

Association between Green Tea Consumption and Risk of Stroke in Middle-Aged and Older Korean Men: The Health Examinees (HEXA) Study

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ABSTRACT: Green tea consumption is known to have varying effects on health and disease. The aim of this study was to investigate the association between green tea consumption and risk of stroke in Korean adult men. Data were obtained from the Health Examinees (HEXA) Study, which included 50,439 subjects aged 40 years and older. Information regarding dietary intake was collected from semi-quantified food frequency questionnaires consisting of 106 items. Green tea consumption was categorized as none, <1 cup/d, 1 to <3 cups/d, and ≥ 3 cups/d. Binary logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CIs) to examine a possible association between green tea consumption and risk of stroke by controlling for potential confounders. Subgroup analyses by age, body mass index, hypertension, diabetes mellitus, smoking status, and alcohol consumption were also performed. Compared with green tea non-drinkers, individuals that consumed 1 to <3 cups/d or ≥ 3 cups/d of green tea had multivariable adjusted OR (CI) of stroke of 0.75 (0.59~0.97) and 0.62 (0.39~0.98), respectively, after adjusting for age and various confounders. In the subgroup analyses, an inverse association between green tea consumption and risk of stroke was identified among younger, non-hypertensive, and non-diabetic men. Higher consumption of green tea was inversely associated with stroke risk in middle-aged and older Korean men.

Keywords: stroke, green tea, Korean

INTRODUCTION

In 2017, cerebrovascular disease was the third leading cause of death in Korea, followed by heart disease and cancer (1). Ten years ago, cerebrovascular disease was the second leading cause of death. Despite a decrease in its incidence, cerebrovascular disease remains a major health concern due to serious side effects and reduced quality of life (2). Generally, stroke is accompanied by severe physical disabilities and other health problems in addition to disease burden (3). Risk factors for stroke include age, family history, race, gender, transient ischemic attack history, a history of cardiac arrest, hypertension, smoking, drinking, diabetes, arterial disease, atrial fibrillation, heart disease, sickle cell disease, hyperlipidemia, poor diet, lack of physical activity, obesity, drug use, stress, and geographic location (4,5).

Tea is one of the most popular natural beverages worldwide. There are various kinds of teas which have different fermentation processes, including non-fermented green

tea, semi-fermented oolong tea, and fully fermented black tea (6). Green tea currently accounts for 20% of the world's tea consumption market and is mainly consumed in Asian countries, including Korea, China, and Japan (6). According to health statistics issued by the Ministry of Health and Welfare and the Korea Centers for Disease Control and Prevention in 2016, average green tea consumption per week is 0.66 cups, with 0.49 cups consumed by women and 0.83 cups consumed by men (7). The relationship between green tea consumption and risk of stroke has previously been studied in Asia. An inverse association between green tea consumption and risk of stroke has previously been identified in a Japanese cohort study (8), a case-control study in Korea (9), and in a cross-sectional study conducted in China (10). In addition, several epidemiological studies have reported that green tea has favorable effects on cardiovascular and ischemic-related diseases (11), blood pressure (12,13), liver cancer (14), and colorectal cancer (15). In meta-analyses published in 2009 (16) and 2016 (11), consumption

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of >1 cup of green tea/d was associated with a lower risk of stroke compared to consumption of <1 cup of green tea/d. However, neither meta-analysis included data from Korea. Therefore, the purpose of this study was to investigate a possible association between green tea consumption and stroke prevalence in Korean adult men by using data available from the large, population-based the Health Examinees (HEXA) baseline Study.

MATERIALS AND METHODS

Study population

HEXA, a large, population-based prospective cohort study, was conducted in Korea from 2004 through 2013 by the Korean Centers for Disease Control and Prevention. Details regarding the methods of this study have previously been described (17). The main objective of this large-scale genomic cohort study was to identify general epidemiological characteristics of major chronic diseases in Korea. A total of 173,357 subjects were enrolled, 40 years of age or older, who were treated at major hospitals ($n=38$) and local health examination centers located in eight regions in Korea. Strict standardized study criteria were employed and socio-demographic characteristics, medical and family history, medication usage, lifestyle factors, diet, and physical activity data were collected from interviews conducted by well-trained research staff.

At baseline, 59,294 men were recruited in the HEXA Study. Among these participants, those without information regarding a stroke diagnosis ($n=258$) and those with a family history of stroke ($n=7,987$) were excluded. After excluding participants who did not report information regarding green tea consumption ($n=610$), data from 50,439 men were analyzed. Written informed consent was obtained from all participants prior to the study start, and the study protocol was approved by the Institutional Review Board of Ewha Womans University in Seoul, Korea (IRB no. 123-14).

