Caffeinated and Decaffeinated Coffee Consumption and Risk of Type 2 Diabetes: A Systematic Review and a Dose-Response Meta-analysis

Ming Ding,[1] Shilpa N. Bhupathiraju,[1] Mu Chen,[1] Rob M. van Dam,[1,2] and Frank B. Hu[1,3,4]

OBJECTIVE

Previous meta-analyses identified an inverse association of coffee consumption with the risk of type 2 diabetes. However, an updated meta-analysis is needed because new studies comparing the trends of association for caffeinated and decaffeinated coffee have since been published.

RESEARCH DESIGN AND METHODS

PubMed and Embase were searched for cohort or nested case-control studies that assessed the relationship of coffee consumption and risk of type 2 diabetes from 1966 to February 2013. A restricted cubic spline random-effects model was used.

RESULTS

Twenty-eight prospective studies were included in the analysis, with 1,109,272 study participants and 45,335 cases of type 2 diabetes. The follow-up duration ranged from 10 months to 20 years. Compared with no or rare coffee consumption, the relative risk (RR; 95% CI) for diabetes was 0.92 (0.90–0.94), 0.85 (0.82–0.88), 0.79 (0.75–0.83), 0.75 (0.71–0.80), 0.71 (0.65–0.76), and 0.67 (0.61–0.74) for 1–6 cups/day, respectively. The RR of diabetes for a 1 cup/day increase was 0.91 (0.89–0.94) for caffeinated coffee consumption and 0.94 (0.91–0.98) for decaffeinated coffee consumption (*P* for difference = 0.17).

CONCLUSIONS

Coffee consumption was inversely associated with the risk of type 2 diabetes in a dose-response manner. Both caffeinated and decaffeinated coffee was associated with reduced diabetes risk.

Diabetes Care 2014;37:569–586 | DOI: 10.2337/dc13-1203

META-ANALYSIS

Type 2 diabetes is a chronic disease with high rates of morbidity and mortality. The worldwide prevalence of type 2 diabetes is increasing, and the global number of people with diabetes is estimated to reach 366 million by the year 2030 (1). The risk of blindness, renal disease, and amputation among those with type 2 diabetes is 20 to 40 times higher than that of people without diabetes. Furthermore, those with type 2 diabetes have a two to five times higher risk of myocardial infarction and two to three times higher risk of stroke (2). Given its significant burden, identifying modifiable lifestyle factors is imperative for the prevention of diabetes.

[1]*Department of Nutrition, Harvard School of Public Health, Boston, MA*
[2]*Saw Swee Hock School of Public Health and Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore*
[3]*Department of Epidemiology, Harvard School of Public Health, Boston, MA*
[4]*Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA*

Corresponding author: Frank B. Hu, nhbfh@channing.harvard.edu.

Received 22 May 2013 and accepted 27 September 2013.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-1203/-/DC1.

Coffee is one of the most widely consumed beverages around the world; thus, investigating its association with various diseases has important public health implications. An inverse association between coffee consumption and risk of type 2 diabetes was first reported in a Dutch population (3). In subsequent years, this finding has been confirmed in most (4–10) but not all (11–13) studies. Two previous meta-analyses of coffee consumption and risk of type 2 diabetes have been published. van Dam and Hu (14) included nine cohort studies and reported a lower risk of type 2 diabetes for high coffee consumption compared with no coffee consumption with little between-study heterogeneity. Huxley et al. (15) included 18 prospective studies and found an inverse monotonous association between the number of cups of coffee consumed and diabetes risk, but they double-counted data from the same cohort (16,17). Since the publication of these meta-analyses, 10 additional prospective studies on the association between coffee consumption and diabetes have been published (6,8,10,12,18–23).

A key issue that remains to be resolved is whether consumption of caffeinated and decaffeinated coffee is similarly associated with the risk of type 2 diabetes. Such results would provide insight into the role of caffeine in the putative relationship between coffee consumption and diabetes risk. The meta-analysis by Huxley et al. (15) included only six studies on decaffeinated coffee, and estimates were less precise than for caffeinated coffee because of lower consumption levels. Eight subsequent prospective studies evaluated the association with decaffeinated coffee, approximately doubling the amount of data on decaffeinated coffee and diabetes risk (8,10,12,18–21,24). We therefore performed an updated systematic review and a dose-response meta-analysis of all available data on the association of both caffeinated and decaffeinated coffee consumption with the risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS

Search Strategy and Selection Criteria

We searched the PubMed and Embase databases for prospective cohort studies or nested case-control studies that evaluated the association between coffee consumption and risk of type 2 diabetes between January 1966 and February 2013. The computer-based searches included the key words *coffee* and *diabetes*. No Medical Subject Headings terms were used because of the clear definitions of coffee and diabetes. Reference lists of retrieved articles were manually scanned for all relevant additional studies and review articles. We restricted the search to studies on humans and written in English.

Study Selection

Studies included in this meta-analysis met the following criteria: *1*) the study design was prospective cohort or nested case-control; *2*) the articles were published in English; *3*) the exposure was categorized coffee consumption, including total coffee, caffeinated coffee, or decaffeinated coffee; and *4*) the outcome was risk of type 2 diabetes. Studies were excluded if they were cross-sectional in design and if information on dose-response modeling was inadequate, including the number of participants and cases, relative risk (RR) and SE for the estimate, and dose of coffee consumption in each exposure category.

Data Extraction and Quality Assessment

One author (M.D.) assessed study eligibility and extracted the data, and another (M.C.) independently double-checked the available data. The following data were extracted from each study: first author's name, year of publication, geographical location, follow-up time, sex, age, number of type 2 diabetes events, number of participants, categories of coffee consumption, type of assessment of type 2 diabetes, covariates adjusted for in the multivariable analysis, and RRs for all categories of coffee consumption. If studies based on the same cohort were published several times, only the most recent article was selected. If a study only reported caffeinated coffee consumption instead of total coffee consumption, caffeinated coffee consumption was also included in the total coffee consumption analysis. The Newcastle-Ottawa quality assessment scale (NOS) was used to evaluate the study quality of the included articles. The scale ranges from 0 to 9 points, with higher points indicating higher study quality. Specifically, loss to follow-up was assessed as an item in the NOS for individual studies. In the present meta-analysis, we assumed that loss to follow-up was random.

To perform a dose-response meta-analysis, we assigned the median or mean coffee consumption in each category of consumption to the corresponding RR for each study. If the mean or median consumption per category was not reported, the midpoint of the upper and lower boundaries in each category was assigned as the mean consumption. If the upper boundary for the highest category was not provided, the assigned mean value was 25% higher than the lower boundary of that category. If the lower boundary for the lowest category was not provided, the assigned mean value was one-half of the upper boundary of that category.

