Tea consumption and risk of stroke in Chinese adults: a prospective cohort study of 0.5 million men and women

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Short running head: Tea consumption and incident stroke in Chinese

Abbreviations:
BMI, body mass index;
CDC, Chinese Center for Disease Control and Prevention;
CIs, confidence intervals;
CKB, China Kadoorie Biobank;
HR, hazard ratios;
ICD-10, the 10th revision of the International Classification of Diseases;
KG, kilogram(s);
MET-hr/day, metabolic equivalent hours per day;
MmHg, millimetres of mercury;
Mmol/L, millimolar per liter;
SD, standard deviation.

ABSTRACT

Background: Many cohort studies have explored the relationship between tea consumption and stroke risk; however, the conclusions have been inconsistent. In addition, evidence is lacking in China, where the patterns and main types of tea consumed differ substantially from those in high-income countries.

Objectives: To systematically assess the association of tea consumption with the risk of stroke based on a Chinese large-scale cohort study.

Methods: A total of 487,377 participants from the China Kadoorie Biobank (CKB) were included in the present study. Detailed information about tea consumption (including frequency, duration, amount, and tea type) was self-reported at baseline. After approximately 4.3 million person-years of follow-up, 38,727 incident cases of stroke were recorded mainly through linkage with mortality and morbidity registries and based on the national health insurance system.

Results: Overall, 128,280 adults (26.3%) reported drinking tea almost daily (41.4% men, 15.9% women), predominantly green tea (86.7%). Tea consumption had an inverse and dose-response relationship with the risk of stroke ($P_{trend} < 0.001$). Compared with nonconsumers, those who consumed tea occasionally, weekly, and daily had adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of 0.96 (0.94, 0.99), 0.94 (0.90, 0.98), and 0.92 (0.89, 0.95) respectively, with little difference by stroke type. Among those who consumed tea daily, the HRs for stroke decreased with the increasing duration and amount of tea consumed (all $P<0.001$). These inverse associations remained significant for green tea but not for other types of tea. Among men, but not women, the inverse relationships could be detected, and the similar inverse associations could be found for male noncurrent alcohol-consumers and noncurrent smokers as well.

Conclusion: Among Chinese adults, a high level of tea consumption, especially green tea, was associated with a reduced risk of ischemic and hemorrhagic stroke.

Keywords: Tea consumption; stroke, risk; association; cohort study; China; CKB.

INTRODUCTION

Tea is one of the most frequently consumed beverages worldwide (1), with the global consumption level increasing annually. In China, a key tea-producing and exporting country worldwide, there are many tea consumers (2). Given the widespread consumption of tea, it is important to understand its potential health effects in diverse populations (1, 3). Over the past decades, exploratory research has reported that tea may influence the risks of numerous diseases, including cardiovascular disease, diabetes mellitus, and cancer (2-4).

In 1989, it was originally proposed that drinking tea might contribute to the prevention of stroke (4).Thereafter, various studies, including experimental and population-based studies, were conducted to explore the relationship between drinking tea and stroke risk (5-7). Experimental evidence has shown that polyphenols, which are important constituents of tea, can inhibit the development of atherosclerosis, have anti-inflammatory properties, improve endothelial function, and contribute to protection against stroke (8, 9). Many previous population-based cohort studies have explored the relationship between tea consumption and stroke risk (1, 10-14). Nevertheless, these prospective studies have failed to reach a consistent conclusion: some studies confirmed the negative correlation between tea intake and stroke risk (13), but the others did not obtain similar results (14). Relatively small sample sizes, lack of reproducibility of tea consumption data, nonrepresentative study populations, and the absence of important modified factors might have led to the above mentioned different results.

The existing cohort studies mainly originated from Western and Japanese populations. The commonly consumed tea types (green tea or black tea), habits of tea drinking (drinking tea with or without milk), production regions and manufacturing technologies of tea (i.e., different technologies for green removing) are very different among populations from various countries (15-17), which might also result in inconsistent associations of tea consumption with stroke risk.

As mentioned above, most of the related cohort studies focusing on tea consumption and stroke risk were conducted in Western and Japanese populations (1, 10-12). However, in China, a country with one of the highest levels of tea consumption, evidence related to this association from a cohort study is still lacking. Moreover, the incidence of hemorrhagic stroke is higher in China than in Western countries (18, 19), where most strokes are of the ischemic type.

Therefore, in this study, based on the large prospective cohort of the China Kadoorie Biobank (CKB) with more than 0.5 million participants, we integrally evaluated the relationship between tea consumption and the risk of stroke, including the different types (including ischemic and hemorrhagic stroke), in the Chinese population.

