Coffee, Decaffeinated Coffee, and Tea Consumption in Relation to Incident Type 2 Diabetes Mellitus

A Systematic Review With Meta-analysis

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Background: Coffee consumption has been reported to be inversely associated with risk of type 2 diabetes mellitus. Similar associations have also been reported for decaffeinated coffee and tea. We report herein the findings of meta-analyses for the association between coffee, decaffeinated coffee, and tea consumption with risk of diabetes.

Methods: Relevant studies were identified through search engines using a combined text word and MeSH (Medical Subject Headings) search strategy. Prospective studies that reported an estimate of the association between coffee, decaffeinated coffee, or tea with incident diabetes between 1966 and July 2009.

Results: Data from 18 studies with information on 457,922 participants reported on the association between coffee consumption and diabetes. Six (N = 225,516) and 7 studies (N = 286,701) also reported estimates of the association between decaffeinated coffee and tea with diabetes, respectively. We found an inverse log-linear relationship between coffee consumption and subsequent risk of diabetes such that every additional cup of coffee consumed in a day was associated with a 7% reduction in the excess risk of diabetes relative risk, 0.93 [95% confidence interval, 0.91-0.95] after adjustment for potential confounders.

Conclusions: Owing to the presence of small-study bias, our results may represent an overestimate of the true magnitude of the association. Similar significant and inverse associations were observed with decaffeinated coffee and tea and risk of incident diabetes. High intakes of coffee, decaffeinated coffee, and tea are associated with reduced risk of diabetes. The putative protective effects of these beverages warrant further investigation in randomized trials.

Arch Intern Med. 2009;169(22):2053-2063

By 2025, the number of individuals estimated to be affected by type 2 diabetes mellitus (DM) will increase by 65% to reach an estimated 380 million individuals worldwide, with the greatest burden being shouldered by the lower- and middle-income countries of the Asia-Pacific region. Diabetes mellitus causes substantial morbidity and mortality in those affected and is associated with enormous economic, health, and societal costs. Moreover, compared with unaffected individuals, those with DM are at greatly elevated risk of other chronic illnesses, including cardiovascular disease, in which cases DM more than doubles the risk of having a heart attack or stroke. Therefore, the identification of modifiable risk factors for the primary prevention of DM is of considerable public health importance.

Despite considerable research attention, the role of specific dietary and lifestyle factors remains uncertain, although obesity and physical inactivity have consistently been reported to raise the risk of DM. Observational epidemiologic studies have also suggested that high dietary intakes of fat, especially trans-fats, and red meat are independently associated with increased risk of DM, and conversely, that high intakes of whole grains may be protective. Other studies have highlighted the potential role that high intakes of coffee and tea may have on reducing the likelihood of developing DM.

An earlier meta-analysis suggested that individuals with the highest level of coffee consumption have approximately one-third the risk of DM compared with those with the lowest levels of consumption. However, since that review was published, the amount of information that is now available on the relationship between coffee consumption and subse-
STUDY SELECTION AND DATA EXTRACTION

Studies were included in this systematic review if they had published quantitative estimates (including variability) of the association between intake of total coffee, decaffeinated coffee, total tea (including green and black) with new-onset (incident) DM. Findings had to be adjusted for at least age and body mass index (BMI). We excluded all animal studies and, in humans, studies of type 1 DM. Given that a disease may plausibly affect dietary intake (reverse causality), we also excluded all cross-sectional studies and those case-control studies with no information on incident DM. Furthermore, we excluded studies that classified consumption only into a binary variable (ie, yes or no) without specifying the number of cups of beverage consumed per day. The literature research and data extraction were conducted by 2 of the us (C.M.Y.L. and L.T.). Where there was disagreement over the eligibility of the study, 3 more of us reviewed the article (R.H., F.B., and S.C.), and a consensus was reached.

DATA SYNTHESIS AND ANALYSIS

Given that most studies reported the association between beverage consumption and DM for more than 1 level of intake, an a priori decision was made to pool the estimates of relative risk (RR) that corresponded as closely as possible to between 3 and 4 cups of coffee, decaffeinated coffee, or tea per day, compared with none. A test for linear trend of effects across coffee consumption categories was performed by regressing each log RR on the ordered categorical variable for coffee in 5 levels using a random-effect meta-regression model. A log-linear association between cups per day and RR was fitted using generalized least squares.

