Differential effects of coffee on the risk of type 2 diabetes according to meal consumption in a French cohort of women: the E3N/EPIC cohort study[1–3]

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ABSTRACT

Background: Coffee consumption has been associated with a lower risk of diabetes, but little is known about the mechanisms responsible for this association, especially related to the time when coffee is consumed.

Objective: We examined the long-term effect of coffee, globally and according to the accompanying meal, and of tea, chicory, and caffeine on type 2 diabetes risk.

Design: This was a prospective cohort study including 69,532 French women, aged 41–72 y from the E3N/EPIC (Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Education Nationale/European Prospective Investigation into Cancer and Nutrition) cohort study, without diabetes at baseline. Food and drink intakes per meal were assessed by using a validated diet-history questionnaire in 1993–1995.

Results: During a mean follow-up of 11 y, 1415 new cases of diabetes were identified. In multivariable Cox regression models, the hazard ratio in the highest category of coffee consumption [$\geq$3 cups (375 mL)/d] was 0.73 (95% CI: 0.61, 0.87; *P* for trend $<$ 0.001), in comparison with no coffee consumption. This inverse association was restricted to coffee consumed at lunchtime (hazard ratio: 0.66; 95% CI: 0.57, 0.76) when comparing $>$1.1 cup (125 mL)/meal with no intake. At lunchtime, this inverse association was observed for both regular and decaffeinated coffee and for filtered and black coffee, with no effect of sweetening. Total caffeine intake was also associated with a statistically significantly lower risk of diabetes. Neither tea nor chicory consumption was associated with diabetes risk.

Conclusions: Our data support an inverse association between coffee consumption and diabetes and suggest that the time of drinking coffee plays a distinct role in glucose metabolism. *Am J Clin Nutr* 2010;91:1002–12.

INTRODUCTION

Coffee is among the most widely consumed beverages in the world and has been associated with a lower risk of type 2 diabetes in $\geq$17 prospective cohorts and in one meta-analysis (1–10). It has been suggested that the benefits of increased coffee consumption result principally from its constituents: magnesium, chlorogenic acids, and lignans (11). Many possible mechanisms for the effects of coffee components on glucose metabolism have been hypothesized. Of the proposed mechanisms, a reduction in glucose absorption, glucose hepatic output, and glucose storage (12, 13) could be influenced by the time of the day when it is consumed. Moreover, the metal chelator effect of polyphenols in coffee could lead to diabetes prevention through lower body iron stores (14), because coffee and tea are potent inhibitors of iron absorption (15). However, no epidemiologic study has investigated whether coffee consumption at different meals or at different times during the day has a distinct effect on diabetes risk.

The benefits of tea on the health profile are also increasingly recognized (16). Although an inverse relation between tea intake and risk of diabetes has been suggested in 3 cohort studies (6, 17, 18), it has not been confirmed in others (19–21); thus, the effect of tea consumption on glucose disturbance remains inconclusive.

In our study, we examined the long-term effect of coffee, chicory (a substitute for coffee traditionally consumed in France), tea, and caffeine intake on the incidence of type 2 diabetes in a large prospective cohort of French women and studied whether the average amount of coffee consumed at different times of the day had distinct effects on diabetes risk. We further examined whether the type of coffee, as well as the addition of sugar and/or milk, plays different roles on the risk of type 2 diabetes.

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SUBJECTS AND METHODS

Study design

The E3N (Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale) is an ongoing prospective cohort study that was designed to investigate the risk of cancers and other chronic diseases according to dietary, hormonal, and lifestyle factors in women (22). The cohort included 98,995 women living in France in 1990, born between 1925 and 1950, who were enrolled in the health insurance plan for employees of the public education system. E3N is the French part of the European Prospective Investigation into Cancer and Nutrition (23). All women signed an informed consent from in compliance with the rules of the French National Commission for Computed Data and Individual Freedom (Commission Nationale Informatique et Libertés), from which approval was obtained. At baseline and at subsequent biannual self-administered follow-up questionnaires, participants provided information on demographic and anthropometric characteristics, physical activity, smoking and drinking habits, use of hormonal treatments, family and personal history of diabetes, personal history of hypertension and hypercholesterolemia, and medication use. For the current analysis, follow-up began when the dietary questionnaire, sent in 1993, was completed, and the endpoint was 2007, when the last available questionnaire was completed.

Dietary data

Usual diet over the previous year was assessed by using a validated 208-item diet-history questionnaire (24), structured according to the French meal pattern. Questions were asked about consumption occasions from breakfast to after-dinner snacks. Usually 2 hot meals are eaten per day in France, lunch and dinner. The frequency and portion sizes of 66 food groups or items were investigated by meal: 38 items for breakfast and in-between snacks, 50 for lunch and dinner, and 13 for aperitifs. Participants were asked to report the frequency and usual serving size of coffee, chicory, and tea that they consumed at breakfast, morning, lunch, afternoon, dinner, and after-dinner and to provide information about the type of coffee consumed (regular/decaffeinated, filtered/instant) and the addition of sugar and/or milk to the beverage. Intakes of espresso or French Press coffee were not specifically assessed; they were included in the total coffee intake. In the validation study, the accuracy of the food intake measure of the questionnaire was tested by comparing it with the average of nine to twelve 24-h recalls (24). The correlation coefficient was 0.69 for coffee intake. Portion sizes were estimated with a validated photo booklet (25). For coffee and tea, 6 different cup sizes could be selected at each meal (70, 150, 200, 250, 300, and 400 mL) and converted into standardized 125-mL cups/d. The total consumption of coffee, chicory, and tea were categorized into 0, $\leq$1.0, 1.1 to 2.9, and $\geq$3.0 cups/d. The consumption by meal was categorized into 0, $\leq$1.0, and $>$1.1 cup/meal.

To convert foods into nutrients, a food-composition table compiled for this study was used, which was derived from a French food-composition table (26). The estimated caffeine contents were 72.8 mg/125 mL coffee, 13.8 mg/125 mL tea, 16.1 mg/125 mL chicory, 17.6 mg/330 mL cola, 2.1 mg/30 g chocolate candy, and 17.8 mg/30 g plain chocolate. For each participant, we calculated the average daily dietary intakes of caffeine, energy, alcohol, saturated fat, fiber, glycemic load, and iron.

Assessment of incident cases of diabetes

A first set of potential cases of diabetes included women who had self-reported either diabetes, a diet to manage diabetes, use of diabetic drugs, or a hospitalization for diabetes in $\geq$1 of the 8 questionnaires up to 2005. A total of 4289 self-reported potential cases were thus identified. Of them, 2315 cases were identified as having been reimbursed for a diabetic drug between 2004 (date when the file became available) and 2007 (endpoint of the present study) from a drug reimbursement file provided by the health insurance plan and were thus considered to be validated. Of the 1974 women without evidence of diabetic drug reimbursement, women alive and with an accurate address (n = 1735) were mailed a questionnaire specifically designed to validate diabetes. It included questions on the circumstances of diagnosis (date of diagnosis, symptoms, and biological data including fasting or random glucose concentrations at diagnosis), current therapy (prescription of diet and/or physical activity, list of diabetes drugs), and monitoring of diabetes (last values of fasting glucose and glycated hemoglobin concentrations). Of the 1480 women who completed this questionnaire (response rate: 84%), 342 potential cases were confirmed, because either reported glucose at diagnosis was consistent with the World Health Organization definition of diabetes [fasting glucose $\geq$7.0 mmol/L (126 mg/dL) or random glucose $\geq$11.1 mmol/L (200 mg/dL)] (27) and/or women reported taking diabetic drugs, and/or their last values of fasting glucose or glycated hemoglobin concentrations were reported to be $\geq$7.0 mmol/L (126 mg/dL) or $\geq$7% respectively (28, 29). Thus, among the 4289 self-reported potential cases, 2657 were validated and subsequently considered as diabetes cases. Of the 1632 nonvalidated cases, 1144 women reported diabetes only once during the follow-up.

