Coffee, tea, and incident type 2 diabetes: the Singapore Chinese Health Study

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ABSTRACT
Background: Increasing coffee intake was inversely associated with risk of type 2 diabetes in populations of European descent; however, data from high-risk Asian populations are lacking as are data on tea intake in general.

Objective: We investigated the prospective associations between intakes of coffee, black tea, and green tea with the risk of type 2 diabetes in Singaporean Chinese men and women.

Design: We analyzed data from 36,908 female and male participants in the Singapore Chinese Health Study aged 45–74 y in 1993–1998 who had multiple diet and lifestyle measures assessed and then were followed up between 1999 and 2004. We used Cox regression models to investigate the association of baseline coffee and tea intakes with incident type 2 diabetes during follow-up, with adjustment for a number of possible confounding or mediating variables.

Results: In multivariate models participants reporting ≥4 cups of coffee/d had a 30% reduction in risk of diabetes [relative risk (RR): 0.70; 95% CI: 0.53, 0.93] compared with participants who reported nondaily consumption. Participants reporting ≥1 cup of black tea/d had a suggestive 14% reduction in risk of diabetes (RR: 0.86; 95% CI: 0.74, 1.00) compared with participants who reported 0 cups/d, and we observed no association with green tea.


INTRODUCTION

Coffee is reported to be one of the most widely consumed beverages in the world, and the potential health effects have been widely studied (1, 2). Recently, data from multiple large prospective studies in Europe and North America have shown that habitual coffee consumption is associated with a decreased risk of type 2 diabetes mellitus (3–8). It is hypothesized that a complex mixture of minerals, antioxidants, and phytonutrient compounds in coffee affect glucose metabolism (9–17). However, the precise mechanisms are unclear.

Tea is also considered one of the world’s most widely consumed beverages, only second to water by some accounts with a per capita estimate of ≈120 mL/d (18). Of the total amount of tea produced, 75% is black, 23% is green, and 2% is oolong (19). The antioxidative and biological properties of tea have led to a developing body of scientific research related to its association with multiple chronic diseases (20, 21). Diabetes-related research has shown the potential for benefits of green and black teas in glucose and insulin metabolism in rats (22–26), unclear associations in cohort studies (5, 7, 27, 28), and inconclusive evidence in trials (29, 30).

The Singapore Chinese Health Study, a population-based, hypothesis-testing, prospective cohort investigation of >63,000 Chinese men and women in Singapore presents a unique and important population in which to examine the association of coffee and green and black tea consumption in relation to the incidence of type 2 diabetes. There has been much study and reasonable consistency on the coffee-diabetes association in Western cultures on populations of similar ethnic homogeneity; however, this cannot rule out some confounding innate to these studies of similar populations. Therefore, data on this topic from studies of other ethnic groups would be highly informative. Second, not many populations outside of white populations drink substantial amounts of coffee. Probably because of its British colonial legacy and its current wealth and cosmopolitan characteristics, Singapore is an Asian country with relatively high consumption of both coffee and tea. There is a wide spectrum of consumption patterns of coffee, black tea, and green tea in this population. As such, the aim of this study was to investigate the nature of the relation between amounts of consumption of coffee, green tea, and black tea with risk of incident type 2 diabetes.

SUBJECTS AND METHODS

Participants were from the Singapore Chinese Health Study, a population-based, prospective cohort of diet and cancer risk. From April 1993 through December 1998 a total of 63,257 Chinese women and men aged 45–74 y enrolled in the study (31). Study subjects were restricted to the 2 major dialect groups of Chinese in Singapore, ie, the Hokkien and the Cantonese, who originated from the contiguous provinces of Fujian and Guangdong in the southern part of China (32). Participants were residents of government-built housing estates, where 86% of the

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Singapore population resided during the enrollment period (31). Recruitment occurred by an initial letter that informed potential participants of the study and invited them to participate. Approximately 5–7 d later, a door-to-door invitation was given; ~85% of eligible subjects who were invited responded positively (32). At recruitment a face-to-face interview was conducted in the subject’s home by a trained interviewer with the use of a structured, scanner-readable questionnaire that requested information on demographics, height, weight, use of tobacco, usual physical activity, menstrual and reproductive history (women only), medical history, and family history of cancer and a 165-item food-frequency section that assessed usual dietary intake (32). A follow-up telephone interview took place between 1999 and 2004 for 52 325 cohort members (83% of recruited cohort), and questions were asked to update tobacco and alcohol use, medical history, and menopausal status of women. The institutional review boards at the National University of Singapore and the University of Minnesota approved this study.