Data collection

Information about the general demographic characteristics, lifestyle factors, and diagnosis of stroke for the cohort examined were obtained from a structured questionnaire. However, stroke was evaluated only based on answers obtained for the question "Have you ever received a diagnosis of stroke by a doctor?". Consequently, the type of stroke (e.g. ischemic vs. hemorrhagic) could not be distinguished and separately analyzed.

Categorization of body mass index (BMI) and definition of hypertension and diabetes mellitus were determined as previously described (18). Obesity was defined as a BMI ≥ 25 kg/m² according to the guidelines of the Steering Committee of the Regional Office for the West-

ern Pacific Region of the World Health Organization (19). Marital status was categorized as married or single (with the latter including unmarried, divorced, separated, cohabiting, and widowed individuals). Education level was classified as middle school or less, high school graduate, and college or above. Household income was categorized as <200, 200 to 400, and >400 (10,000 won/month). Smoking status was categorized as non-smoker, ex-smoker, and current smoker, and alcohol drinking status was categorized as non-drinker, ex-drinker, and current drinker. Regular exercise was evaluated based on responses to the question "Do you regularly exercise enough to the point you are sweating?". Chronic diseases, including hypertension, diabetes, and hyperlipidemia, were defined based on specific criteria of each disease or according to diagnosis by a doctor. Hypertensive subjects were defined as having a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg (20), diabetes was defined as a fasting blood glucose level ≥ 126 mg/dL, and hyperlipidemia was defined as a total cholesterol level ≥ 240 (21). The dietary intake and green tea consumption of participants were estimated based on a semi-quantitative food frequency questionnaire that consisted of 106 food items. This questionnaire was developed by the Korea Centers for Disease Control and Prevention and has previously been assessed for its reliability and validity for the Korean population (22). Participants were queried by trained interviewers regarding their usual intake amount of foods (including green tea) over the previous year. In the questionnaire, green tea consumption was categorized according to frequency (none, once a month, 2 to 3 times a month, 1 to 2 times a week, 3 to 4 times a week, 5 to 6 times a week, once a day, twice a day, or 3 times a day) and average intake per serving (1/2 cup, 1 cup, and 2 cups). However, for the present analysis, we adjusted these categories to consider both intake and frequency as follows: none, <1 cup a day, between 1 and <3 cups a day, and ≥ 3 cups a day.

Statistical analysis

All statistical analyses were performed with SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $P<0.05$. General characteristics of subjects were compared using the Chi-square test for categorical variables and general linear regression for continuous variables.

Based on previously published literature, the following potential confounding factors were analyzed: age, gender, education level, alcohol consumption, regular exercise, BMI, smoking habits, carotid or other artery disease, transient ischemic attacks, hypertension, hyperlipidemia, ethnicity, heart failure, drug abuse, and poor diet (4,5,8,16,23,24). Pearson correlation coefficient and variance inflation factor were used to investigate multicollinearity

between stroke confounding factors. The final model adjusted for age, education level, alcohol consumption, smoking habits, regular exercise, BMI, diagnosis of hypertension, diabetes, hyperlipidemia, intake of vegetables and fruits, red meat intake, coffee consumption, and total energy consumed. Carotid or other artery disease, transient ischemic attacks, ethnicity, heart failure, and drug abuse were not considered to be confounding factors due to lack of information about these factors in present data.

Logistic regression models were used to assess a possible association between green tea consumption and stroke prevalence. Odds ratios (OR) and 95% confidence intervals (CIs) for each category of green tea consumption were calculated using dichotomous logistic regression, and trends were assessed in further analysis. To check additional interactions, stratification analyses according to age, BMI, hypertension, diabetes, smoking status, and alcohol consumption were performed.

RESULTS

General characteristics of the participants according to green tea consumption are presented in Table 1 (none, n = 19,801; <1 cup/d, n = 21,350; 1 to <3 cups/d, n = 7,064; ≥3 cups/d, n = 2,224). The prevalence of stroke in the study population was 1.54% (data not shown). The mean intake of green tea was 0.52 cups/d; 4.4% of men drank ≥3 cups/d, and 39.2% of men did not drink any green tea (data not shown). All of the variables examined (e.g., age group, marital status, education level, household income, BMI, alcohol consumption, smoking status, regular exercise, diabetes, hyperlipidemia, intake of vegetables and fruits, red meat intake, and coffee consumption), except hypertension, showed significant differences based on green tea consumption. Compared with those who did not drink green tea, participants who reported an intake of ≥3 cups of green tea/d were younger in age, had a higher education level and income, and were more likely to be non-smokers. Those who reported higher

Table 1. Baseline characteristics of the Health Examinees Study participants by green tea consumption

