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Original Article

Carbonated Beverage, Fruit Drink, and Water Consumption and Risk of Acute Stroke: the INTERSTROKE Case-Control Study

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Background and Purpose Cold beverage intake (carbonated drinks, fruit juice/drinks, and water) may be important population-level exposures relevant to stroke risk and prevention. We sought to explore the association between intake of these beverages and stroke.

Methods INTERSTROKE is an international matched case-control study of first stroke. Participants reported beverage intake using food frequency questionnaires or were asked "How many cups do you drink each day of water?" Multivariable conditional logistic regression estimated odds ratios (OR) and 95% confidence intervals (CI) for associations with stroke.

Results We include 13,462 cases and 13,488 controls; mean age was 61.7±13.4 years and 59.6% (n=16,010) were male. After multivariable adjustment, carbonated beverages were linearly associated with ischemic stroke (OR 2.39 [95% CI 1.64–3.49]); only consumption once/day was associated with intracerebral hemorrhage (ICH) (OR 1.58 [95% CI 1.23–2.03]). There was no association between fruit juice/drinks and ischemic stroke, but increased odds of ICH for once/day (OR 1.37 [95% CI 1.08–1.75)] or twice/day (OR 3.18 [95% CI 1.69–5.97]). High water intake (>7 cups/day) was associated ischemic stroke (OR 0.82 [95% CI 0.68–0.99]) but not ICH. Associations differed by

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geographical region—increased odds for carbonated beverages in some regions only; opposing directions of association of fruit juices/drinks with stroke in selected regions.
Conclusion Carbonated beverages were associated with increased odds of ischemic stroke and ICH, fruit juice/drinks were associated with increased odds of ICH, and high water consumption was associated with reduced odds of ischemic stroke, with important regional differences. Our findings suggest optimizing water intake, minimizing fruit juice/drinks, and avoiding carbonated beverages.

Keywords Stroke; Carbonated beverages; Fruit juice; Water; Diet

Introduction

Stroke is a leading global cause of death and disability.[1] While dietary modification, focused on solid foods, has been a major target for prevention of stroke, daily beverage intake may represent a similarly important population-level exposure for stroke prevention.[2] Previous studies focus mostly on intake of tea and/or coffee, but other beverages also require consideration given that they are consumed frequently and variably around the world, influenced by social, cultural, behavioral, and economic factors.

Water contributes 60%–75% of human body weight, and plays critical biologic roles in the cardiovascular system through blood volume regulation and impacting blood pressure, heart rate,[3] and vascular contractility.[4] Therefore, overhydration holds the potential to increase blood pressure (a major risk factor for stroke). However, dehydration may increase blood viscosity and increase the risk of cerebral ischemia.[5] Whilst other cold beverages include water as a constituent, their other constituents may have important effects on stroke risk. Although fruit juice contains less fiber and vitamin C[6] than whole fruit, it does contain polyphenols that may reduce cardiovascular risk.[7] However, some fruit drinks contain added sweeteners or preservatives, which may offset these potential benefits. The association between carbonated/soft drinks and health is also complex. Sugar-sweetened beverages (SSB) are associated with higher cardiometabolic risk.[8] Although artificially sweetened beverages (ASB), such as carbonated "diet" beverages, are marketed as healthier alternatives, several large observational studies (Atherosclerosis Risk in Communities [ARIC],[9] Framingham,[10] and Multi-Ethnic Study of Atherosclerosis[11]), report associations of carbonated diet beverages with metabolic syndrome and diabetes mellitus (known cardiovascular risk factors). Taken together, there are complex biological processes underpinning the associations between cold beverage intake and stroke risk.

Therefore, it is first essential that we better understand the associations between the intake of important categories of beverages and stroke. This research will generate hypotheses and potential interventions for stroke prevention that can be further explored using alternative study designs (e.g., clinical trials). The geographically and ethnically diverse INTERSTROKE observational study is ideally placed to explore the associations between cold beverage consumption and stroke (including pathological subtypes) as the next step in this complex research area.

Methods

INTERSTROKE is a large international case-control study whose details were published previously.[12] In brief, cases of first stroke (within 5 days of symptom onset and admitted to hospital within 3 days of presentation) were recruited from 142 centers in 32 countries between March 2007 and July 2015. Neuroimaging was completed in 99.9% of cases. Information was obtained from the patient or a proxy respondent. For each case, a matched control was recruited from the same hospital or community.[13] Controls had no history of stroke and were matched to cases by age (<5 years or <10 years difference if aged >90 years) and sex. In countries with large representation from several ethnic groups, controls were also matched to cases by ethnic origin. Hospital-based controls included visitors, relatives of inpatients, or individuals admitted to hospital or attending hospital outpatients for disorders or procedures not related to stroke or transient ischemic attack.[13]

Risk factors were assessed through standardized structured questionnaires (completed by the participant, proxy, or both) and physical examination. Blood pressure was measured at the time of interview and used to estimate pre-admission level, as previously reported.[12] Self-reported items included medical history, physical activity, diet (assessed using a healthy eating index, with a higher score indicating better diet quality[14]), smoking, and psychological factors.[15] Hypertension was defined as a self-reported history of hypertension or blood pressure ≥140/90 mm Hg (including adjusted admission blood pressure, as previously described[12]). Diabetes mellitus was defined as self-reported history of diabetes or HbA1c ≥6.5%. Countries were grouped: (1) Western Eu-

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rope and North America (Canada, Australia, Germany, Denmark, Sweden, United Kingdom, and Ireland); (2) Eastern and Central Europe and Middle East (Croatia, Poland, Turkey, Iran, United Arab Emirates, Russia, and Saudi Arabia); (3) China; (4) South America (Argentina, Brazil, Chile, Colombia, Ecuador, and Peru); (5) Southeast Asia (Thailand, Philippines, and Malaysia); (6) South Asia (India and Pakistan); and (7) Africa (South Africa, Mozambique, Uganda, Sudan, and Nigeria).

Participants provided information on beverage consumption using two methods. For carbonated beverage and fruit juice/drink consumption, participants completed a food frequency questionnaire (referring to the previous 12 months) and were categorized by frequency (but not quantity) of daily consumption—none, up to once/day, 2/day, or >2/day. Carbonated beverages were defined as cola, non-cola beverages (sweetened and unsweetened), tonic water, or instant iced tea. Separately, participants were asked "How many cups do you drink each day?" of water and categorized as none, 1–2 cups/day, 3–4 cups/day, 5–6 cups/day, 7–8 cups/day, or >8 cups/day. A cup was defined as 250 mL. For tea (Chinese/Japanese green, black, or other) and coffee consumption, participants were asked "How many cups do you drink each day?" and categorized as none, 1–2 cups/day, 3–4 cups/day, or >4 cups/day. All participants answered all questions. All data were transferred to Population Health Research Institute, McMaster University and Hamilton Health Sciences, Canada, for quality control.

Statistical analysis

We calculated means and medians to summarize continuous variables and report proportions for categorical variables. Comparisons are completed using t-test, chi-square test, or nonparametric test, as appropriate. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for all analyses of associations between beverage intake and all stroke, ischemic stroke, and intracerebral hemorrhage (ICH). We built our multivariable-adjusted models in three steps: (1) Model 1 included adjustment for biological factors (age, ethnicity, body mass index [BMI], apolipoprotein B:A ratio [apoB: apoA], diabetes, hypertension, and cardiac risk factors [coronary artery disease, angina, or atrial fibrillation]); (2) Model 2 included additional adjustments for sociocultural factors (education, occupation, physical activity, alcohol intake, smoking, diet quality, and stress); and (3) Model 3 (fully adjusted) included additional adjustments for other beverage intake (fruit juice/drink, carbonated drink, water [as appropriate], tea, and coffee). We explored statistical interactions between different beverage types by adding multiplicative interaction terms to Model 3 (fully adjusted) conditional logistic regression model for all stroke. There were no significant interactions observed (Supplementary Table 1); therefore, no interaction terms were added to multivariable-adjusted models.

For analyses stratified by region, by subgroup, and for all sensitivity analyses, we present fully adjusted (Model 3) associations with all stroke only, and not within stroke subtypes. For analyses stratified by region, we observed limited numbers within categories of beverage consumption; therefore, we chose to dichotomize beverage intake as follows: fruit juice/drink (none vs. any), carbonated drink (none vs. any), and water (≤4 cups vs. >4 cups/day [median intake]). We explored if associations differed by age (hypothesizing that age-related patterns of beverage consumption and comorbidities may alter associations), sex (hypothesizing that sex-related patterns of beverage consumption, muscle mass, and total body water may alter associations), smoking (hypothesizing that smoking may influence choice, and/or pattern of beverage consumption), alcohol consumption (hypothesizing that alcoholic beverages contain biologically active substances that may influence associations and alcoholic beverages may be consumed with, or instead of, other beverages), and hypertension (hypothesizing that total fluid intake and caffeine intake may influence associations). Differential effects between strata were considered statistically significant if the *P*-value for the multiplicative interaction term (P_{int}) between the stratifying variable and beverage estimate was <0.05. As the involvement of a proxy respondent in the completion of some or all of the study questionnaire holds the potential to bias observations (e.g., by over- or under-reporting beverage intake), we chose to complete sensitivity analyses, where cases with the involvement of a proxy respondent (and matched controls) were excluded.