A second set of potential cases of diabetes was identified exclusively from the drug reimbursement file (n = 1216) without prior report of diabetes in any of the 8 study questionnaires. We mailed the diabetes specific questionnaire detailed above to 1139 of them, and 734 women completed it (response rate: 64%). We considered as noncases women who reported to be nondiabetic and who had been reimbursed for diabetic drugs only once before 2007 (n = 233); we validated as diabetic cases women who confirmed diabetes in the diabetes-specific questionnaire (n = 458) and those who did not answer the diabetes-specific questionnaire but who had diabetic drugs reimbursed at least twice (n = 381). Other potential cases were considered to be nonvalidated (n = 144). Altogether, 3496 diabetes cases were validated up to 2007. Nonvalidated potential cases of diabetes were excluded from our analysis. Although this validation procedure did not systematically allow differentiating between type 1 and type 2 diabetes, the age range of our population implied that incident cases considered in our analyses were essentially type 2 diabetes.

Study population

Of the 98,995 women in the cohort, we excluded those who did not complete the dietary questionnaire (n = 24,471), those who

were lost to follow-up (n = 1339), prevalent cases of diabetes (n = 924), those not confirmed as validated cases of diabetes (n = 1349), and those with extreme values for the ratio between energy intake and required energy (ie, the lowest or highest one percentile for the cohort) (n = 1380). A total of 69,532 women were included in the present analysis.

Statistical analysis

Person-years of follow-up were calculated from the date of completion of the dietary questionnaire (1993–1995) to the date of diagnosis of type 2 diabetes, the date that the most recent questionnaire was completed when women were lost to follow-up, or 2007, whichever came first. To test for differences across categories of coffee intake, the analysis of variance was applied. Hazards ratios (HRs) for diabetes and 95% CIs were estimated for each category of coffee, chicory, and tea consumption compared with no intake and for quartiles of caffeine intake according to the study population distribution, by using Cox proportional hazards regression models with age as the time scale and simultaneous adjustment for potential confounders. To test for linear trends across categories of consumption, we modeled the median of each category as a continuous variable.

To investigate the effect of coffee consumption at 6 distinct times of the day, 6 separate models were used. For coffee consumption at each meal, the HR for diabetes was estimated with adjustment for total coffee consumption at other meals (as a continuous variable). Moreover, a further model was tested including coffee intake at lunch and dinner. Furthermore, at each meal, we used 4 separate models according to the type of coffee or additions, including 2 opposite characteristics simultaneously in each model: *1*) regular and decaffeinated coffee, *2*) filtered and instant coffee, *3*) black coffee and coffee with milk, and *4*) coffee with and without sugar. These models were adjusted for total coffee at other meals (as a continuous variable) and for the amount of coffee with missing information about the type of coffee or additions. Nutrient intakes were adjusted for energy intake (excluding energy from alcohol) by the residual method (30). Physical activity was converted into metabolic equivalent task hours (MET-h) per week (31).

For total coffee, chicory, tea, and caffeine intakes, the main model was adjusted for age (time scale); the following variables considered at baseline: history of diabetes in parents (neither, only one, or both), quartiles of physical activity level (≤19.9, 20.0–32.9, 33.0–52.9, or ≥53.0 MET/wk), quartiles of alcohol intake (≤1.34, 1.35–6.15, 6.16–15.63, or ≥15.64 g/d), educational level (≤9, 10–16, or ≥17 y), hypercholesterolemia (self-reported blood cholesterol >5.172 mmol/L or use of cholesterol-lowering drugs: yes or no), hypertension (self-reported or use of antihypertensive drugs: yes or no), smoking (never, former, or current smoker), energy-adjusted fiber and saturated fat (both continuous), total energy without alcohol (continuous), and use of oral contraceptives (ever or never); and for the following time-dependant variables: body mass index (BMI; in kg/m^2) (≤21.9, 22.0–25.0, 25.1–27.0, 27.1–29.9, or ≥30.0), menopause hormonal treatment (yes or no), and menopausal status (pre or post).

Additional models were tested with adjustment for dietary magnesium intake, history of cardiovascular disease, and/or cancer at baseline and/or during follow-up. Moreover, we also tested models in which individuals with a history of cardiovascular disease and/or cancer were excluded. To investigate potential interactions between coffee and tea intake and covariates, we tested models with cross-product terms. The analyses used SPSS (SPSS Inc, Woking, Surrey, United Kingdom) version 14.0 and SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

A total of 1415 new cases of diabetes were identified during a mean follow-up of 11 y. Coffee, chicory, and tea were consumed by 59,222 (85%), 13,368 (19%), and 41,335 (59%) of the women, respectively. Among consumers, the median intakes were 280 mL coffee/d, 140 mL chicory/d, and 214 mL tea/d, which provided 84%, 2%, and 10% of total caffeine intake, respectively. Coffee consumption increased with BMI and smoking. Coffee consumption was also positively associated with dietary intakes of energy, saturated fat, iron, caffeine, and magnesium and was negatively associated with glycemic load in the usual diet (**Table 1**). Higher consumers of tea were younger and leaner. Tea drinking was also positively associated with dietary fiber intake and inversely associated with saturated fat, caffeine, and magnesium intakes. Addition of milk decreased with increasing tea consumption. A lower prevalence of hypertension was found in individuals with higher consumption of tea, and a lower prevalence of hypercholesterolemia was also found for high coffee consumption (Table 1).

The proportions of women drinking coffee were 61% at breakfast, 37% in the morning, 71% at lunchtime, 24% in the afternoon, 15% at dinner, and 6% in the evening. Lunch was the highest daily source of many nutrients in our study, followed by dinner and breakfast. Lunch provided 40% of daily energy (excluding alcohol), 43% of total fat, 46% of protein, 33% of carbohydrates, 41% of fiber, and 42% of iron. Dinner provided 34% of daily energy, 36% of total fat, 37% of protein, 29% of carbohydrates, 33% of fiber, and 15% of daily iron intake. Breakfast provided 18% of daily energy, 10% of total fat, 13% of protein, 27% of carbohydrates, 15% of fiber, and 13% of daily iron intake (data not tabulated). Women with the highest intakes of coffee at all meals were younger, had a higher mean BMI, and were more often smokers. Moreover, women with higher intakes of coffee in the morning and afternoon were less physically active than were women with no coffee intake at these meals (**Table 2**).

Coffee drank at breakfast (n = 40,265) was caffeinated for 74% of women, filtered for 60%, black for 53%, and unsweetened for 47%. Corresponding values for coffee in the morning (n = 23,696) were 60%, 53%, 45% and 85%, respectively; at lunchtime (n = 49,283), 74%, 59%, 85%, and 45% respectively; in the afternoon (n = 16,805), 57%, 47%, 46%, and 64% respectively; at dinner time (n = 10,068) 57%, 54%, 73%, and 27% respectively; and in the evening (n = 4,016), 44%, 44%, 46%, and 65% respectively. Characteristics of coffee consumption were similar at the different meals, except for a higher proportion of women not adding milk at lunch and dinner and a higher proportion of women consuming caffeinated coffee at breakfast and lunchtime.