Data Synthesis and Analysis

To analyze the trend of coffee consumption and risk of type 2 diabetes, we used both semiparametric and parametric methods. For the semiparametric method, four coffee consumption groups were generated, namely lowest, third highest, second highest, and highest. For each included study, the lowest and the highest coffee consumption categories corresponded to the lowest and highest groups, respectively. For studies with four exposure categories, the second and third categories corresponded to the second and third highest groups, respectively. For studies with three exposure categories, the middle category corresponded to either the second or the third highest group, whichever median coffee consumption amount was most similar. If the study had more than four exposure categories, two consumption groups, other than the lowest and highest, were chosen on the basis of their similarity of the amount of coffee consumption in that category to the second and third highest groups. For each group, a random-effects model was used to pool the RR of type 2 diabetes (25). Statistical

heterogeneity in each group was assessed by Cochrane *Q* test, with $P < 0.1$ indicating significant between-study heterogeneity.

For the parametric method, a random-effects dose-response meta-analysis was performed (26). The number of cases and participants in each coffee consumption category was extracted to estimate the covariance of the RR in each study. Together with the observed adjusted variance of the RR, we estimated the variance/covariance matrix of the data. The weight of each study was calculated as the inverse of the variance/covariance matrix. We used generalized least squares models with maximum likelihood method to estimate the coefficients for each study, and we fit a random-effects generalized linear model. Additionally, we tested for potential nonlinearity in the association between coffee consumption and type 2 diabetes by a random-effects restricted cubic spline model with three knots. Stata commands GLST for model fitting and LINCOME for estimating effect were used for the fitted model.

Stratified analyses were performed for study location, sex, diabetes assessment method, and type of coffee (i.e., caffeinated, decaffeinated), and the subgroup difference was tested in the association of coffee consumption with risk of type 2 diabetes. We assessed the potential for publication bias through a formal Egger regression symmetry test. All analyses were conducted with Stata 10 (StataCorp, College Station, TX) statistical software.

RESULTS

Characteristics of Studies

The initial search identified 800 potentially relevant citations. After screening titles and abstracts, we identified 39 studies for further evaluation (Fig. 1). We excluded six studies with a cross-sectional study design, three that were abstracts of conference posters, and two that were repeated in the same cohort. The results of the remaining 28 studies, comprising 1,109,272 study participants and 45,335 cases of type 2 diabetes, were included in the meta-analysis (3–13,17–24,27–35). Characteristics of all 28 studies were shown in Table 1. The duration of follow-up for incident type 2 diabetes ranged from 10 months to 20 years, with a median follow-up of 11 years. Thirteen studies were conducted in the U.S., 11 in Europe, and 4 in Asia. In nine studies, type 2 diabetes was self-reported; the outcome of six studies was assessed by means of a glucose tolerance test, and the outcome of the other studies was confirmed by either medical records or national registries. One study was a nested case-control design, and the remaining 27 were prospective cohort studies. Ten studies assessed both caffeinated and decaffeinated coffee, and only one each assessed caffeinated coffee and decaffeinated coffee. Fifteen studies did not distinguish caffeinated coffee and decaffeinated coffee, and seven assessed caffeine consumption. The mean NOS score was 7 (of a possible 9 points), suggesting a high quality of the studies included in the meta-analysis. The points were mainly lost in exposure assessment and adequacy of follow-up of cohorts: Six studies assessed coffee consumption by structured interview, and five addressed the percentage of loss to follow-up.

Total Coffee Consumption and Risk of Type 2 Diabetes

Figure 2 shows the results of different levels of total coffee consumption

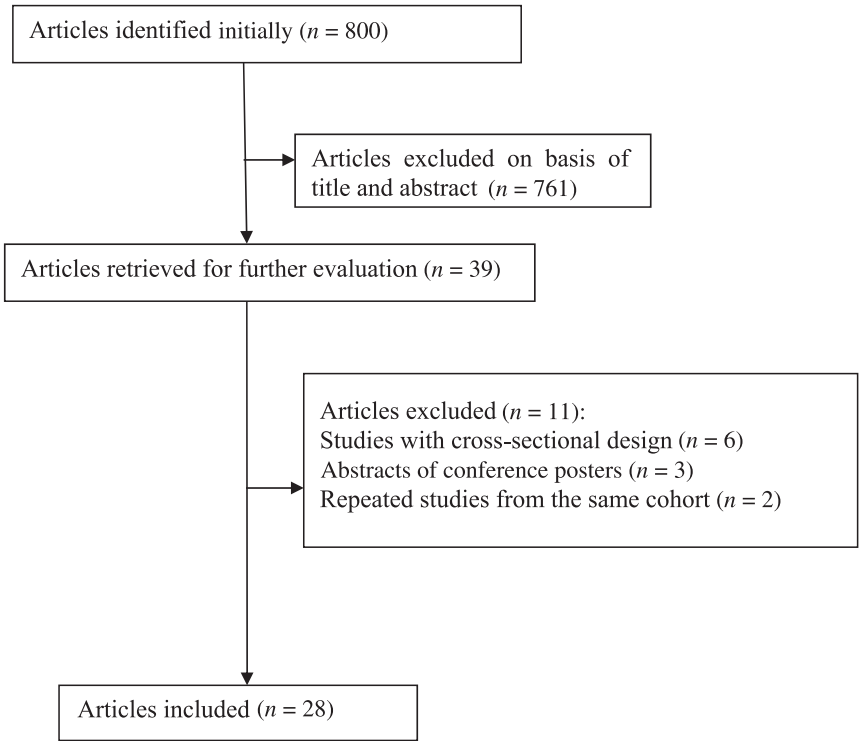

Figure 1—Study selection process of the identified articles.

