Changes in caffeine intake and long-term weight change in men and women[1–3]

Esther Lopez-Garcia, Rob M van Dam, Swapnil Rajpathak, Walter C Willett, JoAnn E Manson, and Frank B Hu

ABSTRACT

Background: The long-term effects of caffeine intake on weight have not been examined prospectively.

Objective: The objective was to assess the relation between caffeine intake and 12-y weight change.

Design: We conducted a prospective study of 18 417 men and 39 740 women, with no chronic diseases at baseline, who were followed from 1986 to 1998. Caffeine intake was assessed repeatedly every 2–4 y. Weight change was calculated as the difference between the self-reported weight in 1986 and in 1998.

Results: The participants reported a change in caffeine intake that varied across quintiles, from decreases of 296 and 342 mg/d to increases of 213 and 143 mg/d in men and women, respectively. Age-adjusted models showed a lower mean weight gain in participants who increased their caffeine consumption than in those who decreased their consumption, but the differences between extreme quintiles were small: −0.43 kg (95% CI: −0.17, −0.69) in men and −0.41 kg (95% CI: −0.20, −0.62) in women. After adjustment for potential confounders and baseline and change in total energy intake and other nutrients and foods, the differences remained similar for men and diminished slightly for women (men: −0.43 kg; 95% CI: −0.17, −0.68; women: −0.35; 95% CI: −0.14, −0.56). An increase in coffee and tea consumption was also associated with less weight gain. In men, the association between caffeine intake and weight was stronger in younger participants (P for interaction < 0.001); in women, the association was stronger in those who had a body mass index (in kg/m^2) ≥25, who were less physically active, or who were current smokers (P for interaction < 0.001).

Conclusion: Increases in caffeine intake may lead to a small reduction in long-term weight gain. *Am J Clin Nutr* 2006;83:674–80.

KEY WORDS Caffeine intake, long-term weight change, prospective study, type 2 diabetes

INTRODUCTION

Although short-term metabolic studies have suggested adverse effects of caffeine on insulin sensitivity (1), long-term studies have linked higher coffee consumption with a lower risk of developing type 2 diabetes mellitus (2). Weight gain is a major determinant of diabetes, and it is possible that a beneficial effect of caffeine on weight might contribute to the inverse association between coffee and diabetes. This hypothesis is supported by previous short-term studies that showed an increased metabolic rate and thermogenesis after caffeine consumption (3).

Supplements containing a combination of caffeine and ephedra alkaloids have been widely used as part of weight-loss treatments. This herbal preparation is the only supplement for which randomized clinical trials indicate some efficacy in weight loss (4). However, these studies had a duration of ≤6 mo (5–9) and did not assess the long-term effect of caffeine. To our knowledge, only one previous study has examined the association between caffeine consumption and weight change retrospectively (10). Therefore, we examined the relation between long-term caffeine intake and 12-y weight change in 2 large prospective cohort studies of men and women.

SUBJECTS AND METHODS

Subjects

The Nurses' Health Study was established in 1976 and included 121 700 female registered nurses aged 30–55 y. Every 2 y, participants are mailed a follow-up questionnaire to update information about their medical history, lifestyle, and other risk factors. A semiquantitative food-frequency questionnaire (FFQ) was first administered in 1980 and every 2–4 y since then. Women who did not complete >10 of 61 items on the 1980 dietary questionnaire or had extreme scores for total daily intake of energy (<500 kcal, or > 3500 kcal) were excluded. In 1984, the FFQ was expanded to include 126 items. The Health Professionals Follow-Up Study was established in 1986 with 51 529 male health professionals, including dentists, optometrists, veterinarians, osteopathic physicians, podiatrists, and pharmacists aged 40–75 y who returned a mailed questionnaire similar to that used in the Nurses' Health Study. Information on the cohort is also updated every 2 y, and newly diagnosed diseases are identified. Participants who did not complete >70 of 131 food items

[1] From the Departments of Nutrition (EL-G, RMvD, WCW, EBR, and FBH) and Epidemiology (WCW, JEM, and FBH), Harvard School of Public Health, Cambridge, MA; the Department of Epidemiology and Population Health, Albert Einstein College of Medicine Bronx, New York, NY (SR); the Channing Laboratory (WCW, JEM, and FBH) and Division of Preventive Medicine (JEM), Harvard Medical School, Cambridge, MA.

[2] Supported by NIH research grants CA87969, P30 DK46200, DK55523, and DK58845. FBH was partially supported by an American Heart Association Established Investigator Award.

[3] Address reprint requests to E Lopez-Garcia, Department of Preventive Medicine, Autonoma University of Madrid, Avda Arzobispo Morcillo, s/n Madrid, Spain. E-mail: esther.lopez@uam.es.

Received August 15, 2005.

Accepted for publication November 14, 2005.

on the 1986 dietary questionnaire or had extreme total daily intakes of energy (<800 kcal, or >4200 kcal) were excluded.

For these analyses we also excluded participants who reported cardiovascular disease, diabetes, or cancer at baseline or during the follow-up and those who did not provide weight measures or information on caffeine intake in 1986 or 1998, which left 39 740 women and 18 417 men who were followed from 1986 to 1998.

Assessment of caffeine intake and other nutrients

On each dietary questionnaire, participants were asked how often on average during the previous year they had consumed caffeinated and decaffeinated coffee, tea, soft drinks, or chocolate. The participants could choose from 9 responses (never, 1–3 times/mo, 1 time/wk, 2–4 times/wk, 5–6 times/wk, 1 time/d, 2–3 times/d, 4–5 times/d, and ≥6 times/d). Using US Department of Agriculture food-composition data (11, 12) supplemented with other sources, we estimated that the caffeine content was 137 mg/cup of caffeinated coffee (1 cup = 237 mL), 47 mg/cup of tea, 46 mg/12-oz (340.19 g) can or bottle of cola beverage, 7 mg/oz (198.45 g) of chocolate candy, and 2 mg/cup of decaffeinated coffee. We assessed the total intake of caffeine by summing the caffeine content for the above specific amounts of each food during the previous year and multiplying this value by a weight proportional to the frequency of its use. In our validation study we obtained high correlations between consumption of coffee and other caffeinated beverages estimated from the FFQ and consumption estimated from repeated 1-wk diet records for men [coffee: $r = 0.83$; tea: $r = 0.62$; low-calorie caffeinated sodas: $r = 0.67$; and regular caffeinated sodas: $r = 0.56$ (13)] and for women [coffee: $r = 0.78$; tea: $r = 0.93$; and caffeinated sodas: $r = 0.85$ (14)]. Change in caffeine intake was calculated as the difference between the intake in 1986 and in 1998.

