

Coffee Consumption and Risk of Type 2 Diabetes Mellitus Among Middle-aged Finnish Men and Women

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CENTURIES OF COFFEE DRINKING has made it the most consumed beverage in the world. During the last decade, research has attempted to make clear health benefits or detriments received from coffee drinking. Effects of coffee and caffeine on cardiovascular disease,¹ hypertension,² neurological diseases,³ different types of cancer,⁴ hormonal changes,⁵⁻⁷ gallstones,⁸ renal stones,⁹ as well as diabetes mellitus (DM)¹⁰⁻¹² have been studied through epidemiological, clinical, or experimental research. Type 2 DM is one of the diseases that is largely determined by lifestyle factors.^{13,14}

The role of coffee in relation to DM has not been investigated thoroughly. A large Dutch cohort study¹² recently showed an inverse association between coffee consumption and the risk of DM. It is well known that caffeine stimulates insulin secretion of the pancreatic beta cells in vivo. However, coffee with its complex compounds may influence many other processes that may take part in the development of DM.

According to international statistics, the Finnish population has the

Context Only a few studies of coffee consumption and diabetes mellitus (DM) have been reported, even though coffee is the most consumed beverage in the world.

Objective To determine the relationship between coffee consumption and the incidence of type 2 DM among Finnish individuals, who have the highest coffee consumption in the world.

Design, Setting, and Participants A prospective study from combined surveys conducted in 1982, 1987, and 1992 of 6974 Finnish men and 7655 women aged 35 to 64 years without history of stroke, coronary heart disease, or DM at baseline, with 175 682 person-years of follow-up. Coffee consumption and other study parameters were determined at baseline using standardized measurements.

Main Outcome Measures Hazard ratios (HRs) for the incidence of type 2 DM were estimated for different levels of daily coffee consumption.

Results During a mean follow-up of 12 years, there were 381 incident cases of type 2 DM. After adjustment for confounding factors (age, study year, body mass index, systolic blood pressure, education, occupational, commuting and leisure-time physical activity, alcohol and tea consumption, and smoking), the HRs of DM associated with the amount of coffee consumed daily (0-2, 3-4, 5-6, 7-9, ≥ 10 cups) were 1.00, 0.71 (95% confidence interval [CI], 0.48-1.05), 0.39 (95% CI, 0.25-0.60), 0.39 (95% CI, 0.20-0.74), and 0.21 (95% CI, 0.06-0.69) (P for trend $< .001$) in women, and 1.00, 0.73 (95% CI, 0.47-1.13), 0.70 (95% CI, 0.45-1.05), 0.67 (95% CI, 0.40-1.12), and 0.45 (95% CI, 0.25-0.81) (P for trend = .12) in men, respectively. In both sexes combined, the multivariate-adjusted inverse association was significant (P for trend $< .001$) and persisted when stratified by younger and older than 50 years; smokers and never smokers; healthy weight, overweight, and obese participants; alcohol drinker and non-drinker; and participants drinking filtered and nonfiltered coffee.

Conclusion Coffee drinking has a graded inverse association with the risk of type 2 DM; however, the reasons for this risk reduction associated with coffee remain unclear.

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highest per capita coffee consumption in the world with 11.3 kg in 2000.¹⁵ Therefore, research into potential health effects of coffee in this population is of particular interest. Our large prospective study aimed at determining whether the suggested inverse relationship between coffee and type 2 DM exists among the Finnish population. In

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See also p 1199.

addition, we evaluated a possible effect modification of the major determinants of type 2 DM and assessed the effects of different types of prepared coffee on the risk of DM.