Standard protocol approvals, registrations, and patient consents

The study was approved by ethics committees in all centers or countries and participants (or proxy) provided written informed consent.

Data availability

Information on the design and rationale of INTERSTROKE has been published previously.[16] The lead author has full access to the data used in the analyses in this manuscript, takes full responsibility for the data, analyses, and interpretation of findings, and has the right to publish these findings. Anonymized data not published within this article may be made available on request from any qualified investigator.[17]

Results

We include 13,462 cases and 13,488 controls from INTERSTROKE, whose characteristics were published previously.[12] Overall, mean age was 61.7 (13.4) years and 59.6% (n=16,010) were male (Table 1). There was representation from seven geographical re-

Table 1. Characteristics of study population stratified by beverage consumption

	Overall (n=26,950)	None (n=1,707)	Water only (n=11,389)	Fruit juice/drink only (n=5,639)	Carbonated beverages only (n=1,531)	Fruit juice/drink & carbonated beverages (n=6,684)	*P*
Age (yr)	61.7±13.4	62.5±11.8	62.5±12.3	64.4±13.7	58.9±13.7	58.7±14.6	<0.001
Female sex	10,894 (40.4)	555 (32.5)	4,882 (42.9)	2,500 (44.3)	566 (37.0)	2,391 (35.8)	<0.001
Education							<0.001
<8 yrs	13,018 (48.3)	809 (47.4)	7,044 (61.9)	2,214 (39.3)	598 (39.1)	2,353 (35.2)	
9–12 yrs	7,034 (26.1)	401 (23.5)	2,701 (23.7)	1,435 (25.5)	491 (32.1)	2,006 (30.0)	
Trade/college/university	6,892 (25.6)	497 (29.1)	1,642 (14.4)	1,989 (35.3)	441 (28.8)	2,323 (34.8)	
Occupation							<0.001
Skilled/gen labour/farmer	13,634 (50.6)	1,059 (62.1)	6,968 (21.2)	2,164 (38.4)	669 (43.7)	2,774 (41.6)	
Police/military/clerical	1,436 (5.3)	63 (3.7)	380 (3.3)	384 (6.8)	108 (7.1)	501 (7.5)	
Professional/business	5,308 (19.7)	302 (17.7)	1,587 (13.9)	1,381 (24.5)	385 (25.2)	1,653 (24.8)	
Housewife	4,366 (16.2)	203 (11.9)	1,880 (16.5)	1,120 (19.9)	204 (13.3)	959 (14.4)	
Disability/social security	657 (2.4)	17 (1.0)	211 (1.9)	178 (3.2)	12 (0.8)	239 (3.6)	
Other	1,531 (5.7)	62 (3.6)	360 (3.2)	407 (7.2)	152 (9.9)	550 (8.2)	
Smoking							<0.001
Never	15,816 (58.7)	877 (51.5)	6,688 (58.7)	3,620 (64.2)	824 (53.8)	3,807 (57.0)	
Former	4,025 (14.9)	178 (10.5)	1,026 (9.0)	1,154 (20.5)	305 (19.9)	1,362 (20.4)	
Current	7,095 (26.3)	648 (38.1)	3,672 (32.3)	862 (15.3)	402 (26.3)	1,511 (22.6)	
Mainly inactive	23,339 (86.7)	1,430 (83.9)	10,459 (91.9)	4,562 (81.0)	1,281 (83.8)	5,607 (83.9)	<0.001
Diet–AHEI tertile							<0.001
1	9,679 (35.9)	683 (40.0)	4,237 (37.2)	1,769 (31.4)	647 (42.3)	2,343 (35.1)	
2	9,074 (33.7)	603 (35.3)	4,020 (35.3)	1,692 (30.0)	465 (30.4)	2,294 (34.3)	
3	8,197 (30.4)	421 (24.7)	3,132 (27.5)	2,178 (38.6)	419 (27.4)	2,047 (30.6)	
BMI (kg/m^2)	25.7±4.8	25.7±4.5	24.5±4.4	26.5±4.8	26.6±5.2	26.9±5.0	<0.001
WHR	0.93±0.08	0.92±0.07	0.91±0.07	0.94±0.08	0.94±0.08	0.94±0.08	<0.001
Hypertension	16,553 (61.4)	1,099 (64.4)	6,752 (59.3)	3,650 (64.7)	933 (60.9)	4,119 (61.6)	<0.001
Diabetes	6,733 (25.0)	403 (23.6)	2,852 (24.8)	1,511 (26.8)	413 (27.0)	1,581 (23.7)	<0.001
Cardiac risk factors	2,557 (9.5)	142 (8.3)	691 (6.1)	806 (14.3)	181 (11.8)	737 (11.0)	<0.001
Myocardial Infarction	940 (3.5)	48 (2.8)	228 (2.0)	308 (5.5)	73 (4.8)	283 (4.2)	<0.001
Atrial fibrillation	869 (3.2)	56 (3.3)	226 (2.0)	295 (5.2)	65 (4.3)	227 (3.4)	<0.001
Beverage intake							
Coffee (cups/day)	0 [0–1]	0 [0–0]	0 [0–0]	1 [0–2]	0 [0–2]	1 [0–2]	<0.001
Black tea (cups/day)	0 [0–0]	0 [0–2]	0 [0–0]	0 [0–2]	0 [0–1]	0 [0–1]	<0.001
Green tea (cups/day)	0 [0–0]	0 [0–2]	0 [0–0]	0 [0–0]	0 [0–0]	0 [0–0]	<0.001
Other tea (cups/day)	0 [0–2]	0 [0–3]	0 [0–2]	0 [0–1]	0 [0–2]	0 [0–1]	<0.001
Water (cups/day)	4 [2–8]	0 [0–0]	5 [2–8]	4 [2–8]	5 [2–8]	5 [3–8]	<0.001
Fruit juice (times/week)	0 [0–1]	0 [0–0]	0 [0–0]	1 [1–1]	0 [0–0]	1 [1–1]	<0.001
Carbonated beverages (times/week)	0 [0–1]	0 [0–0]	0 [0–0]	0 [0–0]	1 [1–1]	1 [1–1]	<0.001

Values are presented as mean±standard deviation, n (%), or median [interquartile range]. Totals for some categories may not sum to the respective group totals due to missing data.
AHEI, Alternative Healthy Eating Index; BMI, body mass index; WHR, waist-to-hip ratio.

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gions of the world, with the largest representations from China (29.5%) and South Asia (21.3%).

Beverage consumption

There were significant regional variations in carbonated beverage and fruit juice/drink consumption; those in South Asia and China were least likely to be consumers compared to other regions where consumption was much higher, with consistent patterns by sex within region (Figure 1 and Supplementary Figure 1). On average, higher carbonated beverage consumers were more likely to be younger, more educated, never-smokers, and more active but with lower diet quality and higher rates of cardiac risk factors (myocardial infarction or atrial fibrillation) and based in Western Europe or North America (Supplementary Table 2). Higher fruit juice/drink consumers were more likely to be male, more educated, non-smokers with higher diet quality, and based in South America or Western Europe/North America (Supplementary Table 3). Higher water consumers were younger, less educated, never smokers, with lower BMI, less likely to have a history of hypertension, myocardial infarction, or atrial fibrillation but more likely to have diabetes and based in Southeast Asia or South Asia (Supplementary Table 4). The prevalence of high water consumption was lowest in those aged >75 years (P<0.001) (Supplementary Figure 2).

Beverage consumption and stroke

The stepwise approach to multivariable adjustment did not materially alter the direction or magnitude of associations between beverages and stroke (Supplementary Table 5). Therefore, we focus our results on the fully adjusted model (Model 3). After multivariable adjustment with no consumption as the reference category, higher carbonated beverage consumption had a significant association with increased odds of all stroke (OR 2.29 [95% CI 1.62–3.24]) and ischemic stroke (OR 2.39 [95% CI 1.64–3.49]) but only up to once/day was significantly associated with increased odds of ICH (OR 1.58 [95% CI 1.23–2.03]) (Figure 2 and Table 2). There was no significant association between fruit juice/drink consumption and all stroke or ischemic stroke, but consumption of up to once/day was significantly associated with increased odds of ICH (OR 1.37 [95% CI 1.08–1.75]), as was twice/day (OR 3.18 [95% CI 1.69–5.97]). For water consumption, higher intake was significantly associated with reduced odds of all stroke (OR 0.84 [95% CI 0.71–0.99] for 7–8 cups/day and OR 0.77 [95% CI 0.65–0.91] for >8 cups/day) and ischemic stroke (OR 0.82 [95% CI 0.68–0.99] for 7–8 cups/day and OR 0.72 [95% CI 0.60–0.87] for >8 cups/day), but there was no significant association between water consumption and ICH.