METHODS

Study population

The details of the prospective cohort design, procedure, population characteristics and other information related to the CKB have been reported elsewhere (20, 21). Overall, 515,681 persons attended the baseline survey between 2004 and 2008. After quality control of the data, a total of 512,891 individuals, from 30 to 79 years old, were recruited (**Supplemental Figure 1**) (20). For this study, we excluded 8884 individuals with stroke or transient ischemic attack, 15,472 persons with heart disease, and 2577 persons with cancer at baseline. After the above exclusions, our final analyses included 487,377 individuals, consisting of 199,294 men and 288,083 women (Supplemental Figure 1).

Prior to the baseline survey, each participant provided written informed consent. The study was approved by the Ethics Review Committee of the Chinese Center for Disease Control and Prevention (CDC), the Oxford Tropical Research Ethics Committee, the University of Oxford, and the institutional research boards at the local CDCs in the ten geographically diverse areas.

Data Collection

At the local assessment clinics, detailed information about demographic and socioeconomic status (age, sex, residential area, education, marital status, and household income), lifestyle behaviors (smoking status, alcohol consumption, physical activity, and intakes of red meat, fresh vegetables and fruits), personal medical history (hypertension and diabetes), family medical history (stroke or transient ischemic attack), and other indexes (height and weight) were collected by trained health workers.

The daily physical activity was calculated for each participant by summing the metabolic equivalent hours per day (MET-hr/day). Body mass index (BMI) was calculated as weight (kilograms; kg) divided by the square of height (square meters; m^2). Habitual dietary intake (including red meat, fresh fruits, and fresh vegetables) over the past 12 months was assessed using a qualitative food frequency questionnaire. The diagnostic criteria for prevalent hypertension in our study included measured systolic blood pressure ≥ 140 millimeters of mercury (mmHg), measured diastolic blood pressure ≥ 90 mmHg, self-reported hypertension, or use of medicine for hypertension at baseline. Diagnostic criteria for prevalent diabetes included measured fasting blood glucose ≥ 7.0 millimolar per liter (mmol/L), measured random blood glucose ≥ 11.1 mmol/L, or self-reported diabetes.

Assessment of tea consumption

All participants were required to answer the question of how often they had consumed tea during the past 12 months, and this question had five choices (never or almost never, only occasionally, only in certain seasons, every month but less than weekly, and usually at least once a week).

Individuals who usually consumed tea at least once a week were further required to answer other questions, including how many days they drank tea in a typical week (1-2 days/week, 3-5 days/week, or daily or almost every day) and which type of tea they consumed most commonly (green tea, oolong tea, black tea, or other tea). In addition, among the above participants, additional data were collected, including the number of cups of tea consumed (based on a 300 ml-sized cup) in a drinking day, tea leaves (in grams) added each time, the number of times that the tea leaves were changed during one consuming day, and the age at which they began to drink tea continuously. Each participant was offered a pictorial guide that showed the size of a standard cup and different grams of tea leaves. The tea leaves added during one drinking day were calculated by multiplying the amount added each time by the number of times the tea leaves were changed.

In the present analyses, according to the frequency of tea consumption, all individuals were classified into four categories: never, occasionally (including only occasionally, only in certain seasons, and every month but less than weekly), weekly (i.e., weekly but less than daily), and daily. In addition to some common indexes (duration, daily cups, and daily grams of tea consumed), we introduced another two indicators to measure the amount of tea consumption, which were generated by multiplying the daily cups of tea consumed by the years of tea drinking, and multiplying the daily grams of tea consumed by years of tea drinking. Furthermore, daily tea drinkers were divided into different classifications on the basis of tertiles of the different tea consumption indexes, including the duration of tea consumption (<19, 19-30, or >30 years), daily grams of tea consumption (<2, 2-4, or >4 grams/day), daily cups of tea consumption (<2, 2-4, or >4 cups/day), number of gram-years of tea consumption (<46, 46-105, or >105 gram-years), and number of cup-years of tea consumption (<35, 35-105, or >105 cup-years).

To test the reproducibility of the tea consumption data, Li et al. analyzed the two investigated results of the frequency of tea consumption for part of the participants at different times, and reported that the weighted kappa coefficient for drinking tea was 0.77 (22). Additionally, the accuracy of the baseline information (including tea consumption) could be guaranteed by several quality control methods, including quality control surveys, monitoring, and re-surveys, and the details have been described in previously published papers (20).