METHODS

Participants

We performed baseline surveys in 2 eastern Finnish provinces, North Karelia and Kuopio, and in the Turku-Loimaa region in southwestern Finland in 1982, 1987, and 1992. The survey was expanded to the Helsinki capital area in 1992. In the 3 surveys, the sample included participants aged 25 to 64 years. The 1982, 1987, and 1992 cohorts were combined in this analysis. The original random sample was stratified by sex and 4 equally large 10-year age groups according to the World Health Organization MONItoring trends and determinants of CARdiovascular disease (MONICA) protocol^{16,17} and consisted of 21 630 participants. The participation rate varied by year from 74% to 88%.¹⁸ Our analysis included 16 670 participants aged 35 to 64 years due to the few cases of type 2 DM in participants aged 25 to 34 years during the follow-up. The final sample comprised 6974 men and 7655 women after excluding participants diagnosed with coronary heart disease or stroke (n=590), participants with known DM at baseline (n=435), and participants with incomplete data on any variables required for this analysis (n=1016). We excluded participants with coronary heart disease and stroke because there may be bias regarding their exposure (coffee drinking due to their disease) or confounding factors (diet and physical activity, their survival probability is lower, and they may be using drugs that trigger DM). These surveys were conducted according to the ethical rules of the National Public Health Institute and the investigations were performed in accordance with the Declaration of Helsinki. At the time the baseline surveys were performed, oral informed consent was obtained from the participants and if not received, the survey data were not collected from these participants (they were considered nonresponders).

Measurements

A self-administered questionnaire was sent to the participants to be completed at home. The questionnaire included questions on medical history, socioeconomic factors, physical activity, smoking habits, and alcohol, coffee, and tea consumption. Education level, measured as the total number of school years, was divided into birth cohort specific tertiles. Physical activity included occupational, commuting, and leisure-time physical activity. A detailed description of the questions is presented elsewhere,¹⁹ and these questions were the same as those used in the studies in the Nordic countries^{19,20} and similar to those used and validated in the Seven Countries study.²¹

The participants reported their occupational physical activity as light, moderate, or active. The daily commuting journey to or from work was grouped into 3 categories: using motorized transportation or not working outside the home (0 minutes of walking or cycling); walking or bicycling 1 to 29 minutes; and walking or bicycling 30 or more minutes. Self-reported leisure-time physical activity was classified as low, moderate, or high. Based on the responses, the participants were classified as never, ex-smokers, or current smokers. Current smokers were categorized into those participants who smoked less than 20 or 20 or more cigarettes per day.

The participants were asked, "How many cups of coffee or tea do you drink per day?" Coffee consumption was categorized into 5 categories: 0 to 2 cups, 3 to 4 cups, 5 to 6 cups, 7 to 9 cups, and 10 or more cups. Tea consumption was categorized as none, 1 to 2 cups, and 3 or more cups because only a few people drank tea. Alcohol consumption was categorized as none, 1 to 100, 101 to 300, or more than 300 g of alcohol per week. Because only a few women drank more than 300 g of alcohol per week, we combined the 2 higher categories in women.

At the study site, specially trained nurses measured height, weight, and blood pressure using the standardized protocol according to the World Health

Organization MONICA project.¹⁷ Blood pressure was measured from the right arm of the participant who was seated for 5 minutes before the measurement was taken using a standard sphygmomanometer. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. In stratified analyses, the participants were classified in 3 categories: normal weight (BMI <25.0), overweight (25 to <30), and obese (≥30).

Diagnosis of DM

We ascertained incident cases of DM from the National Hospital Discharge Register and the Drug Register of the National Social Insurance Institution. These register data were linked to the risk factor survey data with the unique personal identification numbers assigned to every resident of Finland. Antidiabetic drugs prescribed by a physician are free of charge in Finland subject to approval of the application to the National Social Insurance Institution with a case history prepared by the treating physician attached. The physician confirms the diagnosis of DM on the basis of the World Health Organization criteria after 1980²²; before 1980, Finnish national guidelines were applied. All patients receiving free-of-charge medication (either oral antidiabetic agents or insulin) are entered into a register maintained by the National Social Insurance Institution. The National Hospital Discharge Register includes hospitalizations for patients admitted to hospitals with a primary or secondary diagnosis of DM in Finland nationwide. Follow-up of each participant in our present analysis continued until December 31, 1998, or until death.

