

# Coffee Consumption and Risk of Type 2 Diabetes

## A Systematic Review

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**T**YPE 2 DIABETES IS A CHRONIC disease associated with high rates of morbidity and premature mortality.<sup>1</sup> An alarming increase in the prevalence of type 2 diabetes is expected,<sup>2</sup> and the need for preventive action is widely acknowledged. While increased physical activity and restriction of energy intake can substantially reduce the incidence of type 2 diabetes,<sup>3,4</sup> insight into the role of other lifestyle factors may contribute to additional prevention strategies for type 2 diabetes.

Coffee is among the most widely consumed beverages in the world.<sup>5</sup> Knowledge on both the positive and negative health effects of coffee is important to allow individuals to make informed choices regarding coffee consumption. In addition, data on the health effects of different coffee constituents and of different types of coffee can contribute to disease prevention. For example, switching from pot-boiled to filtered coffee lowers serum low-density lipoprotein cholesterol concentrations,<sup>6</sup> which may have contributed to the marked reduction of the incidence of coronary heart disease in Finland.<sup>7</sup> Coffee contains numerous substances; among them, caffeine,<sup>8-14</sup> chlorogenic acid,<sup>15,16</sup>

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**Context** Emerging epidemiological evidence suggests that higher coffee consumption may reduce the risk of type 2 diabetes.

**Objective** To examine the association between habitual coffee consumption and risk of type 2 diabetes and related outcomes.

**Data Sources and Study Selection** We searched MEDLINE through January 2005 and examined the reference lists of the retrieved articles. Because this review focuses on studies of habitual coffee consumption and risk of type 2 diabetes, we excluded studies of type 1 diabetes, animal studies, and studies of short-term exposure to coffee or caffeine, leaving 15 epidemiological studies (cohort or cross-sectional).

**Data Extraction** Information on study design, participant characteristics, measurement of coffee consumption and outcomes, adjustment for potential confounders, and estimates of associations was abstracted independently by 2 investigators.

**Data Synthesis** We identified 9 cohort studies of coffee consumption and risk of type 2 diabetes, including 193 473 participants and 8394 incident cases of type 2 diabetes, and calculated summary relative risks (RRs) using a random-effects model. The RR of type 2 diabetes was 0.65 (95% confidence interval [CI], 0.54-0.78) for the highest ( $\geq 6$  or  $\geq 7$  cups per day) and 0.72 (95% CI, 0.62-0.83) for the second highest (4-6 cups per day) category of coffee consumption compared with the lowest consumption category (0 or  $\leq 2$  cups per day). These associations did not differ substantially by sex, obesity, or region (United States and Europe). In the cross-sectional studies conducted in northern Europe, southern Europe, and Japan, higher coffee consumption was consistently associated with a lower prevalence of newly detected hyperglycemia, particularly postprandial hyperglycemia.

**Conclusions** This systematic review supports the hypothesis that habitual coffee consumption is associated with a substantially lower risk of type 2 diabetes. Longer-term intervention studies of coffee consumption and glucose metabolism are warranted to examine the mechanisms underlying the relationship between coffee consumption and type 2 diabetes.

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quinides,<sup>17</sup> and magnesium<sup>18</sup> have been shown to affect glucose metabolism in animal or metabolic studies. Coffee consumption has been extensively studied in relation to various diseases,<sup>19,20</sup> but not until recently has it been examined in relation to risk of type 2 diabetes. In a Dutch study, higher coffee consumption was associ-

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ated with a substantially lower risk of type 2 diabetes.<sup>21</sup> This finding has been confirmed in several,<sup>22-25</sup> but not all,<sup>26,27</sup> subsequent studies. We systematically reviewed all available epidemiological evidence on the relation between habitual coffee consumption and risk of type 2 diabetes.

## METHODS

### Study Selection and Data Extraction

We searched MEDLINE through January 2005 using key words *coffee* and *caffeine* in combination with *diabetes*, *glucose*, and *insulin* and examined the reference lists of the retrieved articles. Because this review focuses on epidemiological studies of habitual coffee consumption in relation to type 2 diabetes and related outcomes, we excluded studies of type 1 diabetes, animal studies, and studies of short-term

exposure to coffee or caffeine from the meta-analysis. For this systematic review, we identified a total of 15 epidemiological studies, including 9 cohort studies and 7 cross-sectional studies (for 1 study, both longitudinal and cross-sectional data were reported). Information on study design, participant characteristics, measurement of coffee consumption and outcomes, adjustment for potential confounders, and estimates of associations was abstracted independently by 2 investigators. Discrepancies were resolved by discussion and repeated examination of the articles. All cohort studies could be used in the meta-analyses because relative risks (RRs) for type 2 diabetes and information about their variance were provided, and categories of coffee consumption were quantified. Overall RRs and RRs in subgroups according to sex and obesity were extracted.