Table 1—Basic characteristics of the included studies

Authors	Country	Sex	Age at baseline (year)	Follow-up (year)	*N*	*n*	Type 2 diabetes assessment	Coffee exposure (cups/day)	RR (95% CI)	Confounding adjustments	NOS (0–9 points)
van Dam and Feskens 2002 (3)	Europe	Both	30–60	1–13	17,111	306	Self-reported	Total coffee		Educational level, leisure	6
								≤2	1.00 (1.00–1.00)	time physical activity,	
								3–4	0.79 (0.57–1.10)	occupational physical	
								5–6	0.73 (0.53–1.01)	activity, alcohol	
								≥7	0.50 (0.35–0.72)	consumption, cigarette	
										smoking, history of	
										cardiovascular disease,	
										known hypertension,	
										and known	
										hypercholesterolemia	
Reunanen et al. 2003 (11)	Europe	Both	20–98	304,227[a]	19,518	855	Confirmed cases	Total coffee		Age, sex, BMI, smoking,	8
								≤2	1.00 (1.00–1.00)	and leisure time	
								3–4	1.01 (0.81–1.27)	physical activity	
								5–6	0.98 (0.79–1.21)		
								≥7	0.92 (0.73–1.16)		
Carlsson et al. 2004 (7)	Europe	Both	30–60	20	10,652	408	Confirmed cases	Total coffee		Age, sex, BMI, education,	6
								≤2	1.00 (1.00–1.00)	leisure time physical	
								3–4	0.70 (0.48–1.01)	activity, alcohol	
								5–6	0.71 (0.50–1.01)	consumption, and	
								≥7	0.65 (0.44–0.96)	smoking	
Rosengren et al. 2004 (27)	Europe	F	39–65	18	1,361	74	Confirmed cases	Total coffee		Age, smoking, low	8
								≤2	1.00 (1.00–1.00)	physical activity,	
								3–4	0.56 (0.32–0.98)	education, BMI, and	
								5–6	0.45 (0.23–0.90)	serum cholesterol and	
								>6	0.57 (0.26–1.29)	triglycerides	
Salazar-Martinez et al. 2004 (4)	U.S.	Both	M 40–75	M 12	41,934	1,333	Confirmed	Caffeine (men)[b]		Age; total caloric intake;	6
			F 30–55	F 18			self-report	13	1.00 (1.00–1.00)	family history of	
								74	1.06 (0.89–1.26)	diabetes; alcohol	
								172	1. 01 (0.85–1.20)	consumption; smoking	
								323	0.94 (0.78–1.12)	status; menopausal	
								566	0.80 (0.66–0.97)	status and	
					M 84,276			Caffeine (women)[b]		postmenopausal	
					F 4,085			69	1.00 (1.00–1.00)	hormone use; intakes	
								193	1.02 (0.93–1.11)	of glycemic load, *trans*	
								328	0.90 (0.82–0.99)	fat, polyunsaturated	
								432	0.85 (0.77–0.94)	fatty acid, cereal fiber,	
								708	0.70 (0.63–0.79)	and magnesium; BMI;	
										and physical activity	

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Table 1—Continued

Authors	Country	Sex	Age at baseline (year)	Follow-up (year)	*N*	*n*	Type 2 diabetes assessment	Coffee exposure (cups/day)	RR (95% CI)	Confounding adjustments	NOS (0–9 points)
van Dam et al. 2004 (28)	Europe	Both	50–74	6.4	1,312	128	OGTT	Total coffee		Age; sex; BMI; waist-hip ratio; physical activity; alcohol consumption; cigarette smoking; history of cardiovascular disease; use of antihypertensive medication; and intake of fiber, total energy, saturated fat, and polyunsaturated fat	8
								≤2	1.00 (1.00–1.00)		
								3–4	0.94 (0.56–1.55)		
								5–6	0.92 (0.53–1.61)		
								≥7	0.69 (0.31–1.51)		
Greenberg et al. 2005 (35)	U.S.	Both	32–88	8.4	7,006	170	Self-reported	Caffeinated coffee		Per capita income, educational level, race, sex, physical activity, smoking status, alcohol consumption, BMI, age, and type of diet; variables for consumption of caffeine and all three beverages were in the regression model simultaneously	6
								0	1.00 (1.00–1.00)		
								<2	0.82 (0.55–1.23)		
								24	0.75 (0.50–1.13)		
								≥4	0.37 (0.22–0.64)		
								Decaf. coffee			
								0	1.00 (1.00–1.00)		
								<2	0.62 (0.34–1.11)		
								2–4	0.43 (0.20–0.93)		
								Caffeine[b]			
								75	1.00 (1.00–1.00)		
								225	0.69 (0.42–1.11)		
								375	0.73 (0.38–1.41)		
								525	0.65 (0.30–1.42)		
								750	0.65 (0.24–1.77)		
Iso et al. 2006 (9)	Asia	Both	40–65	5	17,413	444	Self-reported	Total coffee		Family history of diabetes, smoking status, alcohol intake, magnesium intake, hours of walking, hours of exercise, and consumption of other beverages	6
								<2	0.82 (0.55–1.23)		
								2–4	0.75 (0.50–1.13)		
								≥4	0.37 (0.22–0.64)		
								≥3	0.58 (0.37–0.90)		
								Caffeine[b]			
								57	1.00 (1.00–1.00)		
								137	1.00 (0.73–1.37)		
								199	0.98 (0.73–1.33)		
								273	1.00 (0.74–1.37)		
								416	0.67 (0.47–0.95)		

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Table 1—Continued

Authors	Country	Sex	Age at baseline (year)	Follow-up (year)	*N*	*n*	Type 2 diabetes assessment	Coffee exposure (cups/day)	RR (95% CI)	Confounding adjustments	NOS (0–9 points)
Paynter et al. 2006 (29)	U.S.	Both	45–64	9	12,204	1,437	Self-reported	Total coffee (men)		Age, race, education,	8
								0	1.00 (1.00–1.00)	family history of	
								<1	1.02 (0.76–1.38)	diabetes, BMI, waist-	
								1	1.01 (0.76–1.34)	hip ratio, total caloric	
								2–3	0.93 (0.70–1.22)	intake, dietary fiber,	
								≥4	0.69 (0.50–0.96)	smoking, alcohol	
								Total coffee (women)		consumption, leisure	
								0	1.00 (1.00–1.00)	activity, and	
								<1	1.23 (0.93–1.62)	hypertension	
								1	1.06 (0.83–1.36)		
								2–3	0.89 (0.68–1.16)		
								≥4	0.66 (0.45–0.96)		
Pereira et al. 2006 (13)	U.S.	F	Mean 61	11	28,812	1,418	Self-reported	Total coffee		Age, education, baseline	6
								0	1.00 (1.00–1.00)	hypertension, alcohol,	
								<1	0.95 (0.77–1.18)	smoking status,	
								1–3	1.01 (0.85–1.19)	cigarette pack-years,	
								4–5	0.85 (0.69–1.04)	BMI, waist-hip ratio,	
								≥6	0.79 (0.61–1.02)	physical activity,	
								Caffeinated coffee		energy intake, total fat,	
								0	1.00 (1.00–1.00)	Keys score, cereal	
								<1	0.92 (0.76–1.11)	fiber, tea	
								1–3	0.88 (0.70–1.12)	consumption, and	
								4–5	0.89 (0.64–1.23)	soda consumption	
								≥6	1.00 (0.84–1.19)		
								Decaf. coffee			
								0	1.00 (1.00–1.00)		
								<1	0.98 (0.83–1.16)		
								1–3	1.01 (0.84–1.21)		
								4–5	0.59 (0.44–0.80)		
								≥6	0.68 (0.43–1.09)		