Statistical Analyses

Sex-specific differences in risk factors based on different levels of coffee consumption were tested using univariate analysis of variance or logistic regression after adjustment for age and study year. The association between coffee consumption at baseline and the risk of type 2 DM was analyzed by using Cox proportional hazards regression

models. Different levels of coffee consumption were included in the models as dummy variables. All analyses were adjusted for age, study year, BMI, systolic blood pressure, education, occupational, commuting, and leisure-time physical activity, alcohol and tea drinking, and smoking. The significance of the trend over different categories of coffee consumption was tested in the same models by giving an ordinal numeric value for each dummy variable. To assess whether the effect differed between the sexes, first-level in-

teractions between coffee consumption and sex were analyzed. Because no statistically significant interactions were found, men and women were combined in subgroup analyses adjusted for sex. Statistical significance was considered to be $P < .05$. All statistical analyses were performed with SPSS version 11.0 (SPSS Inc, Chicago, Ill).

RESULTS

A total of 381 cases of type 2 DM were identified during a mean follow-up of 12 years. In general, older persons were less

likely to drink coffee (TABLE 1). After adjustment for age and study year, higher coffee consumption was associated with higher BMI and cigarette smoking, and lower blood pressure, education level, light occupational physical activity, leisure-time physical activity, tea consumption, and alcohol use.

Coffee Consumption and Risk of Type 2 DM

Age-adjusted and study year-adjusted hazard ratios (HRs) of DM in participants who drank 0 to 2, 3 to 4, 5 to 6, 7

Table 1. Baseline Characteristics Among Men and Women by Volume of Coffee Consumption*

Characteristics	Daily Coffee Consumption, Cups					P Value
	≤2	3-4	5-6	7-9	≥10	
Men						
No. of participants	1251	1732	2185	943	863	
Age, mean (SD), y	49.1 (8.4)	49.0 (8.5)	48.8 (8.4)	47.7 (8.1)	46.3 (7.9)	<.001
Body mass index, mean (SD)†	26.6 (3.7)	27.0 (3.6)	27.1 (3.7)	27.0 (3.7)	27.3 (4.1)	<.001
Blood pressure, mean (SD), mm Hg						
Systolic	143 (19)	143 (19)	144 (19)	144 (18)	143 (23)	.10
Diastolic	89 (12)	88 (11)	88 (11)	87 (12)	86 (12)	<.001
Education, mean (SD), y‡	9.9 (4.2)	9.5 (3.8)	8.9 (3.6)	8.5 (3.2)	8.4 (3.3)	<.001
Physical activity, No. (%)						
Light occupational	573 (46)	737 (43)	852 (39)	307 (33)	279 (32)	<.001
Low leisure time	342 (27)	455 (26)	627 (29)	313 (33)	311 (36)	<.001
Walking or cycling to or from work <30 min	1056 (84)	1472 (85)	1901 (87)	804 (85)	735 (85)	.21
Drinker, No. (%)§						
Tea	847 (68)	766 (44)	539 (25)	124 (13)	91 (11)	<.001
Alcohol	757 (61)	1065 (61)	1283 (59)	533 (57)	482 (56)	.004
Current smoker, No. (%)	211 (17)	379 (22)	655 (30)	370 (39)	481 (56)	<.001
Obesity, No. (%)¶	214 (17)	324 (19)	431 (20)	171 (18)	189 (22)	.008
Women						
No. of participants	1386	2544	2527	819	379	
Age, mean (SD), y	49.3 (8.8)	49.7 (8.5)	49.0 (8.4)	47.1 (8.0)	45.6 (7.6)	<.001
Body mass index, mean (SD)†	26.4 (4.9)	26.4 (4.7)	26.9 (4.8)	27.3 (4.9)	27.5 (5.0)	<.001
Blood pressure, mean (SD), mm Hg						
Systolic	141 (22)	141 (22)	141 (21)	139 (20)	138 (20)	.02
Diastolic	84 (11)	84 (11)	84 (11)	82 (11)	82 (11)	<.001
Education, mean (SD), y‡	10.0 (4.0)	9.6 (3.7)	9.1 (3.4)	8.8 (3.2)	8.6 (3.5)	<.001
Physical activity, No. (%)						
Light occupational	726 (52)	1178 (46)	1036 (41)	300 (37)	128 (34)	<.001
Low leisure time	466 (34)	763 (30)	912 (36)	333 (41)	164 (43)	<.001
Walking or cycling to or from work <30 min	1085 (78)	1890 (74)	1923 (76)	618 (76)	292 (77)	.04
Drinker, No. (%)§						
Tea	920 (66)	1113 (44)	645 (26)	122 (15)	48 (13)	<.001
Alcohol	572 (41)	1051 (41)	905 (36)	302 (37)	145 (38)	.003
Current smoker, No. (%)	93 (7)	229 (9)	346 (14)	148 (18)	147 (39)	<.001
Obesity, No. (%)¶	278 (20)	512 (20)	577 (23)	192 (23)	82 (22)	<.001