Assessment of weight change and other variables

On the baseline questionnaires, we requested information about age, weight, height, smoking status, physical activity, alcohol consumption, and history of chronic diseases. This information, with the exception of height, has been updated on the biennial follow-up questionnaires. Weight change was calculated as the difference between the weight in 1986 and in 1998. Body mass index (BMI) at baseline was calculated as weight in kilograms divided by the square of height in meters. The validity of self-reported height and weight was evaluated previously (15, 16). The correlation coefficients between self-reported weight measurements and the average of 2 standardized measurements were 0.97 for both men and women; the mean difference between measured and self-reported weights was 1.5 kg.

Change in smoking status was categorized as follows: never smoker; past smoker in 1986; smoker in 1986 who quit in 1988, in 1990, in 1992, in 1994, in 1996, or in 1998; and current smoker in 1998 (including those who smoked throughout the follow-up period and those who started smoking at some point during this time). Physical activity was assessed by asking participants about the average time spent per week during the preceding year on specific activities, such as walking or hiking outdoors, jogging, running, bicycling, swimming, tennis, squash, racquetball, rowing, and calisthenics (17). The time spent in each activity in hours per week was multiplied by its typical energy expenditure, expressed in metabolic equivalent tasks (MET) and then summed over all activities to yield a MET-h score. The validity and reproducibility of the physical activity questionnaire were reported previously (18, 19). Alcohol consumption was calculated as the sum of the amount of alcohol in any wine, beer, and liquor consumed, multiplied by the average number of servings per day (11). The validity and reproducibility of alcohol intake were also evaluated (20). Changes in physical activity and alcohol consumption were calculated as the difference between the values reported in 1986 and in 1998.

Statistical analysis

Participants were classified in quintiles according to their levels of change in caffeine intake to avoid a linearity assumption and to reduce the effect of outliers. We used age-adjusted and multivariate linear regression to examine the association between change in caffeine intake and 12-y weight change (kg). We calculated least-squares means for changes in body weight across categories of change in caffeine intake after adjustment for age, change in smoking status, and baseline and change in physical activity (MET-h/wk) and alcohol consumption (g/d). Additionally, we adjusted for BMI at baseline, because weight change can depend on initial weight (21), and for baseline and change in intake of nutrients or foods that were previously associated with an increase or decrease in body weight: total energy intake (kcal/d), *trans* fat intake (% of energy), glycemic load, total fiber (g/d), whole grain intake (g/d), low- and high-calorie soft drinks (servings/d), and fruit and vegetables (servings/d) (17, 22–25). All nutrient values, including caffeine, were energy-adjusted by using the residual method (26). To test for linear trends across categories, we modeled the change in caffeine intake as a continuous variable using the median value of each quintile. We also examined the association of changes in coffee, tea, and decaffeinated coffee consumption with weight change. Finally, we conducted stratified analyses by categories of age, smoking status, BMI, physical activity, and alcohol consumption. All analyses were performed with the use of SAS software (version 8.2; SAS Institute Inc, Cary, NC).

RESULTS

The characteristics of the study populations by quintiles of change in caffeine intake are shown in **Table 1**. Participants in the lower quintiles decreased their caffeine intake between 1986 and 1998 and those in the higher quintiles increased their intake. An increase in caffeine intake was associated with a smaller increase in physical activity and a larger reduction in alcohol consumption in women. Participants in the higher quintiles reduced the total amount of calories in their diets mainly as a result of a lower intake of fat not compensated for an increase in carbohydrate intake. Most of the increase in caffeine consumption came from coffee.

During 12 y of follow-up, participants reported a change in caffeine intake that varied across quintiles from a decrease of 294 mg/d to an increase of 211 mg/d in men and from −317 to 141 mg/d in women (**Table 2**). Age-adjusted models showed less mean weight gain in participants who reported an increment in caffeine consumption than in those who decreased their consumption. However, the differences between extreme quintiles were small: −0.43 kg (95% CI: −0.17, −0.69) in men and −0.41 kg (95% CI: −0.20, −0.62) in women. After adjustment for potential confounders and baseline and change in nutrient and

TABLE 1
Characteristics of the population at baseline (1986) and change (1986–1998) by quintile (Q) of change in caffeine intake in the Health Professionals Follow-Up Study (HPFS) and in the Nurses' Health Study (NHS)[1]