Continued on p. 575

Table 1—Continued

Authors	Country	Sex	Age at baseline (year)	Follow-up (year)	*N*	*n*	Type 2 diabetes assessment	Coffee exposure (cups/day)	RR (95% CI)	Confounding adjustments	NOS (0–9 points)
van Dam et al. 2006 (5)	U.S.	F	26–46	20	88,259	1,263	Self-reported	Total coffee		Age; smoking status; BMI;	5
								0	1.00 (1.00–1.00)	physical activity;	
								<1	0.93 (0.80–1.09)	alcohol consumption;	
								1	0.87 (0.73–1.03)	use of hormone	
								2–3	0.58 (0.49–0.68)	replacement therapy;	
								≥4	0.53 (0.41–0.68)	oral contraceptive use;	
								Caffeinated coffee		family history of type 2	
								0	1.00 (1.00–1.00)	diabetes; history of	
								<1	1.00 (0.86–1.17)	hypertension; history of	
								1	0.89 (0.75–1.07)	hypercholesterolemia;	
								2–3	0.62 (0.52–0.74)	consumption of sugar-	
								≥4	0.61 (0.46–0.81)	sweetened soft drinks;	
								Decaf. coffee		consumption of punch;	
								0	1.00 (1.00–1.00)	and quintiles of	
								<1	0.86 (0.74–0.99)	processed meat	
								1	0.87 (0.68–1.11)	consumption, the	
								2–3	0.52 (0.36–0.74)	polyunsaturated-to-	
								Caffeine[b]		saturated fat intake	
								22	1.00 (1.00–1.00)	ratio, total energy	
								93	0.88 (0.75–1.04)	intake, the glycemic	
								180	0.89 (0.75–1.05)	index, and cereal fiber	
								341	0.74 (0.62–0.89)	intake	
								528	0.55 (0.45–0.67)		
Smith et al. 2006 (30)	U.S.	Both	≥50	8	910	84	OGTT	Total coffee		Sex, age, physical activity,	7
								0	1.00 (1.00–1.00)	BMI, smoking, alcohol,	
								1–2	0.66 (0.38–1.14)	hypertension, and	
								3–4	0.53 (0.26–1.08)	baseline fasting plasma	
								≥5	0.60 (0.26–1.40)	glucose	
Adeney et al. 2007 (24)	U.S.	F	Mean 31	10 mo	1,744	75	OGTT	Caffeinated coffee		Maternal age, smoking	6
								None	1.00 (1.00–1.00)	during pregnancy,	
								Moderate	0.58 (0.33–1.02)	regular alcohol use	
								High	0.76 (0.40–1.46)	before pregnancy,	
										maternal race,	
										prepregnancy BMI,	
										chronic hypertension,	
										and average daily	
										caloric intake	

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Table 1—Continued

Authors	Country	Sex	Age at baseline (year)	Follow-up (year)	*N*	*n*	Type 2 diabetes assessment	Coffee exposure (cups/day)	RR (95% CI)	Confounding adjustments	NOS (0–9 points)
Fuhrman et al. 2009 (31)	U.S.	M	35–79	2.6	4,685	519	OGTT	Total coffee[c]		Age, BMI, smoking status, family history of diabetes, education, alcohol intake, index of physical activity, and milk and sugar intake	7
								1–2	1.00 (1.00–1.00)		
								3	0.79 (0.69–1.00)		
								≥4	0.75 (0.58–0.97)		
Hamer et al. 2008 (32)	Europe	Both	35–55	11.7	5,823	387	OGTT	Total coffee		Five-year age categories, sex, ethnicity, employment grade, plus BMI category, waist-hip ratio, smoking, sex-specific alcohol intake tertiles, physical activity category, family history of diabetes, hypertension, cholesterol, total energy intake, diet pattern, and mutual adjustment for all beverage type	8
								0	1.00 (1.00–1.00)		
								≤1	0.83 (0.60–1.14)		
								2–3	0.85 (0.60–1.20)		
								>3	0.80 (0.54–1.18)		
								Decaf. coffee			
								0	1.00 (1.00–1.00)		
								≤1	1.13 (0.87–1.47)		
						;		2–3	0.87 (0.58–1.30)		
								>3	0.65 (0.36–1.16)		
Odegaard et al. 2008 (33)	Asia	Both	45–74	5.7	36,908	1,889	Confirmed self-report	Total coffee		Age at recruitment, year of interview, sex, dialect, education, hypertension, smoking status, alcohol consumption, BMI, physical activity, dietary variables, and magnesium	9
								<1	1.00 (1.00–1.00)		
								1	0.94 (0.81–1.09)		
								2–3	0.83 (0.68–1.01)		
								≥4	0.70 (0.53–0.93)		
Bidel et al. 2008 (17)	Europe	Both	35–74	5–20	21,826	862	Confirmed cases	Total coffee		Age, BMI, alcohol consumption, smoking, physical activity, and glucose tolerance test	7
								0–2	1.00 (1.00–1.00)		
								3–4	0.85 (0.70–1.04)		
								5–6	0.78 (0.65–0.95)		
								≥7	0.64 (0.51–0.80)		

Continued on p. 577

Table 1—Continued

Authors	Country	Sex	Age at baseline (year)	Follow-up (year)	*N*	*n*	Type 2 diabetes assessment	Coffee exposure (cups/day)	RR (95% CI)	Confounding adjustments	NOS (0–9 points)
Kato et al. 2009 (34)	Asia	Both	40–69	10	55,826	2,694	Confirmed self-report	Total coffee (men)		Age, BMI, smoking status, alcohol drinking, family history of diabetes, physical activity, history of hypertension, perceived mental stress, levels of type A behavior, and hours of sleep	8
								0	1.00 (1.00–1.00)		
								1–2[d]	0.93 (0.80–1.08)		
								3–4[d]	0.84 (0.71–1.01)		
								1–2	0.84 (0.73–0.97)		
								3–4	0.83 (0.68–1.02)		
								≥5	0.82 (0.60–1.11)		
								Total coffee (women)			
								0	1.00 (1.00–1.00)		
								1–2[d]	0.90 (0.76–1.06)		
								3–4[d]	0.95 (0.77–1.17)		
								1–2	0.81 (0.69–0.96)		
								3–4	0.62 (0.45–0.84)		
								≥5	0.40 (0.20–0.78)		
Oba et al. 2010 (10)	Asia	Both	<70	10	13,540	453	Self-reported	Caffeinated coffee (men)		Age, smoking status, BMI, physical activity, length of education in years, alcohol consumption, total energy intake, fat intake, and women's menopausal status to examine beverage and chocolate snacks	6
								0	1.00 (1.00–1.00)		
								1/mo to 6/wk	0.69 (0.50–0.97)		
								≥1	0.69 (0.49–0.98)		
								Caffeinated coffee (women)			
								0	1.00 (1.00–1.00)		
								1/mo to 6/wk	1.08 (0.74–1.60)		
								≥1	0.70 (0.44–1.12)		
								Decaf. coffee (men)			
								0	1.00 (1.00–1.00)		
								≥1[e]	1.09 (0.73–1.61)		
								Decaf. coffee (women)			
								0	1.00 (1.00–1.00)		
								≥1[e]	0.66 (0.36–1.23)		
								Caffeine (men)[b]			
								42	1.00 (1.00–1.00)		
								79	0.81 (0.60–1.10)		
								218	0.95 (0.69–1.30)		
								Caffeine (women)[b]			
								60	1.00 (1.00–1.00)		
								97	1.26 (0.88–1.82)		
								226	0.95 (0.63–1.43)		