*Adjusted for age and study year.

†Calculated as weight in kilograms divided by the square of height in meters.

‡Defined as the total number of school years.

§Defined as drinking 1 or more cups per day of tea or 1 or more grams per week of alcohol.

||Defined as smoking 1 or more cigarettes per day.

¶Defined as body mass index of 30 or higher.

to 9, and 10 or more cups of coffee were 1.00, 0.72 (95% confidence interval [CI], 0.49-1.04), 0.49 (95% CI, 0.32-0.73), 0.47 (95% CI, 0.25-0.87), and 0.26 (95% CI, 0.08-0.85; P for trend = .002) in women, and 1.00, 0.83 (95% CI, 0.54-1.25), 0.88 (95% CI, 0.60-1.30), 0.86 (95% CI, 0.53-1.39), and 0.69 (95% CI, 0.40-1.19; P for trend = .74) in men, respectively (TABLE 2). After further adjustment for BMI, systolic blood pressure, education, occupational, commuting, and leisure-time physical activity, alcohol and tea consumption, and smoking, this inverse association remained highly significant among women (P for trend < .001). In men, a similar trend was observed and the risk of DM was significantly reduced in those participants who drank at least 10 cups of coffee (HR, 0.45; 95% CI, 0.25-0.81). When data for men and women were combined, sex-adjusted and multivariate-adjusted HRs were 1.00, 0.76 (95% CI, 0.57-1.01), 0.54 (95% CI, 0.40-0.73), 0.55 (95% CI, 0.37-0.81), and 0.39 (95% CI, 0.24-0.64; P for trend < .001), respectively.

The risk of DM did not differ between total coffee abstainers and light coffee drinkers (HR, 1.20; 95% CI, 0.74-1.97). Sex-adjusted and multivariate-adjusted (including coffee consumption) HRs of DM by tea consumption of 0, 1 to 2, 3 or more cups were 1.00, 0.81 (95% CI, 0.63-1.05), and 0.98 (95% CI, 0.67-1.42; P for trend = .27), respectively. To avoid the potential bias from subclinical disease, additional analyses were also performed excluding cases of type 2 DM, which occurred during the first 4 years of follow-up ($n=27$). The sex-adjusted and multivariate-adjusted HRs by coffee consumption of 0 to 2, 3 to 4, 5 to 6, 7 to 9, and 10 or more cups did not vary and were 1.00, 0.74 (95% CI, 0.55-1.00), 0.54 (95% CI, 0.39-0.74), 0.54 (95% CI, 0.36-0.81), and 0.41 (95% CI, 0.25-0.68; P for trend < .001).