Assessment of coffee and tea intakes and other covariates

Dietary factors were collected with the use of a semiquantitative food-frequency questionnaire (FFQ) during the interview. The questionnaire assessed 165 food items commonly consumed in the study population, and the respondent referred to accompanying photographs to select from 8 food-frequency categories (ranging from never or hardly ever to 1–3 times/mo, once a week, 2–3 times/wk, 4–6 times/wk, once a day, 2–3 times/d, 4–5 times/d, and ≥6 times/d). The standard serving size was assigned on the questionnaire as 1 cup. Because decaffeinated coffee is rarely consumed in our study population, only caffeinated coffee was assessed; this decision was made during the development of the FFQ specific for this population (31). In addition, specific questions were asked about adding sugar, artificial sweetener, milk (all kinds), and nondairy creamer to coffee and tea with the use of the same 9 frequencies of intake but undefined amounts.

In conjunction with this cohort, the Singapore Food Composition Table was developed, a food-nutrient database that lists the values of 96 nutritive or nonnutritive components (including caffeine) per 100 g of cooked food and beverages in the diet of the Singaporean Chinese. By combining information obtained from the FFQ with nutrient values provided in this food-nutrient database, we were able to compute the mean daily intakes of caffeine and other nutrients for each subject (31).

Other known or suspected risk factors for diabetes assessed with the baseline questionnaire included age (in years), smoking habits or status (age started or quit, amount, frequency, and type), highest educational level reached, self-reported high blood pressure as diagnosed by a physician (yes or no, age, defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), body mass index (BMI; in kg/m²) calculated with the use of self-reported height and weight, frequency of moderate (eg, brisk walking, bicycling on level ground) and strenuous (eg, jogging, bicycling on hills, tennis) physical activity.

Assessment of diabetes

Self-reported diabetes as diagnosed by a physician was evaluated at baseline, and participants with a history of diagnosed diabetes were excluded from analysis. Diabetes status was assessed again by the following question asked during the follow-up telephone interview: “Have you been told by a doctor that you have diabetes (high blood sugar)”? If the answer was yes, then the following question was asked: “Please also tell me the age at which you were first diagnosed?” Participants were classified as having incident diabetes if they reported developing diabetes at any time between the initial enrollment interview and the follow-up telephone interview that occurred between July 1999 and October 2004. The average follow up time was 5.7 y.

A validation study of the incident diabetes mellitus cases used 2 different methods. First, cases were ascertained through linkage with hospital records in a nationwide hospital-based discharge summary database, an administrative database in the Singapore Ministry of Health (35). If subjects in the study had been admitted to hospitals for diagnoses with diabetes-related International Classification of Diseases codes (250.00–250.92) after recruitment into the cohort, they were considered a valid case. A total of 949 cases were validated through the linkage. Cases that did not have hospitalization records available with diabetes-related diagnoses were contacted to answer a supplementary questionnaire about symptoms, diagnostic tests, and hypoglycemic therapy during a telephone interview. A total of 1321 subjects who reported incident diabetes but had no relevant hospitalization records were contacted. Some participants (n = 619) refused or were not available for further interview, whereas 702 (53%) agreed, of which 682 (97%) were considered valid cases. A valid case had the following 3 criteria: 1) confirmed diagnosis later than the baseline interview date, 2) diabetes still present at time of interview, and 3) use of oral medications or insulin injections to treat diabetes. No difference was observed between baseline coffee or tea consumption, age, sex, BMI, education level, or other potential modifying characteristics of the participants and nonparticipants in the validation study.