Variable	Daily green tea consumption (no. of cups)				P-value ¹⁾
	None	<1	1 to <3	≥3	
Participants, n	19,801	21,350	7,064	2,224	
Age group (years)	55.0±9.0	53.5±8.8	52.5±8.6	51.8±8.4	<.0001
Marital status, n (%)					<.0001
Married	17,738 (89.6)	18,859 (88.3)	6,291 (89.1)	1,915 (86.1)	
Single	1,489 (7.5)	1,349 (6.3)	361 (5.1)	118 (5.3)	
Education level, n (%)					<.0001
Under middle school	5,899 (29.8)	4,300 (20.1)	1,038 (14.7)	249 (11.2)	
High school	7,953 (40.2)	8,630 (40.4)	2,637 (37.3)	853 (38.4)	
College or more	5,481 (27.7)	8,036 (37.6)	3,266 (46.2)	1,089 (49.0)	
Household income, n (%) (10,000 won/month)					<.0001
<200	6,035 (30.5)	4,813 (22.5)	1,134 (16.1)	331 (14.9)	
200~400	7,536 (38.1)	8,321 (39.0)	2,740 (38.8)	803 (36.1)	
>400	3,873 (19.6)	5,233 (24.5)	2,126 (30.1)	716 (32.2)	
Body mass index (kg/m ²)	24.2±2.8	24.4±2.7	24.6±2.7	24.7±2.7	<.0001
Smoking status, n (%)					<.0001
Non-smoker	4,884 (24.5)	6,592 (30.9)	2,098 (29.7)	646 (29.1)	
Ex-smoker	7,711 (38.9)	8,566 (40.1)	2,855 (40.4)	892 (40.1)	
Current smoker	7,214 (36.4)	6,145 (28.8)	2,104 (29.8)	683 (30.7)	
Alcohol consumption, n (%)					<.0001
Non-drinker	4,484 (22.7)	4,185 (19.6)	1,229 (17.4)	399 (17.9)	
Ex-drinker	1,545 (7.8)	1,556 (7.3)	435 (6.2)	145 (6.5)	
Current drinker	13,744 (69.4)	15,576 (73.0)	5,391 (76.3)	1,676 (75.4)	
Regular exercise, n (%)	9,713 (49.1)	12,542 (58.7)	4,508 (63.8)	1,493 (67.1)	<.0001
Hypertension, n (%)	6,164 (31.1)	6,582 (30.8)	2,162 (30.6)	695 (31.3)	0.687
Diabetes mellitus, n (%)	2,843 (14.4)	3,275 (15.3)	1,156 (16.4)	338 (15.2)	0.002
Hyperlipidemia, n (%)	3,263 (16.5)	3,546 (16.6)	1,160 (16.4)	388 (17.5)	0.029
Vegetable and fruits intake (g/d)	413.3±276.3	436.4±293.9	521.7±311.8	570.9±396.4	
Red meat intake (g/d)	45.1±52.4	46.4±48.5	52.4±55.3	53.1±60.4	
Coffee consumption (cup/d)	2.0±1.7	1.6±1.6	1.9±1.5	2.1±1.8	
Total energy intake (kcal/d)	1,796.8±547.2	1,848.1±568.7	1,977.2±588.4	2,055.9±713.5	<.0001

Mean±SD.

¹⁾P-values were calculated by Chi-square tests for categorical variables and general linear regression for continuous variables.

Table 2. Odd ratios (OR) and 95% confidence intervals (CIs) of stroke by green tea consumption in the Health Examinees Study

	Daily green tea consumption (no. of cups)				<i>P</i> for trend
	None	<1	1 to <3	≥3	
Male (n=50,439)	(n=19,801)	(n=21,350)	(n=7,064)	(n=2,224)	
Crude OR (95% CI)	1.00	0.75 (0.64~0.87)	0.61 (0.48~0.77)	0.48 (0.31~0.76)	<0.0001
Multivariate OR (95% CI) ¹⁾	1.00	0.82 (0.70~0.96)	0.75 (0.59~0.97)	0.62 (0.39~0.98)	0.0016

¹⁾Adjusted for age, education, alcohol consumption, smoking, regular exercise, body mass index, hypertension, diabetes mellitus, hyperlipidemia, vegetable and fruits intake, red meat intake, coffee consumption, and total energy intake.

frequencies of green tea consumption tended to also undertake more exercise, and have a higher intake of energy, vegetables, fruit, red meat, and coffee.