HRs for type 2 diabetes across categories of coffee, tea, and caffeine intake are shown in **Table 3** and **Table 4**. Whereas there was no association between coffee or caffeine intake and diabetes risk in the age-adjusted model, high coffee intake (≥3 cups/d) was associated with a lower risk of diabetes compared

TABLE 1
Baseline characteristics of the Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Education Nationale/European Prospective Investigation into Cancer and Nutrition (E3N/EPIC) cohort study populations, by usual amounts of coffee and tea consumption (n = 69,532)[1]

	Coffee				Tea			
	0 cups	≤1 cup	1.1–2.9 cups	≥3 cups	0 cups	≤1 cup	1.1–2.9 cups	≥3 cups
Daily intake (cups)[2]	0	0.5	1.9	4.3	0	0.3	2.0	5.4
Coffee (mL/d)	0 (0, 0)[3]	70 (35, 90)	240 (175, 300)	538 (447, 694)	300 (150, 480)	270 (121, 436)	154 (50, 330)	95 (0, 224)
Tea (mL/d)	270 (0, 540)	127 (0, 400)	21 (0, 257)	0 (0, 77)	0 (0, 0)	33 (15, 63)	250 (182, 300)	586 (443, 800)
Characteristics								
n	10,345	12,260	26,966	19,691	28,242	15,623	12,388	13,279
Person-years	113,721	135,150	269,992	218,511	309,355	171,864	136,617	146,537
Incident cases of diabetes (*n*)	198	279	559	379	643	324	245	203
Age (y)	53 ± 6[4]	54 ± 7	53 ± 7	52 ± 6	53 ± 6	53 ± 6	53 ± 6	52 ± 6
BMI (kg/m^2)	22.4 ± 3	22.7 ± 3	22.9 ± 3	23.2 ± 3	23.1 ± 3	22.9 ± 3	22.7 ± 3	22.5 ± 3
Overweight (%)	15.4	18.0	20.3	22.7	22.3	20.4	18.0	15.8
Physical activity (MET-h/wk)	39.6 ± 27	40.2 ± 27	40.0 ± 27	39.8 ± 27	39.2 ± 28	40.6 ± 28	39.9 ± 27	40.6 ± 27
Current smokers (%)	6.6	9.8	13.2	19.7	14.2	12.7	12.2	14.2
Family history of diabetes (%)								
In one parent	9.2	9.0	9.5	9.9	9.6	9.7	9.6	8.8
In both parents	0.7	0.5	0.5	0.6	0.5	0.5	0.5	0.5
Hypertension (%)	12.5	14.1	13.5	12.4	13.8	13.4	13.0	11.5
Hypercholesterolemia (%)	28.8	31.0	31.0	27.1	29.8	29.7	30.2	28.1
Postgraduate (%)	15.7	19.1	17.8	17.5	13.9	18.1	18.9	23.7
Current use of hormone replacement therapy (%)	30.7	33.7	32.6	29.1	30.1	31.9	32.6	33.0
Dietary intake[5]								
Energy without alcohol (kcal/d)	2067 ± 569	2075 ± 551	2076 ± 542	2134 ± 573	2068 ± 564	2142 ± 557	2093 ± 546	2077 ± 552
Saturated fat (% of energy)	14.9 ± 3	15.1 ± 3	15.1 ± 3	15.3 ± 3	15.1 ± 3	15.1 ± 3	15.0 ± 3	15.0 ± 3
Total fiber (g/d)	25.4 ± 8	24.7 ± 8	24.4 ± 8	24.9 ± 8	24.1 ± 8	24.9 ± 8	24.9 ± 8	25.6 ± 8
Glycemic load (g glucose equivalents)	130 ± 54	130 ± 52	129 ± 52	128 ± 54	128 ± 54	133 ± 52	130 ± 51	128 ± 53
Iron (mg/d)	13.6 ± 4	13.7 ± 4	13.8 ± 4	14.4 ± 4	13.8 ± 4	14.1 ± 4	13.9 ± 4	13.9 ± 4
Alcohol (g/d)	3 (0.1, 10)	6 (1, 14)	7 (2, 17)	7 (2, 18)	6 (1.1, 17)	6 (1.8, 15)	6 (1.5, 15)	6 (1.4, 15)
Caffeine (mg/d)	43 (18, 72)	72 (50, 98)	167 (131, 201)	332 (275, 424)	184 (98, 291)	174 (92, 267)	171 (67, 128)	141 (90, 216)
Magnesium (mg/d)	306 ± 92	335 ± 90	402 ± 88	553 ± 140	452 ± 150	444 ± 135	397 ± 132	368 ± 122
Coffee/tea additions								
Sugar (g/d)	0 (0, 2.9)	0.7 (0.6, 8)	0 (0, 10.0)	0 (0, 9.6)	0 (0, 5.0)	0 (0, 8.0)	0.3 (0, 9.0)	0 (0, 8.0)
Milk (mL/d)	0 (0, 51)	30 (0, 180)	11 (0, 120)	0 (0, 46)	0 (0, 118)	21 (0, 150)	0 (0, 90)	0 (0, 47)

[1] MET-h, metabolic equivalent task hours. Statistical test results (ANOVA) for the association between coffee and tea consumption and the covariates were all significant ($P < 0.05$), except for physical activity across categories of coffee intake and hypercholesterolemia across categories of tea intake.
[2] 1 cup = 125 mL.
[3] Median; 25th and 75th percentiles in parentheses (all such values).
[4] Mean ± SD (all such values).
[5] Nutrients were adjusted for energy intake from food by using the residual method.

with no coffee consumption (multivariable HR: 0.73; 95% CI: 0.61, 0.87; *P* for linear trend across categories < 0.001) after multiple adjustment for potential confounders. Similarly, after multiple adjustment, caffeine intake was inversely associated with the risk of diabetes (multivariable HR in the highest compared with the lowest quartile: 0.67; 95% CI: 0.58, 0.78; *P* for trend < 0.001). For both coffee and caffeine intakes, BMI was the most important negative confounder. In contrast, tea consumption, which was inversely related with the risk of diabetes in the age-adjusted model, was no longer significantly associated with diabetes risk after adjustment for confounders, especially BMI (multivariable HR for ≥3 cups/d compared with no tea consumption: 0.89; 95% CI: 0.76, 1.05; *P* for trend = 0.46). No associations between chicory consumption and diabetes risk were found (multivariable HR for ≥3 cups/d compared with no consumption: 0.85; 95% CI: 0.60, 1.19; *P* for trend = 0.21). After further adjustments for dietary magnesium intake and history of cardiovascular disease and cancer at baseline and during follow-up, these results were not modified (multivariable HR for ≥3 cups coffee/d compared with no consumption: 0.76; 95% CI: 0.59, 0.98; *P* for trend 0.03). Moreover, results were similar after exclusion of participants with cancer (n = 4082) or cardiovascular diseases (n = 3046) at baseline or during follow-up (multivariable HR for ≥3 cups coffee/d compared with no consumption: 0.80; 95% CI: 0.66, 0.97; *P* for trend 0.004). No interaction term between coffee or tea intakes and any studied covariate was statistically significant.