Statistical analysis

We excluded from analysis any participants who died before the follow-up interview (7722); reported baseline diabetes (5696); reported cancer, heart disease, or stroke (5975); had missing BMI or physical activity data (6753); reported implausibly high (>5000 kcal) or low (<600 kcal) energy intakes; were missing data on the main exposures of interest; had ≥40 items blank on the FFQ; or were lost to follow-up (<1%). These, along with further exclusion of 20 participants whose diabetes status was not clear after the validation study, left 36 908 participants and 1889 incident cases. Analysis of only diabetes cases who participated in the validation study or had diabetes-related International Classification of Diseases codes in their hospital records did not produce materially different results compared with inclusion of all incident diabetes cases.

Person-years for each participant were calculated from the year of recruitment to the year of reported type 2 diabetes diagnosis or year of follow-up telephone interview for those who did not report a diabetes diagnosis. Relative risks per category of coffee, black tea, and green tea intake were estimated by Cox proportional hazards regression models (PROC PHREG) with simultaneous adjustment for many demographic, lifestyle, and

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dietary variables. All regression analyses were conducted with the use of SAS version 9.1 (SAS Institute, Cary, NC). No evidence was observed that proportional hazards assumptions were violated. Coffee categories were based on round and logical intake cutoffs that would also provide an ample number of participants and cases per category and are as follows: nondaily, 1 cup/d, 2–3 cups/d, and ≥4 cups/d. Black and green tea categories were based on intakes that also allowed for logical cutoffs and provided sufficient participants and cases per category and are as follows: never or monthly (0–3 cups/mo), weekly (1–6 cups/wk), and daily (1 to ≥6 cups/d). Tests for trend were computed with consumption categories as ordinal variables.

Two main models were constructed. Each model included coffee, black tea, and green tea as well as risk factors known to be associated with type 2 diabetes. The first model adjusted for age (<50, 50–54, 55–59, 60–64, ≥65 y), sex, ethnicity (Hokkien compared with Cantonese), year of interview (1993–1995, 1996–1998), education (none, primary, secondary or more), smoking (no, former, current), alcohol intake (no, monthly, weekly, daily), baseline hypertension (yes or no), BMI (continuous quadratic), moderate activity and strenuous activity (h/wk), and dietary covariates of energy intake (kcal/d), fiber intake (g/1000 kcal), total meat intake (g/1000 kcal), saturated fat (g/1000 kcal), soft drink and juice consumption (glasses/wk), and dairy intake (g/1000 kcal) in quintiles. The second model included those variables in model 1 plus components of coffee and tea intakes that may be on the causal pathway between the beverage intakes and type 2 diabetes risk. For coffee, model 2 included magnesium (in mg/d) in quintiles. For the teas, model 2 included intake in quintiles of magnesium (in mg/d) and caffeine (in mg/d) but not coffee. Pearson’s correlation coefficients between coffee and caffeine, black tea and caffeine, green tea and caffeine, and soft drinks and caffeine were 0.821, 0.102, 0.225, and 0.093, respectively. Total caffeine amounts (in mg/d) by beverage intake amount are presented in Table 1. In addition, one last set of models, including the common additions (milk, sugar, artificial sweetener, nondairy creamer in the same frequencies as each beverage) plus the variables in model 1, were run to determine whether they play any potential mechanistic role in single or logical combinations (eg, milk alone or artificial sweetener and milk). However, none of the results materially differed from model 1, so they are not presented.

RESULTS

Of 36 908 men and women, mean (±SD) age of 54.8 ± 7.5 y with 5.7 mean years of follow-up, 1889 developed type 2 diabetes. Selected characteristics of the study population according to consumption of coffee, black tea, and green tea are presented in Table 2. Seventy-one percent of the cohort reported consuming ≥1 cup of coffee/d, whereas =12% reported consuming ≥1 cup of black or green tea daily. Pearson’s correlation coefficients for coffee and black tea, coffee and green tea, and green tea and black tea were −0.146, −0.069, and 0.103, respectively. Weak positive correlations between soft drinks or juice and coffee (0.028) and between soft drinks or juice with black tea (0.092) and green tea (0.009) were observed.

Higher coffee intake was associated with being male, a lower BMI, less education, lower prevalence of hypertension, higher alcohol consumption and smoking, increased energy and decreased fiber intakes, increased caffeine intake, and low amounts of tea consumption. Daily black tea intake was associated with being male, increasing education levels, increasing alcoholic drink consumption and smoking, increasing physical activity time, and increasing energy intake. Daily green tea intake was associated with increasing BMI, prevalent hypertension, alcoholic drink consumption and smoking, physical activity time, and dietary fiber intake. Coffee consumption significantly decreased across increasing amounts of black and green tea consumption; however, both tea groups consumed ≥1 cup of coffee/d regardless of tea consumption.