Table 2 presents ORs and 95% CIs for stroke prevalence according to green tea consumption. Compared with participants who did not drink green tea, the stroke prevalence crude ORs were 0.75 (95% CI, 0.64~0.87), 0.61 (95% CI, 0.48~0.77), and 0.48 (95% CI, 0.31~0.76) for those drinking up to <1 cup/d, 1 to <3 cups/d, and ≥3 cups/d, respectively. After adjusting for confounding variables, higher green tea consumption was

found to reduce stroke prevalence for those drinking <1 cup/d (OR, 0.82; 95% CI, 0.70~0.96), 1 to <3 cups/d (OR, 0.75; 95% CI, 0.59~0.97), and ≥3 cups/d (OR 0.62; 95% CI, 0.39~0.98), versus those who did not drink green tea.

When stratified analyses was performed on the association between stroke prevalence and green tea consumption (Table 3), an inverse association between stroke prevalence and green tea consumption was observed according to age (<65 y), history of hypertension, and history of diabetes. Moreover, an inverse association be-

Table 3. Odd ratios and 95% confidence intervals of stroke by green tea consumption stratified by age, body mass index (BMI), hypertension, diabetes mellitus, smoking status, and alcohol consumption in the Health Examinees Study

	No. of events	Daily green tea consumption (no. of cups)				<i>P</i> for trend
		None	<1	1 to <3	≥3	
Male (n=50,439)						
Age (years) ¹⁾						
<65	512	1.00	0.74 (0.61~0.90)	0.70 (0.52~0.94)	0.48 (0.27~0.84)	0.0002
≥65	252	1.00	0.94 (0.72~1.25)	0.80 (0.49~1.29)	1.02 (0.46~2.23)	0.4962
BMI (kg/m ²) ²⁾						
<25	425	1.00	0.86 (0.71~1.07)	0.81 (0.57~1.13)	0.62 (0.32~1.18)	0.0479
≥25	335	1.00	0.78 (0.61~0.99)	0.65 (0.45~0.96)	0.63 (0.33~1.22)	0.0083
Hypertension ³⁾						
Nonhypertensive	368	1.00	0.87 (0.70~1.10)	0.75 (0.52~1.07)	0.46 (0.21~0.98)	0.0140
Hypertensive	396	1.00	0.77 (0.62~0.97)	0.76 (0.53~1.07)	0.79 (0.44~1.40)	0.0429
Diabetes mellitus ⁴⁾						
Nondiabetic	573	1.00	0.80 (0.67~0.96)	0.72 (0.53~0.96)	0.57 (0.33~0.98)	0.0015
Diabetic	191	1.00	0.89 (0.65~1.24)	0.85 (0.52~1.37)	0.79 (0.34~1.85)	0.3732
Smoking status ⁵⁾						
Never and past	604	1.00	0.84 (0.71~1.01)	0.78 (0.60~1.04)	0.63 (0.38~1.05)	0.0114
Current	157	1.00	0.74 (0.51~1.05)	0.66 (0.36~1.20)	0.63 (0.23~1.74)	0.0591
Alcohol consumption ⁶⁾						
Never and past	356	1.00	0.80 (0.63~1.01)	0.72 (0.49~1.05)	0.59 (0.30~1.18)	0.0152
Current	407	1.00	0.84 (0.68~1.05)	0.79 (0.57~1.11)	0.66 (0.36~1.23)	0.0499

¹⁾Adjusted by education, alcohol consumption, regular exercise, BMI, smoking, hypertension, diabetes mellitus and hyperlipidemia, vegetable and fruits intake, red meat intake, coffee consumption, and total energy intake.

²⁾Adjusted by age, education, alcohol consumption, regular exercise, smoking, hypertension, diabetes mellitus and hyperlipidemia, vegetable and fruits intake, red meat intake, coffee consumption, and total energy intake.

³⁾Adjusted by age, education, alcohol consumption, regular exercise, BMI, smoking, diabetes mellitus and hyperlipidemia, vegetable and fruits intake, red meat intake, coffee consumption, and total energy intake.

⁴⁾Adjusted by age, education, alcohol consumption, regular exercise, BMI, smoking, hypertension and hyperlipidemia, vegetable and fruits intake, red meat intake, coffee consumption, and total energy intake.

⁵⁾Adjusted by age, education, alcohol consumption, regular exercise, BMI, hypertension, diabetes mellitus and hyperlipidemia, vegetable and fruits intake, red meat intake, coffee consumption, and total energy intake.

⁶⁾Adjusted by age, education, regular exercise, BMI, smoking, hypertension, diabetes mellitus and hyperlipidemia, vegetable and fruits intake, red meat intake, coffee consumption, and total energy intake.

tween green tea consumption and stroke prevalence was predominantly observed among participants younger than 65 years (OR, 0.48; 95% CI, 0.27~0.84 for ≥ 3 cups/d vs. none), nonhypertensive participants (OR, 0.46; 95% CI, 0.21~0.98 for ≥ 3 cups/d vs. none), and nondiabetic participants (OR, 0.57; 95% CI, 0.33~0.98 for ≥ 3 cups/d vs. none).