Follow-up for mortality and morbidity

Incident stroke, including mortality and morbidity, was the end point of the present follow-up study. The detailed information of the long-term follow-up was described in the previously published paper (22, 23). Briefly, cause-specific mortality and morbidity were ascertained through electronic linkage via the unique personal identification number to electronic hospital records from the nationwide health insurance system (which has more than 98% coverage across the ten study regions), to established local disease registries and to local death registries. The accuracy of reported stroke types was verified by a review of the original medical records by a panel of certified neurologists and stroke physicians in China. Among the stroke cases selected, more than 90% were confirmed by using brain imaging (23).

The 10^{th} revision of the International Classification of Diseases (ICD-10) was used to code incident strokes, such as ischemic stroke (I63), hemorrhagic stroke (subarachnoid (I60) or intracerebral (I61)) and other or unknown stroke types (I64), by trained staff who were "blinded" to the baseline information.

Statistical analysis

In this study, means (standard deviations; SDs) or percentages were calculated to describe the

baseline characteristics of the participants, adjusting for age, sex, and residential area as appropriate, by using either multiple linear regression (for continuous outcomes) or logistic regression (for binary outcomes). Follow-up time (person-years) was calculated for each participant from the baseline date to the date of the incidence of stroke, loss to follow-up, or December 31, 2015 (the end of follow-up in this study), whichever occurred first. The Cox proportional hazards regression model, stratified jointly by age at baseline in 5-year intervals, sex and study area (ten regions), was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). To determine the proportional hazards assumption for the Cox model, graphs and tests based on Schoenfeld residuals were applied, and no violation was identified. The multivariate adjusted HRs of stroke were estimated with the following adjustments: age (continuous); sex (man or woman); level of education (no formal school, primary school, middle school, high school, technical school/college, or university); marital status (married, widowed, divorced/separated, or never married); household income (<2500, 2500-4999, 5000-9999, 10,000-19,999, 20,000-34,999, or ≥35,000 yuan/year); alcohol consumption (nonconsumer, occasional consumer, ex-consumer, or current regular consumer); smoking status (never smoker, occasional smoker, ex-smoker, or current regular smoker); physical activity (continuous); BMI (continuous); prevalent hypertension or prevalent diabetes at baseline (presence or absence); intake frequencies of red meat, fresh fruits, and vegetables (daily, 4 to 6 days/week, 1 to 3 days/week, monthly, or rarely or never); and family history of stroke (presence or absence). Linear trends of stroke risk related to different tea consumption patterns were calculated by modeling the levels of frequency of tea consumption and the years or the amount of tea consumption as continuous variables in separate models.

For the present study, we explored the relationships between tea consumption and incident stroke in accordance with the frequency, years, and amount of tea consumption using individuals

who never consumed tea during the past year as a reference. Stratified analyses were carried out to examine whether the associations of daily tea consumption with incident stroke differed according to the median age (<50 or ≥50 years), sex (man or woman), residential area (rural or urban), marital status (married or widowed/separated/divorced/never married), education (illiterate/primary school or middle school and above), household income (<35,000 or ≥35,000 yuan/year), smoking status (never or ever), alcohol consumption (never or ever), median physical activity (<18.10 or ≥18.10 MET-hr/day), BMI (<24.00, 24.00-28.00, or ≥28.00 kg/m^2), hypertension (yes or no), or diabetes (yes or no). The test for the interaction was performed using a likelihood ratio test comparing models with and without a cross-product term. We intended to conduct sensitivity analyses by excluding the first two years of follow-up, excluding the participants younger than 40 years of age, and additionally adjusting for waist-to-hip ratio. Additionally, to eliminate residual confounding related to the important effect factors (i.e. smoking), we conducted an association analysis among certain participants (i.e., noncurrently smoking males).

All confidence intervals were estimated at the 95% level. All statistical tests were two-sided and significance was defined as $P < 0.05$. The statistical analyses were performed with R software (Version 3.4.2, 2017-09-28; R Foundation for Statistical Computing, http://www.cran.r-project.org/).

RESULTS

Of the individuals included in this study, 40.9% of the participants (199,294) were male. In both men and women, compared with never tea consumers during the past 12 months, many characteristics of participants who consumed tea more frequently were much different, including residence area, age, household income, smoking, alcohol consumption, etc. (**Table 1**). In total,

128,280 individuals (26.3%) reported drinking tea almost daily among all participants (**Supplementary Table 1**). Approximately 41.4% and 15.9% of individuals consumed tea daily among men and women, respectively. Green tea was the most commonly consumed tea type among daily tea consumers (86.7%). Among all of the daily tea consumers, the males showed a longer duration of tea consumption (25.11 *vs.* 24.15 years) and a greater amount of tea consumed (4.78 *vs.* 3.33 grams/day; 117.00 *vs.* 81.00 gram-years) than the females, as shown in Supplemental Table 1.