	Changes in caffeine intake in men in the HPFS				Changes in caffeine intake in women in the NHS			
	Q1 (n = 3683)	Q3 (n = 3683)	Q5 (n = 3684)	P for trend	Q1 (n = 7945)	Q3 (n = 7952)	Q5 (n = 7948)	P for trend
Caffeine intake in 1986 (mg/d)	550 ± 4.2[2]	105 ± 2.4	180 ± 3.1	< 0.001	493 ± 1.8	195 ± 1.8	197 ± 1.8	< 0.001
Caffeine intake in 1998 (mg/d)	199 ± 3.1	98 ± 2.4	437 ± 4.0	< 0.001	143 ± 1.8	145 ± 1.8	379 ± 1.8	< 0.001
Change in caffeine intake (mg/d)	−351 ± 3.1	−7 ± 0.2	257 ± 2.5	< 0.001	−350 ± 1.4	−50 ± 0.2	182 ± 1.5	< 0.001
Age in 1986 (y)	52.0 ± 0.1	51.7 ± 0.1	50.4 ± 0.1	< 0.001	51.5 ± 0.08	51.8 ± 0.08	51.1 ± 0.08	< 0.001
Age in 1998 (y)	64.0 ± 0.1	63.7 ± 0.1	62.4 ± 0.1	< 0.001	63.5 ± 0.08	63.8 ± 0.08	63.1 ± 0.08	< 0.001
Current smokers in 1986 (%)	12.1	4.5	9.5	< 0.001	23.4	14.8	19.6	< 0.001
Current smokers in 1998 (%)	4.4	2.7	4.7	< 0.001	8.6	6.4	9.2	< 0.001
Hypertension in 1986 (%)	15	15	16	0.63	11	13	12	0.03
Hypertension in 1998 (%)	35	30	30	< 0.001	39	39	35	< 0.001
Hypercholesterolemia in 1986 (%)	10	9	10	0.72	5	7	6	0.004
Hypercholesterolemia in 1998 (%)	46	42	46	0.53	55	55	53	0.003
Physical exercise in 1986 (MET-h/wk)	20.7 ± 0.5	24.5 ± 0.5	22.7 ± 0.5	< 0.001	13.3 ± 0.2	15.1 ± 0.2	15.0 ± 0.2	< 0.001
Change	12.9 ± 0.7	15.8 ± 0.7	11.9 ± 0.7	0.25	4.5 ± 0.3	3.7 ± 0.3	2.8 ± 0.3	< 0.001
Alcohol consumption in 1986 (g/d)	13.1 ± 0.2	9.1 ± 0.2	12.8 ± 0.2	< 0.001	6.7 ± 0.1	6.3 ± 0.1	6.6 ± 0.1	< 0.001
Change	−0.2 ± 0.2	0.3 ± 0.2	−0.6 ± 0.2	0.47	−0.8 ± 0.1	−0.9 ± 0.1	−1.5 ± 0.1	< 0.001
Total energy intake in 1986 (kcal)	1892 ± 9.9	2047 ± 9.9	2008 ± 9.9	< 0.001	1679 ± 5.7	1815 ± 5.7	1731 ± 5.7	< 0.001
Change	119 ± 9.3	−2 ± 9.3	−104 ± 9.3	< 0.001	61 ± 5.5	8 ± 5.5	−140 ± 5.5	< 0.001
Carbohydrate intake in 1986 (% of energy)	45.5 ± 0.1	48.8 ± 0.1	46.5 ± 0.1	< 0.001	47.5 ± 0.1	48.9 ± 0.1	47.9 ± 0.1	< 0.001
Change	4.8 ± 0.1	4.4 ± 0.1	4.3 ± 0.1	< 0.001	6.4 ± 0.1	6.1 ± 0.1	6.0 ± 0.1	0.001
Protein intake in 1986 (% of energy)	18.3 ± 0.1	18.4 ± 0.1	18.5 ± 0.1	0.04	18.7 ± 0.04	18.4 ± 0.04	18.8 ± 0.04	0.04
Change	−0.7 ± 0.1	−0.8 ± 0.1	−1.1 ± 0.1	0.001	−1.6 ± 0.04	−1.5 ± 0.04	−1.7 ± 0.04	0.008
Total fat intake in 1986 (% of energy)	32.7 ± 0.1	31.4 ± 0.1	31.9 ± 0.1	< 0.001	33.2 ± 0.06	32.4 ± 0.06	32.8 ± 0.06	< 0.001
Change	−3.0 ± 0.1	−2.8 ± 0.1	−2.4 ± 0.1	< 0.001	−4.0 ± 0.08	−3.9 ± 0.08	−3.6 ± 0.08	< 0.001
trans Fat intake in 1986 (% of energy)	1.3 ± 0.01	1.2 ± 0.01	1.2 ± 0.01	< 0.001	1.7 ± 0.01	1.7 ± 0.01	1.7 ± 0.01	< 0.001
Change	0.39 ± 0.01	0.37 ± 0.01	0.44 ± 0.01	0.005	−0.11 ± 0.01	−0.11 ± 0.01	−0.06 ± 0.01	< 0.001
Glycemic load in 1986	120 ± 0.4	130 ± 0.4	123 ± 0.4	< 0.001	96 ± 0.2	100 ± 0.2	98 ± 0.2	< 0.001
Change	15 ± 0.4	13 ± 0.4	12 ± 0.4	< 0.001	19 ± 0.2	17 ± 0.2	17 ± 0.2	< 0.001
Total fiber intake in 1986 (g/d)	19.7 ± 0.1	21.9 ± 0.1	20.8 ± 0.1	< 0.001	17.2 ± 0.06	17.8 ± 0.06	17.6 ± 0.06	< 0.001
Change	3.6 ± 0.1	3.2 ± 0.1	2.6 ± 0.1	< 0.001	2.2 ± 0.06	2.0 ± 0.06	1.6 ± 0.06	< 0.001
Whole-grain intake in 1986 (s/d)	19.7 ± 0.3	24.7 ± 0.3	22.5 ± 0.3	< 0.001	13.9 ± 0.2	14.9 ± 0.2	14.5 ± 0.2	< 0.001
Change	12.7 ± 0.4	12.0 ± 0.4	10.8 ± 0.4	< 0.001	12.1 ± 0.2	11.0 ± 0.2	10.7 ± 0.2	< 0.001
Fruit and vegetable intake in 1986 (s/d)	5.0 ± 0.05	5.9 ± 0.05	5.5 ± 0.05	< 0.001	12.4 ± 0.05	13.5 ± 0.06	13.0 ± 0.06	< 0.001
Change	1.2 ± 0.05	0.9 ± 0.05	0.3 ± 0.05	< 0.001	−6.9 ± 0.05	−7.6 ± 0.05	−7.8 ± 0.05	< 0.001
Coffee intake in 1986 (cups/d)	3.1 ± 0.01	0.5 ± 0.02	1.0 ± 0.02	< 0.001	4.8 ± 0.01	1.9 ± 0.02	2.0 ± 0.02	< 0.001
Change	−1.9 ± 0.02	0 ± 0.01	1.57 ± 0.02	< 0.001	−3.9 ± 0.01	−0.9 ± 0.01	0.3 ± 0.02	< 0.001
Tea intake in 1986 (cups/d)	0.7 ± 0.02	0.3 ± 0.01	0.3 ± 0.01	< 0.001	1.4 ± 0.02	1.1 ± 0.02	0.8 ± 0.01	< 0.001
Change	−2.8 ± 0.03	−0.3 ± 0.02	−0.6 ± 0.03	< 0.001	−4.5 ± 0.02	−1.5 ± 0.02	−1.5 ± 0.03	< 0.001
High-calorie soft drink intake in 1986 (s/d)	0.3 ± 0.01	0.3 ± 0.01	0.2 ± 0.01	0.18	0.3 ± 0.01	0.4 ± 0.01	0.3 ± 0.01	< 0.001
Change	−0.04 ± 0.01	−0.04 ± 0.01	−0.03 ± 0.01	0.02	−0.2 ± 0.01	−0.3 ± 0.01	−0.2 ± 0.01	< 0.001
Low-calorie soft drink intake in 1986 (s/d)	0.6 ± 0.02	0.5 ± 0.01	0.6 ± 0.02	0.002	0.9 ± 0.01	0.9 ± 0.01	1.2 ± 0.02	< 0.001
Change	−0.06 ± 0.02	−0.06 ± 0.01	0.05 ± 0.02	< 0.001	−0.4 ± 0.01	−0.4 ± 0.01	−0.5 ± 0.02	< 0.001
Chocolate intake in 1986 (s/d)	0.1 ± 0.01	0.1 ± 0.01	0.1 ± 0.01	0.66	0.2 ± 0.01	0.3 ± 0.01	0.2 ± 0.01	0.03
Change	−0.01 ± 0.01	0 ± 0.01	−0.01 ± 0.01	0.91	−0.1 ± 0.01	−0.1 ± 0.01	−0.1 ± 0.01	0.51