There were significant differences in the associations between beverage intake and all stroke by region. Any carbonated bev-

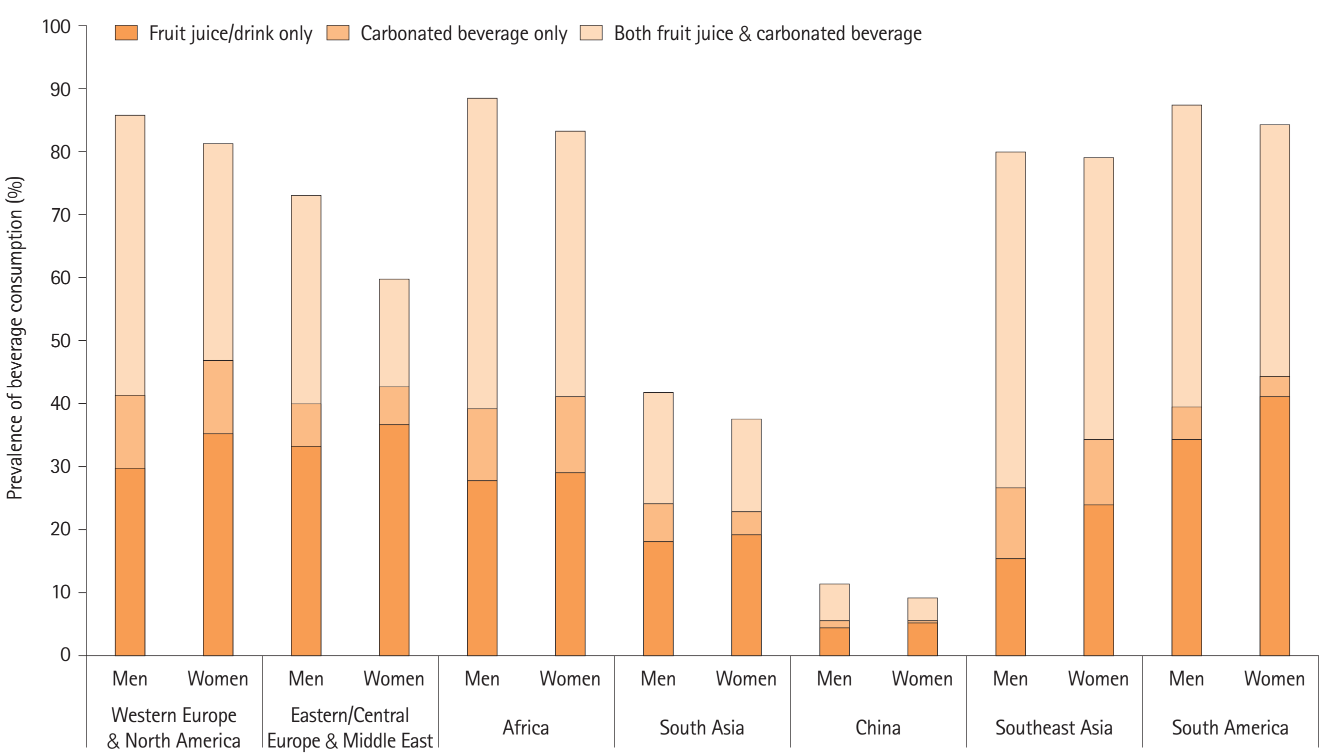

Figure 1. Prevalence of fruit juice/drink, carbonated beverage, or both by sex within seven geographical regions. The stacked columns add up to 100%, with the blank area representing the prevalence of those who consume neither fruit juice/drinks nor carbonated beverages.

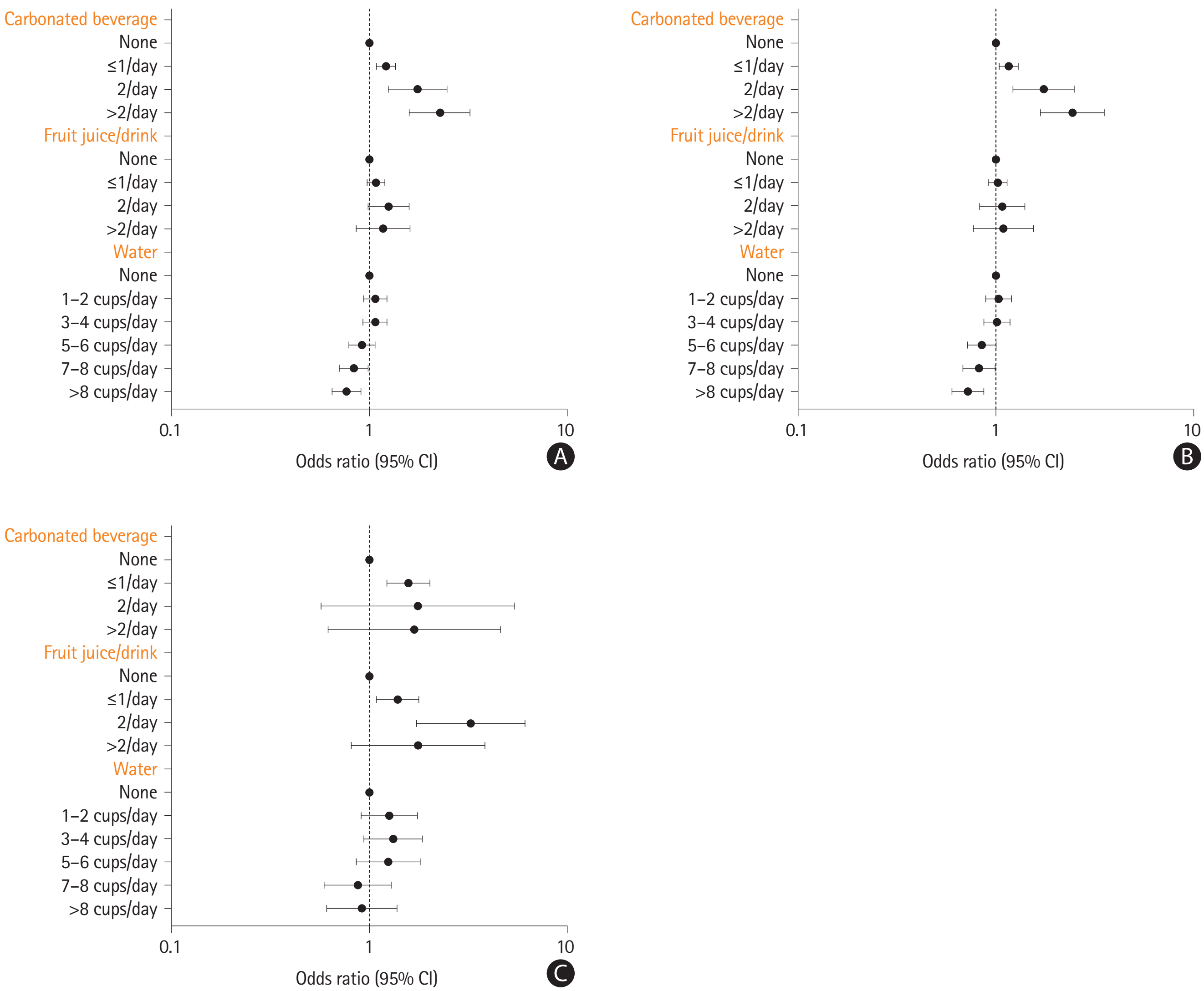

Figure 2. Multivariable adjusted association between beverage intake and stroke. (A) All stroke. (B) Ischemic stroke. (C) Intracerebral hemorrhage. Conditional logistic regression models adjusted for age, ethnicity, education, occupation, body mass index, physical activity, alcohol, smoking, diet (tertile), apolipoprotein B:A ratio, diabetes, hypertension, cardiac risk factors, global stress, and other beverage types. CI, confidence interval.

erage consumption was associated with significantly increased odds of all stroke in Eastern/Central Europe and Middle East, Africa, and South America (P_{int}=0.001) (Table 3). Any fruit juice/drink consumption was associated with reduced odds of all stroke in Western Europe and North America only, with increased odds of all stroke in South Asia (P_{int}=0.001). There were no significant regional differences in the association between water intake and stroke (P_{int}=0.956).