During the 4,289,584 person-years of follow-up, a total of 38,727 incident stroke cases (approximately 9.03 cases/1000 person-years) were identified (including 30,312 ischemic stroke, 6945 hemorrhagic stroke and 1470 other stroke cases). The frequency of tea consumption was inversely associated with the risk of incident stroke in either the age- and sex- or multivariable-adjusted models ($P_{trend} < 0.001$). Compared with individuals who never consumed tea, the multivariable-adjusted HRs (95% CIs) of incident stroke were 0.96 (0.94, 0.99), 0.94 (0.90, 0.98), and 0.92 (0.89, 0.95) for those who consumed tea occasionally, weekly, and daily, respectively. The inverse relationship persisted for both ischemic and hemorrhagic stroke (**Table 2**). Moreover, the risk of incident stroke among daily tea consumers decreased with increasing duration and amount of tea consumed compared with the risk of nonconsumers, which was also the case for both ischemic and hemorrhagic stroke (**Table 3**).

As shown in **Table 4**, the frequency of tea consumption was strongly associated with a reduced risk of incident stroke among male participants: the multivariable adjusted HRs (95% CIs) were 0.94 (0.90, 0.98), 0.88 (0.82, 0.94), and 0.89 (0.85, 0.93) for occasional, weekly, and daily tea consumers versus nonconsumers ($P_{trend} < 0.001$), respectively. For the females, although the association of tea consumption with stroke risk was not obvious for either ischemic or hemorrhagic stroke, the risk of total stroke presented a declining trend as the tea consumption

increased with near statistical significance (P_{trend} = 0.053, Table 4). Furthermore, among daily tea consumers, the risk of stroke significantly decreased with the increased duration and amount of tea consumed in men, while there were no similar findings for women (**Supplemental Table 2** and **Supplemental Table 3**).

We further investigated the associations between different types of tea and stroke risk (**Figure 1** and **Supplemental Table 4**). After multivariate adjustment, the frequency of green tea consumption was inversely related to total stroke and the two main stroke types. In contrast, there was no significant association between nongreen tea consumption and stroke risk. Additionally, consistent results were observed in the relationships between different types of tea and stroke risk, regarding the duration and amount of tea consumed (**Supplemental Table 5** and **Supplemental Table 6**).

We analyzed the relationships of daily tea consumption with stroke risk in specific population subgroups (**Figure 2**). The strength of the associations of tea consumption with the risk of stroke was largely consistent across subgroups, which were classified by age, smoking status, alcohol consumption, physical activity, BMI, hypertension, and diabetes ($P_{heterogeneity}$ > 0.05, Figure 2), but the residential region subgroup was not consistent (rural versus urban) ($P_{heterogeneity}$ = 0.031): stroke risk was significantly lower in the rural areas, but not in the urban regions.

To eliminate residual confounding factors related to important effect factors, we conducted an association analysis among noncurrent smokers (including nonsmokers), and we discovered a negative correlation (**Supplemental Table 7**). In addition, a similar inverse association could also be found for noncurrent alcohol consumer (including nonconsumers) among men (Supplemental Table 7). Excluding the participants younger than 40 years of age did not substantially modify the observed relationship (**Supplementary Table 8**), and the same was true for additional adjustment

for waist-to-hip ratio and excluding the first two years of follow-up (data not shown).

DISCUSSION

In this study, we observed that the frequency of tea consumption was related to a decreased risk of stroke. Compared with nonconsumers, daily tea consumers had an 8% lower risk of stroke. According to the type of tea, green tea consumption was significantly associated with a reduction in stroke risk; however, this was not the case for nongreen tea. The inverse relationships were significant among men but not among women.

Several prior prospective studies have explored the association of tea consumption with stroke (1, 10-14). Nevertheless, previous cohort studies have shown inconsistent results. For instance, Kokubo et al. reported that compared with nonconsumers, the HRs (95% CIs) of stroke were 0.86 (0.78, 0.95) and 0.80 (0.73, 0.95) for tea consumers who drank 2-3 and ≥ 4 cups of tea/day, respectively (with 82,369 participants) (13). No such significant association, however, was identified in the European Prospective Investigation into Cancer and Nutrition study with 37,514 participants (14). A recent meta-analysis of prospective studies involving 513,804 participants identified that an increase in tea consumption of three cups/day was related to a 13% decreased risk of stroke (24). The 14 studies in this meta-analysis were mainly from Japan, Europe and America, where the commonly consumed tea types (black tea in Europe, while green tea is more common in China), tea green removing technologies (stir-frying green in Japan, while steaming green in China), tea-drinking habits (usually drinking tea with milk in Europe, while uncommon in China), and other factors were different from those in China (15-17).