### Statistical Analysis

We used the SAS MIXED Procedure, version 8.2 (SAS Institute, Cary, NC) for meta-regression analysis with the log-RR modeled as dependent variable.<sup>28</sup> Summary RRs were random-effects estimates, which allow each of the studies in the meta-analysis to estimate a different effect size. We conducted separate meta-analyses for different levels of consumption as done previously in a meta-analysis of alcohol consumption.<sup>29</sup> We distinguished 4 levels of coffee consumption: (1) the highest category of coffee consumption (US studies,  $\geq 6$  cups per day<sup>25</sup>; European studies,  $\geq 7$  cups per day<sup>21-24,27,30</sup>); (2) the second highest category of coffee consumption (US studies, 4-5 cups per day<sup>25</sup>; European studies, 5-6 cups per day<sup>21-24,27,30</sup>); (3) the third highest category of coffee consumption (US studies, 1-3 cups per

**Table 1.** Cohort Studies of Coffee Consumption and Risk for Type 2 Diabetes

Source	Country	Sex	Age at Baseline, y	Total N/ No. of Cases	Type 2 Diabetes Assessment	Mean Follow-up, y	Adjustments
van Dam and Feskens, <sup>21</sup> 2002	The Netherlands	M/F	30-60	17 111/306	Self-report	7	Age, sex, town, education, leisure and occupational physical activity, alcohol consumption, smoking, known CVD (risk factors)
Reunanen et al, <sup>27</sup> 2003	Finland	M/F	20-98	19 518/855	Drug-treated diabetes in national registry	16	Age, sex, smoking, BMI, physical activity
Saremi et al, <sup>26</sup> 2003	United States (Pima Indians)	M/F	$\geq 15$ (mean: 27)	2680/824	OGTT	11	Age, sex, BMI
Rosengren et al, <sup>22</sup> 2004	Sweden	F	39-65	1361/74	Self-report and national registry	18	Age, education, smoking, leisure physical activity, BMI
Salazar-Martinez et al, <sup>25</sup> 2004	United States	M	40-75	41 934/1333	Confirmed self-report	12	Age, BMI, family history of diabetes, smoking, leisure physical activity, alcohol consumption, dietary factors
	United States	F	30-55	84 276/4085	Confirmed self-report	18	Age, BMI, family history of diabetes, smoking, leisure physical activity, alcohol consumption, menopausal status, postmenopausal hormone use, dietary factors
Tuomilehto et al, <sup>23</sup> 2004	Finland	M/F	35-64	14 629/381	National registries	12	Age, sex, education, BMI, blood pressure, smoking, leisure and occupational physical activity, alcohol and tea consumption
Carlsson et al, <sup>24</sup> 2004	Finland	M/F	30-60	10 652/408	National registries	20	Age, sex, education, BMI, smoking, leisure physical activity, alcohol consumption
van Dam et al, <sup>30</sup> 2004	The Netherlands	M/F	50-74	1312/128	Newly detected by OGTT	6	Age, sex, BMI, WHR, smoking, leisure physical activity, alcohol consumption, dietary factors, known CVD and antihypertensive medication

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; OGTT, oral glucose tolerance test; WHR, waist-to-hip ratio.

day<sup>25</sup> or  $\geq 3$  cups per day<sup>26</sup>; European studies, 4-5 cups per day<sup>21-24,27,30</sup>); and (4) the reference category (US studies, 0 cups per day<sup>25,26</sup>; European studies,  $\leq 2$  cups per day<sup>21-24,27,30</sup>). For the study by Tuomilehto et al,<sup>23</sup> we used 7 to 9 cups per day instead of 10 or more cups per day for the highest level of coffee consumption to improve the comparability with other studies. We used the results of the original studies from multivariate models with the most complete adjustment for poten-