DISCUSSION

In the present study, an association between the prevalence of stroke and green tea consumption in Korean men over 40 years of age was examined using data from the HEXA baseline Study. After controlling for potential confounding factors, the prevalence of stroke was found to be inversely associated with consumption of green tea. Moreover, a clear dose-response relationship was identified between prevalence of stroke and green tea consumption.

Black tea is very popular in Europe and North America, while green tea or oolong tea remains popular in Asian countries. Studies examining the relationship between green tea intake and stroke have mainly been conducted in Asia, and the results from most of these studies are consistent with the present findings. For example, in a cohort study of 6,358 people aged 40 to 89 years in Japan, the group that consumed ≥ 5 cups of green tea per day had a 59% reduced risk of stroke compared with those who consumed up to 1 cup per week. However, while the risk of stroke was reduced by 73% in men, no significant reduction in stroke risk was observed in women (23). In another cohort study of 82,369 Japanese participants, those who consumed ≥ 4 cups of green tea per day had a 20% reduced risk of stroke compared with those who did not drink green tea (8). In addition, a case-control study of 940 patients who had experienced a hemorrhagic stroke and 940 age-matched controls from the same community in Korea showed a 39% reduced risk of stroke in those who consumed 7 to <14 cups of green tea/week compared with those who did not drink green tea (9). In cross-sectional studies, it was also observed that increased green tea consumption was associated with a decrease in prevalence of stroke in a Chinese population (10). In a meta-analysis published in 2009, which included six observational studies, ≥ 3 cups of green tea per day was found to prevent development of strokes (16). Furthermore, a meta-analysis of nine studies published in 2016 showed that an intake of 1 to 3 cups of green tea per day was inversely associated with risk of myocardial infarction and stroke (11).

The mechanism(s) responsible for the effect of green tea consumption on stroke prevention remain unclear. Polyphenols have been reported to have a positive effect

on a variety of chronic diseases. Catechin is a flavan-3-ol compound and is a major candidate for mediating the beneficial effects of green tea for coronary heart disease (25,26). The four major types of catechins are (–)-epigallocatechin gallate (EGCG), (–)-epigallocatechin (EGC), (–)-epicatechin gallate (ECG), and (–)-epicatechin (EC) (25,27). Among these green tea catechins, EGCG is the most abundant and has been shown to exert positive effects on hypertension, metabolic syndrome, thrombosis, and cardiovascular diseases (12,28,29). It has been hypothesized that the catechin molecules in green tea may prevent vascular diseases and stroke based on the antioxidant, anti-inflammatory, anti-proliferative, and anti-thrombotic effects of catechins (25,30-32). In animal studies, consumption of green tea at an early age prevented the onset of stroke. The authors suggested that green tea also has potential to block onset of hypertension and stroke in the elderly (33). Despite the positive effects, green tea can also cause insomnia, headaches, vomiting, and tachycardia due to the presence of polyphenols, such as caffeine and catechin. The tannin component of green tea may also cause anemia by interfering with absorption of iron (34). However, these polyphenol components may vary depending on the type of green tea and the method by which it is brewed. This heterogeneity may explain the differences in results between studies. Thus, further investigations at the molecular level of anti-stroke mechanisms involving green tea are warranted.

In the present study, the association between green tea consumption and stroke prevalence differed according to gender. A significant association was observed among men but not women (data not shown). This is consistent with results obtained in a previous Japanese study (23). In the present study, it was not possible to identify a clear mechanism for the observed gender-related differences in stroke risk. Gender differences are important risk factors for stroke for multiple reasons, as well as in other chronic diseases. Numerous studies have found that reproductive factors, including hormone replacement therapy use, oral contraceptive use, menopause, and pregnancy, also increase the risk of stroke (35-37). Specific risk factors include excess androgen secretion and decreased estrogen during the menopause transition period, as well as abdominal obesity and levels of triglycerides, total cholesterol, low density lipoprotein cholesterol, and fasting blood glucose (38,39). A cohort study conducted in the United States reported an increased risk of ischemic stroke in men receiving testosterone therapy (40). Other factors, such as the presence of chronic diseases (e.g., diabetes, atherosclerosis, and dyslipidemia), physical activity, absorption rate, bioavailability of green tea consumption, eating habits, and lifestyle differences between genders may also influence this association. Further research is needed to investigate the different risk factors effecting

the association between green tea and stroke prevalence; these studies are warranted to explore gender-related differences in stroke risk.