[1] MET, metabolic equivalents; s, servings. 1 cup = 237 mL. All data, except age, were directly standardized to the age distributions of the entire cohorts.
[2] $\bar{x}$ ± SE (all such values).

food intakes, the differences remained similar. Further adjustment for energy intake, a possible mediator in the relation between caffeine and weight change, did not change the differences between quintiles for men (−0.43 kg; 95% CI: −0.17, −0.68) but did diminish these differences slightly in women (−0.35 kg; 95% CI: −0.14, −0.56). The P values for trend across quintiles were significant for all the models. When we additionally adjusted for sugar intake and whole milk consumption, we obtained similar results.

We examined the association between the main sources of caffeine in the diet and weight change and found that an increase in coffee consumption was inversely associated with weight gain

TABLE 2
Twelve-year weight change (kg) by quintile (Q) of change in caffeine intake (mg/d)

	Change in caffeine intake					*P* for trend[1]
	Q1	Q2	Q3	Q4	Q5	
Men						
Participants (*n*)	3683	3683	3683	3684	3684	
Median intake (mg/d)	−294	−80	−5	36	211	
Age-adjusted model	3.22 ± 0.09[2]	2.70 ± 0.09	2.36 ± 0.09	2.81 ± 0.09	2.79 ± 0.09	0.001
Multivariate model[3]	3.18 ± 0.09	2.71 ± 0.09	2.56 ± 0.09	2.75 ± 0.09	2.68 ± 0.09	< 0.001
Multivariate model[4]	3.14 ± 0.09	2.69 ± 0.09	2.57 ± 0.09	2.78 ± 0.09	2.71 ± 0.09	0.001
Women						
Participants (*n*)	7945	7951	7952	7944	7948	
Median intake (mg/d)	−317	−144	−50	5	141	
Age-adjusted model	4.28 ± 0.07	4.03 ± 0.07	3.89 ± 0.07	3.86 ± 0.07	3.87 ± 0.07	< 0.001
Multivariate model[3]	4.21 ± 0.07	4.07 ± 0.07	3.99 ± 0.07	3.89 ± 0.07	3.76 ± 0.07	< 0.001
Multivariate model[4]	4.17 ± 0.07	4.05 ± 0.07	3.96 ± 0.07	3.93 ± 0.07	3.81 ± 0.07	< 0.001

[1] *P* value from the models in which the change in caffeine intake was modeled as a continuous variable with the use of the median value of each quintile.
[2] $\bar{x}$ ± SE (all such values).
[3] Multivariate linear regression model adjusted for age (5-y categories), BMI at baseline (continuous; in kg/m^2), change in smoking status (never; past smoker in 1986; smoker in 1986 who quit in 1988, in 1990, in 1992, in 1994, in 1996, or in 1998; and current smoker in 1998), baseline and change in physical activity and alcohol intake (quintiles), quintiles of baseline and change in *trans* fat intake, glycemic load, total fiber and whole-grain intakes, and quartiles of baseline and change in low- and high-calorie soft drink intake, and fruit and vegetable consumption.
[4] Multivariate linear regression model with additional adjustment for quintiles of baseline and change in energy intake.

in women but less clearly in men. Similar associations were observed for tea consumption (**Table 3**). In addition, we examined the role of decaffeinated coffee, because it has a small amount of caffeine but all the other components of coffee. Interestingly, we found a modest inverse association with weight gain.

We also examined the association between caffeine intake and weight change stratified by known risk factors for weight gain (**Table 4**). In men, the association was stronger in younger participants (*P* for interaction < 0.001). In women, we observed stronger associations in smokers, women with a BMI ≥ 25, and less physically active persons (*P* for interaction < 0.001).

