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Coffee consumption and risk of cardiovascular events and all-cause mortality among women with type 2 diabetes

W.L. Zhang[1,2], **E. Lopez-Garcia**[1,3], **T. Y. Li**[1], **F. B. Hu**[1,4,5], and **R. M. van Dam**[1,5]

1 *Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts*

2 *Sino-German Laboratory for Molecular Medicine, FuWai Cardiovascular Hospital and Cardiovascular Institute, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China*

3 *Universidad Autónoma de Madrid, Madrid, Spain; and CIBERESP (CIBER of Epidemiology and Public Health), Spain*

4 *Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts*

5 *Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts*

Abstract

Aims/hypothesis—Coffee has been linked to both beneficial and harmful health effects, but data on its relation with cardiovascular disease and mortality in patients with type 2 diabetes are sparse.

Methods—This is a prospective cohort study including 7,170 women with diagnosed type 2 diabetes but free of cardiovascular disease or cancer at baseline. Coffee consumption was assessed in 1980 and then every 2 to 4 years through validated questionnaires. A total of 658 incident cardiovascular events (434 coronary heart disease and 224 stroke) and 734 deaths from all causes were documented between 1980 and 2004.

Results—After adjustment for age, smoking, and other cardiovascular risk factors, the relative risks (RRs) were 0.76 (95% CI, 0.50 to 1.14) for cardiovascular diseases (p trend = 0.09) and 0.80 (95% CI, 0.55 to 1.14) for all-cause mortality (p trend = 0.05) for the consumption of ≥ 4 cups/day caffeinated coffee as compared with nondrinkers. Similarly, multivariable RRs were 0.96 (95% CI, 0.66 to 1.38) for cardiovascular diseases (p trend = 0.84) and 0.76 (95% CI, 0.54 to 1.07) for all-cause mortality (p trend = 0.08) for the consumption of ≥ 2 cups/day decaffeinated coffee as compared with nondrinkers. Higher decaffeinated coffee consumption was associated with lower concentrations of glycosylated hemoglobin (6.2% for ≥ 2 cups/d versus 6.7% for < 1 cup/mo; p trend = 0.02).

Conclusions—These data provides evidence that habitual coffee consumption is not associated with increased risk for cardiovascular diseases or premature mortality among diabetic women.

Keywords

Nutrition and diet; Coffee consumption; Cardiovascular disease; Mortality; Epidemiology

Address correspondence to Rob M. van Dam, Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave., Boston, MA 02115. Tel: 617-432-4975; Fax: 617-432-4711. E-mail: rvandam@hsph.harvard.edu; or Weili Zhang, FuWai Cardiovascular Hospital and Cardiovascular Institute, 167 Beilishi Rd, Beijing 10067, China. Email: weilizhang@sglab.org..

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Introduction

Type 2 diabetes mellitus increases the risk of cardiovascular disease (CVD) and mortality two- to four-fold [1]. Moreover, diabetes increases CVD risk to a greater extent in women as compared with men, and diabetes may eliminate women's protection against coronary heart disease [2].

Coffee drinking is wide-spread across the world; more than 50% of Americans drink coffee, and average per capita intake is about 2 cups per day [3]. Thus, even small health effects of coffee could have a large impact on public health. Habitual coffee consumption has been associated with better glucose tolerance in persons without diabetes [4]. In addition, coffee contains phenolic compounds with antioxidant properties [5], and may favorably affect the process of atherosclerosis through preventing oxidation of LDL- cholesterol [6], and inhibiting platelet aggregation and thrombogenesis [7,8]. On the other hand, caffeine intake acutely raises blood pressure [9,10], homocysteine levels [11], and postprandial glucose levels [12] in short-term trials. Because of these complex physiological effects of coffee and because at least partial tolerance to the hemodynamic effects of caffeine typically develops with long-term use [13], it is difficult to extrapolate findings from short-term metabolic studies to effects of long-term use of coffee.

The relation between coffee consumption and CVD and mortality remains controversial [14, 15]. While most recent prospective studies have suggested that coffee consumption is not associated with an increased risk of coronary heart disease and mortality in the general population [16-20], data among diabetic patients are sparse [21]. Therefore, we prospectively examined the relation between coffee consumption and incidence of coronary heart disease and stroke and all-cause mortality among women with type 2 diabetes in the Nurses' Health Study.