In the present subgroup analyses, the association between green tea consumption and a decreased risk of stroke prevalence was more pronounced in participants younger than 65 years of age and who had never been diagnosed with diabetes mellitus or hypertension. While the mechanistic details of these results remain unclear, we propose several possibilities. As men get older, levels of testosterone decrease. McInnes et al. (41) reported that mice with impaired testosterone function in adipose tissue have a greater tendency to develop insulin resistance compared with uninjured mice. Similarly, in human, low levels of testosterone have been associated with type 2 diabetes (42). Oral consumption of green tea extract significantly improved levels of testosterone in serum of acrylamide-induced testicular-damaged albino rats (43). Based on these results, green tea intake may affect the levels of testosterone.

There is lack of evidence explaining the differing association between green tea consumption and stroke by age. It has been proposed that genetic factors, including genetic predisposition, are more prevalent for younger stroke patients (44). Although clinical risk factors were increased in older patients, other modifiable factors such as dyslipidemia, smoking, physical activity, and diet must be considered (45). The prevalence of diabetes, hypertension, and heart disease differed between young and old stroke patients, which may have affected the risk of stroke (46). The rate of calcium and xanthohumol absorption decreases with age (47,48). Although these are not major components of green tea, absorption of other bioactive components in green tea may also be decreased by age. Future research into the mechanisms of bioactive green tea components are warranted.

A study conducted in Japan reported that administration of the hypertensive drug nadolol in combination with green tea leads to lower plasma nadolol concentrations and an anti-hypertensive effect (49). This supports the observation of our present study, that hypertensive patients that were taking medication did not exhibit any beneficial effects of green tea for risk of stroke. Furthermore, age, hypertension, and diabetes mellitus are well-known risk factors for stroke. In the present study, the participants that consumed ≥ 3 cups of green tea per day were the youngest participants. Therefore, it can be predicted that young, non-diabetic and non-hypertensive individuals have fewer risk factors for stroke, and that lifestyle and multiple unknown factors may explain these data. However, additional mechanistic studies are needed.

Nevertheless, this study has several limitations. First, it was difficult to investigate a cause-and-effect relationship between green tea consumption and stroke risk due

to the cross-sectional study design. To compensate, we adjusted for several confounding factors and stratified the data. Second, information about the types of ischemic and hemorrhagic strokes experienced by the cohort was not collected. Consequently, the possibility that the results are diluted cannot be excluded. Third, each stroke was evaluated according to a self-reported answer about diagnosis by a doctor. Lastly, due to lack of information in the original study, other stroke risk factors (e.g., history of prior stroke, transient ischemic attack, myocardial infarction, carotid disease, peripheral artery disease, atrial fibrillation, heart failure, and drug abuse involving cocaine, amphetamines, and/or heroin), which have been identified by the American Heart Association and American Stroke Association, could not be controlled.

The major strength of this study is the large number of stroke patients that were examined, which provided high statistical power during the analysis. Moreover, to our knowledge, this is the first large-scale study to investigate a possible association between stroke prevalence and green tea consumption in Korea. Recently, coffee consumption has markedly increased in the Korean population. However, many Koreans still enjoy drinking green tea. Therefore, this study provides useful health information that may be of interest to the public.

In conclusion, data from this cross-sectional study indicates that green tea consumption is inversely associated with stroke prevalence in Korean adult men. These results are consistent with previous epidemiological studies, thereby suggesting that green tea intake is beneficial for stroke. Thus, additional long-term cohort studies are warranted to confirm this result.

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AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

REFERENCES

1. Statistics Korea. 2018. Cause of death statistics 2017. Statistics Korea, Daejeon, Korea.
2. You YY, Ahn CS. 2009. A study of the relationships between perceived rehabilitation—motivation and quality of life in patients after a cerebrovascular accident. *J Kor Soc Occup Ther* 17: 1-16.