For studies of specific types of tea (black, green, and oolong), only 1 estimate of the association with DM was reported, and hence, we report on the association with DM comparing tea drinkers with non-tea drinkers. Summary estimates were obtained by means of a random-effects model, and studies were weighted according to an estimate of statistical size defined as the inverse of the variance of the log RR. The percentage of variability across studies attributable to heterogeneity rather than chance was estimated using the I² statistic. Possible sources of heterogeneity were investigated by comparing summary results obtained when studies were grouped according to statistical size, sex, method of diagnosis of DM, and level of adjustment. Publication bias was assessed taking, for each study, the RR and 95% confidence interval (CI) corresponding to the highest category of coffee consumption using the Egger test. All analyses were performed using Stata software, version 10 (StataCorp LP, College Station, Texas).

STUDY CHARACTERISTICS

The search strategy identified a total of 2435 articles, of which 847 were duplicates. After a review of 1588 abstracts, 120 reports were reviewed in full (Figure 1), and 20 of these, all cohort studies, were included in our review. The sample size ranged from 910 to 88259 and totaled 517325 individuals, among whom there were 21897 cases of new-onset DM (Table). Cohorts were drawn from diverse populations, including Singapore, Puerto Rico, the United Kingdom, Finland, the United States, Japan, the Netherlands, and Sweden but included predominantly white populations, with 21% of the data derived from Asian cohorts (n=110147). The studies represented both the general population and specific occupational groups. Age at commencement of the studies ranged from 20 to 98 years, and the median duration of follow-up ranged from 2 to 20 years.

MEASUREMENT OF EXPOSURE AND OUTCOME

Apart from 1 study, which used 24-hour dietary recall to obtain an estimate of coffee consumption, all of the remaining studies used self-reported food frequency or self-administered questionnaires. Diabetes mellitus was ascertained using self-report of physician diagnoses, routinely collected hospital admission records, or direct measurement using an oral glucose tolerance test. Studies quantified the association between beverage intake and DM using RR accom-
panying 95% CIs. With few exceptions, all studies controlled extensively for a range of potential confounders. Although some studies recruited men and women, not all reported sex-specific analyses; those that did were entered separately into the meta-analysis, resulting in a total of 37 estimates of the relationship between coffee, decaffeinated coffee, and tea with risk of DM.

### Table. Characteristics of Studies Reporting on the Association Between Coffee, Decaffeinated Coffee, or Tea and Subsequent Type 2 DM

<table>
<thead>
<tr>
<th>Source</th>
<th>Sex</th>
<th>Age Range, y</th>
<th>Study Size, No. of Subjects</th>
<th>DM Event, No.</th>
<th>Follow-up, y</th>
<th>Assessment of DM</th>
<th>Variables in Multiple Adjustment Beverage Consumption*</th>
<th>Multivariate Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kato et al.40 2009, Japan (JPHC Study Cohort)</td>
<td>M</td>
<td>40-69</td>
<td>24 826</td>
<td>1601</td>
<td>10</td>
<td>SR</td>
<td>Age, BMI, smoking, alcohol, family history, PA, HT, mental stress</td>
<td>Coffee Almost never 1-2/wk 3-4/wk 1-2 3-4 ≥5</td>
</tr>
<tr>
<td>Odegaard et al.20 2008, Singapore (Singapore Chinese Health Study)</td>
<td>M and F</td>
<td>45-74</td>
<td>36 908</td>
<td>1889</td>
<td>5.7</td>
<td>SR</td>
<td>Age, year of interview, sex, dialect, education, HT, smoking, alcohol, BMI, PA, dietary variables</td>
<td>Coffee</td>
</tr>
<tr>
<td>Fuhrman et al.15 2009, Puerto Rico (Puerto Rico Heart Health Program)</td>
<td>M</td>
<td>35-79</td>
<td>4685</td>
<td>519</td>
<td>2.6 (median)</td>
<td>SR</td>
<td>Age, BMI, smoking, family history of DM, education, alcohol, PA, milk and sugar intakes</td>
<td>Coffee</td>
</tr>
<tr>
<td>Hamer et al.17 2008, United Kingdom (Whitehall II Study)</td>
<td>M and F</td>
<td>35-55</td>
<td>5823</td>
<td>387</td>
<td>11.7</td>
<td>SR</td>
<td>Age, sex, ethnicity, employment grade, BMI, WHR, smoking, sex-specific alcohol intake, PA, family history of DM, HT, cholesterol, total energy intake, diet pattern, mutual adjustment for all beverage types</td>
<td>Coffee Decaf 0-2 3-4 5-6 ≥7</td>
</tr>
<tr>
<td>Bidel et al.14 2008, Finland</td>
<td>M</td>
<td>35-74</td>
<td>10 666</td>
<td>483</td>
<td>NR</td>
<td>Age, BMI, alcohol, smoking, PA, GGT</td>
<td>Coffee Decaf 0-2 3-4 5-6 ≥7</td>
<td>1 [Reference] 0.69 (0.68-1.18) 0.77 (0.52-1.140 0.56 (0.36-0.87) 0.72 (0.59-0.86)</td>
</tr>
<tr>
<td>Smith et al.23 2006, United States (Rancho Bernardo Study)</td>
<td>M and F</td>
<td>≥50</td>
<td>910</td>
<td>84</td>
<td>8.3 OGTT</td>
<td>Age, sex, PA, BMI, smoking, alcohol, HT, FPG</td>
<td>Coffee Decaf 0-2 3-4 5-6 ≥7</td>
<td>1 [Reference] 0.66 (0.39-1.14) 0.53 (0.26-1.08) 0.60 (0.26-1.40)</td>
</tr>
</tbody>
</table>