Relative risks of incident type 2 diabetes by consumption of coffee, black tea, and green tea are shown in Table 3 for 2 main regression models. Participants drinking ≥4 cups of coffee/d had a 30% reduction in the risk of diabetes [relative risk (RR): 0.70; 95% CI: 0.53, 0.93] compared with participants who reported nondaily coffee consumption after adjustment for demographic, lifestyle, and dietary confounders (model 1). Further adjustment for magnesium did not alter the association. Exclusion of diabetes cases with <2 y of follow-up time did not materially alter the results. Tests for interaction of coffee consumption by sex, age, or BMI provided no evidence of effect modification.

Among daily drinkers of black tea we observed a suggestive inverse association with risk of incident type 2 diabetes. In model 1, after adjustment for demographic, lifestyle, and dietary factors we observed a RR of 0.86 (95% CI: 0.74, 1.00, P for trend: 0.07) in daily compared with never or monthly consumption of black tea. On further adjustment for caffeine and dietary magnesium in model 2, the association was slightly stronger (RR: 0.84; 95% CI: 0.71, 0.99, P for trend: 0.05). No association was observed between green tea consumption and risk of incident type 2 diabetes. Tests for interaction of black or green tea by sex, age, or BMI offered no evidence of effect modification. Regardless of how caffeine was examined in this population, it had no association with type 2 diabetes (data not shown). The hazard rate ratio from model 2 of the tea analysis for the fifth compared with the first quintile of caffeine was 0.97 (95% CI: 0.83, 1.14).

### Table 2

<table>
<thead>
<tr>
<th>Consumption Category</th>
<th>Coffee intake</th>
<th>Black tea intake</th>
<th>Green tea intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 cup/wk</td>
<td>57.6 (56.5, 58.8)</td>
<td>144.0 (142.7, 145.4)</td>
<td>145.7 (144.4, 147.0)</td>
</tr>
<tr>
<td>1 cup/d</td>
<td>115.9 (115.1, 116.7)</td>
<td>145.0 (142.7, 147.3)</td>
<td>142.5 (139.1, 145.9)</td>
</tr>
<tr>
<td>2–3 cups/d</td>
<td>240.2 (239.1, 241.2)</td>
<td>151.5 (149.1, 153.9)</td>
<td>154.7 (150.0, 159.4)</td>
</tr>
<tr>
<td>≥4 cups/d</td>
<td>437.5 (433.2, 441.7)</td>
<td>180.8 (177.5, 184.1)</td>
<td>181.8 (178.2, 185.4)</td>
</tr>
</tbody>
</table>