Methods

Study population

The Nurses' Health Study (NHS) cohort was established in 1976 when 121,700 female registered nurses, 30 to 55 years old and residing in 11 large US states, completed a mailed questionnaire about their medical history and lifestyle. The present study included the 7,170 women who reported physician-diagnosed type 2 diabetes on any questionnaire from 1976 to 2004 (1,552 prevalent diabetic women in 1980 and 5,618 incident diabetic women during the follow-up). Women with diabetes diagnosed before the age of 30 years, or with a history of CHD (including myocardial infarction, angina, and/or coronary revascularization), stroke, or cancer reported on the 1980 questionnaire (when diet was first assessed), or before, were excluded at baseline. This study was approved by the institutional review board at Brigham and Women's Hospital and return of the questionnaires was assumed to imply informed consent.

Confirmation of *diabetes mellitus*

A supplementary questionnaire was mailed to women who indicated on any biennial questionnaire that they had been diagnosed as diabetes. Consistent with the criteria of the National Diabetes Data Group [22], diagnosed cases required (1) an elevated glucose concentration (fasting plasma glucose of ≥7.8 mmol/l, random plasma glucose ≥11.1 mmol/l, or plasma glucose ≥11.1 mmol/l after an oral glucose load), and at least one symptom related to diabetes (excessive thirst, polyuria, weight loss, or hunger); (2) no symptoms, but elevated glucose concentrations on two occasions; and (3) treatment with insulin or oral hypoglycemic medication. For cases of type 2 diabetes identified after 1998, the cut-off point used for fasting

plasma glucose concentrations was lowered to 7.0 mmol/l according to the American Diabetes Association criteria [23]. Our validation study showed a high confirmation (98%) of self-reported type 2 diabetes [24].

Assessment of coffee consumption

Dietary questionnaires were sent to the NHS participants in 1980, 1984, 1986, 1990, 1994, 1998, and 2002. On each questionnaire, participants were asked how often on average during the previous year they had consumed coffee and tea. Decaffeinated coffee and different types of caffeinated soft drinks were first assessed in 1984. We also assessed total caffeine intake as described previously [25]. In our validation study, we obtained high correlations between consumption of coffee and other caffeinated beverages estimated from the food frequency questionnaire and consumption estimated from repeated 1-week diet records (coffee, r=0.78; tea, r=0.93; and caffeinated sodas, r=0.85) [26].

Ascertainment of end points

The end points were incident CHD (defined as nonfatal myocardial infarction or fatal CHD), stroke, and all-cause mortality. We requested permission to review the medical records of women who reported having a nonfatal myocardial infarction or stroke on a follow-up questionnaire. Myocardial infarction was confirmed if it met the criteria of the World Health Organization of symptoms and the patient's records showed diagnostic electrocardiographic changes or elevated cardiac enzyme levels [27]. Fatal CHD was defined as fatal myocardial infarction if this was confirmed by hospital records or autopsy, or if coronary disease was listed as the cause of death on the certificate. Sudden death within 1 hour of onset of symptoms in women with no other plausible cause other than coronary disease was also included. Stroke was confirmed by medical records according to the criteria of the National Survey of Stroke [28], which define it as a constellation of neurologic deficits, sudden or rapid in onset, lasting at least 24 hours or until death.

Deaths were reported by next of kin or the postal system or ascertained through the National Death Index. Follow-up for the death was more than 98% complete [29]. We obtained copies of death certificates and medical records and determined causes of death (classified according to the categories of the International Classification of Diseases, Ninth Revision [ICD-9]).

Laboratory methods

Blood was drawn in 1989-1990. Concentrations of glycosylated hemoglobin (HbA1c) were based on turbidimetric immunoinhibition with hemolyzed whole blood or packed red cells with less than 3.0% CV. The concentrations of total cholesterol, HDL L-cholesterol, and triglycerides were measured simultaneously on the Hitachi 911 analyzer (Roche Diagnostics, Indianapolis, IN); the CVs for these measurements were less than 1.8%. Concentrations of LDL cholesterolL- were measured using a homogenous direct method (Genzyme, Cambridge, MA) with a CV less than 3.1%. Concentrations of apoB-100 were measured in an immunonephelometric assay (Wako Chemicals, Richmond, VA) with a CV less than 5.0%.