In multivariable models of coffee consumption according to meals (**Table 5**), drinking coffee at lunchtime was associated with a lower risk of diabetes [multivariable HR for ≤1 and >1.1 cup/meal, respectively, compared with no coffee consumption: 0.84 (95% CI: 0.74, 0.95) and 0.66 (95% CI: 0.57, 0.76); *P* for trend < 0.001] in models adjusted for all considered variables. The relative risk per additional cup (125 mL) was 0.80 (95% CI: 0.73, 0.87; *P* for trend < 0.001). Coffee consumed at dinner time was also associated with a lower risk of diabetes [multivariable HR for ≤1 and >1.1 cup/meal, respectively, compared with no coffee consumption: 0.86 (95% CI: 0.75, 0.99) and 0.74 (95% CI: 0.58, 0.93); *P* for trend < 0.001]; however, it was no longer statistically significant after further adjustment for coffee consumption in other meals [multivariable HR for ≤1 and >1.1 cup/meal, respectively, compared with no coffee consumption: 0.84 (95% CI: 0.69, 1.02) and 0.81 (95% CI: 0.58, 1.12); *P* for trend < 0.001]. On further analysis, coffee intake at lunch and dinner was included simultaneously in the same model, which did not affect the association between lunchtime coffee and diabetes [multivariable HR for ≤1 and >1.1 cup/meal, respectively, compared with no coffee consumption at lunch: 0.85 (95% CI: 0.75, 0.96) and 0.68 (95% CI: 0.59, 0.79); *P* for trend < 0.001]. In this same model, dinner time coffee remained unassociated with diabetes [multivariable HR for ≤1 and >1.1 cup/meal, respectively, compared with no coffee consumption at dinner: 0.86 (95% CI: 0.71, 1.04) and 0.86 (95% CI: 0.62, 1.20); *P* for trend 0.11]. No associations were found between the risk of diabetes and the coffee consumed at other times of the day (Table 5), even after stratification for types of coffee and the addition of milk and/or sugar (data not tabulated).

We then investigated characteristics of the coffee consumed at lunchtime (**Table 6**). Both caffeinated and decaffeinated coffee were associated with significantly lower risks of diabetes [multivariable HR for >1.1 cup/meal of regular and decaffeinated coffee, respectively, compared with no coffee consumption: 0.67 (95% CI: 0.57, 0.78) and 0.67 (95% CI: 0.47, 0.95)]. Both coffee with and coffee without sugar were associated with significantly lower risks [multivariable HR for >1.1 cup/meal of coffee with and without sugar, respectively, compared with no consumption: 0.69 (95% CI: 0.55, 0.87) and 0.60 (95% CI: 0.50, 0.73)]. Filtered coffee, but not instant coffee, was associated with a statistically significant lower risk of diabetes [multivariable HR for >1.1 cup/meal of filtered and instant coffee, respectively, compared with no consumption: 0.65 (95% CI: 0.55, 0.77) and 0.82 (95% CI: 0.62, 1.08)], but the CIs largely overlapped. Similarly, black coffee but not coffee with milk was associated with a statistically significant lower risk of diabetes [multivariable HR for >1.1 cup/meal of black and coffee with milk, respectively, compared with no coffee consumption: 0.71 (95% CI: 0.61, 0.82) and 1.06 (95% CI: 0.53, 2.15)] (Table 6).

DISCUSSION

In this large prospective study of French women, coffee, especially at lunchtime, and caffeine intakes were inversely associated with the risk of diabetes, whereas there was no significant association with tea or chicory intakes. At lunch, both regular and decaffeinated coffee were inversely associated with diabetes risk, whereas the association was restricted to black coffee as opposed to coffee with milk, and was independent of sweetening.

Our findings of an overall association between coffee and risk of diabetes are consistent with previous reports from prospective studies (3–10, 17, 19, 32–35). The association was of the same order of magnitude as the one described in a meta-analysis of prospective studies (1), that is, 34% for ≥4 or more cups/d as compared with none. We also observed an inverse association between caffeine intake and the risk of diabetes, which is also in line with previous cohort studies (17, 20). Given the high correlation between coffee and caffeine intakes (r = 0.8), and considering that coffee provided 84% of the caffeine in this population, it was not possible to test for independent effects of coffee and caffeine on diabetes risk. However, the inverse association between lunchtime coffee and diabetes risk was similar for regular and decaffeinated coffee, in line with previous studies (19, 20). This suggests the importance of components in coffee other than caffeine. Addition of sugar to coffee did not modify the association between coffee intake and diabetes risk, similarly to a report from a Dutch cohort study (33).

In agreement with previous studies (19, 32, 33), a high consumption of coffee was associated with an unhealthy lifestyle (eg, high proportion of current smokers, high BMI, and high saturated fat intake). In our study, adjustment for potential confounders, especially BMI, strengthened the association between the risk of diabetes and coffee or caffeine intake. In contrast, tea drinking was associated with a healthy lifestyle, and, after multiple adjustments, especially for BMI, the inverse association between tea and diabetes risk disappeared. Although we could not discriminate the type of tea drank, most of the tea consumed in France is traditionally black tea; thus, our results do not agree with previous studies (17, 18).

TABLE 2
Baseline selected lifestyle characteristics of the Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Education Nationale/European Prospective Investigation into Cancer and Nutrition (E3N/EPIC) cohort study populations, by categories of coffee intake by meals (n = 69,532)[1]

	Coffee intake			
	0 cups/d	≤1 cup/d	>1.1 cup/d	P^2
Breakfast				
n	29,267	10,323	29,942	—
Cases/person-years	543/323,272	221/113,457	651/327,643	—
Age (y)	52.9 ± 6[3]	53.1 ± 6	52.6 ± 6	<0.001
BMI (kg/m^2)	22.6 ± 3	23.0 ± 3	23.1 ± 3	<0.001
Physical activity (MET-h/wk)	39.8 ± 27	39.6 ± 27	40.1 ± 28	0.18
Current smokers (%)	10.6	12.7	16.6	<0.001
Morning				
Intake (mL/d)	0 (0, 0)[4]	43 (20, 70)	150 (150, 320)	—
n	44,001	19,074	6457	—
Cases/person-years	945/483,668	340/210,145	130/70,560	—
Age (y)	54.1 ± 7	50.7 ± 6	50.3 ± 5	<0.001
BMI (kg/m^2)	22.8 ± 3	22.8 ± 3	23.3 ± 3	<0.001
Physical activity (MET-h/wk)	40.8 ± 28	38.6 ± 27	38.1 ± 27	<0.001
Current smokers (%)	9.8	18.3	24.8	<0.001
Lunch				
Intake (mL/d)	0 (0, 0)	70 (40, 70)	150 (150, 200)	—
n	20,249	27,642	21,641	—
Cases/person-years	493/221,430	558/304,326	364/238,617	—
Age (y)	53.0 ± 7	52.9 ± 7	52.6 ± 6	<0.001
BMI (kg/m^2)	22.7 ± 3	22.8 ± 3	23.1 ± 3	<0.001
Physical activity (MET-h/wk)	39.7 ± 28	39.9 ± 27	40.1 ± 28	0.21
Current smokers (%)	9.8	14.0	16.3	<0.001
Afternoon				
Intake (mL/d)	0 (0, 0)	29 (10, 64)	171 (150, 225)	—
n	52,727	13,146	3659	—
Cases/person-years	1067/580,476	272/144,036	76/39,861	—
Age (y)	53.1 ± 7	52.0 ± 6	51.8 ± 6	<0.001
BMI (kg/m^2)	22.7 ± 3	23.2 ± 3	23.5 ± 3	<0.001
Physical activity (MET-h/wk)	40.1 ± 27	39.3 ± 27	39.3 ± 28	0.003
Current smokers (%)	12.1	17.0	21.7	<.001
Dinner				
Intake (mL/d)	0 (0, 0)	15 (5, 57)	150 (150, 200)	—
n	59,405	76,39	2488	—
Cases/person-years	1246/653,196	129/83,800	40/27,378	—
Age (y)	53.0 ± 7	52.0 ± 6	51.3 ± 6	<0.001
BMI (kg/m^2)	22.8 ± 3	23.1 ± 3	23.1 ± 3	<0.001
Physical activity (MET-h/wk)	39.9 ± 27	40.3 ± 28	39.4 ± 27	0.32
Current smokers (%)	12.1	20.7	25.1	<0.001
Evening				
Intake (mL/d)	0 (0, 0)	10 (5, 43)	179 (150, 225)	—
n	65,407	3477	648	—
Cases/person-years	1338/719,150	63/38,163	14/7060	—
Age (y)	52.9 ± 7	51.6 ± 6	51.3 ± 6	<0.001
BMI (kg/m^2)	22..9 ± 3	23.0 ± 3	23.3 ± 4	<0.001
Physical activity (MET-h/wk)	39.9 ± 27	40.1 ± 27	40.8 ± 30	0.65
Current smokers (%)	12.9	21.7	27.6	<0.001