3. Ezzati M1, Hoorn SV, Rodgers A, Lopez AD, Mathers CD, Murray CJ; Comparative Risk Assessment Collaborating Group. 2003. Estimates of global and regional potential health gains from reducing multiple major risk factors. *Lancet* 362: 271-280.
4. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, Creager MA, Eckel RH, Elkind MS, Fornage M, Goldstein LB, Greenberg SM, Horvath SE, Iadecola C, Jauch EC, Moore WS, Wilson JA; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. 2014. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 45: 3754-3832.
5. Sacco RL, Benjamin EJ, Broderick JP, Dyken M, Easton JD, Feinberg WM, Goldstein LB, Gorelick PB, Howard G, Kittner SJ, Manolio TA, Whisnant JP, Wolf PA. 1997. American Heart Association Prevention Conference. IV. Prevention and rehabilitation of stroke. Risk factors. *Stroke* 28: 1507-1517.
6. Siddiqui IA, Afaq F, Adhami VM, Ahmad N, Mukhtar H. 2004. Antioxidants of the beverage tea in promotion of human health. *Antioxid Redox Signal* 6: 571-582.
7. KCDC. 2017. Korea Health Statistics 2016. Korea Centers for Disease Control and Prevention, Cheongju, Chungbuk, Korea.
8. Kokubo Y, Iso H, Saito I, Yamagishi K, Yatsuya H, Ishihara J, Inoue M, Tsugane S. 2013. The impact of green tea and coffee consumption on the reduced risk of stroke incidence in Japanese population: the Japan public health center-based study cohort. *Stroke* 44: 1369-1374.
9. Lee SM, Choi NK, Yoon BW, Park JM, Han MK, Park BJ. 2015. The impact of green tea consumption on the prevention of hemorrhagic stroke. *Neuroepidemiology* 44: 215-220.
10. Chen Z, Li Y, Zhao LC, Zhou BF, Yang J, Wang ZW, Guo M, Wu YF. 2004. A study on the association between tea consumption and stroke. *Zhonghua Liu Xing Bing Xue Za Zhi* 25: 666-670.
11. Pang J, Zhang Z, Zheng TZ, Bassig BA, Mao C, Liu X, Zhu Y, Shi K, Ge J, Yang YJ, Huang D, Bai M, Peng Y. 2016. Green tea consumption and risk of cardiovascular and ischemic related diseases: a meta-analysis. *Int J Cardiol* 202: 967-974.
12. Peng X, Zhou R, Wang B, Yu X, Yang X, Liu K, Mi M. 2014. Effect of green tea consumption on blood pressure: a meta-analysis of 13 randomized controlled trials. *Sci Rep* 4: 6251.
13. Khalesi S, Sun J, Buys N, Jamshidi A, Nikbakht-Nasrabadi E, Khosravi-Boroujeni H. 2014. Green tea catechins and blood pressure: a systematic review and meta-analysis of randomized controlled trials. *Eur J Nutr* 53: 1299-1311.
14. Huang YQ, Lu X, Min H, Wu QQ, Shi XT, Bian KQ, Zou XP. 2016. Green tea and liver cancer risk: a meta-analysis of prospective cohort studies in Asian populations. *Nutrition* 32: 3-8.
15. Wang ZH, Gao QY, Fang JY. 2012. Green tea and incidence of colorectal cancer: evidence from prospective cohort studies. *Nutr Cancer* 64: 1143-1152.
16. Arab L, Liu W, Elashoff D. 2009. Green and black tea consumption and risk of stroke: a meta-analysis. *Stroke* 40: 1786-1792.
17. Health Examinees Study Group. 2015. The Health Examinees (HEXA) study: rationale, study design and baseline characteristics. *Asian Pac J Cancer Prev* 16: 1591-1597.
18. Lee J, Lee JE, Kim Y. 2017. Relationship between coffee consumption and stroke risk in Korean population: the Health Examinees (HEXA) Study. *Nutr J* 16: 7.
19. WHO. 2000. Obesity: Preventing and managing the global epidemic. WHO Technical Report Series 894, World Health Organization, Geneva, Switzerland.
20. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. 2003. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 289: 2560-2572.
21. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 2002. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 106: 3143-3421.
22. Ahn Y, Kwon E, Shim JE, Park MK, Joo Y, Kimm K, Park C, Kim DH. 2007. Validation and reproducibility of food frequency questionnaire for Korean genome epidemiologic study. *Eur J Clin Nutr* 61: 1435-1441.
23. Tanabe N, Suzuki H, Aizawa Y, Seki N. 2008. Consumption of green and roasted teas and the risk of stroke incidence: results from the Tokamachi-Nakasato cohort study in Japan. *Int J Epidemiol* 37: 1030-1040.
24. Mineharu Y, Koizumi A, Wada Y, Iso H, Watanabe Y, Date C, Yamamoto A, Kikuchi S, Inaba Y, Toyoshima H, Kondo T, Tamakoshi A; JACC study Group. 2011. Coffee, green tea, black tea and oolong tea consumption and risk of mortality from cardiovascular disease in Japanese men and women. *J Epidemiol Community Health* 65: 230-240.
25. Khan N, Mukhtar H. 2007. Tea polyphenols for health promotion. *Life Sci* 81: 519-533.
26. Arts IC, Hollman PC, Feskens EJ, Bueno de Mesquita HB, Kromhout D. 2001. Catechin intake might explain the inverse relation between tea consumption and ischemic heart disease: the Zutphen Elderly Study. *Am J Clin Nutr* 74: 227-232.
27. McKay DL, Blumberg JB. 2002. The role of tea in human health: an update. *J Am Coll Nutr* 21: 1-13.
28. Marventano S, Salomone F, Godos J, Pluchinotta F, Del Rio D, Mistretta A, Grosso G. 2016. Coffee and tea consumption in relation with non-alcoholic fatty liver and metabolic syndrome: a systematic review and meta-analysis of observational studies. *Clin Nutr* 35: 1269-1281.
29. Kim A, Chiu A, Barone MK, Avino D, Wang F, Coleman CI, Phung OJ. 2011. Green tea catechins decrease total and low-density lipoprotein cholesterol: a systematic review and meta-analysis. *J Am Diet Assoc* 111: 1720-1729.
30. Babu PV, Liu D. 2008. Green tea catechins and cardiovascular health: an update. *Curr Med Chem* 15: 1840-1850.
31. Hofmann CS, Sonenshein GE. 2003. Green tea polyphenol epigallocatechin-3 gallate induces apoptosis of proliferating vascular smooth muscle cells via activation of p53. *FASEB J* 17: 702-704.
32. Lee W, Min WK, Chun S, Lee YW, Park H, Lee DH, Lee YK, Son JE. 2005. Long-term effects of green tea ingestion on atherosclerotic biological markers in smokers. *Clin Biochem* 38: 84-87.
33. Ikeda M, Suzuki C, Umegaki K, Saito K, Tabuchi M, Tomita T. 2007. Preventive effects of green tea catechins on spontaneous stroke in rats. *Med Sci Monit* 13: BR40-BR45.
34. Fan FS. 2016. Iron deficiency anemia due to excessive green tea drinking. *Clin Case Rep* 4: 1053-1056.
35. Shekhar S, Travis OK, He X, Roman RJ, Fan F. 2017. Menopause and ischemic stroke: a brief review. *MOJ Toxicol* 3:

