical activity and dietary fiber and folate intakes and a decrease in total energy intake may be important in men. Intervention studies should be performed to confirm these observations.

REFERENCES

1. Refsum H, Ueland PM, Nygard O, Vollset SE. Homocysteine and cardiovascular disease. Annu Rev Med 1998;49:31–62.
2. den Heijer M, Rosendaal FR, Blom HJ, Gerrits WBJ, Bos GMJ. Hyperhomocysteinemia and venous thrombosis: a meta-analysis. Thromb Haemost 1998;80:874–7.
3. Kang SS, Passen EL, Ruggie N, Wong N, Sora H. Thermolablie defect of methylenetetrahydrofolate reductase in coronary artery disease. Circulation 1993;88:1463–9.
4. Nygard O, Vollset SE, Refsum H, et al. Total plasma homocysteine and cardiovascular risk profile. The Hordaland Homocysteine Study. JAMA 1995;274:1526–33.
5. Lussier-Cacan S, Xhignesse M, Piolot A, Selhub J, Davignon J, Genest J. Plasma total homocysteine in healthy subjects: sex-specific relation with biological traits. Am J Clin Nutr 1996;64:587–93.
6. Nygard O, Refsum H, Ueland PM, Vollset SE. Major lifestyle determinants of plasma total homocysteine distribution: the Hordaland Homocysteine Study. Am J Clin Nutr 1998;67:263–70.
7. Rasmussen LB, Ovesen L, Bülow I, Knudsen N, Laurberg P, Perrild H. Folate intake, lifestyle factors, and homocysteine concentrations in younger and older women. Am J Clin Nutr 2000;72:1156–63.
8. Jacques PF, Bostom AG, Wilson PWF, Rich S, Rosenberg IH, Selhub J. Determinants of plasma total homocysteine concentration in the Framingham Offspring cohort. Am J Clin Nutr 2001;73:613–21.
9. Saw SM, Yan JM, Ong CN, et al. Genetic, dietary, and other lifestyle determinants of plasma homocysteine concentrations in middle-aged and older Chinese men and women in Singapore. Am J Clin Nutr 2001;73:232–9.
10. Giles WH, Kittner SJ, Croft JB, et al. Distribution and correlates of elevated total homocyst(e)ine: the Stroke Prevention in Young Women Study. Ann Epidemiol 1999;9:307–13.
11. de Bree A, Verschuren WMM, Kromhout D, Blom HJ. Biological cariovascular risk factors and plasma homocysteine levels in the general Dutch population. Atherosclerosis 2001;154:513–4.
12. Hercberg S, Preziosi P, Briancon S, et al. A primary prevention trial of nutritional doses of antioxidant vitamins and minerals on cardiovascular diseases and cancers in general population: the SU.VI.MAX Study. Design, methods and participants characteristics. Control Clin Trials 1998;19:336–51.
13. Le Moullec N, Deheeger M, Preziosi P, et al. Validation du manuel-photos utilisé pour l'enquête alimentaire de l'étude SU.VI.MAX. (Validation of the photo manual used for the collection of dietary data in the SU.VI.MAX Study.) Cah Nutr Diet 1996;31:158–64 (in French).
14. Chango A, Potier de Courcy G, Boisson F, et al. 5,10-Methylenetetrahydrofolate reductase common mutations, folate status and plasma homocysteine in healthy French adults of the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX) cohort. Br J Nutr 2000;84:891–6.
15. Favier JC, Ireland-Ripert J, Toque C, Feinberg M. Répertoire général des aliments. Table de composition. (Food composition table.) Paris: Institut National de Recherche Agronomique, Centre National d'étude Vétérinaire et Agricole, Centre Informatique sur la Qualité des Aliments, 1995 (in French).
16. Brattström L, Wilcken DEL. Homocysteine and cardiovascular disease: cause or effect? Am J Clin Nutr 2000;72:315–23.
17. Homocysteine Lowering Trialists' Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. BMJ 1998;316:894–8.
18. Morris MS, Jacques PF, Selhub J, Rosenberg IH. Total homocysteine and estrogen status indicators in the Third National Health and Nutrition Examination Survey. Am J Epidemiol 2000;152:140–8.
19. Serdula MK, Byers T, Mokdad AH, Simoes E, Mendlein JM, Coates RJ. The association between fruit and vegetable intake and chronic disease risk factors. Epidemiology 1996;7:161–5.
20. Stolzenberg-Solomon R, Miller ER III, Maguire MG, Selhub J, Appel LJ. Association of dietary protein intake and coffee consumption with serum homocysteine concentrations in an older population. Am J Clin Nutr 1999;69:467–75.
21. Oshaug A, Bugge KH, Refsum H. Diet, and independent determinant for plasma total homocysteine. A cross sectional study of Norwegian workers on platforms in the North Sea. Eur J Clin Nutr 1998;52:7–11.
22. Nygard O, Refsum H, Ueland PM, et al. Coffee consumption and plasma total homocysteine: the Hordaland Homocysteine Study. Am J Clin Nutr 1997;65:136–43.
23. Olthof MR, Hollman PCH, Zock P, Katan MB. Consumption of high doses of chlorogenic acid, present in coffee, or of black tea increases plasma total homocysteine concentrations in humans. Am J Clin Nutr 2001;73:532–8.