[1] 1 cup = 125 mL. MET-h, metabolic equivalent task hours.
[2] Significant differences between categories of coffee intake were tested by ANOVA.
[3] Mean ± SD (all such values).
[4] Median; 25th and 75th percentiles in parentheses (all such values).

Several pathways have been proposed to explain the protective effect of coffee consumption on diabetes risk. Coffee is rich in magnesium, which has been related to improved insulin sensitivity (36). Our data do not support this hypothesis, because adjustment for dietary magnesium intake did not modify the observed association, consistent with previous studies (4, 19, 34). A protective effect of coffee through its lignan and chlorogenic acid content has been suggested in experimental studies and deserves to be further explored in epidemiologic studies. Chlorogenic acid has antioxidant properties (37, 38) and has been associated in experimental studies with improved insulin sensitivity (39) and in rats with a reduction of glucose concentration

TABLE 3
Incident type 2 diabetes according to total coffee and tea intakes: Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Education Nationale/European Prospective Investigation into Cancer and Nutrition cohort study (E3N/EPIC) populations, France (1993–2007; n = 69,532)[1]

	0 cups/d	≤1 cup/d	1.1–2.9 cups/d	≥3 cups/d	P for trend[2]
Coffee intake					
Daily intake (mL)	0 ± 0[3]	63 ± 34	241 ± 72	613 ± 255	—
n	10,345	12,260	26,966	19,691	—
Cases/person-years	198/113,721	279/135,150	559/296,992	379/218,511	—
Age-adjusted model[4]	1.00 (Ref)	1.12 (0.94,1.35)	1.06 (0.90,1.24)	1.09 (0.92,1.30)	0.98
Multivariable model 1[4,5]	1.00 (Ref)	1.13 (0.94,1.36)	1.04 (0.88,1.22)	1.00 (0.84,1.19)	0.60
Multivariable model 2[4,6]	1.00 (Ref)	1.04 (0.87,1.26)	0.86 (0.73,1.02)	0.73 (0.61,0.87)	<0.001
Tea intake					
Daily intake (mL)	0 ± 0	44 ± 34	245 ± 70	680 ± 345	—
n	28,242	15,623	12,388	13,279	—
Cases/person-years	643/309,355	324/171,864	245/136,617	203/146,537	—
Age-adjusted model[4]	1.00 (Ref)	0.90 (0.79,1.03)	0.86 (0.74,0.99)	0.68 (0.58,0.80)	<0.001
Multivariable model 1[4,5]	1.00 (Ref)	0.97 (0.85,1.11)	0.94 (0.81,1.09)	0.78 (0.67,0.92)	0.14
Multivariable model 2[4,6]	1.00 (Ref)	0.99 (0.87,1.14)	1.02 (0.88,1.19)	0.89 (0.76,1.05)	0.46

[1] 1 cup = 125 mL. Ref, reference.
[2] To test for linear trends across categories, we modeled the median of each category of coffee and tea intakes as continuous variables.
[3] Mean ± SD (all such values).
[4] Values are hazard ratios; 95% CIs in parentheses.
[5] Adjusted for age (time scale), history of diabetes in ascendants (none, only one parent, or both parents), quartiles of physical activity level (≤19.9, 20.0–32.9, 33.0–52.9, or ≥53.0 metabolic equivalent tasks/wk), quartiles of alcohol intake (≤1.34, 1.35–6.15, 6.16–15.63, or ≥15.64 g/d), educational level (≤9, 10–16, or ≥17 y), hypercholesterolemia (self-reported blood cholesterol >2 g/L or use of cholesterol-lowering drugs: yes or no), hypertension (self-reported or use of antihypertensive drugs: yes or no), smoking (never, former, or current smoker), energy-adjusted fiber and saturated fat (continuous), total energy without alcohol (continuous), menopausal status (pre or post), hormone replacement therapy as a time-dependent variable (yes or no), and use of oral contraceptives at baseline (ever or never).
[6] Adjusted for the same variables as in model 1 with the addition of BMI category (in kg/m^2) as a time-dependent variable (≤21.9, 22.0–25.0, 25.1–27.0, 27.1–29.9, or ≥30.0).

(40) and of glucose absorption, thus lowering post load glucose concentrations (12). The lignan secoisolariciresinol has also been shown to prevent diabetes development in experimental models through a possible antioxidant pathway (41).

The most original finding of our study is a selective association between diabetes risk and coffee consumed at lunchtime. Our data showed that having coffee at lunch would be sufficient to benefit from the putative protective effect of coffee on diabetes, and the coffee intake at dinner or other meals did not change the estimation for lunchtime coffee and diabetes. Whereas lunchtime coffee consumption represented <60% of daily coffee for 75% of our population, our findings strongly suggest that only coffee

TABLE 4
Incident type 2 diabetes according to caffeine intakes: Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Education Nationale/European Prospective Investigation into Cancer and Nutrition (E3N/EPIC) cohort study populations, France (1993–2007; n = 69,532)[1]

	Caffeine intake				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend[2]
Daily intake (mg)	48 ± 25[3]	126 ± 21	209 ± 28	397 ± 150	—
n	17,382	17,384	17,384	17,382	—
Cases/person-years	393/191,100	355/192,134	344/191,123	323/190,017	—
Age-adjusted model[4]	1.00 (Ref)	0.89 (0.78,1.04)	0.90 (0.78,1.04)	0.90 (0.78,1.05)	0.19
Multivariable model 1[4,5]	1.00 (Ref)	0.92 (0.79,1.06)	0.91 (0.78,1.05)	0.89 (0.77,1.04)	0.14
Multivariable model 2[4,6]	1.00 (Ref)	0.84 (0.72,0.96)	0.77 (0.66,0.89)	0.67 (0.58,0.78)	<0.001

[1] Ref, reference.
[2] To test for linear trends across categories, we modeled the median of caffeine intake as a continuous variable.
[3] Mean ± SD (all such values).
[4] Values are hazard ratios; 95% CIs in parentheses.
[5] Adjusted for age (time scale), history of diabetes in ascendants (none, only one parent, or both parents), quartiles of physical activity level (≤19.9, 20.0–32.9, 33.0–52.9, or ≥53.0 metabolic equivalent tasks/wk), quartiles of alcohol intake (≤1.34, 1.35–6.15, 6.16–15.63, or ≥15.64 g/d), educational level (≤9, 10–16, or ≥17 y), hypercholesterolemia (self-reported blood cholesterol >2 g/L or use of cholesterol-lowering drugs: yes or no), hypertension (self-reported or use of antihypertensive drugs: yes or no), smoking (never, former, or current smoker), energy-adjusted fiber and saturated fat (continuous), total energy without alcohol (continuous), menopausal status (pre or post), hormone replacement therapy as a time-dependent variable (yes or no), and use of oral contraceptives at baseline (ever or never).
[6] Adjusted for the same variables as in model 1 with the addition of BMI category (in kg/m^2) as a time-dependent variable (≤21.9, 22.0–25.0, 25.1–27.0, 27.1–29.9, or ≥30.0).