Currently, there is no standard population-based prospective study focusing on the association of drinking tea with stroke in a Chinese population. A Chinese case-control study reported that a significant decline in the risk of ischemic stroke was associated with tea

consumption (25). A similar negative relationship was observed in our current study. In addition to using a cohort study design with stronger causal verification ability and involving a larger sample size (0.5 million), our study analyzed the main types of stroke (ischemic and hemorrhagic stroke), controlled confounding factors more stringently, and included stricter quality control than the above mentioned case-control study.

Tea is divided into three main categories, i.e., green, black, and oolong tea, according to the degree of fermentation during processing: green tea is nonoxidized and black and oolong tea are oxidized and partially oxidized, respectively (26). The different manufacturing processes could affect the components of tea and further influence the functions of tea related to stroke (27). For example, green tea had higher antioxidant properties than nongreen tea, indicating possibly different effects on stroke risk. In accord with the above mentioned situation, our study identified the different effects of green and nongreen tea on stroke risk. Similar to our results, Tanabe et al. found that green tea consumption was associated with reduced stroke risk, but an inverse relationship could not be observed between other kinds of tea and stroke risk (11). In addition, a meta-analysis revealed that green tea consumption was related to stroke risk, but did not find similar effects of other types of tea (3). In our study, the minority of tea drinkers consumed black and oolong tea, which might affect our further exploration of the effects of the two kinds of tea on stroke risk.

We found that tea consumption was strongly associated with a reduced stroke risk among men, while similar evidence was lacking for women. The proportion of tea consumers was 80.8% and 45.8% among males and females, respectively. Additionally, compared with women, the proportion of daily tea consumers and the duration and the amount of tea consumption for male tea consumers were both significantly greater, which might partly explain why the protective effects of tea consumption on stroke were more significant for men. It was reported that

differences in risk factors between men and women could strongly affect stroke risk. Alcohol abuse and cigarette smoking were proposed to be leading risk factors for men (28, 29). Both factors were adjusted in our analyses and to avoid residual confounding, we limited the analyses only to male noncurrent smokers/noncurrent alcohol consumers, and the results still revealed a negative relationship between tea consumption and stroke risk. For women, it has been reported that two factors, atrial fibrillation and stress, were more prevalent (28, 29). Nevertheless, due to lack of related information, the two above effect factors were not adjusted, which might somewhat modify the results among women.

Increasing evidence has shown that the protective effects of tea on stroke risk might have different biological bases (5-7). Tea polyphenols, which are the most important components in tea, especially green tea, could exert a wide spectrum of beneficial effects, including modulating the plasma lipid profile, decreasing plasma glucose, and reducing the risk of atherosclerosis, all of which are vital risk factors for stroke (8, 9, 30). Furthermore, catechin, a major category of polyphenols, might block increases in the serum nitric oxide concentration and improve endothelial function, which could also reduce stroke risk (31, 32). Additionally, tea could significantly reduce blood pressure, which is the most predominant risk factor for stroke (31, 32).

The results of this prospective study with 0.5 million participants from ten geographic areas might be a good representation of the situation of some Chinese adults. Moreover, the indicator, grams of tea consumed, was a vital analysis index in our study and might better reflect the amount of tea consumed than other indexes. In addition, based on daily grams/cups and years of tea drinking, we proposed new indexes to indicate the accumulated amount of tea consumed. This study also has some limitations. First, although we adjusted for many influencing factors in the analyses according to previously published studies (22, 33), residual confounding caused by other dietary patterns, total energy intake, blood cholesterol level, etc. still persisted due to a lack

of related information, which might affect our results to some extent. In order to achieve the real causality of associations, in future studies, more detailed information about dietary factors should be gathered and randomized controlled trials should be considered. Second, coffee might confound our results as well. In China, apart from tea, the major beverage might be water, at least among middle-aged or elderly populations, with very little consumption of coffee based on the findings of other nationwide surveys during the early 2000s (34). Additionally, both resurveys (one during 2008; the other during 2013-2014) showed that less than 2% of randomly chosen participants consumed coffee at least once a week (22, 35). Third, information on tea consumption at baseline was collected based on self-report by using a simple qualitative questionnaire. According to the previously published CKB study, the weighted kappa coefficient for drinking tea was 0.77, which means that the consistency is quite satisfactory (22). However, further validation against gold standards including circulating biomarkers of tea metabolites could not be conducted. Fourth, although the *P* value for the trend test showed statistical significance, there was limited evidence of the dose-response relationship between tea consumption and stroke risk. First, the protective effect of tea consumption was relatively modest; second, some other unavailable risk factors might have a certain impact on the relationship.