In additional analyses, we excluded participants who reported having hypertension or hypercholesterolemia at baseline or during the follow-up because they could have changed their caffeine intake in response to the diagnosis. The differences in weight gain between extreme quintiles of change in caffeine intake did not vary significantly in men (multivariate adjusted mean: −0.40 kg; 95% CI: −0.03, −0.70) or in women (multivariate adjusted mean: 0.38 kg; 95% CI: −0.03, −0.74). We also performed an analysis in which we excluded participants who reported to have lost ≥5 kg before 1986, because weight loss has been shown to be associated with a subsequent greater weight gain (27), and the results were similar.

DISCUSSION

In this large longitudinal study, an increase in caffeine intake during 12 y was associated with slightly smaller weight gains in men and women. In addition, an increase in coffee or tea consumption was also associated with a smaller weight gain.

Randomized clinical trials have found that the combination of caffeine and ephedrine is modestly effective in short-term weight loss (5–7, 9). Ephedrine is an adrenergic alkaloid with thermogenic and appetite-suppressant properties (28), which is obtained from the plant ma huang (*Ephedra sinica*). Caffeine is often combined with ephedrine because it boosts ephedrine's thermogenic effect (8, 29). However, dietary supplements containing ephedra alkaloids have also been associated with adverse cardiovascular outcomes (30). For this reason, the National Institutes of Health guidelines recommend against the use of herbal preparations as part of a weight-loss program (31).

Caffeine alone has several important metabolic effects. Caffeine is an adenosine-receptor antagonist (32), and all tissues with adenosine receptors can be affected by caffeine exposure. Spriet et al (33) reported that caffeine stimulates fat utilization in muscle tissue during exercise. In addition, Astrup et al (3) reported a dose-dependent increase in basal energy expenditure with caffeine intake in healthy subjects who had moderate habitual caffeine consumption. They attributed this effect to an increase in lactate and triacylglycerol production and increased vascular smooth muscle tone. Acheson et al (34) suggested that caffeine may stimulate thermogenesis by increasing lipid turnover. All the above mechanisms suggest a beneficial effect of caffeine on energy metabolism. In addition, because we adjusted our analyses for total energy intake and soft drink consumption, we believe that the inverse association between caffeine and weight cannot be due to a replacement of high-calorie food consumption by low-calorie fluid ingestion. Finally, epidemiologic studies have consistently reported a decreased risk of developing type 2 diabetes in heavy coffee drinkers (35–38). Although it is unlikely that the modest association between caffeine and weight change can explain the beneficial effect of coffee on type 2 diabetes, it may contribute to it.

The observed association between decaffeinated coffee and smaller weight gain may indicate that the effect of coffee could be due to compounds other than caffeine. For example, chlorogenic acid in coffee is able to attenuate glucose absorption in the digestive track, which could help control weight (39). The stronger effect of caffeine in female smokers is interesting because there is evidence of a synergistic effect between caffeine and smoking on energy expenditure (40). In a clinical trial with 12 healthy normal-weight subjects who were advised to chew 7 types of gum containing different doses of nicotine and caffeine,

TABLE 3
Twelve-year weight change (kg) by quintile (Q) of change in consumption of foods containing caffeine[1]

	Change in consumption					*P* for trend[2]
	Q1	Q2	Q3	Q4	Q5	
Men						
Caffeinated coffee						
Median (cups/d)	−2.0	−0.3	0	0.2	1.5	
Age-adjusted model	2.99 ± 0.09[3]	2.69 ± 0.14	2.67 ± 0.06	2.66 ± 0.15	2.88 ± 0.09	0.24
Multivariate model[4]	3.01 ± 0.11	2.70 ± 0.15	2.81 ± 0.07	2.66 ± 0.15	2.69 ± 0.10	0.07
Multivariate model[5]	3.02 ± 0.11	2.71 ± 0.15	2.81 ± 0.07	2.65 ± 0.15	2.68 ± 0.10	0.04
Tea						
Median (cups/d)	−2.5	−1.7	−0.4	0	0.4	
Age-adjusted model	3.04 ± 0.09	2.78 ± 0.10	2.89 ± 0.10	2.55 ± 0.09	2.61 ± 0.09	< 0.001
Multivariate model[4]	2.61 ± 0.16	2.80 ± 0.13	3.02 ± 0.13	2.78 ± 0.13	2.86 ± 0.13	0.40
Multivariate model[5]	2.61 ± 0.16	2.81 ± 0.13	3.01 ± 0.13	2.78 ± 0.13	2.85 ± 0.13	0.42
Decaffeinated coffee						
Median (cups/d)	−1.5	−0.08	0	0.06	0.65	
Age-adjusted model	3.22 ± 0.09	3.00 ± 0.12	2.64 ± 0.06	2.19 ± 0.43	2.67 ± 0.09	< 0.001
Multivariate model[4]	3.12 ± 0.10	2.95 ± 0.12	2.71 ± 0.06	2.17 ± 0.42	2.65 ± 0.09	< 0.001
Multivariate model[5]	3.14 ± 0.10	2.94 ± 0.12	2.71 ± 0.06	2.20 ± 0.42	2.63 ± 0.09	< 0.001
Women						
Caffeinated coffee						
Median (cups/d)	−3.5	−2.0	−1.5	−0.08	0.3	
Age-adjusted model	4.27 ± 0.07	3.76 ± 0.07	3.81 ± 0.09	4.06 ± 0.08	3.94 ± 0.08	0.03
Multivariate model[4]	4.26 ± 0.09	3.80 ± 0.09	3.80 ± 0.09	4.16 ± 0.11	3.82 ± 0.09	0.005
Multivariate model[5]	4.28 ± 0.09	3.80 ± 0.09	3.80 ± 0.09	4.16 ± 0.11	3.80 ± 0.09	0.002
Tea						
Median (cups/d)	−4.5	−4.4	−2.4	−0.08	0.4	
Age-adjusted model	4.09 ± 0.07	4.04 ± 0.09	3.78 ± 0.08	4.05 ± 0.08	3.95 ± 0.08	0.43
Multivariate model[4]	4.18 ± 0.14	4.30 ± 0.15	3.88 ± 0.12	3.85 ± 0.16	3.75 ± 0.15	0.05
Multivariate model[5]	4.21 ± 0.14	4.33 ± 0.15	3.89 ± 0.12	3.82 ± 0.16	3.71 ± 0.15	0.03
Decaffeinated coffee						
Median (cups/d)	−4.07	−1.0	−0.14	−0.08	0.35	
Age-adjusted model	4.41 ± 0.08	4.01 ± 0.08	4.02 ± 0.16	3.95 ± 0.06	3.82 ± 0.08	0.007
Multivariate model[4]	4.04 ± 0.08	3.98 ± 0.08	4.03 ± 0.15	4.00 ± 0.06	3.86 ± 0.07	0.24
Multivariate model[5]	4.09 ± 0.08	4.00 ± 0.08	4.05 ± 0.15	4.00 ± 0.06	3.79 ± 0.08	0.07