tial confounders; the covariables included in these models are shown in TABLE 1 and TABLE 2.<sup>31-36</sup> *P* values for heterogeneity of study results were calculated as described by Greenland.<sup>37</sup> To examine sources of heterogeneity, we conducted meta-regression analysis with "region" (United States/Europe), "sex" (men/women), and "obesity" (obese/ leanest reported group) as independent variables. We used funnel plots, plots of study results against precision, to assess potential publica-

tion bias, and tested symmetry of the funnel plot as suggested by Egger et al.<sup>38</sup> To estimate whether publication bias (if present) would explain the observed associations, we calculated fail-safe numbers using a weighted method.<sup>39</sup> A fail-safe number indicates the number of studies of average precision with null results that would need to be added to the meta-analysis to reduce the overall statistically significant observed result to nonsignificance.<sup>39,40</sup>

**Table 2.** Cross-Sectional Studies of Coffee Consumption in Relation to Hyperglycemia, Insulin Sensitivity, and Insulin Secretion

Source	Country	Sex	Age, y	N	Outcome Measure	Coffee Consumption	Adjusted OR (95% CI)	Adjustments	Other Results
Isogawa et al, <sup>31</sup> 2003	Japan	M/F	40-50	4620	Newly detected fasting hyperglycemia	Nonuse Use	1.00 0.61 (0.47-0.80)	Age, sex, BMI, family history of diabetes	
van Dam et al, <sup>32</sup> 2003	The Netherlands	M	69-89	419	Newly OGTT detected IGT/ type 2 diabetes (n = 88)	$\leq 2$ cups/d 3-4 cups/d $\geq 5$ cups/d	1.00 0.63 (0.35-1.14) 0.35 (0.16-0.74)	Age, family history of diabetes, smoking, alcohol intake, leisure physical activity, BMI, subscapular skinfold thickness, and dietary factors	No substantial association with fasting insulin
Agardh et al, <sup>33</sup> 2004	Sweden	M	35-56	3128	Newly OGTT detected type 2 diabetes (n = 55)	$\leq 2$ cups/d 3-4 cups/d $\geq 5$ cups/d	1.00 0.52 (0.27-1.00) 0.36 (0.18-0.74)	Age, smoking, leisure physical activity (no change after adjustment for SES, family history of diabetes)	Inverse association with prevalence IGT and HOMA-IR
		F	35-56	4821	Newly OGTT detected type 2 diabetes (n = 52)	$\leq 2$ cups/d 3-4 cups/d $\geq 5$ cups/d	1.00 0.41 (0.22-0.76) 0.28 (0.12-0.65)	Age, smoking, leisure physical activity (no change after adjustment for SES, family history of diabetes)	Inverse association with prevalence IGT and HOMA-IR
Soriguer et al, <sup>34</sup> 2004	Spain	M/F	18-65	1226	Newly OGTT detected IGT/ type 2 diabetes	<1 cup/d $\geq 1$ cups/d	1.00 0.66 (0.48-0.92)	Age, sex, obesity, smoking	Inverse association with 2-h glucose and insulin; no association with HOMA-IR or fasting glucose and insulin
Yamaji et al, <sup>35</sup> 2004	Japan	M	46-59	3224	Newly detected type 2 diabetes (n = 171)	<1 cup/d 1-2 cups/d 3-4 cups/d $\geq 5$ cups/d	1.00 0.6 (0.4-1.0) 0.8 (0.5-1.2) 0.8 (0.5-1.3)	BMI, smoking, leisure physical activity, alcohol intake, region, rank, parental history of diabetes, green tea	Inverse association with IGT and fasting and 2-h glucose concentrations, but not with IFG
Ärnlov et al, <sup>36</sup> 2004	Sweden	M	69-74	936		Per cups/d*		BMI, smoking, alcohol consumption, leisure physical activity, tea, added sugar, milk, and cookies (no change after adjustment for age)	Positive association with insulin sensitivity (clamp); no association with early insulin response (OGTT)
van Dam et al, <sup>30</sup> 2004	The Netherlands	M/F	50-74	2280		Per cups/d*		Age, sex, BMI, WHR, smoking, leisure physical activity, alcohol intake, dietary factors, known CVD and antihypertensive medication	Inverse association with 2-h glucose, fasting and 2-h insulin and HOMA-IR; no association with fasting glucose

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HOMA-IR, homeostasis model assessment for insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; OR, odds ratio; SES, socioeconomic status; WHR, waist-to-hip ratio.