Subgroup and sensitivity analyses

By age, there were no significant interactions between carbonated beverages or fruit juice/drinks and stroke; only in those aged ≥65 years with higher water intake were the odds of stroke reduced (P_{int}=0.002) (Supplementary Table 6). By sex, there were no significant interactions between carbonated beverages or water and stroke; only in females with higher fruit juice/drink intake were the odds of stroke increased (P_{int}=0.004) (Supplementary Table 7). By smoking, there were no significant interactions between carbonated beverages or fruit juice/drinks and stroke; in current smokers, there was a statistically significant interaction but inconsistent pattern of association between water intake and stroke (P_{int}=0.014) (Supplementary Table 8). By alcohol consumption, there was a statistically significant interaction but inconsistent patterns of association between carbonated beverage intake and stroke (P_{int}=0.044) and between fruit juice/drink intake and stroke (P_{int}=0.018); there was no significant interaction between water intake and stroke (Supplementary Table 9). By hypertension, there were no significant interactions between carbonated beverage and stroke; for water intake and stroke, there was a statistically significant but not clinically meaningful

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Table 2. Primary analyses: associations between beverage intake and stroke

Carbonated drink	None	≤1/day		2/day	>2/day	
Cases of all stroke	9,271	3,763		186	242	
Unadjusted	1.00 (Ref)	1.04 (0.97–1.11)		1.75 (1.37–2.22)	2.05 (1.59–2.63)	
Fully adjusted*	1.00 (Ref)	1.22 (1.10–1.34)		1.76 (1.25–2.48)	2.29 (1.62–3.24)	
Cases of ischemic stroke	7,130	2,889		164	219	
Unadjusted	1.00 (Ref)	1.02 (0.95–1.10)		1.84 (1.42–2.38)	2.34 (1.80–3.05)	
Fully adjusted*	1.00 (Ref)	1.17 (1.04–1.30)		1.76 (1.22–2.54)	2.39 (1.64–3.49)	
Cases of ICH	2,141	874		22	23	
Unadjusted	1.00 (Ref)	1.13 (0.96–1.32)		1.32 (0.70–2.51)	1.63 (0.81–3.30)	
Fully adjusted*	1.00 (Ref)	1.58 (1.23–2.03)		1.75 (0.57–5.44)	1.29 (0.44–3.77)	
Fruit juice/drink	**None**	**≤1/day**		**2/day**	**>2/day**	
Cases of all stroke	7,295	5,656		338	173	
Unadjusted	1.00 (Ref)	1.00 (0.93–1.06)		1.06 (0.89–1.25)	0.97 (0.76–1.22)	
Fully adjusted*	1.00 (Ref)	1.08 (0.98–1.19)		1.26 (0.99–1.58)	1.13 (0.83–1.55)	
Cases of ischemic stroke	5,456	4,519		283	144	
Unadjusted	1.00 (Ref)	0.96 (0.89–1.04)		1.03 (0.86–1.24)	1.05 (0.82–1.36)	
Fully adjusted*	1.00 (Ref)	1.02 (0.92–1.14)		1.08 (0.83–1.40)	1.07 (0.76–1.52)	
Cases of ICH	1,839	1,137		55	29	
Unadjusted	1.00 (Ref)	1.18 (1.01–1.38)		1.22 (0.81–1.85)	1.16 (0.69–1.96)	
Fully adjusted*	1.00 (Ref)	1.37 (1.08–1.75)		3.18 (1.69–5.97)	1.52 (0.68–3.41)	
Water	**None**	**1–2 cups**	**3–4 cups**	**5–6 cups**	**7–8 cups**	**>8 cups**
Cases of all stroke	1,706	2,515	2,792	2,359	1,745	2,345
Unadjusted	1.00 (Ref)	1.11 (1.01–1.22)	1.09 (0.99–1.21)	0.98 (0.88–1.09)	0.85 (0.75–0.95)	0.83 (0.74–0.94)
Fully adjusted*	1.00 (Ref)	1.07 (0.94–1.23)	1.07 (0.93–1.23)	0.92 (0.79–1.07)	0.84 (0.71–0.99)	0.77 (0.65–0.91)
Cases of ischemic stroke	1,474	1,962	2,170	1,803	1,262	1,731
Unadjusted	1.00 (Ref)	1.08 (0.97–1.21)	1.04 (0.93–1.16)	0.91 (0.81–1.02)	0.82 (0.72–0.93)	0.80 (0.70–0.92)
Fully adjusted*	1.00 (Ref)	1.03 (0.89–1.20)	1.01 (0.87–1.18)	0.85 (0.72–1.00)	0.82 (0.68–0.99)	0.72 (0.60–0.87)
Cases of ICH	232	553	622	556	483	614
Unadjusted	1.00 (Ref)	1.28 (0.94–1.76)	1.48 (1.07–2.06)	1.44 (1.02–2.03)	1.02 (0.70–1.49)	1.02 (0.70–1.48)
Fully adjusted*	1.00 (Ref)	1.26 (0.91–1.75)	1.32 (0.94–1.86)	1.25 (0.86–1.81)	0.88 (0.59–1.30)	0.92 (0.61–1.38)

Values are presented as odds ratios (95% confidence intervals) unless otherwise indicated.
ICH, intracerebral hemorrhage.
*Conditional logistic regression models adjusted for age, ethnicity, body mass index, apolipoprotein B:A ratio, diabetes, hypertension, cardiac risk factors, education, occupation, physical activity, alcohol intake, smoking, diet (tertile), global stress, and other beverage types.

interactions for fruit juice/drink (P_{int}=0.044) and water (P_{int}<0.001) (Supplementary Table 10). Our primary findings were essentially unchanged with the exclusion of proxy respondents (Supplementary Table 11).

Discussion

In this large international study, we report considerable regional variation in the patterns of beverage consumption and characteristics of consumers across the world. Interestingly, we observed a particularly low prevalence of fruit drink and carbonated beverage consumption in China, broadly consistent with other studies.[18] All levels of carbonated beverage consumption were significantly associated with increased odds of all stroke, ischemic stroke, and ICH. There was a significant association between fruit juice/drink consumption and ICH, but not ischemic stroke. Water consumption >7 cups/day was associated with reduced odds of ischemic stroke, but not ICH. There were significant regional differences in our observed associations. Carbonated beverage consumption was associated with increased odds of all stroke in Eastern/Central Europe and Middle East, Africa, and South America; and, fruit juice/drink consumption was associated with reduced odds of all stroke in Western Europe and North America but increased odds in South Asia.

Table 3. Association* between tea/coffee and all stroke by region

	Western Europe, North America	Eastern/Central Europe, Middle East	Africa	South Asia	China	Southeast Asia	South America	P_{int}
Fruit juice/drink								0.001
None								
Cases	598	542	225	1,795	3,600	290	263	
OR (95% CI)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	
Any								
Cases	1,319	852	748	1,070	387	565	1,208	
OR (95% CI)	0.74 (0.60–0.92)	1.06 (0.83–1.35)	1.43 (0.99–2.08)	1.37 (1.03–1.82)	1.17 (0.87–1.57)	0.87 (0.58–1.30)	1.20 (0.89–1.61)	
Carbonated drink								0.001
None								
Cases	920	890	406	2,311	3,760	344	661	
OR (95% CI)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	
Any								
Cases	997	504	567	554	227	511	810	
OR (95% CI)	0.98 (0.81–1.19)	1.44 (1.10–1.89)	1.46 (1.02–2.10)	0.78 (0.56–1.08)	1.19 (0.81–1.73)	1.01 (0.69–1.48)	1.83 (1.45–2.31)	
Water								0.956
≤4 cups per day								
Cases	1,278	905	417	480	3,038	88	807	
OR (95% CI)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	
>4 cups per day								
Cases	639	489	556	2,385	949	767	664	
OR (95% CI)	0.98 (0.79–1.20)	0.62 (0.47–0.80)	1.15 (0.78–1.69)	1.03 (0.76–1.41)	0.65 (0.54–0.78)	1.08 (0.67–1.76)	0.98 (0.78–1.23)	

OR, odds ratio; CI, confidence interval.
*Conditional logistic regression models adjusted for age, ethnicity, education, occupation, body mass index, physical activity, alcohol, smoking, diet (tertile), apolipoprotein B:A ratio, diabetes, hypertension, cardiac risk factors, global stress, and other beverage types.

Carbonated beverages, or soft drinks, include both SSB and ASB. Soft drink consumption is often proposed to be a surrogate marker of an "unhealthy" diet and lifestyle, including adverse dietary pattern, smoking, poor physical activity, and higher BMI.[19] Our observations are not entirely consistent with this hypothesis. Whilst high carbonated beverage consumers had lower diet quality and higher prevalence of cardiac risk factors, they were also younger, more educated, never-smokers, and more active. We report that carbonated beverage consumption had a positive linear association with all stroke and ischemic stroke, with lower magnitude of association with ICH. Our findings are broadly consistent with those reported by two Swedish cohorts,[20] where >2 servings/day of carbonated beverages was associated with increased risk of total stroke and cerebral infarction, but not hemorrhagic stroke. Mechanisms such as increased weight, obesity, and diabetes are well established risk factors for ischemic stroke but not ICH.[21] We report no significant differences in the associations between carbonated beverages and stroke by age or sex, unlike a Japanese cohort study.[22]

Importantly, we do not have separate data on SSB and ASB within INTERSTROKE. In particular, SSB are associated with higher cardiometabolic risk,[8] weight gain, metabolic syndrome, diabetes,[23] hypertension,[24] plaque stability, and thrombosis.[25] Although ASB are often marketed as "healthier" alternatives to SSB, they are also associated with cardiovascular risk through weight gain, increased adiposity,[26] and hyperinsulinemia.[27] In addition, reverse causation may, at least in part, contribute to ASB consumption instead of SSB, as those at increased risk of cardiometabolic complications may switch from SSB to ASB. Previous studies of SSB intake report inconsistent results. The Framingham Heart Study[28] and the Northern Manhattan Study[29] reported no association with stroke, but a systematic review, including nine prospective cohort studies, reports an increase in risk of stroke, particularly in women.[30] In contrast, multiple studies including the Northern Manhattan Study,[29] Nurses Health Study and Health Professionals Follow-Up Study,[31] and the Framingham Heart Study[28] report an increased risk of stroke with ASB, confirmed by systematic review and meta-analysis.[30] We report significant variations in the association between carbonated drinks and stroke by geographical region, which may reflect differences in

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the prevalence of ASB versus SSB consumption, or the level of sugar content in SSB. However, we do not have data in INTERSTROKE to interrogate this further.