- 00059.
36. Caso V, Falorni A, Bushnell CD, Acciarresi M, Remohí J, Sprigg N, Gerli S. 2017. Pregnancy, hormonal treatments for infertility, contraception, and menopause in women after ischemic stroke: a consensus document. *Stroke* 48: 501-506.
 37. Bath PM, Gray LJ. 2005. Association between hormone replacement therapy and subsequent stroke: a meta-analysis. *BMJ* 330: 342.
 38. The Lancet Neurology. 2014. Sex differences and stroke prevention. *Lancet Neurol* 13: 339.
 39. Lisabeth L, Bushnell C. 2012. Stroke risk in women: the role of menopause and hormone therapy. *Lancet Neurol* 11: 82-91.
 40. Vigen R, O'Donnell CI, Barón AE, Grunwald GK, Maddox TM, Bradley SM, Barqawi A, Woning G, Wierman ME, Plomondon ME, Rumsfeld JS, Ho PM. 2013. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 310: 1829-1836.
 41. McInnes KJ, Smith LB, Hunger NI, Saunders PT, Andrew R, Walker BR. 2012. Deletion of the androgen receptor in adipose tissue in male mice elevates retinol binding protein 4 and reveals independent effects on visceral fat mass and on glucose homeostasis. *Diabetes* 61: 1072-1081.
 42. Farrell JB, Deshmukh A, Baghaie AA. 2008. Low testosterone and the association with type 2 diabetes. *Diabetes Educ* 34: 799-806.
 43. Yassa HA, George SM, Refaiy Ael R, Moneim EM. 2014. *Camellia sinensis* (green tea) extract attenuate acrylamide induced testicular damage in albino rats. *Environ Toxicol* 29: 1155-1161.
 44. Terni E, Giannini N, Brondi M, Montano V, Bonuccelli U, Mancuso M. 2014. Genetics of ischaemic stroke in young adults. *BBA Clin* 3: 96-106.
 45. Cook NL, Mensah GA. 2015. Eliminating health disparities: what can we learn from the veterans health administration?. *Circulation* 132: 1519-1521.
 46. Smajlović D. 2015. Strokes in young adults: epidemiology and prevention. *Vasc Health Risk Manag* 11: 157-164.
 47. Nordin BE, Need AG, Morris HA, O'Loughlin PD, Horowitz M. 2004. Effect of age on calcium absorption in postmenopausal women. *Am J Clin Nutr* 80: 998-1002.
 48. Zamzow DR, Elias V, Legette LL, Choi J, Stevens JF, Magnusson KR. 2014. Xanthohumol improved cognitive flexibility in young mice. *Behav Brain Res* 275: 1-10.
 49. Misaka S, Yatabe J, Müller F, Takano K, Kawabe K, Glaeser H, Yatabe MS, Onoue S, Werba JP, Watanabe H, Yamada S, Fromm MF, Kimura J. 2014. Green tea ingestion greatly reduces plasma concentrations of nadolol in healthy subjects. *Clin Pharmacol Ther* 95: 432-438.