\*Coffee consumption was modeled as a continuous variable (the presented beta in these studies represented the change in the outcome measure for each x cups/d higher coffee consumption).

## RESULTS

We identified 9 cohort studies of coffee consumption and risk of type 2 diabetes, including 193 473 participants and 8394 incident cases of type 2 diabetes (Table 1). The FIGURE shows the results of the cohort studies for different levels of coffee consumption compared with the lowest level of coffee consumption. The RR of type 2 diabetes for all cohort studies combined was 0.65 (95% confidence interval [CI], 0.54-0.78;  $P < .001$ ) for the highest category, 0.72 (95% CI, 0.62-0.83;  $P < .001$ ) for the second highest category, and 0.94 (95% CI, 0.88-1.01;  $P = .07$ ) for the third highest category of coffee consumption compared with the lowest category of coffee consumption (TABLE 3). The  $P$  values for heterogeneity in results were .07, .03, and .18, respectively. The study by Reunanen et al<sup>27</sup> contributed substantially to heterogeneity in results for the highest and second highest level of coffee consumption ( $P$  for heterogeneity, .60 and .37, respectively, after exclusion of that study). Exclusion of the study that was published first<sup>21</sup> did not materially change the findings (RR, 0.68; 95% CI, 0.57-0.82, for the highest vs the lowest level of coffee consumption).

In 5 of the cross-sectional studies, including a total of 17 438 participants, higher coffee consumption was consistently associated with a lower prevalence of newly detected hyperglycemia<sup>31-35</sup> (Table 2). For the studies that reported on the association between coffee consumption and type 2 diabetes,<sup>33,35</sup> the summary odds ratio (OR) was 0.48 (95% CI, 0.28-0.82) for 5 or more cups per day and 0.60 (95% CI, 0.42-0.85) for 3 to 4 cups per day compared with the lowest level of coffee consumption ( $\leq 2$  cups per day<sup>33</sup> or  $< 1$  cups per day<sup>35</sup>). The corresponding summary ORs for impaired glucose tolerance (IGT) in these studies<sup>33,35</sup> were 0.54 (95% CI, 0.42-0.68) and 0.61 (95% CI, 0.51-0.72). One of the cohort studies also reported an inverse association between coffee consumption and incidence of IGT (RR, 0.37; 95% CI, 0.16-0.84 for  $\geq 7$  cups per day vs  $\leq 2$

cups per day;  $P$  for trend = .001).<sup>30</sup> In contrast to these results for IGT, no association between coffee consumption and impaired fasting glucose was observed.<sup>30,35</sup> Consistent with this observation, associations with coffee consumption were stronger for postload than for fasting glucose concentrations.<sup>30,34,35</sup> Higher coffee consumption was associated with higher insulin sensitivity in several<sup>30,33,36</sup> but not all<sup>32,34</sup> cross-sectional studies.

### Characteristics of the Study Population

The inverse association between coffee consumption and glucose intolerance/type 2 diabetes was observed in various populations (the United States,<sup>25</sup> northern Europe,<sup>21-24,30,32,33</sup> southern Europe,<sup>34</sup> Japan,<sup>31,35</sup>) including predominantly Asian<sup>31,35</sup> and white (in the other studies) participants. In meta-regression analyses, we examined whether results differed for US compared with European cohort studies. For the highest and second highest level of coffee consumption, associations were similar for US and European cohorts, but for the third highest level of consumption, the association was stronger in the European cohorts (Table 3). The association between coffee consumption and risk of type 2 diabetes was similar for men and women and for obese and nonobese participants (Table 3). Several studies also reported consistent associations across strata of smoking,<sup>21-23,25</sup> physical activity,<sup>21,25</sup> and alcohol consumption.<sup>21,23</sup>

### Confounding Factors

The potential confounders that were adjusted for are shown in Table 1 and Table 2. In all studies, age, sex, and obesity were considered as potential confounders. However, associations in a study of Pima Indians<sup>26</sup> and a study in Japan<sup>31</sup> were not adjusted for potential confounding by lifestyle factors, and associations in a Spanish study were only adjusted for smoking.<sup>34</sup> This is of importance, as higher coffee consumption tends to be associated with cigarette smoking,<sup>21-23,25,33</sup> lower leisure

physical activity,<sup>21-23,25,33</sup> and an unfavorable diet,<sup>21,25</sup> and adjustment for lifestyle factors generally strengthened the inverse association between coffee consumption and type 2 diabetes.<sup>21,23,24,33</sup>