Fruit juice has varying definitions. Pure fruit juice is defined as 100% juice that is freshly squeezed and bottled without added sugars, artificial sweeteners, flavorings, or preservatives.[6] However, many products marketed as fruit juice are made from concentrates and contain added sugars and preservatives (e.g., fruit drinks). Potential health benefits associated with fruit juice are likely to be less than whole fruit (as juice contains less fiber and vitamin C). Similar to whole fruit consumption, intake and access to fruit juice are likely to be impacted by socioeconomic status and geographic region. Some report that higher fruit juice consumption was observed in those of lower socioeconomic status,[32] whilst the Global Burden of Disease reports highest intake in high-income countries.[33] Taken together, these factors may explain the differences in our observations between regions. Fruit juice/drink consumption was associated with significantly reduced odds of stroke in Western Europe and North America only and significantly increased odds in South Asia only (P_{int}=0.001). This may also explain our observations that high fruit juice/drink consumers were female, more educated, non-smokers with higher diet quality, and based in South America or Western Europe/North America. We report no significant association between fruit juice/drink consumption and all stroke or ischemic stroke, but increased odds of ICH. This contrasts with other studies: two Dutch cohorts reported reduced risk of stroke (1–8 glasses of fruit juice per week[34]); a systematic review (including 81 cohorts and >4 million individuals) reported a lower risk of stroke mortality in those consuming fruit juice[35]; and another systematic review (21 prospective cohort studies) reported a non-linear association with stroke risk, but a lower risk with intake of <200 mL/day.[20] The potential impact of socioeconomic factors and global variations observed within INTERSTROKE are likely to be particularly important, and may explain, in part, the difference in our findings from previous studies. In INTERSTROKE, high fruit juice/drink consumers tended to be more educated and with high diet quality; this may suggest that these individuals were of higher socioeconomic standing. Importantly, such individuals may also have additional access to healthcare and be more likely to be diagnosed with stroke. Our regional analyses, with significant variations in the association between fruit drinks and all stroke, may reflect differences in the definition of fruit drinks or sugar/preservative content in fruit drinks between regions. However, we do not have data in INTERSTROKE to interrogate this further.

Previous studies demonstrate that water intake varies significantly across the world.[36,37] Water intake is influenced by many factors: (1) health-conscious individuals with higher physical activity may drink more water; (2) those with comorbidities, such as diabetes, may have increased thirst[38]; and (3) sanitation,[39] water cleanliness, and the affordability of bottled water[40] significantly impact intake. On average, our high water consumers were younger, less educated individuals with lower cardiovascular risk factor burdens. Importantly, high water consumers were also more likely to have diabetes mellitus and be based in Southeast Asia or South Asia. Adequate hydration is associated with lower rates of chronic kidney disease[41] and coronary heart disease,[42] but the association with cardiovascular mortality is inconsistent.[43-45] Dehydration increases whole-blood viscosity, plasma viscosity, fibrinogen and hematocrit,[46] contributing to vascular collapse[47] and vessel spasm,[48] which may lead to cerebral events. Therefore, higher water intake (and adequate hydration) may offset these increases in blood viscosity and reduce risk of cerebral infarction.[49] These mechanisms support our observations that higher water intake was associated with reduced odds of all stroke and ischemic stroke (but not ICH). Although females have smaller blood volumes and blood viscosity may react differently to the same volume of water,[50] we report no differences in odds of stroke between males and females. Importantly, thirst is triggered by increased osmolarity and hypovolemia and occurs only after dehydration (when stroke risk may have already risen); this may be more marked in older individuals, where thirst decreases.[51] Whilst increased age is a risk factor for stroke, we observed that the reduced odds of stroke with higher water intake were restricted to those aged ≥65 years, perhaps suggesting that the maintenance of regular water intake may play a role in reducing risk of stroke in older age.[52] We observed a significant reduction in the prevalence of water consumption >8 cups/day with increasing age, which may be related to comorbidity and introduces the potential for reverse causation to impact our findings, although one would expect bias towards the null. Given these uncertainties, there may be a role for clinical trials of water intake, particularly in older adults, for stroke prevention.

The major strength of this study is the large number of individuals included from a range of countries across regions of the world and ethnicity. The case-control design provided a practical approach to achieving a level of diversity and ensuring global representation, including populations generally excluded from previous studies. We have a large volume of data, with ability to control for many covariates to minimize the effects of confounding and facilitate different analytic approaches.

Our study has limitations. As it is a case-control study, it may be impacted by recall bias particularly if there is differential recollection of beverage intake between cases and controls, or exacerbated where the questionnaire was completed by or with the assistant of a proxy. Therefore, we completed sensitivity analyses excluding the contribution of proxy respondents, which was consistent with our primary analyses. Recall bias leading to under- or over-reporting of beverage intake is likely to be randomly distributed within cases. Selection bias may have resulted from the approach to recruiting controls but we reduced this by excluding those with a hospital referral or diagnosis related to stroke. In addition, data was collected in a standardized manner which was identical in cases and controls. Controls were recruited from both community-based and hospital-based sources; ideally, we would have recruited controls from the general population without stroke and in the same catchment areas (as hospital-based controls may underestimate the true association for risk factors[13]). However, this approach was impractical in many settings. There was limited variation in the intake of individual beverages, likely reflecting regional, geographical, or socioeconomic differences between populations. We were unable to adjust multivariable models for total energy intake (kcal/day) as that information is not typically available from a 12-month food frequency questionnaire. Similarly, our estimates of carbonated beverages and fruit juice/drinks lack quantitative dimensions including but not limited to volume, mineral, or sweetener content. Although we can approximately quantify water intake (1 cup=250 mL), we cannot do so for other beverages, and therefore, it limits our ability to complete quantitative dose-response analyses. However, we do present analyses based on increasing frequency of consumption. Our data on cold beverage consumption was limited to those presented here; we did not have data on other cold beverages (e.g., milk) and cannot comment on total quantitative fluid intake. We have separately reported on the associations between tea and coffee intake and stroke.[53] As an observational study, causality cannot be firmly established and although we adjusted for multiple confounders, our findings may be influenced by residual confounding or unmeasured confounders. Our study was confined to those who survived long enough to reach the hospital, rather than all individuals with stroke, and we could not include the most severe (fatal) strokes. Even a large study like INTERSTROKE may have limited power to quantify the impacts of beverages within some countries or regions.

Conclusions

We report increased odds of stroke associated with carbonated beverage intake and fruit juice/drink (ICH only) but reduced odds of stroke associated with high water consumption. We observed important regional differences in our associations, suggesting that geographical and sociocultural factors would need to be considered in the design of future studies. We encourage individuals to maintain adequate levels of hydration and generate hypotheses that the future risk of stroke could be reduced by optimizing water intake, minimizing fruit juice/drinks, and avoiding carbonated beverages. In order to determine if our observed associations between beverage intake and stroke are causally linked, future studies with different methodological frameworks (such as testing interventions in clinical trials) are required.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2024.01543.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: AS, SY, MOD. Study design: AS, SY, MOD. Methodology: AS, SY, MOD. Data collection: GJH, AD, HKI, SO, FA, PL, DX, PLJ, AO, AC, FL, DR, XW, AR. Investigation: AS, CM, CR, MOD. Statistical analysis: AS. Writing—original draft: AS. Writing—review & editing: AS, GJH, PL, CM, CR, SY, MOD. Funding acquisition: SY, MOD. Approval of final manuscript: all authors.

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Supplementary Table 1. Interaction terms between beverage types for association with stroke

	Carbonated beverage	Fruit juice/drink	Water	Tea	Coffee
Carbonated beverage	-	0.12	0.08	0.21	0.10
Fruit juice/drink	0.12	-	0.46	0.73	0.42
Water	0.08	0.46	-	0.32	0.89
Tea	0.21	0.73	0.32	-	-
Coffee	0.10	0.42	0.89	-	-

P for interaction presented based on conditional logistic regression model for all stroke including multiplicative interaction term and multivariable adjustment for age, ethnicity, education, occupation, body mass index, physical activity, alcohol, smoking, diet (tertile), apolipoprotein B:A ratio (apoB:apoA), diabetes, hypertension, cardiac risk factors, global stress, and other beverage types (as appropriate).