Coffee Consumption and Risk of Type 2 DM in Subgroup Analyses

Multivariate-adjusted inverse association between coffee consumption and

DM risk was present in participants aged 35 to 49 years (P for trend = .23) and 50 to 64 years (P for trend = .001; TABLE 3). Similarly, the inverse association was observed in nonsmokers (P for trend = .001), in overweight participants (P for trend = .01), and in nondrinkers (P for trend < .001). A nonsignificant association was observed in smokers (P for trend = .07), in healthy weight participants (P for trend = .35), in participants who were obese (P for trend = .05), in alcohol drinkers (P for trend = .25), in filtered coffee drinkers (P for trend = .07), and in pot-boiled coffee drinkers (P for trend = .06). There were 22 incident cases of DM among participants aged 25 to 34 years at baseline who were not included in the analyses. An additional analysis including the youngest age group also did not change the results.

The type of coffee consumption was assessed in the surveys from 1987 and 1992. More than 80% of Finnish coffee consumers used filtered coffee at baseline. There was no interaction be-

Table 2. Development of Type 2 Diabetes by Volume of Coffee Consumption

	Daily Coffee Consumption, Cups					<i>P</i> Value for Trend
	≤2	3-4	5-6	7-9	≥10	
Men						
No. of new cases	41	48	67	28	19	
Person-years	14 191	20 054	25 704	11 480	10 426	
Adjustment for age and study year, HR (95% CI)	1.00	0.83 (0.54-1.25)	0.88 (0.60-1.30)	0.86 (0.53-1.39)	0.69 (0.40-1.19)	.74
Multivariate adjustment, HR (95% CI)*	1.00	0.73 (0.47-1.13)	0.70 (0.45-1.05)	0.67 (0.40-1.12)	0.45 (0.25-0.81)	.12
Women						
No. of new cases	46	68	48	13	3	
Person-years	15 821	30 367	32 036	10 523	4980	
Adjustment for age and study year, HR (95% CI)	1.00	0.72 (0.49-1.04)	0.49 (0.32-0.73)	0.47 (0.25-0.87)	0.26 (0.08-0.85)	.002
Multivariate adjustment, HR (95% CI)*	1.00	0.71 (0.48-1.05)	0.39 (0.25-0.60)	0.39 (0.20-0.74)	0.21 (0.06-0.69)	<.001
Men and Women Combined†						
No. of new cases	87	116	115	41	22	
Person-years	30 112	50 421	57 740	22 003	15 406	
Adjustment for age and study year, HR (95% CI)	1.00	0.79 (0.59-1.04)	0.67 (0.50-0.88)	0.66 (0.46-0.96)	0.53 (0.33-0.85)	.02
Multivariate adjustment, HR (95% CI)*	1.00	0.76 (0.57-1.01)	0.54 (0.40-0.73)	0.55 (0.37-0.81)	0.39 (0.24-0.64)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio.

*Adjusted for age, study year, body mass index, systolic blood pressure, education, occupational physical activity (light, moderate, and active), walking or cycling to or from work (0, 1-29, and ≥30 min/d), leisure time physical activity (low, moderate, and high), cigarette smoking (never, past, and current smoking of 1-19 or ≥20 cigarettes/d), alcohol consumption (0, 1-100, 101-300, and >300 g/wk), and tea consumption (none, 1-2, and ≥3 cups/d).

†Also adjusted for sex.

tween the type of coffee and the amount of coffee for the risk of type 2 DM ($\chi^2_1 = 2.63$, 0.85, and 2.13 for men, women, and for men and women combined, respectively; all $P > .10$). Men and women who drank pot-boiled coffee without filtering showed a similar inverse trend in risk of type 2 DM vs participants who drank filtered coffee (Table 3). However, men who drank pot-boiled coffee showed a 2.9 times higher risk for development of DM (HR,

2.86; 95% CI, 1.76-4.63) compared with men who drank filtered coffee after multivariate adjustment for risk factors of DM, including the amount of coffee consumed (TABLE 4). This association was also observed among men and women combined.