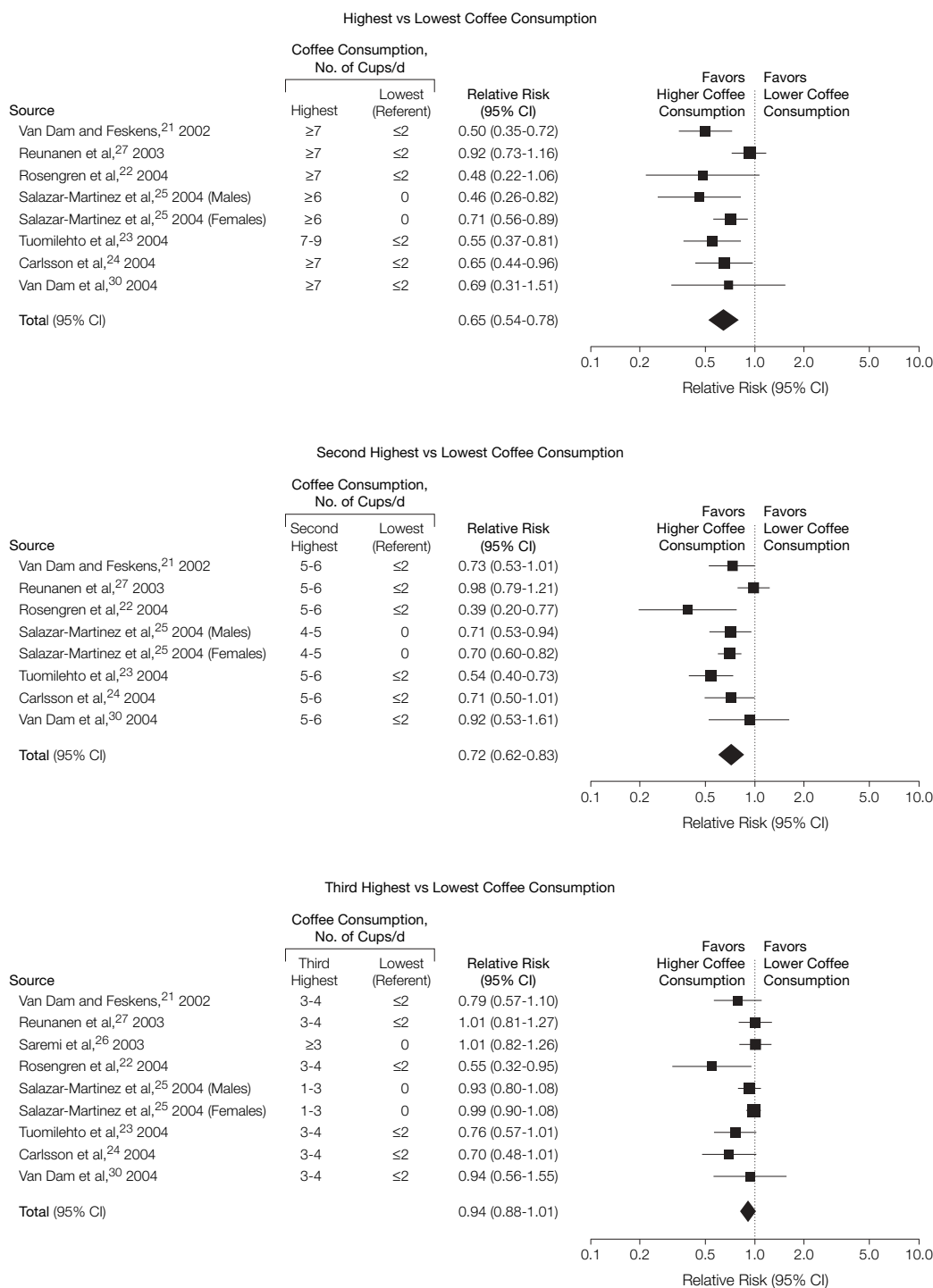
### Type of Coffee

The distinction between filtered and boiled coffee may be relevant for risk of type 2 diabetes. The Finnish study that did not observe an association between coffee consumption and risk of type 2 diabetes assessed coffee consumption in a period in which pot-boiled coffee was the most commonly consumed type of coffee in Finland.<sup>27</sup> In another Finnish study, higher consumption of both boiled and filtered coffee was associated with a lower risk of type 2 diabetes.<sup>23</sup> However, for the same amount of coffee, risk was lower for participants who consumed filtered coffee than for those who consumed pot-boiled coffee. Except for these Finnish studies,<sup>23,27</sup> consumption of unfiltered coffee such as boiled, Turkish/Greek, or cafetiere coffee was low in the included study populations,<sup>41</sup> and except for Japan and the United States,<sup>42</sup> instant coffee consumption was also low relative to total coffee consumption. Thus, the current findings mostly reflect consumption of drip-filtered coffee.