Supplementary Table 2. Population characteristics by carbonated beverage consumption

	None (n=18,735)	≤1/day (n=7,561)	2/day (n=301)	>2/day (n=376)	*P*
Age (yr)	63.1±12.7	58.7±14.5	59.4±14.0	59±13.4	<0.001
Male sex	10,786 (57.6)	4,828 (63.9)	203 (67.4)	227 (64.3)	0.009
Education					<0.001
<8 years	10,067 (53.7)	2,798 (37.0)	66 (21.9)	87 (24.7)	
9–12 years	4,537 (24.2)	2,249 (29.8)	120 (39.9)	128 (36.3)	
Trade/college/university	4,128 (22.0)	2,511 (33.2)	115 (38.2)	138 (39.1)	
Occupation					<0.001
Skilled/gen labour/farmer	10,191 (54.4)	3,137 (41.5)	121 (40.2)	185 (52.6)	
Police/military/clerical	827 (4.4)	573 (7.6)	20 (6.6)	16 (4.6)	
Professional/business	3,270 (17.5)	1,867 (24.7)	83 (27.6)	88 (25.0)	
Housewife	3,203 (17.1)	1,120 (14.8)	25 (8.3)	18 (5.1)	
Disability/social security	406 (2.2)	242 (3.2)	3 (1.0)	6 (1.7)	
Other	829 (4.4)	614 (8.1)	49 (16.3)	39 (11.1)	
Smoking					<0.001
Never	11,185 (59.7)	4,381 (58.0)	112 (37.2)	138 (39.1)	
Former	2,358 (12.6)	1,464 (19.4)	96 (31.9)	107 (30.3)	
Current	5,182 (27.7)	1,712 (22.7)	93 (30.9)	108 (30.6)	
Mainly inactive	16,451 (87.9)	6,387 (84.5)	241 (80.1)	260 (73.7)	<0.001
Diet–AHEI tertile					<0.001
1	6,689 (35.7)	2,694 (35.6)	124 (41.2)	172 (48.7)	
2	6,315 (33.7)	2,599 (34.4)	81 (26.9)	79 (22.4)	
3	5,731 (30.6)	2,268 (30.0)	96 (31.9)	102 (28.9)	
BMI (kg/m^2)	25.2±4.6	26.7±4.9	28.4±6.1	28.3±5.9	<0.001
WHR	0.92±0.07	0.94±0.08	0.96±0.08	0.95±0.10	<0.001
Hypertension	11,501 (61.4)	4,622 (61.1)	193 (64.1)	237 (67.1)	0.041
Diabetes	4,739 (25.3)	1,819 (24.1)	77 (25.7)	98 (27.9)	0.107
Cardiac risk factors	1,639 (8.8)	802 (10.6)	57 (18.9)	59 (16.7)	<0.001
Myocardial infarction	584 (3.1)	305 (4.0)	22 (7.3)	29 (8.2)	<0.001
Atrial fibrillation	577 (3.1)	242 (3.2)	23 (7.6)	27 (7.7)	<0.001

Values are presented as mean±standard deviation or n (%). Totals for some categories may not sum to the respective group totals due to missing data.
AHEI, Alternative Healthy Eating Index; BMI, body mass index; WHR, waist-to-hip ratio.

Supplementary Table 3. Population characteristics by fruit juice/drink consumption

	None (n=14,627)	≤1/day (n=11,346)	2/day (n=660)	>2/day (n=317)	*P*
Age (yr)	62.1±12.5	61.2±14.4	63.3±14.7	61.3±15.9	<0.001
Male sex	8,624 (59.0)	6,877 (60.6)	367 (55.6)	188 (59.3)	0.009
Education					<0.001
<8 years	8,451 (57.8)	4,243 (37.4)	231 (35.0)	93 (29.3)	
9–12 years	3,593 (24.6)	3,164 (27.9)	180 (27.3)	97 (30.6)	
Trade/college/university	2,580 (17.6)	3,936 (34.7)	249 (37.7)	127 (40.1)	
Occupation					<0.001
Skilled/gen labour/farmer	8,696 (59.5)	4,622 (40.8)	222 (33.6)	94 (29.7)	
Police/military/clerical	551 (3.8)	810 (7.2)	52 (7.9)	23 (7.3)	
Professional/business	2,274 (15.6)	2,758 (24.3)	180 (27.3)	96 (30.3)	
Housewife	2,287 (15.6)	1,934 (17.1)	97 (14.7)	48 (15.1)	
Disability/social security	240 (1.6)	354 (3.1)	42 (6.4)	21 (6.6)	
Other	574 (3.9)	855 (7.5)	67 (10.2)	35 (11.0)	
Smoking					<0.001
Never	8,389 (57.4)	6,900 (60.9)	369 (55.9)	158 (49.8)	
Former	1,509 (10.3)	2,227 (19.6)	186 (28.2)	103 (32.5)	
Current	4,722 (32.3)	2,212 (19.5)	105 (15.9)	56 (17.7)	
Mainly inactive	13,170 (90.1)	9,435 (83.2)	486 (73.6)	248 (78.2)	<0.001
Diet–AHEI tertile					<0.001
1	5,567 (38.1)	3,839 (33.8)	184 (27.9)	89 (28.1)	
2	5,088 (34.8)	3,712 (32.7)	191 (28.9)	83 (26.2)	
3	3,972 (27.2)	3,795 (33.5)	285 (43.2)	145 (45.7)	
BMI (kg/m^2)	24.9±4.6	26.6±4.8	27.4±5.3	27.6±5.7	<0.001
WHR	0.92±0.07	0.94±0.08	0.94±0.08	0.94±0.09	<0.001
Hypertension	8,784 (60.1)	7,145 (63.0)	430 (65.2)	194 (61.2)	<0.001
Diabetes	3,641 (24.9)	2,873 (25.3)	159 (24.1)	60 (18.9)	0.064
Cardiac risk factors	1,014 (6.9)	1,374 (12.1)	119 (18.0)	50 (15.8)	<0.001
Myocardial infarction	349 (2.4)	526 (4.6)	45 (6.8)	20 (6.3)	<0.001
Atrial fibrillation	347 (2.4)	457 (4.0)	47 (7.1)	18 (5.7)	<0.001

Values are presented as mean±standard deviation or n (%). Totals for some categories may not sum to the respective group totals due to missing data.
AHEI, Alternative Healthy Eating Index; BMI, body mass index; WHR, waist-to-hip ratio.

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Supplementary Table 4. Population characteristics by water consumption

	0 cups/day (n=3,442)	1–2 cups/day (n=4,889)	3–4 cups/day (n=5,410)	5–6 cups/day (n=4,717)	7–8 cups/day (n=3,651)	>8 cups/day (n=4,841)	*P*
Age (yr)	62.6±12.7	64.6±13.1	63±13.5	61.8±13.6	60±13.3	58±13.1	<0.001
Male sex	2,287 (66.4)	2,921 (59.8)	2,960 (54.7)	2,549 (54.0)	2,082 (57.0)	3,257 (67.3)	<0.001
Education							<0.001
<8 years	1,364 (39.7)	2,393 (49.0)	2,597 (48.0)	2,269 (48.1)	1,754 (48.1)	2,641 (54.6)	
9–12 years	889 (25.8)	1,312 (26.8)	1,443 (26.7)	1,252 (26.7)	1,010 (27.7)	1,128 (23.3)	
Trade/college/university	1,187 (34.5)	1,184 (24.2)	1,369 (25.3)	1,194 (25.3)	886 (24.3)	1,072 (22.1)	
Occupation							<0.001
Skilled/gen labour/farmer	1,780 (51.8)	2,632 (53.9)	2,719 (50.3)	2,221 (47.1)	1,791 (49.1)	2,491 (51.5)	
Police/military/clerical	192 (5.6)	200 (4.1)	234 (4.3)	235 (5.0)	229 (6.3)	346 (7.2)	
Professional/business	769 (22.4)	1,031 (21.1)	1,132 (21.0)	941 (20.0)	633 (17.3)	802 (16.6)	
Housewife	453 (13.2)	646 (13.2)	829 (15.3)	905 (19.2)	746 (20.4)	787 (16.3)	
Disability/social security	55 (1.6)	117 (2.4)	183 (3.4)	143 (3.0)	61 (1.7)	98 (2.0)	
Other	187 (5.4)	262 (5.4)	307 (5.7)	270 (5.7)	190 (5.2)	315 (6.5)	
Smoking							<0.001
Never	1,856 (54.0)	2,659 (54.4)	3,308 (61.2)	3,019 (64.0)	2,247 (61.6)	2,727 (56.3)	
Former	518 (15.1)	863 (17.7)	872 (16.1)	737 (15.6)	525 (14.4)	510 (10.5)	
Current	1,062 (30.9)	1,366 (28.0)	1,227 (22.7)	960 (20.4)	877 (24.0)	1,603 (33.1)	
Mainly inactive	2,771 (80.6)	4,163 (85.3)	4,689 (86.7)	4,146 (88.0)	3,278 (89.8)	4,292 (88.7)	<0.001
Diet–AHEI tertile							<0.001
1	1,270 (36.9)	2,032 (41.6)	1,955 (36.1)	1,443 (30.6)	1,288 (35.3)	1,691 (34.9)	
2	1,169 (34.0)	1,685 (34.5)	1,904 (35.2)	1,603 (34.0)	1,215 (33.3)	1,498 (30.9)	
3	1,003 (29.1)	1,172 (24.0)	1,551 (28.7)	1,671 (35.4)	1,148 (31.4)	1,652 (34.1)	
BMI (kg/m^2)	26.4±4.7	25.5±4.6	25.8±4.7	26.1±4.8	25.6±4.9	25.0±5.1	<0.001
WHR	0.93±0.08	0.92±0.07	0.92±0.08	0.93±0.08	0.93±0.08	0.93±0.08	<0.001
Hypertension	2,135 (62.0)	3,092 (63.2)	3,429 (63.4)	2,993 (63.5)	2,228 (61.0)	2,676 (55.3)	<0.001
Diabetes	786 (22.9)	887 (18.2)	1,144 (21.2)	1,220 (25.9)	1,124 (30.8)	1,572 (32.5)	<0.001
Cardiac risk factors	374 (10.9)	519 (10.6)	602 (11.1)	460 (9.8)	290 (7.9)	312 (6.4)	<0.001
Myocardial infarction	143 (4.2)	191 (3.9)	214 (4.0)	161 (3.4)	108 (3.0)	123 (2.5)	<0.001
Atrial fibrillation	137 (4.0)	197 (4.0)	228 (4.2)	152 (3.2)	79 (2.2)	76 (1.6)	<0.001

Values are presented as mean±standard deviation or n (%). Totals for some categories may not sum to the respective group totals due to missing data.
AHEI, Alternative Healthy Eating Index; BMI, body mass index; WHR, waist-to-hip ratio.