[1] 1 cup = 237 mL.
[2] *P* value from the models in which the change in caffeine intake was modeled as a continuous variable with the use of the median value of each quintile.
[3] $\bar{x}$ ± SE (all such values).
[4] Multivariate linear regression model adjusted for age (5-y categories), BMI at baseline (continuous; in kg/m^2), change in smoking status (never; past smoker in 1986; smoker in 1986 who quit in 1988, in 1990, in 1992, in 1994, in 1996, or in 1998; and current smoker in 1998), baseline and change in physical activity and alcohol intake (quintiles), quintiles of baseline and change in *trans* fat intake, glycemic load, total fiber and whole-grain intakes, and quartiles of baseline and change in low- and high-calorie soft drink intake, and fruit and vegetable consumption. Caffeinated coffee, decaffeinated coffee, and tea were adjusted simultaneously.
[5] Multivariate linear regression model with additional adjustment for quintiles of baseline and change in energy intake. Caffeinated coffee, decaffeinated coffee, and tea were adjusted simultaneously.

the addition of 50 mg caffeine to 1 or 2 mg nicotine significantly enhanced the thermogenic effect of nicotine and also reduced appetite (41). This synergism might be explained by the complementary physiologic effects of nicotine and caffeine: nicotine increases norepinephrine release, which stimulates β-adrenoceptors in the thermogenic target tissues, whereas caffeine acts by amplifying the postreceptor signal via antagonism of the effect of adenosine and inhibition of cyclic AMP (42).

Although we have focused on changes in caffeine intake during follow-up, it is possible that the effect of caffeine might also be observed in the participants who decreased their caffeine consumption. Dulloo et al (43) showed that the administration of 100 mg caffeine (less than the amount of caffeine in a cup of coffee) increased the resting metabolic rate by 3–4% and improved diet-induced thermogenesis in lean and obese subjects. When we performed the analyses by adjusting for baseline caffeine intake, the increase in caffeine intake was still associated with less weight gain. A limitation of our study was that information on weight was self-reported. However, our validation study indicated that self-reported weight was highly correlated with measured weight (15, 16). Some measurement error in the assessment of caffeine intake will also have occurred because we estimated caffeine intake from self-reported food consumption. However, the validation data showed that coffee and tea, the main sources of caffeine, were among the more accurately reported foods in the FFQ (13, 14). Finally, because this was an

TABLE 4
Twelve-year weight change (kg) by quintile (Q) of change in caffeine intake, stratified by age, smoking, BMI, physical activity, and alcohol consumption in 1986[1]

	Change in caffeine intake					*P* for interaction[2]
	Q1	Q2	Q3	Q4	Q5	
Men						
Participants (*n*)	3683	3683	3683	3684	3684	
Median intake (mg/d)	−294	−80	−5	36	211	
Age (y)[3]						
<50	4.88 ± 0.14[4]	4.01 ± 0.14	3.96 ± 0.14	4.00 ± 0.13	4.01 ± 0.13	< 0.001
≥50	1.64 ± 0.12	1.40 ± 0.12	1.24 ± 0.12	1.67 ± 0.13	1.58 ± 0.13	
Smoking status						
Never	3.16 ± 0.14	2.59 ± 0.12	2.54 ± 0.11	2.72 ± 0.11	2.64 ± 0.13	0.33
Past	2.93 ± 0.13	2.56 ± 0.15	2.39 ± 0.17	2.65 ± 0.16	2.66 ± 0.14	
Current	4.27 ± 0.35	3.71 ± 0.43	3.01 ± 0.57	3.98 ± 0.49	3.06 ± 0.39	
BMI (kg/m^2)						
<25	2.84 ± 0.11	2.34 ± 0.10	2.35 ± 0.10	2.56 ± 0.10	2.62 ± 0.11	0.64
25–29.9	3.43 ± 0.14	3.12 ± 0.14	2.90 ± 0.16	2.93 ± 0.15	2.65 ± 0.14	
≥30	3.45 ± 0.62	2.77 ± 0.61	2.67 ± 0.76	3.10 ± 0.71	3.91 ± 0.64	
Physical activity (MET-h/wk)[3]						
<13.6	3.09 ± 0.14	2.62 ± 0.14	2.34 ± 0.15	2.62 ± 0.14	2.60 ± 0.14	0.74
≥13.6	3.20 ± 0.12	2.78 ± 0.12	2.72 ± 0.12	2.92 ± 0.12	2.88 ± 0.12	
Alcohol consumption (g/d)						
0–4.9	3.08 ± 0.15	2.59 ± 0.14	2.71 ± 0.13	2.87 ± 0.14	2.83 ± 0.15	0.82
5–9.9	3.38 ± 0.23	2.83 ± 0.22	2.43 ± 0.23	2.79 ± 0.23	3.03 ± 0.21	
≥10.0	2.82 ± 0.23	2.84 ± 0.23	2.35 ± 0.25	2.61 ± 0.23	2.58 ± 0.22	
Women						
Participants (*n*)	7945	7951	7952	7944	7948	
Median intake (mg/d)	−317	−144	−50	5	141	
Age (y)[3]						
<50	6.07 ± 0.12	5.79 ± 0.12	5.91 ± 0.12	5.77 ± 0.12	5.61 ± 0.11	0.68
≥50	2.61 ± 0.10	2.52 ± 0.10	2.25 ± 0.10	2.35 ± 0.10	2.23 ± 0.10	
Smoking status						
Never	3.78 ± 0.12	3.72 ± 0.10	3.64 ± 0.10	3.58 ± 0.09	3.69 ± 0.11	< 0.001
Past	3.90 ± 0.12	3.91 ± 0.12	3.84 ± 0.12	4.01 ± 0.13	3.78 ± 0.12	
Current	5.76 ± 0.18	5.25 ± 0.20	5.00 ± 0.22	4.76 ± 0.24	4.10 ± 0.19	
BMI (kg/m^2)						
<25	3.91 ± 0.08	3.97 ± 0.07	3.88 ± 0.07	3.79 ± 0.08	4.06 ± 0.08	< 0.001
25–29.9	4.86 ± 0.15	4.56 ± 0.15	4.36 ± 0.15	4.60 ± 0.15	4.04 ± 0.15	
≥30	3.75 ± 0.38	3.17 ± 0.36	3.60 ± 0.35	3.25 ± 0.35	1.85 ± 0.36	
Physical activity (MET-h/wk)[3]						
<7.9	4.32 ± 0.11	3.93 ± 0.11	3.86 ± 0.12	3.80 ± 0.12	3.65 ± 0.11	< 0.001
≥7.9	3.99 ± 0.10	4.18 ± 0.10	4.04 ± 0.10	4.08 ± 0.10	3.96 ± 0.10	
Alcohol consumption (g/d)						
0–4.9	4.29 ± 0.09	4.29 ± 0.10	4.12 ± 0.09	4.17 ± 0.09	4.03 ± 0.09	0.19
5–9.9	4.40 ± 0.20	3.89 ± 0.21	4.27 ± 0.21	4.00 ± 0.23	3.98 ± 0.21	
≥10.0	3.81 ± 0.20	3.65 ± 0.21	3.51 ± 0.21	3.43 ± 0.23	3.37 ± 0.21	