Continued on p. 578

Table 1—Continued

Authors	Country	Sex	Age at baseline (year)	Follow-up (year)	*N*	*n*	Type 2 diabetes assessment	Coffee exposure (cups/day)	RR (95% CI)	Confounding adjustments	NOS (0–9 points)
Zhang et al. 2011 (23)	U.S.	Both	45–74	7.6	1,141	188	OGTT	Total coffee		Age, sex, smoking, alcohol	7
								0	1.00 (1.00–1.00)	use, family history of	
								1–2	0.93 (0.55–1.57)	diabetes, physical	
								3–4	0.87 (0.53–1.44)	activity, and BMI	
								5–7	0.72 (0.43–1.23)		
								8–11	0.78 (0.44–1.37)		
								≥12	0.33 (0.13–0.81)		
van Dieren et al. 2009 (22)	Europe	Both	49–70	10	40,011	918	Confirmed	Total coffee		Cohort, sex, age, BMI,	6
							self-report	0–1	1.00 (1.00–1.00)	highest education,	
								1–2	0.88 (0.69–1.11)	physical activity, family	
								2–3	0.94 (0.75–1.17)	history of diabetes,	
								3–4	0.75 (0.60–0.92)	smoking, alcohol	
								4–6	0.74 (0.61–0.91)	intake, energy intake,	
								>6	0.84 (0.65–1.08)	energy-adjusted	
										saturated fat intake,	
										energy-adjusted fiber	
										intake, energy-	
										adjusted vitamin C	
										intake,	
										hypercholesterolemia,	
										and hypertension	
Boggs et al. 2010 (21)	U.S.	F	30–69	12	46,906	3,671	Self-reported	Caffeinated coffee		Age, questionnaire cycle,	6
								0[e]	1.00 (1.00–1.00)	energy intake,	
								1 cup/mo to		education, family	
								<1 cup/day	0.94 (0.86–1.04)	history of diabetes,	
								1	0.90 (0.81–1.01)	vigorous activity,	
								2–3	0.82 (0.72–0.93)	smoking, glycemic	
								≥4	0.83 (0.69–1.01)	index, cereal fiber,	
								Decaf. coffee		sugar-sweetened soft	
								0[e]	1.00 (1.00–1.00)	drinks, BMI, history of	
								1 cup/mo to		hypertension, and	
								<1 cup/day	1.04 (0.93–1.16)	history of high	
								1	1.07 (0.92–1.25)	cholesterol	
								2–3	1.01 (0.83–1.24)		
								≥4	1.10 (0.81–1.49)		

Continued on p. 579

Table 1—Continued

Authors	Country	Sex	Age at baseline (year)	Follow-up (year)	*N*	*n*	Type 2 diabetes assessment	Coffee exposure (cups/day)	RR (95% CI)	Confounding adjustments	NOS (0–9 points)
Sartorelli et al. 2010 (20)	Europe	F	41–72	11	69,532	1,415	Confirmed self-report	Total coffee		Age, history of diabetes in ascendants, quartiles of physical activity level, quartiles of alcohol intake, educational level, hypercholesterolemia, hypertension, smoking, energy-adjusted fiber and saturated fat, total energy without alcohol, menopausal status, hormone replacement therapy as a time-dependent variable, use of oral contraceptives at baseline, and time-dependent BMI	7
								0	1.00 (1.00–1.00)		
								≤1	1.04 (0.87–1.26)		
								1.1–2.9	0.86 (0.73–1.02)		
								≥3	0.73 (0.61–0.87)		
								Caffeinated coffee			
								0	1.00 (1.00–1.00)		
								≤1	0.85 (0.74–0.97)		
								>1	0.67 (0.57–0.78)		
								Decaf. coffee			
								0	1.00 (1.00–1.00)		
								≤1	0.69 (0.51–0.93)		
								>1	0.67 (0.47–0.95)		
								Caffeine[b]			
								48	1.00 (1.00–1.00)		
								126	0.84 (0.72–0.96)		
								209	0.77 (0.66–0.89)		
								397	0.67 (0.58–0.78)		
Goto et al. 2011 (12)	U.S.	F	Mean 60	10	718	359	Confirmed self-report	Caffeinated coffee		Age, race, duration of follow-up, time of blood draw, smoking status, physical activity, family history of diabetes, alcohol use, total calories, and BMI	7
								0	1.00 (1.00–1.00)		
								≤1	0.92 (0.46–1.84)		
								2–3	0.96 (0.48–1.94)		
								≥4	0.71 (0.31–1.61)		
								Decaf. coffee			
								0	1.00 (1.00–1.00)		
								≤1	1.31 (0.84–2.03)		
								2–3	0.91 (0.42–2.00)		
								≥4	0.92 (0.26–3.27)		
								Caffeine[b]			
								13	1.00 (1.00–1.00)		
								140	1.53 (0.71–3.30)		
								366	1.70 (0.79–3.62)		
								656	1.32 (0.61–2.82)		
Hjellvik et al. 2011 (6)	Europe	Both	40–45	5–20	362,045	9,886	Confirmed cases	Total coffee		Year of birth and, where relevant, sex, BMI, smoking, education, and physical activity	7
								<1	1.00 (1.00–1.00)		
								1–4	0.84 (0.79–0.89)		
								5–8	0.65 (0.61–0.70)		
								>9	0.63 (0.58–0.69)		