COMMENT

This study revealed unequivocal evidence for an inverse and graded association between coffee consumption

and type 2 DM independent of other risk factors for type 2 DM. Because the Finnish population drinks more coffee than other populations,¹⁵ we had power to determine the risk of DM at high levels of coffee consumption. The significant inverse association between coffee consumption and the risk of type 2 DM was found in both sexes.

In a previous study among the Finnish population,²³ no association between the coffee consumption and in-

Table 3. Development of Type 2 Diabetes by Volume of Coffee Consumption Among Various Subpopulations*

Hazard Ratio (95% Confidence Interval)	Daily Coffee Consumption, Cups					P Value for Trend
	≤2	3-4	5-6	7-9	≥10	
Age, y						
35-49	1.00	0.65 (0.37-1.13)	0.63 (0.37-1.11)	0.57 (0.29-1.15)	0.42 (0.20-0.91)	.23
50-64	1.00	0.82 (0.59-1.16)	0.53 (0.37-0.76)	0.57 (0.35-0.92)	0.38 (0.20-0.74)	.001
Smoking						
Never	1.00	0.77 (0.53-1.12)	0.44 (0.29-0.66)	0.41 (0.22-0.76)	0.42 (0.18-1.00)	.001
Ever or current	1.00	0.71 (0.45-1.13)	0.69 (0.44-1.09)	0.71 (0.41-1.22)	0.39 (0.21-0.73)	.07
Body mass index†						
<25	1.00	0.53 (0.19-1.45)	0.65 (0.25-1.66)	0.36 (0.09-1.48)	0.15 (0.02-1.29)	.35
25-29.9	1.00	0.74 (0.46-1.18)	0.48 (0.29-0.80)	0.53 (0.28-1.01)	0.26 (0.10-0.68)	.01
≥30	1.00	0.86 (0.58-1.28)	0.59 (0.39-0.88)	0.59 (0.35-1.01)	0.56 (0.31-1.02)	.05
Alcohol						
None	1.00	0.79 (0.55-1.13)	0.46 (0.32-0.68)	0.40 (0.23-0.70)	0.45 (0.25-0.83)	<.001
Drinker	1.00	0.79 (0.47-1.32)	0.78 (0.47-1.32)	0.97 (0.53-1.78)	0.38 (0.16-0.93)	.25
Type of coffee‡						
Filtered	1.00	0.63 (0.34-1.16)	0.51 (0.27-0.96)	0.47 (0.19-1.17)	0.15 (0.03-0.66)	.07
Pot-boiled without filter	1.00	0.90 (0.40-2.01)	0.39 (0.17-0.90)	0.48 (0.18-1.28)	0.33 (0.09-1.18)	.06

*Adjusted for age, study year, body mass index, systolic blood pressure, education, occupational physical activity (light, moderate, and active), walking or cycling to or from work (0, 1-29, and ≥30 min/d), leisure time physical activity (low, moderate, and high), cigarette smoking (never, past, and current smoking of 1-19 or ≥20 cigarettes/d), alcohol consumption (0, 1-100, 101-300, and >300 g/wk), tea consumption (none, 1-2, and ≥3 cups/d), and sex.

†Calculated as weight in kilograms divided by the square of height in meters.

‡This analysis only includes surveys conducted from 1987 and 1992.