Statistical analyses

The follow-up period started at the date of return of the questionnaire on which type 2 diabetes diagnosis was first reported until the occurrence of CHD, stroke, death, or the end of the study period (June 1, 2004). Women who reported having cardiovascular disease on previous questionnaires were excluded from subsequent follow-up.

Cox proportional hazard regression was used to investigate the association between coffee consumption and incidence of CVD events and all-cause mortality. Multivariable models were

first adjusted for age and smoking status. Furthermore, we adjusted for BMI, physical activity, alcohol intake, use of hormone therapy for women, parental history of myocardial infarction (MI), history of hypertension and hypercholesterolemia, duration of diabetes, insulin or other hypoglycemic therapy, total energy intake, and use of multivitamin and vitamin E supplements. An additional analysis was further adjusted for dietary factors. The median value of each category of coffee consumption was used as a continuous variable to test for linear trends.

To represent long-term intake of coffee and to reduce measurement error, we conducted analyses using cumulative updated coffee intake from all available dietary questionnaires up to the start of each 2-year follow-up interval [30]. To determine whether there were different effects of long-term and short-term effects of coffee consumption, we also used the most recent report of coffee intake in relation to incidence of CVD events. In addition, we studied the association between caffeine intake, decaffeinated coffee and tea consumption, and CVD risk.

As a complementary study, we examined the association of caffeinated and decaffeinated coffee and plasma concentrations of lipids and HbA1c by conducting a cross-sectional analysis in the subgroup including 663 diabetic women who provided blood samples in 1989-1990 and had a confirmed diagnosis of type 2 diabetes mellitus but not of cardiovascular disease or cancer [31]. There was no substantially difference between the total group and the subsample in coffee consumption and baseline characteristics. We used dietary information from the 1990 food frequency questionnaire. Multivariable-adjusted geometric means (95%CI) of plasma lipids and HbA1c across categories of coffee consumption were calculated. All analyses were performed with SAS software, version 8.2 (SAS Institute Inc, Cary, NC). The authors had full access to the data and take responsibility for its integrity. All authors have approved the manuscript as written.

Results

Between 1980 and 2004 (62,722 person-years of follow-up), we documented 658 incident cases of cardiovascular disease (434 CHD and 224 stroke), and 734 deaths from all causes (282 from CHD or stroke, 182 from cancer, and 270 from other causes). Higher coffee consumption was strongly associated with cigarette smoking and alcohol use (Table 1).

In both age and smoking adjusted analyses and multivariable analyses adjusting for cardiovascular risk factors, we found no significant association between long-term caffeinated coffee consumption and risk for CHD or stroke (Table 2). Further adjustment for other dietary factors, suggested a tendency of inverse association between coffee consumption and risk of CHD (p for trend=0.06), particularly fatal CHD (p for trend=0.07). A sensitivity analysis adjusting for tea, sugar-sweetened soft drinks, and dairy food intake did not substantially change the results. Additional analyses also showed no direct association between coffee consumption and CVD risk in any subgroups stratified by risk factor status, including obesity, smoking status, and duration of diabetes (see the supplementary Table1).

Compared with coffee intake of less than 1 cup/month, caffeinated coffee consumption of 4 cups/day or more appeared to be associated with a slightly lower risk for all-cause mortality after adjustment for cardiovascular risk factors, lifestyle and dietary factors (RR, 0.80; 95% CI, 0.55-1.14; p for trend=0.05; Table 2). This was due to an inverse association between coffee and cardiovascular death (RR, 0.62; 95%CI, 0.33-1.17; p for trend=0.01). Coffee consumption was not associated with non-cardiovascular death (RR, 0.94; 95%CI, 0.60-1.46; p for trend=0.70). We conducted a sensitivity analysis where we updated coffee consumption using the most recent data in relation to CVD risk and mortality yielding very similar results (results not shown).