ASSOCIATION BETWEEN COFFEE CONSUMPTION AND DM

A total of 23 estimates from 18 studies (5 studies reported sex-specific...
There was evidence of a significant inverse log-linear association such that every additional cup of coffee consumed in a day was associated with a 7% reduction in the excess risk of DM (RR, 0.93 [95% CI, 0.91-0.95]) (P < .001) (Figure 2). In categorical analysis, the pooled summary estimate from these studies indicated that drinking 3 to 4 cups of coffee per day was associated with
an approximate 25% lower risk of DM than drinking none or 2 or fewer cups per day (RR, 0.76 [95% CI, 0.69-0.82]) (Figure 3). There was evidence of significant heterogeneity across studies (P = 0.01) that was not explained by differences in the strength of effect between men and women (RR, 0.78 [95% CI, 0.70-0.87] and 0.71 [95% CI, 0.62-0.81], respectively) (P = .24 for heterogeneity); the region where the study was conducted (Europe RR, 0.84 [95% CI, 0.75-0.94] vs the United States RR, 0.73 [95% CI, 0.62-0.85]) (P = 0.15 for heterogeneity); or the method of diagnosis (national register or oral glucose tolerance test RR, 0.85 [95% CI, 0.74-0.98] vs self-report RR, 0.72 [95% CI, 0.66-0.79]) (P = 0.05 for heterogeneity).

Restriction of the analysis to those 11 studies that reported both age- and sex-adjusted estimates and estimates that were adjusted for other potential confounders (Table) indicated that the observed association was unaffected by the level of adjustment in the crude model (RR,
0.75 [95% CI, 0.67-0.85]) vs in the maximally adjusted model (RR, 0.76 [95% CI, 0.70-0.84]) (P = .81 for heterogeneity).

There was some evidence of publication bias found by the Egger test (P = .08) such that the smaller studies tended to report greater effect sizes than did the larger studies (P = .01 for trend) (Figure 4). The summary risk estimate from the 6 largest estimates (defined as having a statistical study weight >35) of drinking 3 to 4 cups of coffee per day compared with drinking none or fewer than 2 cups per day was RR, 0.85 (95% CI, 0.75-0.96), while from the 7 smallest estimates (defined as having a statistical study weight <20), it was RR, 0.62 (95% CI, 0.48-0.79).