[1] Adjusted for age (5-y categories), BMI at baseline (continuous; kg/m^2), change in smoking status (never; past smoker in 1986; smoker in 1986 who quit in 1988, in 1990, in 1992, in 1994, in 1996, or in 1998; and current smoker in 1998), baseline and change in physical activity and alcohol intake (quintiles), quintiles of baseline and change in *trans* fat intake, glycemic load, total fiber and whole-grain intakes, and quartiles of baseline and change in low- and high-calorie soft drinks and fruit and vegetable consumption, except for the stratification variable in each model. MET, metabolic equivalents.

[2] *P* value from the Wald test calculated for the estimate of the interaction term between coffee intake and each stratification variable.

[3] We used the median of age and physical activity in men and women to create the dichotomous stratification variables.

[4] $\bar{x}$ ± SE (all such values).

observational study, we cannot infer causality for the association between caffeine and weight change.

In conclusion, this study suggests that an increase in caffeine intake was associated with a smaller weight gain over 12 y of follow-up. Although this study does not support the use of caffeine as a weight-loss strategy, its effect on the population might have public health relevance given the widespread intake of caffeinated beverages.

EL-G, RMvD, SR, WCW, JEM, and FBH were responsible for the study concept and design. WCW, JEM, and FBH collected the data, obtained the funding, and provided administrative, technical, or material support. EL-G, RMvD, and FBH analyzed and interpreted the data, drafted the manuscript, and provided statistical expertise. EL-G, RMvD, SR, WCW, JEM, and FBH critically revised the manuscript for important intellectual content. FBH supervised the study.

None of the authors had a conflict of interest.