Possible differences between the effects of regular and decaffeinated coffee are also of interest. In the European studies, no distinction was made between regular and decaffeinated coffee. The results of these studies most likely reflect consumption of regular coffee because decaffeinated coffee consumption was relatively low.<sup>21</sup> Regular and decaffeinated coffee were examined separately in 2 US cohort studies only.<sup>25</sup> In these studies, higher decaffeinated coffee consumption was also associated with a reduction in risk of type 2 diabetes (men: RR, 0.74; 95% CI, 0.48-1.12 for  $\geq 4$  vs 0 cups per day;  $P$  for trend = .048; women: RR, 0.85; 95% CI, 0.61-1.17 for  $\geq 4$  vs 0 cups per day;  $P$  for trend = .008).<sup>25</sup>

In a Swedish study, adding sugar to coffee or tea was associated with lower

**Figure.** Relative Risks for the Association Between Coffee Consumption for Individual Cohort Studies and All Cohort Studies Combined



Relative risks were incidence density ratios from proportional hazards models, except for the study by van Dam et al,<sup>30</sup> which used odds ratios obtained by logistic regression analysis to estimate relative risks. CI indicates confidence interval. The size of the data markers (squares) corresponds to the weight of the study in the meta-analysis.



**Table 3.** Summary Relative Risks for the Association Between Coffee Consumption and Type 2 Diabetes in Cohort Studies

	Coffee Consumption, Relative Risk (95% CI)*			
	Low	Third Highest	Second Highest	Highest
All studies (n = 9)†	1.00	0.94 (0.88-1.01)	0.72 (0.62-0.83)	0.65 (0.54-0.78)
Stratification by region				
Europe (n = 6)	1.00	0.82 (0.71-0.96)	0.72 (0.58-0.89)	0.65 (0.51-0.82)
United States (n = 3)†	1.00	0.98 (0.91-1.05)	0.70 (0.61-0.80)	0.67 (0.54-0.83)
P Value difference‡		.04	.80	.88
Stratification by sex				
Men (n = 3)	1.00	0.91 (0.79-1.04)	0.71 (0.57-0.87)	0.60 (0.44-0.81)
Women (n = 4)	1.00	0.78 (0.61-1.00)	0.58 (0.44-0.76)	0.50 (0.34-0.72)
P Value difference‡		.63	.51	.57
Stratification by obesity				
Nonobese (n = 4)	1.00	0.95 (0.78-1.15)	0.75 (0.57-0.98)	0.50 (0.34-0.72)
Obese (n = 4)	1.00	0.94 (0.86-1.04)	0.60 (0.51-0.71)	0.62 (0.46-0.82)
P Value difference‡		.95	.19	.23

Abbreviation: CI, confidence interval.

\*The highest level denotes 6 or more<sup>25</sup> or 7 or more<sup>21-24,27,30</sup> cups per day; the second highest level denotes 4 to 5 cups per day<sup>25</sup> or 5 to 6 cups per day<sup>21-24,27,30</sup>; the third highest level denotes 1 to 3 cups per day,<sup>25</sup> 3 or more cups per day,<sup>26</sup> or 4 to 5 cups per day<sup>21-24,27,30</sup>; and the lowest level of consumption denotes 0 cups per day<sup>25,26</sup> or 2 or less cups per day<sup>21-24,27,30</sup>.

†Number of studies is 1 lower for the second highest and highest category, because 1 study<sup>26</sup> did not include these higher levels of consumption.

‡P Values for the difference in strength of the association between coffee consumption and risk of type 2 diabetes between the strata.

insulin sensitivity, whereas adding milk/cream to coffee or tea was not associated with insulin sensitivity.<sup>36</sup> However, for most people the amount of sugar and milk added to coffee is small compared to other food sources. In Dutch studies, inverse associations with 2-hour postload glucose concentrations<sup>30</sup> and risk of type 2 diabetes<sup>21</sup> were observed for coffee with or without sugar and for coffee with or without milk/cream.