Continued on p. 580

Table 1—Continued

Authors	Country	Sex	Age at baseline (year)	Follow-up (year)	*N*	*n*	Type 2 diabetes assessment	Coffee exposure (cups/day)	RR (95% CI)	Confounding adjustments	NOS (0–9 points)
Floegel et al. 2012 (8)	Europe	Both	35–65	8.9	42,659	1,432	Confirmed self-report	Caffeinated coffee		Age, center, sex, smoking, alcohol intake, physical activity, education, employment, vitamin and mineral supplement use during past 4 wk, total energy intake, tea intake, decaf. coffee intake, BMI, waist-hip ratio, and prevalent hypertension	7
								<1	1.00 (1.00–1.00)		
								1–2	0.89 (0.69–1.16)		
								2–3	0.92 (0.76–1.13)		
								3–4	0.82 (0.65–1.02)		
								≥4	0.77 (0.63–0.94)		
								Decaf. coffee			
								<1	1.00 (1.00–1.00)		
								1–2	0.97 (0.68–1.39)		
								2–3	1.11 (0.84–1.48)		
								3–4	0.70 (0.41–1.19)		
								≥4	0.70 (0.46–1.06)		
Bhupathiraju et al. 2013 (19)	U.S.	Both	M 40–75 F 30–55	M 22 F 24	39,059	2,865	Confirmed self-report	Caffeinated coffee (men)		Age; total caloric intake; family history of diabetes; alcohol consumption; smoking status; menopausal status; postmenopausal hormone use; intake of glycemic load, *trans* fat, polyunsaturated fatty acid, cereal fiber, and magnesium; BMI; and physical activity	6
								<1	1.00 (1.00–1.00)		
								1–3	0.95 (0.88–1.03)		
								4–5	0.92 (0.82–1.05)		
								≥6	0.65 (0.49–0.85)		
								Caffeinated coffee (women)			
								<1	1.00 (1.00–1.00)		
								1–3	0.91 (0.86–0.95)		
								4–5	0.78 (0.72–0.85)		
								≥6	0.65 (0.58–0.73)		
					M 74,749 F 7,370			Decaf. coffee (men)			
								0	1.00 (1.00–1.00)		
								<1	0.92 (0.84–1.01)		
								1–3	0.84 (0.75–0.93)		
								≥4	0.84 (0.68–1.03)		
								Decaf. coffee (women)			
								0	1.00 (1.00–1.00)		
								<1	0.95 (0.89–1.00)		
								1–3	0.86 (0.81–0.92)		
								≥4	0.73 (0.64–0.84)		

Continued on p. 581

Table 1—Continued

Authors	Country	Sex	Age at baseline (year)	Follow-up (year)	*N*	*n*	Type 2 diabetes assessment	Coffee exposure (cups/day)	RR (95% CI)	Confounding adjustments	NOS (0–9 points)
Doo et al. 2013 (18)	U.S.	Both	45–75	14	75,140	8,582	Confirmed cases	Total coffee (men)		Age and adjusted for	9
								0	1.00 (1.00–1.00)	ethnicity, BMI, physical	
								<1	1.12 (1.01–1.24)	activity, education,	
								1	1.06 (0.97–1.17)	history of	
								2	1.05 (0.95–1.16)	hypertension, energy,	
								≥3	0.95 (0.84–1.08)	alcohol intake,	
								Total coffee (women)		smoking status,	
								0	1.00 (1.00–1.00)	sugared sodas, dietary	
								<1	1.08 (0.98–1.19)	fiber per 4,184 kJ, and	
								1	0.96 (0.87–1.05)	processed meat per	
								2	0.82 (0.74–0.91)	4,184 kJ	
								≥3	0.69 (0.59–0.81)		
								Caffeinated coffee (men)			
								0	1.00 (1.00–1.00)		
								<1	1.07 (0.98–1.18)		
								1	1.02 (0.93–1.11)		
								2	0.99 (0.91–1.09)		
								≥3	0.86 (0.75–0.98)		
								Caffeinated coffee (women)			
								0	1.00 (1.00–1.00)		
								<1	1.02 (0.94–1.12)		
								1	0.93 (0.86–1.01)		
								2	0.75 (0.68–0.83)		
								≥3	0.65 (0.54–0.78)		
								Decaf. coffee (men)			
								0	1.00 (1.00–1.00)		
								<1	1.08 (1.00–1.16)		
								1	1.03 (0.93–1.15)		
								≥2	1.07 (0.93–1.23)		
								Decaf. coffee (women)			
								0	1.00 (1.00–1.00)		
								<1	1.07 (0.99–1.15)		
								1	1.03 (0.92–1.14)		
								≥2	0.85 (0.72–1.01)		

Decaf., decaffeinated; F, female; M, male; mo, month; OGGT, oral glucose tolerance test; wk, week. [a]In person-years. [b]In mg/day. [c]In servings/day. [d]In cups/week. [e]In cups/month.

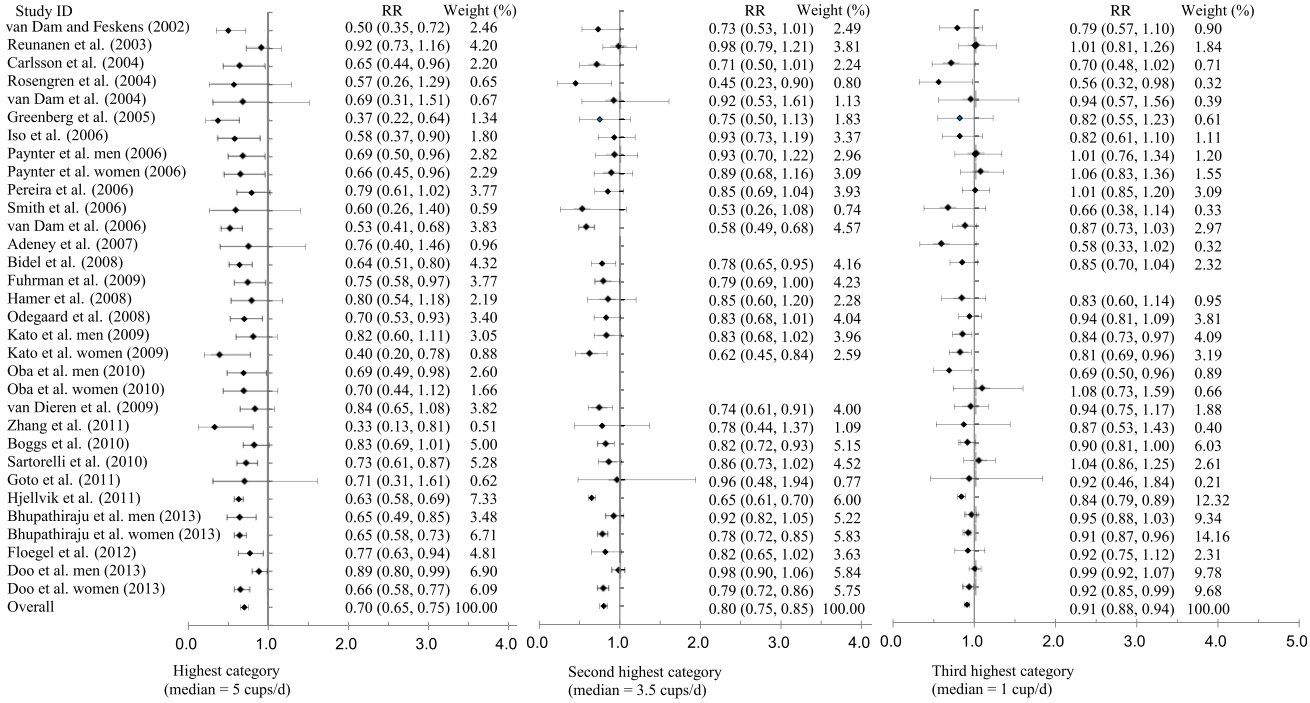

Figure 2—Forest plot of the associations between total coffee consumption and risk of type 2 diabetes. Compared with the lowest category (median consumption 0 cups/day), the pooled RR for incident type 2 diabetes was 0.70 (95% CI 0.65–0.75, I^2 = 50%, *P* for heterogeneity = 0.001) for the highest category of consumption, 0.80 (0.75–0.85, I^2 = 71%, $P < 0.001$) for the second highest, and 0.91 (0.88–0.94, I^2 = 19%, *P* = 0.17) for the third highest category of coffee consumption.