Table. Characteristics of Studies Reporting on the Association Between Coffee, Decaffeinated Coffee, or Tea and Subsequent Type 2 DM (continued)

<table>
<thead>
<tr>
<th>Source and Population</th>
<th>Sex</th>
<th>Age Range, y</th>
<th>Study Size, No. of Subjects</th>
<th>DM Event, No.</th>
<th>Follow-up, y</th>
<th>Assessment of DM</th>
<th>Variables in Multiple Adjustment Beverage Consumption</th>
<th>Multivariate Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carlsson et al.31 2004, Finland (Finnish Twin Cohort)</td>
<td>M and F</td>
<td>30-60</td>
<td>10 652</td>
<td>408</td>
<td>20</td>
<td>NR</td>
<td>Age, sex, BMI, education, leisure, time PA, alcohol, smoking</td>
<td>Coffee ≤2 3-4 5-6 ≥7</td>
</tr>
<tr>
<td>van Dam et al.32 2004, the Netherlands (Hoorn Study)</td>
<td>M and F</td>
<td>50-74</td>
<td>1312</td>
<td>128</td>
<td>6</td>
<td>OGTT</td>
<td>Age, sex, BMI, WHR, PA, alcohol, smoking, history of CVD, use of antihypertensive medication, intake of fiber, total energy, saturated fat, polyunsaturated fat</td>
<td>Coffee ≤2 3-4 5-6 ≥7</td>
</tr>
<tr>
<td>Rosengren et al.33 2004, Sweden (BEDA study)</td>
<td>F</td>
<td>39-65</td>
<td>1361</td>
<td>74</td>
<td>18</td>
<td>SR and NR</td>
<td>Age, smoking, low PA, education, BMI, serum cholesterol, triglycerides</td>
<td>Coffee ≤2 3-4 5-6 ≥7</td>
</tr>
<tr>
<td>Salazar-Martinez et al.34 2004, United States (Health Professionals Follow-up Study and Nurses’ Health Study)</td>
<td>M</td>
<td>40-75</td>
<td>41 934</td>
<td>1333</td>
<td>12</td>
<td>SR</td>
<td>Age, smoking, low PA, education, BMI, serum cholesterol, triglycerides, history of CVD, use of antihypertensive medication, intake of fiber, total energy, saturated fat, polyunsaturated fat</td>
<td>Coffee 0 1-3 4-5 ≥6</td>
</tr>
<tr>
<td>Salazar-Martinez et al.35 2004, the Netherlands (AGIS Study)</td>
<td>M</td>
<td>30-55</td>
<td>84 276</td>
<td>4085</td>
<td>18</td>
<td>SR</td>
<td>Age, BMI, total caloric intake, family history of DM, alcohol, smoking, intakes of glycemic load, trans-fat, polyunsaturated fatty acid, cereal fiber, magnesium</td>
<td>Coffee 0 1-3 4-5 ≥6</td>
</tr>
<tr>
<td>Decaf coffee 0 1-3 4-5 ≥6</td>
<td>0.96 (0.88-1.05) 0.88 (0.80-0.97) 0.85 (0.61-1.17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tea 0 1-3 1.05 (0.97-1.15)</td>
<td>1.01 (0.92-1.11) 0.91 (0.72-1.16)</td>
<td>0.96 (0.88-1.05) 0.88 (0.80-0.97) 0.85 (0.61-1.17)</td>
<td>1.01 (0.92-1.11) 0.91 (0.72-1.16)</td>
<td></td>
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</table>
ASSOCIATION BETWEEN DECAFFEINATED COFFEE CONSUMPTION AND SUBSEQUENT RISK OF DM

Six studies (N = 225,516 participants) reported on the association between decaffeinated coffee consumption and subsequent risk of DM. The pooled summary estimates from these studies indicated that individuals who drank more than 3 to 4 cups of decaffeinated coffee per day had an approximate one-third lower risk of DM than those consuming no decaffeinated coffee (RR, 0.64 [95% CI, 0.54-0.77]) (Figure 3). There was little evidence for either significant heterogeneity across included studies (P = .31) or publication bias (P = .57 for Egger test).

ASSOCIATION BETWEEN TEA CONSUMPTION AND SUBSEQUENT RISK OF DM

A total of 7 studies (N = 286,701 participants) reported on the association between tea consumption and subsequent risk of DM. Pooled summary estimates indicated that individuals who drank more than 3 to 4 cups of tea per day had an approximate one-fifth lower risk of DM than those consuming no tea (RR, 0.82 [95% CI, 0.73-0.94]) (Figure 3). There was little evidence for significant heterogeneity across included studies (P = .46) and no evidence to indicate the presence of publication bias (P = .11 for Egger test). For studies of tea and decaffeinated coffee, there was insufficient data to permit examination of a dose-response relation. It was also not possible to examine the potential effect of confounding on the relationship because none of the studies reported both age- and multivariate-adjusted estimates.