REFERENCES

1. Thong FS, Graham TE. Caffeine-induced impairment of glucose tolerance is abolished by beta-adrenergic receptor blockade in humans. J Appl Physiol 2002;92:2347–52.
2. van Dam RM, Hu FB. Coffee consumption and risk of type 2 diabetes: a systematic review. JAMA 2005;294:97–104.
3. Astrup A, Toubro S, Cannon S, Hein P, Breum L, Madsen J. Caffeine: a double-blind, placebo-controlled study of its thermogenic, metabolic, and cardiovascular effects in healthy volunteers. Am J Clin Nutr 1990; 51:759–67.
4. Allison DB, Fontaine KR, Heshka S, Mentore JL, Heymsfield SB. Alternative treatments for weight loss: a critical review. Crit Rev Food Sci Nutr 2001;41:1–28 (discussion 39–40).
5. Boozer CN, Daly PA, Homel P, et al. Herbal ephedra/caffeine for weight loss: a 6-month randomized safety and efficacy trial. Int J Obes Relat Metab Disord 2002;26:593–604.
6. Boozer CN, Nasser JA, Heymsfield SB, Wang V, Chen G, Solomon JL. An herbal supplement containing ma huang-guarana for weight loss: a randomized, double-blind trial. Int J Obes Relat Metab Disord 2001;25: 316–24.
7. Coffey CS, Steiner D, Baker BA, Allison DB. A randomized double-blind placebo-controlled clinical trial of a product containing ephedrine, caffeine, and other ingredients from herbal sources for treatment of overweight and obesity in the absence of lifestyle treatment. Int J Obes Relat Metab Disord 2004;28:1411–9.
8. Astrup A, Breum L, Toubro S, Hein P, Quaade F. The effect and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine and placebo in obese subjects on an energy restricted diet. A double blind trial. Int J Obes Relat Metab Disord 1992;16:269–77.
9. Greenway FL, De Jonge L, Blanchard D, Frisard M, Smith SR. Effect of a dietary herbal supplement containing caffeine and ephedra on weight, metabolic rate, and body composition. Obes Res 2004;12:1152–7.
10. Greenberg JA, Axen KV, Schnoll R, Boozer CN. Coffee, tea and diabetes: the role of weight loss and caffeine. Int J Obes Relat Metab Disord 2005;29:1121–9.
11. US Department of Agriculture, Agricultural Research Service. Nutrient Data Laboratory: home page. USDA nutrient database for standard reference, release 10. 1993. Internet: http://www.nal.usda.gov/fnic/foodcomp (accessed 23 December 2005).
12. US Department of Agriculture, Agricultural Research Service. Nutrient Data Laboratory: home page. USDA nutrient database for standard reference, release 14. 2001. Internet: http://www.nal.usda.gov/fnic/foodcomp (accessed 23 December 2005).
13. Feskanich D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc 1993;93:790–6.
14. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol 1989;18:858–67.
15. Palta M, Prineas RJ, Berman R, Hannan P. Comparison of self-reported and measured height and weight. Am J Epidemiol 1982;115:223–30.
16. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1990;1:466–73.
17. Koh-Banerjee P, Chu NF, Spiegelman D, et al. Prospective study of the association of changes in dietary intake, physical activity, alcohol consumption, and smoking with 9-y gain in waist circumference among 16 587 US men. Am J Clin Nutr 2003;78:719–27.
18. Chasan-Taber S, Rimm EB, Stampfer MJ, et al. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. Epidemiology 1996;7:81–6.
19. Wolf AM, Hunter DJ, Colditz GA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. Int J Epidemiol 1994;23:991–9.
20. Giovannucci E, Colditz G, Stampfer MJ, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. Am J Epidemiol 1991;133:810–7.
21. Kahn HS, Tatham LM, Rodriguez C, Calle EE, Thun MJ, Heath CW Jr. Stable behaviors associated with adults' 10-year change in body mass index and likelihood of gain at the waist. Am J Public Health 1997;87: 747–54.
22. Wannamethee SG, Field AE, Colditz GA, Rimm EB. Alcohol intake and 8-year weight gain in women: a prospective study. Obes Res 2004;12: 1386–96.
23. Koh-Banerjee P, Franz M, Sampson L, et al. Changes in whole-grain, bran, and cereal fiber consumption in relation to 8-y weight gain among men. Am J Clin Nutr 2004;80:1237–45.
24. Schulze MB, Manson JE, Ludwig DS, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA 2004;292:927–34.
25. He K, Hu FB, Colditz GA, Manson JE, Willett WC, Liu S. Changes in intake of fruits and vegetables in relation to risk of obesity and weight gain among middle-aged women. Int J Obes Relat Metab Disord 2004; 28:1569–74.
26. Willett W. Nutritional epidemiology. 2nd ed. New York, NY: Oxford University Press, 1998.
27. Field AE, Manson JE, Taylor CB, Willett WC, Colditz GA. Association of weight change, weight control practices, and weight cycling among women in the Nurses' Health Study II. Int J Obes Relat Metab Disord 2004;28:1134–42.
28. Ryan DH. Use of sibutramine and other noradrenergic and serotonergic drugs in the management of obesity. Endocrine 2000;13:193–9.
29. Dulloo AG, Miller DS. The thermogenic properties of ephedrine/methylxanthine mixtures: human studies. Int J Obes 1986;10:467–81.
30. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. N Engl J Med 2000;343:1833–8.
31. National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—The Evidence Report. Obes Res 1998;6(suppl):51S–209S.
32. Van Soeren MH, Graham TE. Effect of caffeine on metabolism, exercise endurance, and catecholamine responses after withdrawal. J Appl Physiol 1998;85:1493–501.
33. Spriet LL, MacLean DA, Dyck DJ, Hultman E, Cederblad G, Graham TE. Caffeine ingestion and muscle metabolism during prolonged exercise in humans. Am J Physiol 1992;262:E891–8.
34. Acheson KJ, Gremaud G, Meirim I, et al. Metabolic effects of caffeine in humans: lipid oxidation or futile cycling? Am J Clin Nutr 2004;79: 40–6.
35. Salazar-Martinez E, Willett WC, Ascherio A, et al. Coffee consumption and risk for type 2 diabetes mellitus. Ann Intern Med 2004;140:1–8.
36. van Dam RM, Feskens EJ. Coffee consumption and risk of type 2 diabetes mellitus. Lancet 2002;360:1477–8.
37. Tuomilehto J, Hu G, Bidel S, Lindstrom J, Jousilahti P. Coffee consumption and risk of type 2 diabetes mellitus among middle-aged Finnish men and women. JAMA 2004;291:1213–9.
38. Rosengren A, Dotevall A, Wilhelmsen L, Thelle D, Johansson S. Coffee and incidence of diabetes in Swedish women: a prospective 18-year follow-up study. J Intern Med 2004;255:89–95.
39. Johnston KL, Clifford MN, Morgan LM. Coffee acutely modifies gastrointestinal hormone secretion and glucose tolerance in humans: glycemic effects of chlorogenic acid and caffeine. Am J Clin Nutr 2003; 78:728–33.
40. Jessen AB, Toubro S, Astrup A. Effect of chewing gum containing nicotine and caffeine on energy expenditure and substrate utilization in men. Am J Clin Nutr 2003;77:1442–7.
41. Jessen A, Buemann B, Toubro S, Skovgaard IM, Astrup A. The appetite-suppressant effect of nicotine is enhanced by caffeine. Diabetes Obes Metab 2005;7:327–33.
42. Dulloo AG, Seydoux J, Girardier L. Potentiation of the thermogenic antiobesity effects of ephedrine by dietary methylxanthines: adenosine antagonism or phosphodiesterase inhibition? Metabolism 1992;41:1233–41.
43. Dulloo AG, Geissler CA, Horton T, Collins A, Miller DS. Normal caffeine consumption: influence on thermogenesis and daily energy expenditure in lean and postobese human volunteers. Am J Clin Nutr 1989;49:44–50.