Supplementary Table 5. Associations between beverage intake and stroke

Carbonated drink	None	≤1/day	2/day	>2/day
Cases of all stroke	9,292	3,763	186	221
Unadjusted	1.00 (Ref)	1.04 (0.97–1.11)	1.75 (1.37–2.22)	2.05 (1.59–2.63)
Model 1[*]	1.00 (Ref)	1.20 (1.10–1.32)	1.97 (1.44–2.70)	2.78 (2.02–3.84)
Model 2[†]	1.00 (Ref)	1.24 (1.13–1.37)	1.83 (1.30–2.58)	2.24 (1.58–3.16)
Model 3 (fully adjusted[‡])	1.00 (Ref)	1.22 (1.10–1.34)	1.76 (1.25–2.48)	2.29 (1.62–3.24)
Cases of ischemic stroke	7,144	2,889	164	205
Unadjusted	1.00 (Ref)	1.02 (0.94–1.10)	1.82 (1.41–2.37)	2.15 (1.65–2.80)
Model 1[*]	1.00 (Ref)	1.16 (1.05–1.28)	2.03 (1.45–2.85)	3.06 (2.18–4.31)
Model 2[†]	1.00 (Ref)	1.17 (1.06–1.31)	1.83 (1.27–2.63)	2.48 (1.71–3.60)
Model 3 (fully adjusted[‡])	1.00 (Ref)	1.17 (1.04–1.30)	1.75 (1.22–2.54)	2.39 (1.64–3.49)
Cases of ICH	2,148	874	22	16
Unadjusted	1.00 (Ref)	1.12 (0.95–1.31)	1.29 (0.68–2.45)	1.20 (0.53–2.72)
Model 1[*]	1.00 (Ref)	1.48 (1.19–1.83)	1.42 (0.55–3.69)	1.10 (0.41–3.03)
Model 2[†]	1.00 (Ref)	1.67 (1.32–2.12)	1.83 (0.58–5.78)	1.15 (0.40–3.33)
Model 3 (fully adjusted[‡])	1.00 (Ref)	1.58 (1.23–2.03)	1.75 (0.57–5.44)	1.29 (0.44–3.77)

Fruit juice/drink	None	≤1/day	2/day	>2/day
Cases of all stroke	7,313	5,656	338	155
Unadjusted	1.00 (Ref)	1.00 (0.93–1.06)	1.06 (0.89–1.25)	0.97 (0.76–1.22)
Model 1[*]	1.00 (Ref)	0.97 (0.89–1.06)	1.08 (0.87–1.35)	0.91 (0.68–1.22)
Model 2[†]	1.00 (Ref)	1.12 (1.01–1.23)	1.29 (1.02–1.63)	1.18 (0.87–1.61)
Model 3 (fully adjusted[‡])	1.00 (Ref)	1.08 (0.98–1.19)	1.26 (0.99–1.58)	1.13 (0.83–1.55)
Cases of ischemic stroke	5,467	4,519	283	133
Unadjusted	1.00 (Ref)	0.96 (0.89–1.03)	1.02 (0.85–1.23)	0.96 (0.75–1.24)
Model 1[*]	1.00 (Ref)	0.93 (0.84–1.03)	0.97 (0.76–1.23)	0.91 (0.66–1.25)
Model 2[†]	1.00 (Ref)	1.04 (0.94–1.16)	1.10 (0.85–1.42)	1.12 (0.80–1.58)
Model 3 (fully adjusted[‡])	1.00 (Ref)	1.02 (0.92–1.14)	1.08 (0.83–1.40)	1.07 (0.76–1.52)
Cases of ICH	1,846	1,137	55	22
Unadjusted	1.00 (Ref)	1.17 (1.00–1.37)	1.21 (0.80–1.82)	0.94 (0.53–1.67)
Model 1[*]	1.00 (Ref)	1.17 (0.95–1.45)	1.96 (1.12–3.45)	1.11 (0.56–2.21)
Model 2[†]	1.00 (Ref)	1.50 (1.19–1.89)	3.29 (1.77–6.10)	1.64 (0.76–3.51)
Model 3 (fully adjusted[‡])	1.00 (Ref)	1.37 (1.08–1.75)	3.18 (1.69–5.97)	1.52 (0.68–3.41)

Water	None	1–2 cups	3–4 cups	5–6 cups	7–8 cups	>8 cups
Cases of all stroke	1,706	2,515	2,792	2,359	1,745	2,345
Unadjusted	1.00 (Ref)	1.11 (1.01–1.22)	1.09 (0.99–1.21)	0.98 (0.88–1.09)	0.85 (0.75–0.95)	0.83 (0.74–0.94)
Model 1[*]	1.00 (Ref)	1.05 (0.93–1.19)	1.08 (0.95–1.22)	0.91 (0.80–1.04)	0.82 (0.71–0.95)	0.75 (0.65–0.88)
Model 2[†]	1.00 (Ref)	1.10 (0.96–1.25)	1.14 (1.00–1.30)	1.00 (0.87–1.15)	0.91 (0.77–1.06)	0.84 (0.71–0.99)
Model 3 (fully adjusted[‡])	1.00 (Ref)	1.07 (0.94–1.23)	1.07 (0.93–1.23)	0.92 (0.79–1.07)	0.84 (0.71–0.99)	0.77 (0.65–0.91)
Cases of ischemic stroke	1,474	1,962	2,170	1,803	1,262	1,731
Unadjusted	1.00 (Ref)	1.08 (0.97–1.21)	1.04 (0.93–1.16)	0.91 (0.81–1.02)	0.82 (0.72–0.93)	0.80 (0.70–0.92)
Model 1[*]	1.00 (Ref)	1.00 (0.87–1.15)	1.01 (0.88–1.16)	0.83 (0.72–0.96)	0.79 (0.66–0.93)	0.69 (0.58–0.83)
Model 2[†]	1.00 (Ref)	1.06 (0.91–1.22)	1.07 (0.92–1.23)	0.91 (0.78–1.07)	0.88 (0.74–1.06)	0.78 (0.65–0.94)
Model 3 (fully adjusted[‡])	1.00 (Ref)	1.03 (0.89–1.20)	1.01 (0.87–1.17)	0.85 (0.72–1.00)	0.82 (0.68–0.99)	0.72 (0.60–0.87)

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Supplementary Table 5. Continued

Water	None	1–2 cups	3–4 cups	5–6 cups	7–8 cups	>8 cups
Cases of ICH	232	553	622	556	483	614
Model 1*	1.00 (Ref)	1.27 (1.01–1.60)	1.37 (1.08–1.72)	1.36 (1.06–1.74)	1.02 (0.79–1.33)	1.02 (0.78–1.34)
Model 2†	1.00 (Ref)	1.31 (0.97–1.75)	1.34 (0.99–1.81)	1.27 (0.92–1.76)	0.97 (0.69–1.38)	1.00 (0.70–1.43)
Model 3 (fully adjusted‡)	1.00 (Ref)	1.28 (0.94–1.76)	1.48 (1.07–2.06)	1.44 (1.02–2.03)	1.02 (0.70–1.48)	1.05 (0.72–1.55)
Adjusted‡	1.00 (Ref)	1.26 (0.91–1.75)	1.32 (0.94–1.86)	1.25 (0.86–1.81)	0.88 (0.59–1.30)	0.92 (0.61–1.38)

Values are presented as odds ratios (95% confidence intervals) unless otherwise indicated.
ICH, intracerebral hemorrhage.
*Conditional logistic regression models adjusted for age, ethnicity, body mass index (BMI), apolipoprotein B:A ratio (apoB:apoA), diabetes, hypertension, and cardiac risk factors; †Conditional logistic regression models adjusted for age, ethnicity, BMI, apoB:apoA, diabetes, hypertension, cardiac risk factors, education, occupation, physical activity, alcohol intake, smoking, diet (tertile), and global stress; ‡Conditional logistic regression models adjusted for age, ethnicity, BMI, apoB:apoA, diabetes, hypertension, cardiac risk factors, education, occupation, physical activity, alcohol intake, smoking, diet (tertile), global stress, and other beverage types.