1. Note: 95% CI in parentheses (all such values).
<table>
<thead>
<tr>
<th></th>
<th>Coffee</th>
<th>Black tea</th>
<th>Green tea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nondaily (n = 10 737)</td>
<td>Never or monthly (n = 25 672)</td>
<td>Never or monthly (n = 25 677)</td>
</tr>
<tr>
<td></td>
<td>1 cup/d (n = 13 353)</td>
<td>Weekly (n = 6833)</td>
<td>Weekly (n = 6652)</td>
</tr>
<tr>
<td></td>
<td>2–3 cups/d (n = 11 381)</td>
<td>Daily (n = 4403)</td>
<td>Daily (n = 4579)</td>
</tr>
<tr>
<td></td>
<td>≥4 cups/d (n = 1437)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td>0.08</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>54.5 ± 7.6 ± 2</td>
<td>55.2 ± 7.6 ± 0.08</td>
<td>54.9 ± 7.5 ± 2</td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>59.0 ± 63.0 ± 1</td>
<td>62.0 ± 48.0 ± 0.08</td>
<td>59.0 ± 52.0 ± 0.08</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.0 ± 3.5 ± 2</td>
<td>23.0 ± 3.5 ± 0.001</td>
<td>22.8 ± 3.5 ± 0.0001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>21.0 ± 21.0 ± 3</td>
<td>19.0 ± 21.0 ± 0.001</td>
<td>19.0 ± 21.0 ± 0.001</td>
</tr>
<tr>
<td>Secondary education (%)</td>
<td>40.0 ± 32.0 ± 3</td>
<td>30.0 ± 41.0 ± 0.0001</td>
<td>31.0 ± 40.0 ± 0.0001</td>
</tr>
<tr>
<td>Alcohol (drinks/wk)</td>
<td>0.8 ± 0.9 ± 1.1</td>
<td>0.9 ± 1.0 ± 1.3</td>
<td>0.9 ± 1.0 ± 1.2</td>
</tr>
<tr>
<td>Ever smoked (%)</td>
<td>19.0 ± 23.0 ± 350 ± 57.0</td>
<td>26.0 ± 28.0 ± 33.0 ± 0.001</td>
<td>27.0 ± 26.0 ± 31.0 ± 0.001</td>
</tr>
<tr>
<td>Strenuous activity (min/wk)</td>
<td>16.0 ± 11.0 ± 14.0 ± 18.0 ± 13.0 ± 69.0</td>
<td>11.0 ± 60.0 ± 18.0 ± 75.0 ± 20.0 ± 76.0</td>
<td>11.0 ± 58.0 ± 18.0 ± 75.0 ± 20.0 ± 79.0</td>
</tr>
<tr>
<td>Saturated fat (% kcal)</td>
<td>8.8 ± 9.0 ± 9.1 ± 2.5 ± 9.3 ± 2.5</td>
<td>8.9 ± 9.3 ± 9.1 ± 2.5</td>
<td>8.9 ± 9.3 ± 8.9 ± 2.5</td>
</tr>
<tr>
<td>Dietary fiber (g/1000 kcal)</td>
<td>9.0 ± 8.5 ± 7.6 ± 2.3 ± 6.8 ± 2.2</td>
<td>8.3 ± 8.4 ± 8.2 ± 2.6</td>
<td>8.2 ± 8.6 ± 8.7 ± 2.8</td>
</tr>
<tr>
<td>Coffee (cups/d)</td>
<td>0.1 ± 0.2 ± 1.0 ± 0.1 ± 2.5 ± 0.3 ± 4.9 ± 0.8</td>
<td>1.5 ± 1.4 ± 5.0 ± 1.1</td>
<td>1.5 ± 1.4 ± 1.2 ± 1.1</td>
</tr>
<tr>
<td>Black tea (cups/d)</td>
<td>0.4 ± 0.4 ± 0.2 ± 0.5 ± 0.2 ± 0.5</td>
<td>0.01 ± 0.02 ± 0.3 ± 0.2 ± 1.5 ± 0.8</td>
<td>0.2 ± 0.5 ± 0.3 ± 0.5 ± 0.3 ± 0.7</td>
</tr>
<tr>
<td>Green tea (cups/d)</td>
<td>0.4 ± 0.9 ± 0.3 ± 0.7 ± 0.2 ± 0.7</td>
<td>0.3 ± 0.8 ± 0.4 ± 0.8</td>
<td>0.01 ± 0.02 ± 0.3 ± 0.2</td>
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</tbody>
</table>

* x ± SD (all such values).
and dietary variables. A recent clinical study found that glucose intolerance because of caffeine consumption was associated (8) and more strongly inversely associated than caffeine with incident type 2 diabetes (38). In addition, a more plausible mechanism from a recent meta-analysis and prospective cohort study may be that coffee drinking may be inversely associated with type 2 diabetes risk in our cohort; thus, it did not change the relative risks for coffee intake. Caffeine’s possible role in type 2 diabetes risk is still unclear, and caffeine and coffee may be too highly correlated to take any mechanistic analysis approach. Hypotheses on specific bioactive components are driven by laboratory and clinical studies relating to chlorogenic acid, a phenolic compound in coffee (9, 48, 49), quinides (12), and the potential of polyphenolic compounds contributing to a lower iron status (50, 51). Moreover, another hypothesis is coffee’s high antioxidant activity, and a high antioxidant contribution to the diet may reduce free radical oxidative stress or potentially promoting insulin sensitivity in the peripheral tissues (17).