compared with the lowest category. Compared with the lowest category (median consumption 0 cups/day), the pooled RR for incident type 2 diabetes for individuals in the highest category of consumption (5 cups/day) was 0.70 (95% CI 0.65–0.75, I^2 = 50%, *P* for heterogeneity = 0.001). The corresponding RRs were 0.80 (0.75–0.85, I^2 = 71%, $P < 0.001$) for the second highest category (3.5 cups/day) and 0.91 (0.88–0.94, I^2 = 19%, *P* = 0.17) for the third highest category (1 cup/day) of coffee consumption. Thus, there was evidence for substantial between-study heterogeneity in results for the highest two categories of coffee consumption.

Dose-Response Analyses of Total Coffee Consumption and Risk of Diabetes

We performed a dose-response meta-analysis in 27 studies to test for a linear trend between total coffee consumption and risk of type 2 diabetes and to estimate RRs for specific amounts of coffee consumption. One study included coffee consumption of >12 cups/day for the highest category (23); we treated this observation as an outlier and excluded it from the dose-response analysis. There was a strong inverse association between coffee consumption and risk of type 2 diabetes (Fig. 3). A cubic spline model accounted for more variance in the outcome than did a linear model (likelihood ratio test $P < 0.001$), suggesting that the association was not fully linear. Compared with participants with no coffee consumption, the RR estimated directly from the cubic spline model for 1–6 cups/day was 0.92 (95% CI 0.90–0.94), 0.85 (0.82–0.88), 0.79 (0.75–0.83), 0.75 (0.71–0.80), 0.71 (0.65–0.76), and 0.67 (0.61–0.74), respectively.

To test whether the inverse association between coffee consumption and risk of type 2 diabetes was different for unadjusted and adjusted RRs, we performed a dose-response meta-analysis of the unadjusted data in 27 studies (Supplementary Fig. 1). The spline curve of the unadjusted data was similar to that of the multivariable-adjusted data, indicating that adjustment for potential confounders minimally affected effect estimates for the association between coffee consumption and a lower risk of diabetes.

Comparison of Associations for Caffeinated and Decaffeinated Coffee

Both caffeinated and decaffeinated coffee consumption was inversely associated with risk of type 2 diabetes (Supplementary Fig. 2). Compared with participants with the lowest level of caffeinated coffee consumption, the RR for incident type 2 diabetes was 0.74 (95% CI 0.67–0.81, I^2 = 56%, *P* for heterogeneity = 0.005) for the highest category (median consumption 5 cups/day), 0.82 (0.75–0.91, I^2 = 74%, $P < 0.001$) for the second highest category (3.5 cups/day), and 0.92 (0.89–0.96, I^2 = 6.6%, *P* = 0.38) for the third highest category (1 cup/day). Compared with those with the lowest level of decaffeinated coffee consumption, the combined RR for incident type 2 diabetes was 0.80 (0.70–0.91, I^2 = 62%, *P* = 0.001) for the highest category

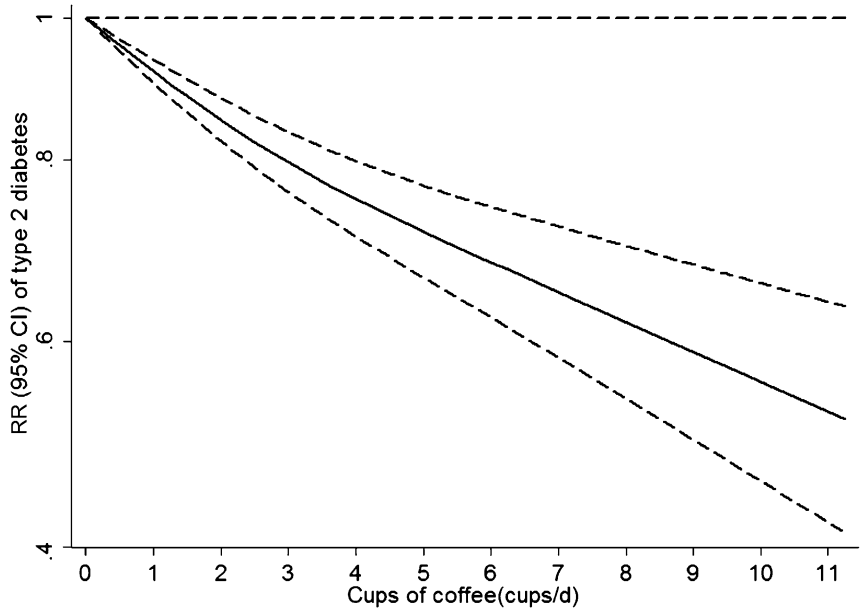

Figure 3—Dose-response analysis of the association between coffee consumption and risk of type 2 diabetes. For the overall association between coffee consumption and risk of diabetes, $P < 0.001$; for the goodness of fit of the model, $P = 0.14$; and for the likelihood ratio test compared with the nested linear model, $P < 0.001$.

(4 cups/day), 0.95 (0.88–1.02, I^2 = 53%, P = 0.02) for the second highest category (2 cups/day), and 0.98 (0.92–1.05, I^2 = 62%, P = 0.003) for the third highest category (0.5 cups/day). Heterogeneity was shown for five of the six subgroups. Seven of 12 studies adjusted for caffeinated and decaffeinated coffee consumption simultaneously. The association was slightly stronger for caffeinated coffee consumption than for decaffeinated coffee consumption (P = 0.03 for the second highest group, P = 0.07 for the highest group) (Supplementary Table 1).

We conducted a linear dose-response analysis for caffeinated and decaffeinated coffee consumption separately (11 studies). For a 1 cup/day increase in caffeinated coffee consumption, the RR for type 2 diabetes was 0.91 (95% CI 0.89–0.94), and for a 1 cup/day increase in decaffeinated coffee consumption, the RR was 0.94 (0.91–0.98, P for difference = 0.17). We performed a dose-response analysis between caffeine consumption and type 2 diabetes risk based on seven of the included studies (4,9,12,17,21,22,35) and found that for every 140 mg/day (~1 cup/day coffee) higher caffeine consumption, the RR for type 2 diabetes was 0.92 (0.90–0.94). Of note, none of the included studies controlled for coffee intake when modeling caffeine intake and diabetes.