The findings from this meta-analysis, based on over 500,000 individuals with over 21,000 cases of new-onset DM, confirm an inverse association between coffee consumption and subsequent risk of DM: every additional cup of coffee consumed in a day was associated with 5% to 10% lower risk of incident DM after adjustment for potential confounders. However, this may be an overestimate of the true magnitude of the association owing to the presence of small-study bias. Furthermore, in the first overview of which we are aware, we were able to demonstrate similar inverse associations between consumption of decaffeinated coffee and tea with risk...
of incident DM. For example, individuals consuming more than 3 to 4 cups of tea a day had a one-fifth lower risk of subsequent DM than non-tea drinkers; those consuming a similar amount of decaffeinated coffee had a one-third lower risk than nonconsumers. However, in the study by Greenberg and colleagues, consumption of decaffeinated coffee was associated with a significant 40% reduction in the risk of DM only in those aged 60 years or younger. In older individuals, the direction of association was reversed such that there was a significant 40% increase in risk. The observed age-related effect may have been a statistical artifact driven by subgroup analysis. However, we were unable to examine the effect by age, and the possibility that the association between coffee and DM risk is age dependent warrants further investigation.

That the apparent protective effect of tea and coffee consumption appears to be independent of a number of potential confounding variables raises the possibility of direct biological effects. Our findings suggest that any protective effects of coffee and tea are unlikely to be solely effects of caffeine, but rather, as has been speculated previously, they likely involve a broader range of chemical constituents present in
these beverages, such as magnesium,41 lignans,42 and chlorogenic acids.43 The effects of these coffee components on glucose metabolism and insulin sensitivity from both animal studies and in vitro experiments have been extensively reviewed elsewhere.44 While these components have been demonstrated to have beneficial effects on biological pathways intimately involved in glucose homeostasis and insulin secretion, how these findings relate to in vivo effects in humans is uncertain. Because most of the studies included in this review did not provide data on the effects of these beverages or their components on measures of hyperglycemia and insulin sensitivity, we cannot provide further evidence on the mechanisms involved. In studies that reported data on insulin sensitivity, findings were conflicting, with some suggesting that coffee use increased sensitivity to insulin,45,46 while others reported no effect.46 There have been few randomized trials of the effects of coffee on glucose and insulin, but 1 randomized crossover trial of 4 weeks’ duration of high coffee consumption reported an increase in fasting insulin levels but no effect on fasting glucose concentration.47

Possible mechanisms of action for tea on DM may involve 1 or more physiologic pathways. For example, tea catechins have been shown to inhibit the carbohydrate digestive enzymes, which suggests that glucose production may be decreased in the gastrointestinal system resulting in lower levels of glucose and insulin.48 Black, green, and oolong tea have also been reported to increase insulin sensitivity by increasing insulin-stimulated glucose uptake in adipocytes.49 There has also been the suggestion that green tea may prevent damage to pancreatic beta cells.50,51 There have been several small clinical intervention studies conducted that have examined the effects of tea consumption on biomarkers of glucose regulatory control, but the results from these studies have been inconsistent. Some studies have reported a significant reduction in plasma glucose and hemoglobin A1c levels,52,53 while others have reported no effect on any aspect of glucose-coregulatory control.54 Given that dietary polyphenols are rapidly metabolized, one explanation for the discrepant findings between these studies may have been the measurement of the effects of tea on biomarkers at different times after its consumption. For example, catechin concentrations in human plasma reach their maximum level at 2 hours after ingestion of green tea but are undetectable after 24 hours.55

That there is a causal inverse association between coffee consumption and subsequent risk of DM is further supported by the presence of a dose-response relationship. In those consuming more than 6 cups of coffee per day, the risk of new-onset DM was reduced by approximately 40% compared with non–coffee drinkers, while among those who drank less than 1 cup per day, the risk was only marginally reduced to about 4% compared with coffee abstainers. Moreover, estimates were quite similar across studies despite the diversity in populations. Of note, this similarity was presence in spite of the likely presence of marked variation between studies in types of coffee and tea and their preparation (eg, filtered vs unfiltered, cup size, cup strength, addition of milk or sugar, and other variations). Finally, the results were consistent between studies regardless of which method of diagnosis of DM was used (ie, self-report vs national register or oral glucose tolerance test).