### Assessment of Publication Bias

The Egger test provided no evidence for publication bias for the analyses for the highest ( $P = .10$ ) and second highest ( $P = .62$ ) level of coffee consumption. The Egger test, however, indicated that stronger associations were observed for smaller studies for the third highest level of coffee consumption ( $P = .03$ ), but this may have been due to regional differences: the US studies were larger and showed weaker associations for this level of coffee consumption. We also calculated the number of studies with null results that would need to be added to the meta-analysis to reduce the overall observed associations to nonsignificance. This fail-safe

number was 62 for the highest level of coffee consumption, and 76 for the second highest level of coffee consumption. These numbers are robust according to a commonly used criterion that requires a fail-safe number greater than 50 ( $5n + 10$ , where  $n$  is the original number of studies in the analysis) for the current analyses.<sup>39</sup>

### COMMENT

The current meta-analysis of cohort studies supports a significant inverse association between coffee consumption and risk of type 2 diabetes. Participants who drank 4 to 6 cups and more than 6 to 7 cups of coffee per day had a 28% and 35% lower risk of type 2 diabetes compared with those who drank less than 2 cups per day. Similar inverse associations between coffee consumption and IGT or type 2 diabetes were observed in cross-sectional studies.

### Validity of the Studies

The possibility that the observed inverse association between coffee consumption and type 2 diabetes was due to bias should be considered. The prospective design and minimal loss to fol-

low-up in most studies strongly reduced the probability of selection bias. In addition, coffee consumption was not associated with response to a follow-up questionnaire in a Dutch study.<sup>21</sup> It has been suggested that diagnostic bias could explain the inverse association between coffee consumption and risk of diagnosed type 2 diabetes.<sup>26</sup> However, the supportive findings of cohort<sup>30</sup> and cross-sectional<sup>31-35</sup> studies that measured blood glucose concentrations in all participants strongly argues against the possibility that diagnostic bias can explain the observed associations. One could argue that subclinical diabetes may have affected coffee consumption in the cohort studies. However, exclusion of the first 4 or 10 years<sup>21,22,25</sup> of follow-up did not substantially change the results, and coffee consumption was also inversely associated with incidence of IGT.<sup>30</sup> In addition, residual confounding cannot be fully excluded as a potential explanation for findings in observational studies. However, higher coffee consumption was generally associated with a less healthy lifestyle. As a result, more complete adjustment for potential confounders generally strengthened the observed associations.

Several validation studies suggested that coffee consumption was assessed with a relative high validity and reproducibility.<sup>21,35,43,44</sup> The correlations between coffee consumption assessed by questionnaire and by diet records were 0.75 for Japanese men,<sup>35</sup> 0.78 in US women,<sup>44</sup> and 0.93 in US men.<sup>43</sup> However, except for 3 cohort studies,<sup>24,25</sup> coffee consumption was assessed only once, and changes in coffee consumption may have weakened the observed associations given the long follow-up period of many of the cohort studies. Serving sizes for coffee and strength of the coffee brew can differ substantially within and between countries. Particularly, the size of standard coffee cups is larger in the United States ( $\approx 250$  mL<sup>45</sup>), compared with Europe (125-150 mL<sup>30,36</sup>). However, this is compensated for by the generally much

weaker coffee brew in the United States<sup>45</sup> relative to Europe.<sup>46</sup>

### Mechanisms

Several plausible mechanisms for a beneficial effect of coffee on glucose metabolism exist. Coffee has been shown to be a major contributor to the total in vitro antioxidant capacity of the diet,<sup>47,48</sup> which may be relevant as oxidative stress can contribute to the development of type 2 diabetes.<sup>49</sup> Coffee is the major source of the phenol chlorogenic acid.<sup>50</sup> Intake of chlorogenic acid has been shown to reduce glucose concentrations in rats,<sup>15,16</sup> and intake of quinides, degradation products of chlorogenic acids, increased insulin sensitivity in rats.<sup>17</sup> Chlorogenic acid contributes to the antioxidant effects of coffee,<sup>50</sup> may reduce hepatic glucose output through inhibition of glucose-6-phosphatase,<sup>51</sup> and may improve tissue mineral distribution through its action as a metal chelator.<sup>16</sup> In addition, chlorogenic acid acts as a competitive inhibitor of glucose absorption in the intestine.<sup>50</sup> Indeed, decaffeinated coffee seemed to delay intestinal absorption of glucose and increased glucagon-like peptide-1 concentrations in an intervention study in humans.<sup>52</sup> Glucagon-like peptide-1 is well known for its beneficial effects on glucose-induced insulin secretion and insulin action.<sup>53</sup> This effect may explain the observation that higher coffee consumption was associated with lower postload, rather than fasting, glucose concentrations.<sup>30,34,35</sup>