Unlike most other studies on this topic, we specifically assessed green and black teas, whereas past studies have typically grouped tea types into one category and have reported null findings (5, 7, 27, 53). A retrospective cohort study in a Japanese population showed that a high intake of green tea, but not black tea, was associated with a decreased risk of type 2 diabetes (28). However, there are potential methodologic concerns in that study with respect to population selection and follow-up because the final analysis included only 17,413 of the original 110,792 participants. Of note, that study did observe a much higher intake of green tea than in our study.

In our study we were not able to assess specific mechanisms beyond any contribution magnesium and caffeine may play in the tea-diabetes association. Although our results in the main model are only suggestive of an inverse association between black tea intake and risk of type 2 diabetes, if there is a true causal relation, it may be explained by a number of plausible mechanisms from...
laboratory and clinical investigations related to improved glucose metabolism (22–26), antiinflammatory activity (54), insulin-potentiating activity (55), and the ability of tea extracts to induce malabsorption of carbohydrates in humans (30). Those studies all considered tea from the plant *Camellia sinensis*, as opposed to herbal teas that do not contain any leaves from the plant.

To our knowledge this is the first large prospective study addressing the topic of coffee, black tea, and green tea consumption and incident type 2 diabetes in an Asian population. Other strengths of this study include the high participant response rate, <1% lost to follow-up, data obtained through a detailed face-to-face interview that included a FFQ specific to this population, and validated diabetes case status with a high positive predictive value obtained through the validation study.

Limitations include potential misclassification of the exposures because of poor self-report, biases, and other errors; this would probably bias the results toward the null, assuming it is nondifferential in nature. Residual confounding as an explanation also needs to be considered, yet this appears unlikely to play an important role because of the observation that the relative risk for the coffee and diabetes association was strengthened (away from the null) when we adjusted for lifestyle and dietary factors. In addition, we have not estimated the negative predictive value of our diabetes definition, although missing cases in this manner would tend to bias the relative risks toward the null; this is a relatively benign threat to the validity of the study given the findings for coffee and diabetes risk. In addition, although we were able to study both black and green tea consumption, our results only apply to a smaller range of intake compared with coffee.

In conclusion, we observed a significant inverse association between coffee consumption and risk of incident type 2 diabetes mellitus in middle-aged Chinese men and women of Singapore. We also observed a suggestive inverse association between black tea consumption and incident type 2 diabetes in a population at high risk of developing type 2 diabetes. These findings are important because coffee and tea are 2 of the most commonly consumed beverages worldwide and other prospective studies on this topic have been restricted to essentially European-based populations, whereas Asians have among the world’s highest rates of type 2 diabetes. Second, we were able to take advantage of our rich data set and the unique dietary patterns in Singapore to simultaneously examine the associations of coffee, black tea, and green tea in the same analysis. The associations we observed are noteworthy because they provide evidence that the coffee findings in other prospective cohort studies are not likely artifacts of the reported dietary patterns, nor are they likely to be explained by residual confounding. Further human studies, especially clinical trials, are needed to investigate the role of long-term coffee and tea consumption, and their innate bioactive compounds, in relation to the risk of type 2 diabetes mellitus. Indeed, diet plays an important role in the prevention of diabetes. Given the high consumption of coffee and tea worldwide and the growing type 2 diabetes epidemic, especially in Asia, these findings convey a potential high significance for public health. However, it is too early to recommend increasing coffee and tea consumption until there is more thorough data from clinical trials related to the topic, with respect to not only the possible benefits but possible side effects or harm as well.

We thank Ms. Siew-Hong Low (National University of Singapore) for supervising the field work of the Singapore Chinese Health Study and Ms. Kazuko Arakawa (University of Minnesota) for the development and management of the cohort study database.

The author’s responsibilities were as follows—AOO: contributed to the study design, conducted the statistical analysis, and wrote the first draft of the paper along with editing of further drafts; MAP (guarantor): contributed to the study design, statistical analysis, and writing and editing of the paper; W-PK and MCY: contributed to the study design and writing and editing of the paper; KA: contributed to the statistical analysis and editing of the paper; H-PL: made important contributions to the writing of the paper. None of the authors had a personal or financial conflict of interest.

REFERENCES