An inherent weakness of all observational studies and meta-analyses thereof is the possibility that any association is due to the presence of confounding. However, because high levels of coffee and tea consumption have been reported to be associated with risk behaviors that are positively associated with the risk of developing DM (such as low levels of physical activity56 and cigarette smoking57), it might be speculated that adjustment for such risk factors would strengthen the relationship as has been reported. We examined the impact of confounding on the relationship between coffee consumption and subsequent risk of DM by comparing crude and adjusted estimates of effect from only those studies that reported both estimates and observed that adjustment for potential confounders had no material impact (either a strengthening or a weakening) on the estimate of effect. However, we were unable to conduct a similar analysis for tea consumption because studies only reported the adjusted estimate. Tea drinkers may be more health conscious than coffee drinkers, and it is therefore plausible that some of the observed beneficial effect of tea on DM risk is due in part to other health-promoting behaviors (eg, regular physical activity, weight maintenance, and nonsmoking) that may or may not have been taken into consideration in the original studies.

A further major limitation of this analysis is the reliance on published data, which precluded more detailed analysis of the effect of adjustment for confounders at an individual level or for specific confounders separately. In this regard, it is possible that individuals who consume extreme quantities of coffee differ in other important di-

Figure 4. Impact of study size on summary estimates of the relative risk between coffee consumption and subsequent type 2 diabetes mellitus adjusted in all cases at least for age, sex, and body mass index. The center of each black square is placed at the summary point estimate; the area of the square is proportional to the statistical size; and each horizontal line shows the 95% confidence interval about the summary estimate.

<table>
<thead>
<tr>
<th>Statistical size of study</th>
<th>Estimates People</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>7 33825</td>
</tr>
<tr>
<td>Medium</td>
<td>10 259165</td>
</tr>
<tr>
<td>Large</td>
<td>6 164982</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
</tr>
</tbody>
</table>

Relative Risk

Test for trend

\[ \chi^2 = 6.32, \ P_{\text{trend}} = .01 \]
etary and sociologic aspects from more moderate coffee consumers, but to examine this issue any further would require an individual participant data meta-analysis. Therefore, the possibility that coffee consumption may be acting as a surrogate marker of some other dietary or lifestyle risk factor cannot be fully excluded.

Finally, although the studies included in this review were all population based, only 20% of the cohorts were from nonwhite populations, which somewhat limits the generalizability of the study findings to largely Western populations. This is an important consideration given that the pattern of beverage consumption and background risk of DM may differ across ethnic groups.

In conclusion, high intake of coffee, decaffeinated coffee, and/or tea is associated with a material reduction in the risk of new-onset DM. If such beneficial effects were observed in interventional trials to be real, the implications for the millions of individuals who have DM, or who are at future risk of developing it, would be substantial. For example, the identification of the active components of these beverages would open up new therapeutic pathways for the primary prevention of DM. It could also be envisaged that we will advise our patients most at risk for DM to increase their consumption of tea and coffee in addition to increasing their levels of physical activity and weight loss.

Accepted for Publication: August 14, 2009.

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Author Contributions: Dr Huxley had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Huxley, Czer- nichow, Perkovic, and Grobbee. Acquisition of data: Timmermeister. Analysis and interpretation of data: Huxley, Lee, Barzi, Timmermeister, Perkovic, Batty, and Woodward. Drafting of the manuscript: Huxley, Barzi, Timmermeister, Czer- nichow, Grobbee, Batty, and Woodward. Critical revision of the manuscript for important intellectual content: Huxley, Lee, Czer- nichow, Perkovic, Grobbee, and Batty. Statistical analysis: Lee, Barzi, Grobbee, and Woodward. Administrative, technical, and material support: Perkovic. Study supervision: Huxley and Barzi.

Financial Disclosure: None reported.

Funding/Support: Dr Huxley is supported by a Career Development Award from the National Heart Foundation of Australia. This work was additionally supported by grant 402903 from the National Health and Medical Research Council of Australia (Dr Lee); a Research Career Development Fellowship from the UK Wellcome Trust (Dr Batty); and a research grant from Institut Servier, France and Assistance Publique-Hopitaux de Paris (Dr Czer- nichow).

REFERENCES