TABLE 5
Incident type 2 diabetes according to categories of coffee intake, by meals: Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Education Nationale/European Prospective Investigation into Cancer and Nutrition (E3N/EPIC) cohort study populations, France (1993–2007; n = 69,532 women)[1]

	Categories of intake			
Coffee consumption by meal	0 cup/d	≤1 cup/d	>1.1 cup/d	P for trend[2]
Breakfast				
n	29,267	10,323	29,942	—
Cases/person-years	543/323,272	221/113,457	651/327,643	—
Coffee intake (mL/d)[3]	0 (0, 0)	66 (30, 90)	280 (200, 320)	—
Multivariable model 1[4,5]	1.00 (Ref)	1.08 (0.92,1.26)	1.10 (0.97,1.25)	0.30
Multivariable model 2[4,6]	1.00 (Ref)	0.96 (0.85,1.17)	1.04 (0.92,1.17)	0.47
Morning				
n	44,001	19,074	6457	—
Cases/person-years	945/483, 668	340/210,145	130/70,560	—
Coffee intake (mL/d)[3]	0 (0, 0)	43 (20, 70)	150 (150, 320)	—
Multivariable model 1[4,5]	1.00 (Ref)	0.99 (0.87,1.12)	1.15 (0.96,1.39)	0.28
Multivariable model 2[4,6]	1.00 (Ref)	0.98 (0.85,1.12)	0.97 (0.79,1.19)	0.93
Lunch				
n	20,249	27,642	21,641	—
Cases/person-years	493/221,430	558/304,326	364/238,617	—
Coffee intake (mL/d)[3]	0 (0, 0)	70 (40, 70)	150 (150, 200)	—
Multivariable model 1[4,5]	1.00 (Ref)	0.83 (0.74,0.94)	0.67 (0.58,0.77)	<0.001
Multivariable model 2[4,6]	1.00 (Ref)	0.84 (0.74,0.95)	0.66 (0.57,0.76)	<0.001
Afternoon				
n	52,727	13,146	3659	—
Cases/person-years	1067/580,476	272/144,036	76/39,861	—
Coffee intake (mL/d)[3]	0 (0, 0)	29 (10, 64)	171 (150, 225)	—
Multivariable model 1[4,5]	1.00 (Ref)	1.05 (0.91,1.96)	1.03 (0.81,1.30)	0.80
Multivariable model 2[4,6]	1.00 (Ref)	0.96 (0.84,1.11)	0.89 (0.69,1.15)	0.64
Dinner				
n	59,405	7639	2488	—
Cases/person-years	1246/653,196	129/83,800	40/27,378	—
Coffee intake (mL/d)[3]	0 (0, 0)	15 (5, 57)	150 (150, 200)	—
Multivariable model 1[4,5]	1.00 (Ref)	0.86 (0.75,0.99)	0.74 (0.58,0.93)	<0.001
Multivariable model 2[4,6]	1.00 (Ref)	0.84 (0.69,1.02)	0.81 (0.58,1.12)	0.12
Evening				
n	65,407	3477	648	—
Cases/person-years	1338/719,150	63/38,163	14/7060	—
Coffee intake (mL/d)[3]	0 (0, 0)	10 (5, 43)	179 (150, 225)	—
Multivariable model 1[4,5]	1.00 (Ref)	0.92 (0.80,1.05)	0.90 (0.70,1.15)	0.38
Multivariable model 2[4,6]	1.00 (Ref)	0.98 (0.75,1.26)	1.18 (0.69,2.03)	0.81

[1] 1 cup = 125 mL. Ref, reference.
[2] To test for linear trends across categories, we modeled the median of each category of coffee consumption as a continuous variable.
[3] Values are medians; 25th and 75th percentiles in parentheses.
[4] Values are hazard ratios; 95% CIs in parentheses.
[5] Adjusted for age (time scale), history of diabetes in ascendants (none, only one parent, or both parents), BMI categories (in kg/m^2) as a time-dependent variable (≤21.9, 22.0–25.0, 25.1–27.0, 27.1–29.9, or ≥30.0), quartiles of physical activity level (≤19.9, 20.0–32.9, 33.0–52.9, or ≥53.0 metabolic equivalent tasks/wk), quartiles of alcohol intake (≤1.34, 1.35–6.15, 6.16–15.63, or ≥15.64 g/d), educational level (≤9, 10–16, or ≥17 y), hypercholesterolemia (self-reported blood cholesterol >2 g/L or use of cholesterol-lowering drugs: yes or no), hypertension (self-reported or use of antihypertensive drugs: yes or no), smoking (never, former, or current smoker), energy-adjusted fiber and saturated fat (continuous), total energy without alcohol (continuous), menopausal status (pre or post), hormone replacement therapy as a time-dependent variable (yes or no), and use of oral contraceptives at baseline (ever or never). Six separate models were carried out for categories of coffee consumption at each of the 6 meals.
[6] Adjusted for the same variables as in model 1 with further adjustment for coffee consumption at other meals as a continuous variable.

taken with lunch may reduce diabetes risk. Breakfast was the second most frequent meal for drinking coffee (57.8% of women), but no association with diabetes was found. Coffee consumed at dinner time was no longer significantly inversely associated with diabetes risk after adjustment for coffee intake at other meals, especially lunch. However, because a limited number of women had coffee at dinner time, there was possibly insufficient statistical power to show this association independently of coffee at other meals. Some nutritional aspects specific to lunch might interfere in the relation between coffee consumed at these meals and diabetes risk. First, according to Hurrel et al (42), polyphenol-containing beverages such as coffee and tea, are potent inhibitors of iron absorption, but this effect has only been verified when coffee and the iron source are consumed simultaneously (15). High body iron stores have been related to an increased risk of diabetes (14, 43) and for the metabolic

TABLE 6
Incident type 2 diabetes according to characteristics of coffee intake at lunchtime: Etude Epidémiologique auprès de Femmes de la Mutuelle Générale de l'Education Nationale/European Prospective Investigation into Cancer and Nutrition (E3N/EPIC) cohort study populations, France (1993–2007; n = 69,532 women)[1]