In summary, the large Chinese cohort study demonstrated that a high level of tea consumption, especially green tea, was inversely related to the risks of total stroke and different stroke types, including ischemic and hemorrhagic stroke. Further experimental studies are required to explore the causal relationship.

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The CKB data access policy and procedures are available at www.ckbiobank.org. And all researchers can apply to use the CKB data by registering and applying at the website: http://www.ckbiobank.org/site/Data+Access.

The authors' contributions were as follows—TT, HS and ZH: conceived and designed the research; TT and GJ: performed the statistical analyses; all authors: contributed to interpretation of the results; TT and GJ: drafted the manuscript; JL, HS, ZC and LL: supervised the conduct of research and had primary responsibility for final content; and all authors: reviewed the manuscript for important intellectual content, and read and approved the final manuscript.

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Table 1. Baseline characteristics of the study participants according to the frequency of tea consumption.[1]

Characteristics	Men (N=199,294)				Women (N=288,083)			
	Never	Occasional	Weekly	Daily	Never	Occasional	Weekly	Daily
Participants, n	38,360	58,527	19,940	82,467	131,974	94,595	15,701	45,813
Age, years (SD)	51.95±11.23	51.88±10.59	51.82±10.46	51.75±10.52	50.92±10.61	50.45±9.88	49.99±9.81	49.52±10.18
Rural area, %	58.95	58.05	57.15	56.25	55.05	56.72	58.39	60.03
Married, %	92.95	93.39	93.80	94.19	92.31	92.63	92.93	93.23
Middle school and higher, %	64.00	61.84	59.63	57.38	35.54	41.51	47.75	54.05
Household income≥35 000yuan/year, %	13.81	17.00	20.76	25.09	15.04	16.45	17.98	19.61
Ever smoker, [2] %	79.09	83.96	87.87	90.93	3.49	4.11	4.82	5.65
Ever alcohol consumer,[3] %	80.68	81.09	81.50	81.89	34.80	36.23	37.69	39.17
Physical activity, MET-hr/day (SD)	22.64±16.79	22.62±15.68	22.61±14.08	22.59±14.47	22.02±13.53	20.71±12.53	19.40±12.01	18.09±11.11
Body mass index, [4] kg/m^2 (SD)	23.42±3.17	23.40±3.20	23.38±3.26	23.36±3.27	23.65±3.44	23.76±3.36	23.86±3.38	23.97±3.56
Average weekly consumption [5]								
Red meat, day (SD)	3.39±2.61	3.73±2.53	4.07±2.39	4.41±2.43	3.18±2.53	3.57±2.49	3.95±2.39	4.34±2.41
Fresh vegetables, day (SD)	6.84±0.78	6.84±0.74	6.84±1.04	6.84±0.72	6.79±0.89	6.84±0.70	6.89±0.75	6.93±0.53
Fresh fruits, day (SD)	2.06±2.31	2.17±2.31	2.28±2.32	2.40±2.31	2.49±2.47	2.79±2.59	3.09±2.64	3.39±2.61
Diabetes, %	4.39	4.34	4.30	4.26	4.46	4.54	4.62	4.70
Hypertension, %	34.40	34.72	35.04	35.36	30.36	29.80	29.25	28.70
Family history of stroke, %	21.41	19.14	17.06	15.16	18.33	17.31	16.33	15.40

[1]The results are presented as the means±standard deviations (SDs) or percentages, which were adjusted for age and residential region, as appropriate, by using either multiple linear regression (for continuous outcomes) or logistic regression (for binary outcomes). All baseline characteristics were associated with the frequency of tea consumption, with $P<0.001$ across categories, except for physical activity ($P=0.468$), body mass index ($P=0.002$), fresh vegetable intake ($P=0.250$), and diabetes ($P=0.213$) among men and diabetes ($P=0.019$) among women.

[2] Ever smokers included occasional smokers, ex-smokers, and current regular smokers.

[3] Ever alcohol consumers included occasional alcohol consumers, ex-alcohol consumers, and current regular alcohol consumers.

[4] Body mass index was defined as the body weight divided by the square of the height.

[5]Average weekly intakes of red meat, fresh vegetables and fresh fruits were calculated by assigning participants to the midpoint of their consumption category (daily, 4-6 days/week, 1-3 days/week, monthly, or rarely or never).
MET-hr/day, metabolic equivalent hours per day.

Table 2. Association of frequency of tea consumption with the risk of stroke among 487,377 participants.