Stratified Analysis

In stratified analyses, the inverse associations between coffee consumption and risk of diabetes were similar by geographical region (U.S., Europe, and Asia), sex, and diabetes assessment method (P for interaction > 0.05 for all groups) (Supplementary Table 1).

Sensitivity Analysis

For the dose-response analysis of total coffee consumption with diabetes, after we included the observation with extremely high coffee consumption (23), the results did not change. Significant heterogeneity was found for the highest and second highest total coffee consumption, which might be attributable to the heterogeneous amount of coffee consumption in these categories. The dose-response analysis accounted for the heterogeneous consumption amount of individual studies and showed an appropriate goodness of fit (P = 0.14).

Heterogeneity was also found in separate analyses of caffeinated and decaffeinated coffee consumption. In addition to considering different consumption amounts, we stratified the analyses by whether the studies included caffeinated and decaffeinated coffee consumption simultaneously in the same model. In these analyses, the heterogeneity at each level of caffeinated and decaffeinated coffee consumption decreased significantly, with even more inverse results for both caffeinated and decaffeinated coffee consumption (Supplementary Fig. 3).

Publication Bias

The Egger test provided no evidence of publication bias at any levels of total coffee, caffeinated coffee, and decaffeinated coffee consumption (Supplementary Table 2).

CONCLUSIONS

The findings from this systematic review and meta-analysis, based on 1,109,272 study participants and 45,335 cases of type 2 diabetes, demonstrate a robust inverse association between coffee consumption and risk of diabetes. Compared with no coffee consumption, consumption of 6 cups/day of coffee was associated with a 33% lower risk of type 2 diabetes. Caffeinated coffee and decaffeinated coffee consumption were both associated with a lower risk of type 2 diabetes. The association between

coffee consumption and diabetes risk was consistent for men and women and for European, U.S., and Asian populations.

There has been some debate about the role of caffeine in the development of insulin resistance and diabetes. Short-term studies in humans have shown that caffeine intake results in an acute reduction of insulin sensitivity, which may be due to adenosine receptor antagonism and increased epinephrine release caused by caffeine (36). Other studies have found that when controlling for total coffee intake, caffeine intake was no longer associated with diabetes risk (5,19). Nonetheless, these results need to be interpreted with caution because the high correlation between coffee and caffeine consumption makes it more difficult to separate their effects. The present meta-analysis shows that both caffeinated and decaffeinated coffee consumption is associated with a lower risk of diabetes. The results were more inverse when only including the studies adjusting for caffeinated and decaffeinated coffee simultaneously in the model. Because caffeinated coffee consumption is inversely related to decaffeinated coffee consumption, caffeinated coffee is a positive confounder for the association of decaffeinated coffee with diabetes and vice versa. Thus, the association is strengthened when both variables are adjusted simultaneously. Moreover, because the consumption of caffeinated coffee is much higher than decaffeinated coffee, the results appear to be more robust for caffeinated coffee. However, the difference for continuous analysis between caffeinated and decaffeinated coffee (1 cup/day increment) was not statistically significant. These results suggest that components of coffee other than caffeine are responsible for this putative beneficial effect. Although the present results show that higher caffeine consumption is inversely associated with the risk of diabetes, this association is likely to be confounded by other components of coffee because of the collinearity of caffeine and those components.

Plausible biological mechanisms that may contribute to the inverse association between coffee consumption and diabetes risk have been demonstrated in animal models and in vitro studies implicating several coffee components in reducing insulin resistance and improving glucose metabolism. Chlorogenic acid, a phenolic compound, is a major component of coffee and has been shown to reduce blood glucose concentrations in animal experiments (37). Chlorogenic acid may reduce glucose absorption in the intestines by competitively inhibiting glucose-6-phosphate translocase and reducing sodium-dependent glucose transport in the brush border membrane vesicles (38), by reducing oxidative stress as a result of its antioxidant properties, and by reducing liver glucose output (39). Other components of coffee may also improve glucose metabolism, including lignans, quinides, and trigonelline (40–42). Coffee is also a good source of magnesium, which has been associated with a lower risk of type 2 diabetes (43). However, adjustment for magnesium intake did not substantially attenuate the inverse association (4,5), suggesting that other bioactive compounds in coffee may also be responsible. In addition, because some of the compounds, such as lignans and magnesium, also exist in other foods, it is difficult to attribute the benefits of coffee on diabetes to these specific compounds only.

This meta-analysis has several significant strengths. The mean NOS score of 7 of 9 ensured the relatively high quality of the included studies. All 28 studies used a prospective design; thus, the differential misclassification of coffee consumption attributable to recall bias was minimized. Given the observational nature of the studies, residual confounding might be an explanation for the findings. However, higher coffee consumption was generally associated with a less healthy lifestyle, including a high prevalence of cigarette smoking, less physical activity, and a less healthy diet. Thus, the true association between coffee and diabetes risk might be stronger than observed. Indeed, the similarity found in the present adjusted and unadjusted results indicates that the association is unlikely to be substantially confounded by known diabetes risk factors. Nonetheless, it is difficult to establish the causality between coffee consumption and diabetes solely based on observational evidence.

Because most of the studies coffee was assessed through self-reported dietary questionnaires, misclassification of coffee intake is inevitable. However, the misclassification is likely to be nondifferential with respect to the outcome because of the prospective design of the studies, which might have attenuated the observed association. Only five studies addressed the loss to follow-up percentage. However, the loss to follow-up is unlikely to be associated with coffee consumption and may have resulted in selection bias. Coffee brewing methods were not assessed in the studies. However, most coffee is likely to be filtered coffee, and the results from studies conducted in various populations, including U.S., European, and Asian, were similar, indicating consistency of the results despite potentially different preparation and processing methods. In addition, none of the studies assessed the amount of sugar and dairy added to coffee. However, the amount of sugar and dairy added to coffee is likely to be small compared with other food sources. Finally, because of the observational nature of the studies, a causal relationship cannot be established with these data alone.

In conclusion, this meta-analysis provides strong evidence that higher consumption of coffee is associated with a significantly lower risk of diabetes. Both caffeinated coffee and decaffeinated coffee are associated with reduced diabetes risk. Longer-term randomized controlled trials are needed to establish causality and to elucidate the underlying mechanisms.

Funding. This research was supported by National Institutes of Health grant DK-58845.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. M.D. contributed to the data research, extraction, and analyses and wrote the manuscript. M.D., S.N.B., M.C., R.M.v.D., and F.B.H. contributed substantially to the study

conception and design, data analysis and interpretation, and drafting and critical revision of the manuscript for important intellectual content. S.N.B. contributed to the manuscript organization and reviewed and edited the manuscript. M.C. double-checked the extracted data and reviewed the manuscript. R.M.v.D. and F.B.H. contributed to the introduction and discussion and reviewed and edited the manuscript. F.B.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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