We also examined caffeine intake in relation to risk for CVD and all-cause mortality and did not observe significant associations. The multivariable adjusted RRs (95%CI) for quintiles of caffeine intake were 1.0, 1.11(0.74-1.69), 0.98(0.51-1.80), 1.09(0.71-1.66), and 0.90 (0.70-1.15) (*p* for trend=0.73) for cardiovascular diseases, and 1.0, 0.93(0.63-1.38), 0.71 (0.39-1.32), 1.25(0.84-1.86), and 0.96(0.76-1.23) (*p* for trend=0.36) for all-cause mortality. Decaffeinated coffee consumption tended to be associated with a lower risk of all-cause mortality, but this association was not significant. No substantial associations were observed for tea (supplementary table 2).

In a cross-sectional analysis for biomarker, higher decaffeinated coffee consumption was associated with lower concentrations of HbA1c (6.2% for ≥2 cups/d versus 6.7% for <1 cup/mo; *p* for trend=0.02). Neither caffeinated nor decaffeinated coffee was associated with blood lipid levels, including total cholesterol, LDL-C, and HDL-C, Apo B-100, and triglycerides (Table 3).

Discussion

In this prospective study in diabetic women, higher coffee consumption was not associated with a higher risk of cardiovascular diseases or all-cause mortality. Higher decaffeinated, but not caffeinated, coffee consumption was associated with lower glycosylated hemoglobin levels. Neither caffeinated nor decaffeinated coffee consumption was associated with blood lipid levels.

The strengths of the study included large number of diabetic women, prospective design, and long follow-up period. Also, we controlled for severity of diabetes by adjusting for duration of diabetes and hypoglycemic medications. The food frequency questionnaire that we used in the dietary assessment has been previously evaluated as a reasonable reflection of long-term diet [32]. We reduced error by measuring coffee consumption repeatedly during follow-up. Because coffee drinking is often thought to be an unhealthy habit, people may reduce the consumption of coffee after developing a disease. These changes in coffee habits would dilute a possible positive association between coffee and CVD risk. To reduce bias from this source, we excluded women with hypertension, hypercholesterolemia, or cardiovascular diseases at baseline. We used coffee consumption after the diagnosis of diabetes thus incorporating possible changes in intake as a result of the diagnosis. Different brewing strength may have led to some misclassification of coffee intake; nevertheless, we could study a large contrast in coffee intake (4 or more cups per day versus none) that will remain large even in the presence of variation in brew strength.

Type 2 diabetes is characterized by insulin resistance, lipid metabolism abnormalities, increased platelet aggregation and clotting, and high oxidative stress, all of which are associated with accelerated cardiovascular incidence [33]. A growing body of evidence shows that coffee intake may favorably affect the process of atherosclerosis through reducing oxidation of LDL cholesterolL- [6], inhibiting platelet aggregation and thrombogenesis [7,8], and preventing inflammation and endothelial dysfunction [31]. In randomized trials, consumption of unfiltered coffee such as boiled or French Press coffee increased serum LDL-cholesterol concentrations, whereas paper-filtered coffee did not have substantial effects on cholesterol concentrations [34]. In our cohort, women predominantly consumed paper-filtered coffee [19] and the lack of association between coffee consumption and blood lipid levels is thus consistent with findings from randomized trials.

Coffee contains various components that may improve glucose metabolism [35,36]. The phenol chlorogenic acid has been shown to reduce glucose concentrations in rats [37] and may stimulate secretion of glucagon-like peptide-1 [38]. Glucagon-like peptide-1 is well known for

its beneficial effects on glucose-induced insulin secretion and insulin action [39]. These mechanisms may explain our findings that higher decaffeinated coffee consumption was associated with lower HbA1c levels, a marker of glycemic control. The results from this cross-sectional analysis should be interpreted with caution, because 'reverse causation' with better treated and more health-concerned participants switching to decaffeinated coffee may have biased the results. Longer-term trials of caffeinated, decaffeinated coffee and glycemic control in diabetic patients are needed.

Concerns have been raised that caffeine acutely increases blood pressure [40] and plasma homocysteine concentrations [41]. However, the results of prospective cohort studies suggest that long-term coffee consumption is not substantially associated with a risk of hypertension [42]. The detrimental short-term effects of caffeine intake on blood pressure may be reduced by the development of partial tolerance with long-tern use and the counteracting effects of other coffee components [43]. In contrast, the effects of coffee on homocysteine appear to remain after long-term consumption [44]. It is unclear, however, whether homocysteine has a causal effect on the development of CHD or is merely an innocent bystander [45].