Caffeine ingestion can acutely reduce glucose storage,<sup>8</sup> but beneficial effects of caffeine on lipid oxidation and uncoupling protein-3 expression have also been suggested.<sup>54</sup> In US studies, decaffeinated coffee consumption was inversely associated with risk of type 2 diabetes.<sup>25</sup> In addition, in a Japanese study, the inverse association with hyperglycemia was stronger for coffee than for caffeine.<sup>31</sup> These observations suggest that coffee components other than caffeine may have beneficial effects on risk of type 2 diabetes. Coffee also contains sub-

stantial amounts of magnesium, which has been linked to better insulin sensitivity and insulin secretion.<sup>18</sup> However, adjustment for magnesium intake did not explain the association between coffee consumption and risk of type 2 diabetes.<sup>25,30</sup>

### Findings From Short-term Intervention Studies

Recent studies have shown that caffeine acutely lowers insulin sensitivity measured by a hyperinsulinemic-euglycemic clamp<sup>8-10</sup> due to reduced carbohydrate storage.<sup>8</sup> Several studies also showed that caffeine intake acutely increased postload glucose concentrations.<sup>11-14</sup> Randomized controlled studies of caffeine intake for 4 days,<sup>55</sup> 5 days,<sup>56</sup> 2 weeks,<sup>57</sup> and 24 weeks<sup>58</sup> did not show effects on plasma glucose concentrations. Findings from short-term caffeine intervention studies cannot be extrapolated to the effects of chronic coffee consumption on risk of type 2 diabetes. First, physiological effects of coffee can be different from those of caffeine. It has been shown that intake of caffeine results in a larger increase in epinephrine concentrations than intake of the same amount of caffeine in coffee, despite similar effects on blood caffeine concentrations.<sup>59</sup> Possibly, quinides in coffee counteract this effect of caffeine by raising extracellular adenosine concentrations.<sup>60</sup> In addition, coffee contains many substances other than caffeine for which an effect on glucose metabolism is plausible. Second, the acute effects of caffeine on glucose metabolism may wane after chronic coffee consumption. This is plausible because the effect of caffeine on insulin sensitivity may be mediated through increased epinephrine concentrations,<sup>9,61</sup> and the effects of caffeine (750 mg) on epinephrine have been shown to disappear within 7 days of caffeine intake.<sup>62</sup> In a trial of very high coffee consumption (providing  $\approx$  1100 mg of caffeine), however, increased fasting insulin concentrations were found after 4 weeks,<sup>57</sup> a finding that could represent effects on insulin secretion or reduced hepatic insulin clearance in-

stead of insulin sensitivity<sup>57</sup> and this requires further study.

### CONCLUSIONS

This systematic review supports the hypothesis that habitual coffee consumption is associated with a substantially lower risk of type 2 diabetes. It is not clear what mechanisms may be responsible for the observed association, but animal and in vitro studies have suggested several plausible pathways. Paradoxically, caffeine intake acutely lowered insulin sensitivity and increased glucose concentrations in short-term intervention studies. Our meta-analysis of observational studies cannot prove causality. Longer-term intervention studies of coffee consumption, including appropriate measures of postprandial hyperglycemia and insulin sensitivity, are warranted. In addition, studies of different coffee constituents are worthwhile because this may lead to the development of coffees that can maximize health benefits. Currently, it is premature to recommend increasing coffee consumption as a public health strategy to prevent type 2 diabetes, and other health effects of coffee should also be considered.

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**Study concept and design:** van Dam, Hu.

**Acquisition of data:** van Dam.

**Analysis and interpretation of data:** van Dam, Hu.

**Drafting of the manuscript:** van Dam.

**Critical revision of the manuscript for important intellectual content:** van Dam, Hu.

**Statistical analysis:** van Dam.

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