Stroke type	No. of participants	Frequency of tea consumption				P_{trend} [4]
		Never	Occasional	Weekly	Daily	
No. of participants	487,377	170,334	153,122	35,641	128,280	
No. of person years	4,289,584	1,492,052	1,353,461	316,773	1,127,298	
Total stroke [1]						
No. of cases	38,727	16,283	10,628	2341	9475	
Model 1 [2]		1.00	**0.95 (0.93, 0.98)**	**0.94 (0.90, 0.99)**	**0.94 (0.91, 0.97)**	**<0.001**
Model 2 [3]		1.00	**0.96 (0.94, 0.99)**	**0.94 (0.90, 0.98)**	**0.92 (0.89, 0.95)**	**<0.001**
Ischemic stroke						
No. of cases	30,312	13,291	8394	1798	6829	
Model 1 [2]		1.00	**0.96 (0.93, 0.98)**	0.96 (0.91, 1.01)	**0.96 (0.93, 0.999)**	**0.040**
Model 2 [3]		1.00	**0.96 (0.93, 0.98)**	**0.94 (0.90, 0.995)**	**0.92 (0.89, 0.96)**	**<0.001**
Hemorrhagic stroke						
No. of cases	6945	2421	1836	449	2239	
Model 1 [2]		1.00	**0.92 (0.86, 0.98)**	**0.86 (0.77, 0.95)**	**0.85 (0.79, 0.92)**	**<0.001**
Model 2 [3]		1.00	0.96 (0.90, 1.03)	**0.89 (0.80, 0.99)**	**0.86 (0.80, 0.93)**	**<0.001**

Values were obtained from a Cox proportional hazards analysis.

[1] Including hemorrhagic stroke, ischemic stroke and stroke of unknown type.

[2] Model 1: Hazard ratios (95% confidence intervals) was achieved after adjusting for age and sex.

[3] Model 2: Hazard ratios (95% confidence intervals) was achieved after adjusting for age; sex; marital status; education; annual household income; smoking status; alcohol consumption; physical activity; BMI; history of hypertension; history of diabetes; intake frequencies of red meat, fresh fruits and fresh vegetables; and family history of stroke.

[4] P_{trend}, P for the linear trend test.

Table 3. Association of tea consumption with stroke risk according to duration and amount of tea consumed.

Variables of tea consumption[1]	Total stroke [2]		Ischemic stroke		Hemorrhagic stroke	
	HR (95% CI) [3]	P_{trend} [4]	HR (95% CI) [3]	P_{trend} [4]	HR (95% CI) [3]	P_{trend} [4]
Never	1.00		1.00		1.00	
Duration of tea consumption (years)		**<0.001**		**0.002**		**<0.001**
<19	**0.95 (0.91, 0.998)**		0.97 (0.92, 1.02)		**0.88 (0.79, 0.98)**	
19-30	**0.89 (0.84, 0.94)**		**0.89 (0.84, 0.96)**		**0.85 (0.75, 0.97)**	
>30	**0.92 (0.87, 0.97)**		**0.93 (0.88, 0.99)**		**0.81 (0.72, 0.91)**	
Amount of tea consumed (grams/day)		**<0.001**		**0.002**		**<0.001**
<2	0.96 (0.91, 1.00)		0.96 (0.91, 1.02)		**0.90 (0.81, 0.99)**	
2-4	**0.91 (0.87, 0.95)**		**0.93 (0.88, 0.98)**		**0.82 (0.74, 0.91)**	
>4	**0.91 (0.87, 0.96)**		**0.92 (0.87, 0.98)**		**0.82 (0.72, 0.92)**	
Amount of tea consumed (gram-years)		**<0.001**		**0.001**		**<0.001**
<46	0.95 (0.91, 1.00)		0.96 (0.91, 1.01)		**0.90 (0.80, 0.996)**	
46-105	**0.92 (0.88, 0.97)**		**0.94 (0.89, 0.997)**		**0.83 (0.74, 0.93)**	
>105	**0.90 (0.86, 0.94)**		**0.91 (0.86, 0.96)**		**0.81 (0.73, 0.91)**	
Amount of tea consumed (cups/day)						
<2	**0.93 (0.89, 0.98)**	**<0.001**	0.95 (0.90, 1.01)	**0.002**	**0.88 (0.79, 0.98)**	**<0.001**
2-4	**0.93 (0.89, 0.98)**		0.96 (0.90, 1.01)		**0.88 (0.79, 0.98)**	
>4	**0.92 (0.87, 0.97)**		**0.91 (0.86, 0.97)**		**0.78 (0.69, 0.88)**	
Amount of tea consumed (cup-years)						
<34	0.95 (0.90, 1.01)	**<0.001**	0.94 (0.89, 1.01)	**0.009**	0.92 (0.82, 1.03)	**<0.001**
34-105	**0.93 (0.88, 0.97)**		**0.93 (0.88, 0.99)**		**0.80 (0.71, 0.89)**	
>105	**0.91 (0.86, 0.95)**		**0.94 (0.89, 0.996)**		**0.83 (0.74, 0.93)**	

Values were obtained from a Cox proportional hazards analysis.