Coffee consumption was correlated with smoking in this study, consistent with observations in other study populations [21,46]. However, we did not find an interaction between smoking and coffee in relation to CVD risk. Our study showed a modest inverse association between coffee and CVD incidence and mortality although this was only borderline significant. This inverse association was more clearly observed in a previous study in Finnish persons with diabetes [21].

In conclusion, in this large prospective study, our findings do not support the hypothesis that habitual caffeinated coffee consumption increases the risk of cardiovascular events and mortality among persons with type 2 diabetes. Further research should evaluate whether consumption of decaffeinated coffee may improve glycemic control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CVD, Cardiovascular disease; NHS, The Nurses' Health Study; HbA1c, Glycosylated hemoglobin; MI, Myocardial infarction.

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Table 1

Baseline characteristics according to caffeinated coffee consumption among women with type 2 diabetes [a] (n=7,170)

Variables	Caffeinated coffee consumption, Cups					
	< 1/mon	1/mon to 4/wk	5 to 7/wk	2 to 3/d	≥ 4/d	p for trend
Participants, n	1451	1076	2302	1717	624	
Age, y	48	48	49	49	48	0.26
Risk factors						
BMI, kg/m^2	29.9	30.7	30.2	29.5	28.4	0.12
Current smokers, %	11	8	12	20	39	<0.001
History of hypertension, %	42	51	46	40	37	0.11
History of hypercholesterolemia, %	36	43	40	34	29	0.15
Parental history of myocardial infarction, %	22	22	24	22	22	0.87
Postmenopausal hormone use, %	20	24	21	17	13	0.74
Aspirin use, % [b]	15	16	18	16	16	0.67
Physical activity, h/wk	2.4	2.2	2.1	2.2	2.4	0.36
Alcohol, g/d	2.4	2.8	4.2	5.2	4.8	0.005
Dietary daily intake						
Saturated fat, % energy	13.5	12.9	13.2	14.0	14.9	0.13
Polyunsaturated fat, % energy	5.6	5.8	5.8	5.7	5.7	0.56
Trans fat, % energy	1.9	1.9	2.0	2.0	2.2	0.10
Total n-3 fatty acids, % energy	0.61	0.63	0.64	0.63	0.61	0.75
Cereal fiber, g/d	3.3	3.7	3.5	3.3	3.0	0.39
Folate, µg/d	404.8	397.9	387.7	369.6	344.3	0.03
Glycemic load	98.8	99.6	95.8	90.3	85.4	0.002
Caffeine, mg/d	101.7	139.3	269.2	467.1	775.8	<0.001
Sugar-sweetened soft drinks, servings/d	1.1	1.0	1.2	0.9	1.0	0.10
Dairy, servings/d	2.0	2.6	2.9	3.5	3.9	0.007
Tea consumption, cups	1.1	0.9	0.7	0.6	0.5	0.01
Supplements						
Multivitamins, %	37	42	41	37	29	0.02
Vitamin E, %	25	31	30	23	17	0.01

Variables	Caffeinated coffee consumption, Cups					p for trend
	< 1/mon	1/mon to 4/wk	5 to 7/wk	2 to 3/d	≥ 4/d	

[a] Data were from different periods based on the diagnostic time of type 2 diabetes during follow-up (1980-2004). Values are means unless otherwise indicated.

[b] Aspirin use denotes 1 or more times per week.

Table 2

Relative risks (95% CI) for cardiovascular diseases and all-cause mortality by caffeinated coffee consumption among women with type 2 diabetes (1980-2004) [a]