	Categories of intake			
Characteristics of coffee consumption	0 cups/meal	≤1 cup/meal	>1.1 cup/meal	P for trend[2]
Regular coffee				
Intake (mL/d)[3]	0 (0, 0)	70 (42, 70)	150 (150, 200)	—
n	24,218	20,308	16,202	—
Cases/person-years	570/264,966	391/223,923	260/178,995	—
Multivariable[4]	1.00	0.85 (0.74,0.97)	0.67 (0.57,0.78)	<0.001
Decaffeinated coffee				
Intake (mL/d)[3]	0 (0, 0)	60 (21, 70)	150 (150, 210)	—
n	56,485	2536	1707	—
Cases/person-years	1139/62,1331	48/27,838	34/18,714	—
Multivariable model[4]	1.00	0.69 (0.51,0.93)	0.67 (0.47,0.95)	0.006
Filtered coffee				
Intake (mL/d)[3]	0 (0, 0)	70 (42, 70)	150 (150, 200)	—
n	26,496	16,494	13,054	—
Cases/person-years	622/289,997	329/182,010	218/144,350	—
Multivariable model[4]	1.00	0.85 (0.73,0.98)	0.65 (0.55,0.77)	<0.001
Instant coffee				
Intake (mL/d)[3]	0 (0, 0)	70 (35, 70)	150 (150, 200)	—
n	49,291	3949	2804	—
Cases/person-years	1031/542,232	82/43,497	56/30,627	—
Multivariable model[4]	1.00	0.86 (0.68,1.08)	0.82 (0.62,1.08)	0.19
Black coffee				
Intake (mL/d)[3]	0 (0, 0)	70 (43, 70)	150 (150, 200)	—
n	19,384	22,497	19,426	—
Cases/person-years	462/212,614	431/248,032	321/214,697	—
Multivariable model[4]	1.00	0.88 (0.76,1.01)	0.71 (0.61,0.82)	<0.001
Coffee with milk added				
Intake (mL/d)[3]	0 (0, 0)	49 (21, 75)	167 (140, 210)	—
n	61348	680	226	—
Cases/person-years	1212/675,753	21/7356	8/2404	—
Multivariable model[4]	1.00	1.12 (0.72,1.73)	1.06 (0.53,2.15)	0.91
Coffee with sugar				
Intake (mL/d)[3]	0 (0, 0)	70 (40, 70)	150 (150, 200)	—
n	40480	11,258	6848	—
Cases/person-years	829/445,335	176/124,769	89/76,161	—
Multivariable model[4]	1.00	0.88 (0.74,1.05)	0.69 (0.55,0.87)	0.017
Coffee without sugar				
Intake (mL/d)[3]	0 (0, 0)	70 (42, 70)	150 (150, 210)	—
n	36,160	11,658	10,768	—
Cases/person-years	680/399,140	250/128,307	164/118,818	—
Multivariable model[4]	1.00	0.88 (0.75,1.04)	0.60 (0.50,0.73)	<0.001

[1] 1 cup = 125 mL.
[2] To test for linear trends across categories, we modeled the median of each category of coffee consumption as a continuous variable.
[3] Values are medians; 25th and 75th percentiles in parentheses.
[4] Values are hazard ratios; 95% CIs in parentheses. Adjusted for age (time scale), history of diabetes in ascendants (none, only one parent, or both parents), BMI categories (in kg/m^2) as a time-dependent variable (≤21.9, 22.0–25.0, 25.1–27.0, 27.1–29.9, or ≥30.0), quartiles of physical activity level (≤19.9, 20.0–32.9, 33.0–52.9, or ≥53.0 metabolic equivalent tasks/wk), quartiles of alcohol intake (≤1.34, 1.35–6.15, 6.16–15.63, or ≥15.64 g/d), educational level (≤9, 10–16, or ≥17 y), hypercholesterolemia (self-reported blood cholesterol >2 g/L or use of cholesterol lowering drugs: yes or no), hypertension (self-reported or use of antihypertensive drugs: yes or no), smoking (never, former, or current smoker), energy-adjusted fiber and saturated fat (continuous), total energy without alcohol (continuous), menopausal status (pre or post), hormone replacement therapy as a time-dependent variable (yes or no), use of oral contraceptives at baseline (ever or never). Four different models were carried out according to the type of coffee or additions: *1*) regular/decaffeinated, *2*) filtered/instant, *3*) black coffee/with milk, and *4*) with/without sugar, adjusted for coffee consumption at other meals as a continuous variable. The models were also adjusted on the amount of coffee consumption at the same meal without available information on the type of coffee and/or addition of milk.

syndrome both among men and among pre- and postmenopausal women (44). Iron acts as a catalyst in the formation of hydroxyl radicals, prooxidants that attack cellular membranes, lipids, proteins, and nucleic acids (45). Moreover, excess iron is usually stored in the liver, muscle, and pancreas and might cause organ-specific oxidative damage leading to insulin resistance and β cell dysfunction (14). In our study, no data on iron stores were available. According to the dietary questionnaire, lunch

provided 47% of the total daily iron intake. It can be suggested that coffee intake at lunch is inversely associated with diabetes via reduced iron absorption. However, it has been shown that tea intake has an even stronger inhibitory effect on iron absorption than coffee (46). In the present study, no association between tea intake, overall or by meal (data not shown), and diabetes was found; thus, our findings do not support the iron hypothesis. Second, milk added to coffee may neutralize some active components of coffee, as suggested by the absence of association between coffee consumed with milk at lunch and diabetes risk, compared with the lower risk associated with black coffee. However, there are some limitations to our interpretation. There were few white coffee drinkers at lunch, which possibly limited the statistical power to show an association with white coffee, if any exists; further, there were no differential associations between black coffee and coffee with milk at other meals, in particular at breakfast (data not tabulated). Third, the chlorogenic acids in coffee can delay intestinal glucose absorption through inhibition of Na^+-dependent transport across the brush border membranes (47). Experimental studies conducted in both rodents and humans showed that chlorogenic acids may reduce the blood glucose response to an oral-tolerance test (47). This suggests that the putative protective effect of coffee consumption at larger meals, such as lunch and dinner, on diabetes could be related to the reduced glucose absorption by the chlorogenic acid content of coffee.

To our knowledge, this was the first prospective study to address the timing of coffee intake and diabetes risk. Our data suggest that the time of drinking coffee, or alternatively the accompanying meal, might play a role in diabetes protection and suggest that mechanisms involving interactions with other meal components may be relevant. Limitations of our study include the absence of information on the type of tea consumed and incomplete information on coffee type. In particular, we did not specifically assess espresso coffee intake and the absence of biochemical data and recorded diet and beverages only once, which opened the possibility that participants changed their habits during follow-up. Moreover, despite careful adjustment for potential confounders, residual confounding due to unadjusted lifestyle factors cannot be ruled out. However, such potential misclassification of exposure would probably weaken, not bias the associations. Finally, our results are restricted to women.

In conclusion, our prospective study of French women further supports an inverse association between coffee intake and risk of type 2 diabetes and suggests that this association may be independent of caffeine content and be influenced by the meal when coffee is drunk. Further research is warranted to fully understand the role of time of drinking coffee and the association with specific nutrients of the diet on the risk of type 2 diabetes.