Table 4. Development of Type 2 Diabetes by Different Type of Coffee Consumption According to Sex and Age*

	No. of New Diabetes Cases		Person-Years		Hazard Ratio (95% Confidence Interval)	
	Filtered Coffee	Pot-Boiled Coffee Without Filter	Filtered Coffee	Pot-Boiled Coffee Without Filter	Filtered Coffee	Pot-Boiled Coffee Without Filter
Men	40	36	25 410	6915	1.00	2.86 (1.76-4.63)
Age, y						
35-49	17	11	16 001	2923	1.00	3.89 (1.65-9.21)
50-64	23	25	9409	3992	1.00	2.72 (1.49-4.96)
Women	38	26	29 462	7943	1.00	1.30 (0.76-2.24)
Age, y						
35-49	6	4	18 032	3067	1.00	2.11 (0.45-9.99)
50-64	32	22	11 430	4876	1.00	1.29 (0.72-2.33)
Men and women combined†	78	62	54 871	14 858	1.00	2.04 (1.43-2.92)
Age, y						
35-49	23	15	34 034	5990	1.00	2.71 (1.33-5.53)
50-64	55	47	20 837	8868	1.00	1.87 (1.24-2.82)

*Adjusted for age, study year, body mass index, systolic blood pressure, education, occupational physical activity (light, moderate, and active), walking or cycling to or from work (0, 1-29, and ≥30 min/d), leisure time physical activity (low, moderate, and high), cigarette smoking (never, past, and current smoking of 1-19 or ≥20 cigarettes/d), alcohol consumption (0, 1-100, 101-300, and >300 g/wk), tea consumption (none, 1-2, and ≥3 cups/d), and coffee consumption (0-2, 3-4, 5-6, 7-9, ≥10 cups/d). This analysis only includes surveys conducted from 1987 and 1992.

†Also adjusted for sex.

cidence of type 2 DM was observed. One possible explanation for the different results is that at the time of their baseline survey, in 1973 and 1977, most Finnish individuals drank pot-boiled coffee. At the end of the 1960s, 75% of the Finnish population drank boiled coffee²⁴ but by 1987 this proportion had decreased to 24%, although 69% drank filtered coffee.²⁵ However, although we were able to determine the type of the coffee consumed in our surveys in 1987 and 1992, there was no interaction effect between type of coffee and amount of coffee on the risk of type 2 DM in either men or women. Nevertheless, there was a significant, almost 3-fold, increase in the risk of diabetes among men who drank pot-boiled coffee compared with men who drank filtered coffee.

Van Dam and Feskens¹² investigated the association between coffee consumption and risk of type 2 DM in a prospective study. They also obtained similar inverse associations between coffee consumption and the risk of type 2 DM, similar to our results. Recently, data from large US cohorts of men and women also showed that long-term coffee consumption and total caffeine intake were significantly associated with a reduced risk of type 2 DM.²⁶ A Japanese cross-sectional study comprising 1916 men and 2704 women aged 40 to 50 years found that coffee intake or caffeine intake from coffee was inversely associated with the prevalence of fasting hyperglycemia (fasting plasma glucose, ≥ 110 mg/dL [≥ 6.1 mmol/L]).²⁷

Although the biological mechanism behind the inverse association between coffee consumption and the risk of DM is unknown, several putative mechanisms can be proposed. The protective effect of coffee may be due to the inhibition of glucose-6-phosphatase activity by chlorogenic acid.²⁸ Hepatic glucose-6-phosphatase may be a key control site in the homeostatic regulation of blood glucose concentration,^{29,30} and glucose-6-phosphatase is widely held to be a significant factor in the abnormally high rates of hepatic glucose pro-

duction observed in the diabetic state. Reduced glucose-6-phosphatase hydrolysis or its inhibition may reduce plasma glucose output leading to reduced plasma glucose concentration.²⁸ Hypoglycemic effect of chlorogenic acid has been presented in streptozotocin-induced diabetic rats as well.³¹ Johnston et al³² also suggest that chlorogenic acid might have an antagonistic effect on glucose transport. It is possible that habitual differences between the coffee consumers and different manufacturing process of coffee from green seeds may also result in different effects. For instance, roasting and some other manipulation of processing coffee will partly destroy chlorogenic acid and may oxidize some other compounds to form new compounds,³³ leading subsequently to differential metabolic effects.