Variables	Caffeinated coffee consumption, cups					*p* for trend
	< 1/mon	1/mon to 4/wk	5 to 7/wk	2 to 3/d	≥ 4/d	
Total cardiovascular events						
Person years	12262	10853	21351	13754	4504	
Cases, n	114	114	261	131	38	
Age-, and smoking-adjusted	1.0	0.97 (0.75-1.26)	1.05 (0.84-1.31)	0.86 (0.66-1.10)	0.82 (0.56-1.19)	0.11
Multivariable I [b]	1.0	1.02 (0.79-1.33)	1.14 (0.91-1.43)	0.94 (0.73-1.23)	0.82 (0.55-1.21)	0.18
Multivariable II [c]	1.0	1.04 (0.80-1.36)	1.14 (0.91-1.44)	0.92 (0.70-1.20)	0.76 (0.50-1.14)	0.09
Total coronary **heart disease**						
Cases, n	77	69	178	82	28	
Age-, and smoking-adjusted	1.0	0.89 (0.64-1.23)	1.07 (0.82-1.41)	0.78 (0.57-1.07)	0.85 (0.55-1.33)	0.19
Multivariable I [b]	1.0	0.91 (0.65-1.26)	1.13 (0.86-1.50)	0.83 (0.60-1.15)	0.79 (0.50-1.26)	0.16
Multivariable II [c]	1.0	0.94 (0.67-1.30)	1.14 (0.86-1.50)	0.80 (0.57-1.12)	0.70 (0.43-1.14)	0.06
Nonfatal MI						
Cases, n	41	25	99	37	15	
Age-, and smoking-adjusted	1.0	0.61 (0.37-1.02)	1.15 (0.79-1.67)	0.66 (0.42-1.04)	0.80 (0.43-1.48)	0.31
Multivariable I [b]	1.0	0.60 (0.36-0.99)	1.15 (0.79-1.68)	0.70 (0.44-1.11)	0.77 (0.41-1.47)	0.40
Multivariable II [c]	1.0	0.60 (0.36-1.00)	1.16 (0.79-1.70)	0.69 (0.43-1.13)	0.74 (0.38-1.45)	0.38
Fatal CHD						
Cases, n	36	44	79	45	13	
Age-, and smoking-adjusted	1.0	1.18 (0.76-1.84)	0.99 (0.66-1.48)	0.92 (0.59-1.43)	0.91 (0.47-1.74)	0.38
Multivariable I [b]	1.0	1.31 (0.83-2.04)	1.11 (0.74-1.67)	0.99 (0.63-1.57)	0.82 (0.42-1.60)	0.26
Multivariable II [c]	1.0	1.41 (0.90-2.22)	1.12 (0.74-1.69)	0.91 (0.56-1.46)	0.67 (0.33-1.36)	0.07
Stroke						
Cases, n	37	45	83	49	10	
Age-, and smoking-adjusted	1.0	1.14 (0.74-0.77)	1.01 (0.68-1.49)	1.02 (0.66-1.57)	0.73 (0.36-1.50)	0.37
Multivariable I [b]	1.0	1.24 (0.80-1.93)	1.14 (0.77-1.71)	1.19 (0.76-1.86)	0.85 (0.41-1.77)	0.75
Multivariable II [c]	1.0	1.24 (0.80-1.93)	1.13 (0.76-1.70)	1.16 (0.73-1.85)	0.86 (0.40-1.84)	0.74
All-cause mortality						

Variables	Caffeinated coffee consumption, cups					*p* for trend
	< 1/mon	1/mon to 4/wk	5 to 7/wk	2 to 3/d	≥ 4/d	
Person years	12342	10911	21506	13841	4526	
Deaths, n	136	135	267	146	50	
Age-, and smoking-adjusted	1.0	0.92 (0.73-1.17)	0.86 (0.70-1.06)	0.78 (0.62-0.99)	0.92 (0.66-1.28)	0.22
Multivariable I [b]	1.0	1.08 (0.85-1.38)	1.04 (0.84-1.28)	0.89 (0.70-1.13)	0.82 (0.59-1.15)	0.06
Multivariable II [c]	1.0	1.10 (0.86-1.40)	1.04 (0.84-1.30)	0.87 (0.67-1.12)	0.80 (0.55-1.14)	0.05

[a] Total coronary heart disease includes nonfatal MI and fatal CHD. Total cardiovascular events include total coronary heart disease and stroke.

[b] Adjusted for: age (5-year categories), smoking status (never, past, and current 1-14, 15-24, and ≥25 cigarettes/day), BMI (<23.0, 23.0 -24.9, 25.0-27.9, 28.0-29.9, or ≥ 30.0 kg/m^2), alcohol intake (0, 0.1-4.9, 5-14, ≥15 g/d), parental history of MI, history of hypertension, hypercholesterolemia, menopausal status and use of hormone therapy, physical activities (<1, 1-1.9, 2-3.9, 4-6.9, ≥7 h/wk), multivitamin use and vitamin E supplement use, total energy intake, duration of diabetes (<5, 5-10, 11-15, ≥15 y), and hypoglycemic medication.