[1] Variables of tea consumption (duration and amount of tea consumed) were only calculated among daily tea consumers.

[2] Including hemorrhagic stroke, ischemic stroke and stroke of unknown type.

[3] Adjusted for age; sex; marital status; education; annual household income; smoking status; alcohol consumption; physical activity; BMI; history of hypertension; history of diabetes; intake frequencies of red meat, fresh fruits and fresh vegetables; and family history of stroke.

[4] P_{trend}, P for the linear trend test.

HR, hazard ratio; 95% CI, 95% confidence interval.

Table 4. Association of frequency of tea consumption with the risk of stroke among male and female participants.

Sex	Stroke type	No. of participants	Frequency of tea consumption				P_{trend} [3]
			Never	Occasional	Weekly	Daily	
Men	No. of participants	199,294	38,360	58,527	19,940	82,467	
	No. of person years	1,722,946	322,076	507,410	175,236	718,224	
	No. of cases	18,038	5095	5061	1417	6465	
	HR (95% CI) [1]						
	Total stroke [2]		1.00	**0.94 (0.90, 0.98)**	**0.88 (0.82, 0.94)**	**0.89 (0.85, 0.93)**	**<0.001**
	Ischemic stroke		1.00	**0.93 (0.89, 0.97)**	**0.87 (0.81, 0.94)**	**0.89 (0.85, 0.94)**	**<0.001**
	Hemorrhagic stroke		1.00	0.92 (0.84, 1.02)	**0.85 (0.73, 0.97)**	**0.82 (0.74, 0.90)**	**<0.001**
Women	No. of participants	288,083	131,974	94,595	15,701	45,813	
	No. of person years	2,566,640	1,169,977	846,051	141,537	409,075	
	No. of cases	20,689	11,188	5567	924	3010	
	HR (95% CI) [1]						
	Total stroke [2]		1.00	0.97 (0.94, 1.00)	1.01 (0.94, 1.09)	**0.95 (0.90, 0.998)**	0.053
	Ischemic stroke		1.00	0.97 (0.93, 1.01)	1.03 (0.95, 1.11)	0.95 (0.89, 1.01)	0.120
	Hemorrhagic stroke		1.00	0.97 (0.89, 1.06)	0.92 (0.77, 1.10)	0.92 (0.82, 1.04)	0.177

Values were obtained from a Cox proportional hazards analysis.

[1] Adjusted for age; marital status; education; annual household income; smoking status; alcohol consumption; physical activity; BMI; history of hypertension; history of diabetes; intake frequencies of red meat, fresh fruits and fresh vegetables; and family history of stroke.

[2] Including hemorrhagic stroke, ischemic stroke and stroke of unknown type.

[3] P_{trend}, *P* for the linear trend test.

HR, hazard ratio; 95% CI, 95% confidence interval.

Figure legends

Figure 1. Association of frequency of tea consumption with the risk of stroke according to type of tea. (A) Results for the relationships of green tea consumption to risks of total, ischemic, and hemorrhagic stroke; (B) results for the relationships of non-green tea consumption to risks of total, ischemic, and hemorrhagic stroke. Values were obtained from a Cox proportional hazards analysis. Analyses were adjusted for age; sex; marital status; education; annual household income; smoking status; alcohol consumption; physical activity; BMI; history of hypertension; history of diabetes; intake frequencies of red meat, fresh fruits and fresh vegetables; and family history of stroke. Total stroke included hemorrhagic stroke, ischemic stroke and stroke of unknown type. Round dots represented the HRs (hazard ratios), and vertical lines represented the corresponding 95% CIs (confidence intervals).

Figure 2. Subgroup analysis of associations between daily tea consumption and stroke risk according to potential baseline risk factors. HRs and 95% CIs for stroke were obtained by the comparation between daily tea consumers and individuals who never consumed tea during the past year. Values were obtained from a Cox proportional hazards analysis. Analyses were adjusted for age; sex; marital status; education; annual household income; smoking status; alcohol consumption; physical activity; BMI; history of hypertension; history of diabetes; intake frequencies of red meat, fresh fruits and fresh vegetables; and family history of stroke, except for the stratification factor. Round dots represented the HRs (hazard ratios), and horizontal lines represented the corresponding 95% CIs (confidence intervals). BMI, body mass index; MET-hr/day, metabolic equivalent hours per day.