In addition to the inhibitory effects of chlorogenic acid on glucose-6-phosphatase affecting glucose regulation at hepatic stage, it has also been reported to inhibit glucose transporters (sodium-dependent glucose transporter) at the intestinal stage.³⁴ Coffee may also influence the secretion of gastrointestinal peptides such as glucagon-like peptide 1 and gastric inhibitory polypeptide, both of which are known for their glucose lowering effects.^{35,36}

Coffee also contains magnesium, approximately 11 mg per 100 g of dry coffee. This component is another possible factor, which may result in positive effects on glucose tolerance and prevention of type 2 DM. There is a significant inverse correlation between serum magnesium and the incidence of type 2 DM; both serum and ionized magnesium were consistently found to be decreased in patients with DM.³⁷⁻⁴⁰

It is well known that caffeine and theophylline are strong stimulants of pancreatic beta cells.⁴¹ Stimulation of insulin secretion may be beneficial in people at risk of type 2 DM who usually have impaired insulin secretion.¹¹ In addition, caffeine may increase insulin sensitivity.⁴² It has also been suggested that the thermogenic effect of caffeine may overcome the energy imbalance accom-

panied by unfavorable lifestyle and improve glucose homeostasis.

The inverse association between coffee consumption and the risk of DM tended to be stronger in women than in men, although the sex-interaction was not statistically significant. Previous studies have revealed that caffeine may be positively associated with plasma estrogen, plasma estradiol, and sex hormone-binding globulin levels and inversely related with testosterone among postmenopausal women.^{5,6} In addition phytoestrogens may have beneficial effects in patients with DM. Phytoestrogens content of coffee and effects of caffeine on hormonal level may explain the effects of coffee on the risk of diabetes in women. Nevertheless, in most populations, the prevalence of type 2 DM is lower in women than in men at premenopausal age.^{43,44}

A limitation of our study was that a glucose tolerance test was not performed in the baseline and follow-up surveys. Therefore, we could have missed some cases of asymptomatic and diet-treated diabetes, although the clinical diagnosis of diabetes from the hospital discharge register may have in part avoided this potential underdiagnosis. Another source of misclassification may be that we used self-report for data on coffee intake. However, the misclassification of exposure is most probably not systematically related to the outcome and vice versa. Therefore, it should not cause biased results but may only weaken the observed association. Finally, we cannot completely exclude the effects of residual confounding due to measurement error in the assessment of confounding factors and unmeasured factors such as diet (whole grain consumption, intake of fiber, saturated and polyunsaturated fat, glyce-mic load of the diet, and total energy intake). The Finnish population typically drink their coffee without milk or only add a very small volume of milk.

In conclusion, we found a strong and graded inverse relationship between coffee consumption and the risk of type 2 DM among Finnish men and women, a population with the highest coffee

consumption in the world. The mechanisms or process by which coffee contents may exert their beneficial effects on DM are nevertheless unclear. Several components of coffee may affect glucose regulation, such as chlorogenic acid on glucose-6-phosphatase, antioxidant activity of polyphenols on α -glucosidase, caffeine on insulin secretion on pancreatic beta cells, cumulative effects of phytoestrogens, and magnesium, which are suggested as the

biological basis of our findings. Expanded investigation is required to explore these mechanisms, including randomized controlled trials.

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Study concept and design: Tuomilehto, Hu, Jousilahti. **Acquisition of data:** Tuomilehto, Hu.

Analysis and interpretation of data: Tuomilehto, Hu, Bidel, Lindstrom.

Drafting of the manuscript: Tuomilehto, Hu, Bidel, Lindstrom, Jousilahti.

Critical revision of the manuscript for important intellectual content: Hu, Bidel, Jousilahti.

Statistical expertise: Tuomilehto, Hu, Lindstrom.

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