[c] Adjusted for factors cited above and polyunsaturated, saturated, and trans fat, n-3, glycemic load, dietary cereal fiber and folate intake (all in quintiles).

Table 3

Cross-sectional analysis of the relation between coffee and plasma concentrations of lipids and HbA1c among diabetic women (*n* = 663) [a]

Beverage drinking, Cups	*n*	HbA1c, % [b]	Total cholesterol, mg/dl	HDL-C, mg/dl	LDL-C, mg/dl [c]	ApoB-100, mg/dl	Triglycerides, mg/dl
Caffeinated coffee							
< 1/mon	174	6.5 (6.3, 6.7)	227.1 (220.7, 233.6)	50.1 (48.1, 52.1)	135.3 (129.5, 141.3)	102.8 (99.2, 106.5)	178.5 (164.5, 193.6)
1 /mon to 4 /wk	140	6.6 (6.3, 6.8)	226.0 (218.9, 233.3)	47.8 (45.7, 50.0)	135.6 (129.2, 142.3)	101.6 (97.7, 105.7)	188.0 (171.6, 205.9)
5 to 7/wk	251	6.7 (6.5, 6.9)	224.0 (218.7, 229.3)	47.2 (45.7, 48.8)	136.3 (131.5, 141.3)	102.6 (99.6, 105.7)	180.2 (168.3, 192.9)
≥ 2/day	98	6.3 (6.0, 6.6)	227.3 (218.8, 236.1)	46.7 (44.2, 49.2)	140.7 (132.8, 149.1)	103.6 (98.8, 108.6)	187.1 (167.7, 208.6)
p for linear trend [d]		0.52	0.98	0.18	0.46	0.88	0.83
Decaffeinated coffee							
< 1/mon	252	6.7 (6.5, 6.9)	226.6 (221.3, 232.0)	48.2 (46.6, 49.8)	138.5 (133.6, 143.5)	102.9 (100.0, 106.0)	181.3 (169.5, 193.9)
1 /mon to 4 /wk	214	6.5 (6.3, 6.7)	226.8 (221.1, 232.6)	46.3 (44.6, 47.9)	137.4 (132.2, 142.8)	104.6 (101.4, 108.0)	189.4 (176.1, 203.7)
5 to 7/wk	149	6.5 (6.3, 6.8)	226.0 (219.1, 233.0)	50.1 (48.0, 52.3)	133.2 (127.1, 139.5)	100.6 (96.8, 104.5)	179.5 (164.4, 196.0)
≥ 2/day	48	6.2 (5.8, 6.6)	215.6 (204.2, 227.6)	48.5 (45.0, 52.4)	133.2 (122.7, 144.7)	98.1 (91.8, 105.0)	167.0 (142.9, 195.1)
p for linear trend [d]		0.02	0.40	0.08	0.52	0.15	0.21

[a] A cross-sectional analysis was conducted in the subgroup including 663 women who provided blood sample in 1989-1990 and had a confirmed diagnosis of type 2 diabetes mellitus but not of cardiovascular disease. Adjusted geometric mean (95% CI) plasma concentrations of lipids and HbA1c was calculated with the use of multiple linear regression models (in PROC GLM) controlling for age (5-year categories), smoking status (never, past, and current 1-14, 15-24, and ≥25 cigarettes/day), BMI (<23.0, 23.0 -24.9, 25.0-27.9, 28.0-29.9, or ≥ 30.0 kg/m^2), alcohol intake (0, 0.1-4.9, 5-14, ≥15 g/d), physical activities (<1, 1-1.9, 2-3.9, 4-6.9, ≥7 h/wk), menopausal status and use of hormone therapy, and aspirin use in 1990.

[b] Data on HbA1c were missing for 12 women.

[c] Data on LDL-C were missing for 3 women.

[d] From multiple linear regression models for the relation between beverage consumption (cups/d) and log-transformed markers.