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REFERENCES

1. Van Dam RM, Hu F. Coffee consumption and risk of type 2 diabetes: a systematic review. JAMA 2005;294:97–104.
2. Greenberg JA, Boozer CN, Geliebter A. Coffee, diabetes, and weight control. Am J Clin Nutr 2006;84:682–93.
3. Paynter NP, Yeh HC, Voutilainen S, et al. Coffee and sweetened beverage consumption and the risk of type 2 diabetes mellitus. Am J Epidemiol 2006;164:1075–84.
4. Pereira MA, Parker ED, Folsom AR. Coffee consumption and risk of type 2 diabetes mellitus. Arch Intern Med 2006;166:1311–6.
5. Bidel S, Silventoinen K, Hu G, Lee D-H, Kaprio J, Tuomilehto J. Coffee consumption, serum γ-glutamyltransferase and risk of type 2 diabetes. Eur J Clin Nutr 2008;62:178–85.
6. Odegaard AO, Pereira MA, Koh WP, Arakawa K, Lee HP, Yu MC. Coffee, tea, and incident type 2 diabetes: the Singapore Chinese Health Study. Am J Clin Nutr 2008;88:979–85.
7. Oba S, Nagata C, Nakamura K, et al. Consumption of coffee, green tea, oolong tea, black tea, chocolate snacks and the caffeine content in relation to risk of diabetes in Japanese men and women. Br J Nutr (Epub ahead of print 12 October 2009).
8. Smith B, Wingard DL, Smith TC, Kritz-Silverstein D, Barrett-Connor E. Does coffee consumption reduce the risk of type 2 diabetes in individuals with impaired glucose? Diabetes Care 2006;29:2385–90.
9. van Dieren S, Uiterwaal CSPM, van der Schouw YT, et al. Coffee and tea consumption and risk of type 2 diabetes. Diabetologia 2009;52:2561–9.
10. Fuhrman BJ, Smit E, Crespo CJ, Garcia-Palmieri MR. Coffee intake and risk of incident diabetes in Puerto Rican men: results from the Puerto Rico Heart Health Program. Public Health Nutr 2009;12:842–8.
11. Van Dam RM. Coffee and type 2 diabetes: from beans to beta-cells. Nutr Metab Cardiovasc Dis 2006;16:69–77.
12. Scalbert A, Manach C, Morand C, Remesy C. Dietary polyphenols and the prevention of diseases. Crit Rev Food Sci Nutr 2005;45:287–306.
13. Greer F, Hudson R, Ross R, Graham T. Caffeine ingestion decreases glucose disposal during a hyperinsulinemic-euglycemic clamp in sedentary humans. Diabetes 2001;50:2349–54.
14. Jiang R, Manson JE, Meigs JB, Ma J, Rifai N, Hu FB. Body iron stores in relation to risk of type 2 diabetes in apparently health women. JAMA 2004;291:711–7.
15. Fleming DJ, Jacques PF, Dallal GE, Tucker KL, Wilson PWF, Wood RJ. Dietary determinants of iron stores in a free-living elderly population; the Framingham Heart Study. Am J Clin Nutr 1998;67:722–33.
16. McKay DL, Blumberg JB. The role of tea in human health: an update. J Am Coll Nutr 2002;21:1–13.
17. Greenberg JA, Axen KV, Schnoll R, Boozer CN. Coffee, tea and diabetes: the role of weight loss and caffeine. Int J Obes 2005;29:1121–9.
18. Iso H, Date C, Wahai K, Fukui M, Tamakoshi A, for the JACC Study Group. The relationship between green tea and total caffeine intake and risk for self-reported type 2 diabetes among Japanese adults. Ann Intern Med 2006;144:554–62.
19. Salazar-Martinez E, Willett WC, Aschiero A, et al. Coffee consumption and risk for type 2 diabetes mellitus. Ann Intern Med 2004;140:1–8.
20. van Dam RM, Willett WC, Manson JE, Hu FB. Coffee, caffeine, and risk of type 2 diabetes. Diabetes Care 2006;29:398–403.
21. Hu G, Jousilahti P, Peltonen M, Bidel S, Tuomilehto J. Joint association of coffee consumption and other factors to the risk of type 2 diabetes: a prospective study in Finland. Int J Obes 2006;30:1742–9.
22. Clavel-Chapelon F. Cumulative number of menstrual cycles and breast cancer risk: results from the E3N cohort study of French women. Cancer Causes Control 2002;13:831–8.
23. Slimani N, Kaaks R, Ferrari P, et al. European Prospective Investigation into Cancer and Nutrition (EPIC) calibration study: rationale, design and population characteristics. Public Health Nutr 2002;5:1125–45.
24. Van Liere MJV, Lucas F, Clavel F, Slimani N, Villeminot S. Relative validity and reproducibility of a French dietary history questionnaire. Int J Epidemiol 1997;26(suppl 1):128S–36S.
25. Lucas F, Niravong M, Villeminot S, Kaaks R, Clavel-Chapelon F. Estimation of food portion size using photographs: relative validity,

strengths, weaknesses and recommendations. J Hum Nutr Diet 2008;8: 65–74.
26. Favier JC, Ireland-Ripert J, Toque C, Feinberg M. Répertoire Général des Aliments. Table de composition. [Composition tables.] INRA, CIQUAL-REGAL, editors. 2nd ed. Paris, France: Tec & Doc Lavoisier, 1995 (in French).
27. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Geneva, Switzerland: World Health Organization / International Diabetes Federation, 2006.
28. Kilpatrick ES. Haemoglobin A1c in the diagnosis and monitoring of diabetes mellitus. J Clin Pathol 2008;61:977–82.
29. Saudek CD, Herman WH, Sacks DB, Bergenstal RM, Edelman D, Davidson MB. A new look at screening and diagnosing diabetes mellitus. J Clin Endocrinol Metab 2008;93:2447–53.
30. Willett W, Stampfer M. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27.
31. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32(suppl 9):S498–504.
32. 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.
33. Van Dam RM, Feskens EJ. Coffee consumption and risk of type 2 diabetes mellitus. Lancet 2002;360:1477–8.
34. van Dam RM, Dekker JM, Nijpels G, Stehouwer CD, Bouter LM, Heine RJ. Coffee consumption and incidence of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes: the Hoorn Study. Diabetologia 2004;47:2152–9.
35. Carlsson S, Hammar N, Grill V, Kaprio J. Coffee consumption and risk of type 2 diabetes in Finish twins. Int J Epidemiol 2004;33:616–7.
36. deValk HW. Magnesium in diabetes mellitus. Neth J Med 1999;54: 139–46.
37. Svilaas A, Sakhi AK, Andersen LF, et al. Intake of antioxidants in coffee, wine, and vegetables are correlated with plasma carotenoids in humans. J Nutr 2004;134:562–7.
38. Johansen JS, Harris AK, Rychly DJ, Ergeil A. Oxidative stress and the use of antioxidants in diabetes: linking basic science to clinical practice. Cardiovasc Diabetol 2005;4:5–15.
39. Shearer J, Farah A, Paulis T, et al. Quinides of roasted coffee enhance insulin action in conscious rats. J Nutr 2003;133:3529–32.
40. Arion WJ, Canfield WK, Ramos FC, et al. Chlorogenic acid and hydroxynitrobenzaldehyde: new inhibitors of hepatic glucose 6-phosphatase. Arch Biochem Biophys 1997;339:315–22.
41. Prasad K, Mantha SV, Muir AD, Westcott ND. Protective effect of secoisolariciresinol diglucoside against streptozotocin-induced diabetes and its mechanism. Mol Cell Biochem 2000;206:141–9.
42. Hurrell RF, Reddy M, Cook JD. Inhibition of non-haem iron absorption in man by polyphenolic-containing beverages. Br J Nutr 1999;81:289–95.
43. Fumeron F, Péan F, Driss F, et al. Ferritin and transferrin are both predictive of the onset of hyperglycemia in men and women over 3 years. Diabetes Care 2006;29:2090–4.
44. Vari IS, Balkau B, Kettaneh A, et al. Ferritin and transferrin are associated with metabolic syndrome abnormalities and their change over time in a general population. Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR). Diabetes Care 2007;30:1795–801.
45. Perron NR, Brumaghim JL. A review of the antioxidant mechanisms of polyphenol compounds related to iron binding. Cell Biochem Biophys 2009;53:75–100.
46. Hallberg L, Hulthén L. Prediction of dietary iron absorption: an algorithm for calculating absorption and bioavailability of dietary iron. Am J Clin Nutr 2000;71:1147–60.
47. Tunnicliffe JM, Shearer J. Coffee, glucose homeostasis, and insulin resistance: physiological mechanisms and mediators. Appl Physiol Nutr Metab 2008;33:1290–300.