Supplementary Table 6. Association* between beverage intake and all stroke: stratified by age

Carbonated drink	None	≤1/day		2/day		>2/day	P_{int}
Overall	1.00 (Ref)	1.22 (1.10–1.34)		1.76 (1.25–2.48)		2.29 (1.62–3.24)	-
<65 years	1.00 (Ref)	1.18 (1.02–1.36)		1.40 (0.89–2.21)		2.37 (1.48–3.80)	0.469
≥65 years	1.00 (Ref)	1.33 (1.14–1.56)		2.46 (1.31–4.61)		1.85 (0.97–3.52)	
Fruit juice/drink	**None**	**≤1/day**		**2/day**		**>2/day**	P_{int}
Overall	1.00 (Ref)	1.08 (0.98–1.19)		1.26 (0.99–1.58)		1.13 (0.83–1.55)	-
<65 years	1.00 (Ref)	1.06 (0.92–1.22)		1.36 (0.96–1.91)		1.03 (0.66–1.62)	0.079
≥65 years	1.00 (Ref)	1.09 (0.93–1.27)		1.20 (0.84–1.72)		1.10 (0.67–1.83)	
Water	**None**	**1–2 cups**	**3–4 cups**	**5–6 cups**	**7–8 cups**	**>8 cups**	P_{int}
Overall	1.00 (Ref)	1.07 (0.94–1.23)	1.07 (0.93–1.23)	0.92 (0.79–1.07)	0.84 (0.71–0.99)	0.77 (0.65–0.91)	-
<65 years	1.00 (Ref)	1.09 (0.89–1.33)	1.21 (0.99–1.48)	1.04 (0.84–1.29)	0.97 (0.77–1.22)	0.88 (0.70–1.11)	0.002
≥65 years	1.00 (Ref)	1.09 (0.89–1.32)	0.99 (0.80–1.22)	0.86 (0.68–1.08)	0.72 (0.55–0.95)	0.70 (0.53–0.93)	

Values are presented as odds ratios (95% confidence intervals).
P_{int}, *P* for interaction.
*Conditional logistic regression models adjusted for ethnicity, education, occupation, body mass index, physical activity, alcohol, smoking, diet (tertile), apolipoprotein B:A ratio (apoB:apoA), diabetes, hypertension, cardiac risk factors, global stress, and other beverage types.

Supplementary Table 7. Association* between beverage intake and all stroke: stratified by sex

Carbonated drink	None	≤1/day		2/day		>2/day	P_{int}
Overall	1.00 (Ref)	1.22 (1.10–1.34)		1.76 (1.25–2.48)		2.29 (1.62–3.24)	-
Male	1.00 (Ref)	1.22 (1.07–1.39)		1.96 (1.31–2.94)		1.94 (1.28–2.94)	0.585
Female	1.00 (Ref)	1.22 (1.04–1.44)		1.29 (0.66–2.52)		3.19 (1.63–6.25)	
Fruit juice/drink	**None**	**≤1/day**		**2/day**		**>2/day**	P_{int}
Overall	1.00 (Ref)	1.08 (0.98–1.19)		1.26 (0.99–1.58)		1.13 (0.83–1.55)	-
Male	1.00 (Ref)	0.97 (0.85–1.10)		1.12 (0.82–1.53)		0.88 (0.59–1.32)	0.004
Female	1.00 (Ref)	1.25 (1.07–1.47)		1.50 (1.03–2.19)		1.82 (1.08–3.07)	
Water	**None**	**1–2 cups**	**3–4 cups**	**5–6 cups**	**7–8 cups**	**>8 cups**	P_{int}
Overall	1.00 (Ref)	1.07 (0.94–1.23)	1.07 (0.93–1.23)	0.92 (0.79–1.07)	0.84 (0.71–0.99)	0.77 (0.65–0.91)	-
Male	1.00 (Ref)	1.05 (0.89–1.23)	1.10 (0.93–1.30)	0.93 (0.77–1.13)	0.84 (0.68–1.04)	0.78 (0.63–0.96)	0.940
Female	1.00 (Ref)	1.15 (0.91–1.46)	1.08 (0.85–1.37)	0.94 (0.73–1.20)	0.90 (0.68–1.19)	0.80 (0.60–1.08)	

Values are presented as odds ratios (95% confidence intervals).
P_{int}, *P* for interaction.
*Conditional logistic regression models adjusted for age, ethnicity, education, occupation, body mass index, physical activity, alcohol, smoking, diet (tertile), apolipoprotein B:A ratio (apoB:apoA), diabetes, hypertension, cardiac risk factors, global stress, and other beverage types.

Supplementary Table 8. Association* between beverage intake and all stroke: stratified by smoking

Carbonated drink	None	≤1/day		2/day		>2/day	P_{int}
Overall	1.00 (Ref)	1.22 (1.10–1.34)		1.76 (1.25–2.48)		2.29 (1.62–3.24)	-
Never/former smoker	1.00 (Ref)	1.21 (1.07–1.36)		1.90 (1.20–2.99)		1.86 (1.16–2.99)	0.900
Current smoker	1.00 (Ref)	1.01 (0.66–1.55)		3.11 (0.81–12.0)		4.18 (1.11–15.8)	
Fruit juice/drink	**None**	**≤1/day**		**2/day**		**>2/day**	P_{int}
Overall	1.00 (Ref)	1.08 (0.98–1.19)		1.26 (0.99–1.58)		1.13 (0.83–1.55)	-
Never/former smoker	1.00 (Ref)	1.12 (1.00–1.27)		1.33 (1.01–1.77)		1.41 (0.97–2.04)	0.683
Current smoker	1.00 (Ref)	1.04 (0.70–1.55)		1.17 (0.28–4.94)		0.36 (0.10–1.32)	
Water	**None**	**1–2 cups**	**3–4 cups**	**5–6 cups**	**7–8 cups**	**>8 cups**	P_{int}
Overall	1.00 (Ref)	1.07 (0.94–1.23)	1.07 (0.93–1.23)	0.92 (0.79–1.07)	0.84 (0.71–0.99)	0.77 (0.65–0.91)	-
Never/former smoker	1.00 (Ref)	1.03 (0.86–1.22)	1.02 (0.85–1.22)	0.86 (0.71–1.03)	0.86 (0.70–1.07)	0.75 (0.61–0.94)	0.014
Current smoker	1.00 (Ref)	1.29 (0.87–1.92)	1.33 (0.86–2.05)	1.11 (0.66–1.88)	0.64 (0.35–1.16)	0.64 (0.35–1.16)	

Values are presented as odds ratios (95% confidence intervals).
P_{int}, *P* for interaction.
*Conditional logistic regression models adjusted for age, ethnicity, education, occupation, body mass index, physical activity, alcohol, diet (tertile), apolipoprotein B:A ratio (apoB:apoA), diabetes, hypertension, cardiac risk factors, global stress, and other beverage types.

Supplementary Table 9. Association* between beverage intake and all stroke: stratified by alcohol consumption

Carbonated drink	None	≤1/day		2/day		>2/day	P_{int}
Overall	1.00 (Ref)	1.22 (1.10–1.34)		1.76 (1.25–2.48)		2.29 (1.62–3.24)	-
Never/former drinker	1.00 (Ref)	1.28 (1.11–1.46)		1.03 (0.57–1.86)		2.06 (1.13–3.76)	0.044
Current drinker	1.00 (Ref)	1.03 (0.79–1.34)		2.37 (1.23–4.57)		1.48 (0.78–2.82)	
Fruit juice/drink	**None**	**≤1/day**		**2/day**		**>2/day**	P_{int}
Overall	1.00 (Ref)	1.08 (0.98–1.19)		1.26 (0.99–1.58)		1.13 (0.83–1.55)	-
Never/former drinker	1.00 (Ref)	1.23 (1.08–1.40)		1.62 (1.15–2.30)		1.83 (1.12–3.00)	0.018
Current drinker	1.00 (Ref)	0.90 (0.69–1.17)		1.20 (0.68–2.11)		0.96 (0.49–1.89)	
Water	**None**	**1–2 cups**	**3–4 cups**	**5–6 cups**	**7–8 cups**	**>8 cups**	P_{int}
Overall	1.00 (Ref)	1.07 (0.94–1.23)	1.07 (0.93–1.23)	0.92 (0.79–1.07)	0.84 (0.71–0.99)	0.77 (0.65–0.91)	-
Never/former drinker	1.00 (Ref)	1.22 (1.01–1.46)	1.12 (0.92–1.35)	0.98 (0.80–1.19)	0.84 (0.68–1.05)	0.78 (0.62–0.98)	0.081
Current drinker	1.00 (Ref)	0.95 (0.68–1.34)	1.32 (0.93–1.87)	0.96 (0.65–1.41)	1.00 (0.63–1.58)	0.81 (0.50–1.31)	

Values are presented as odds ratios (95% confidence intervals).
P_{int}, *P* for interaction.
*Conditional logistic regression models adjusted for age, ethnicity, education, occupation, body mass index, physical activity, smoking, diet (tertile), apolipoprotein B:A ratio (apoB:apoA), diabetes, hypertension, cardiac risk factors, global stress, and other beverage types.

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Supplementary Table 10. Association* between beverage intake and all stroke: stratified by hypertension status

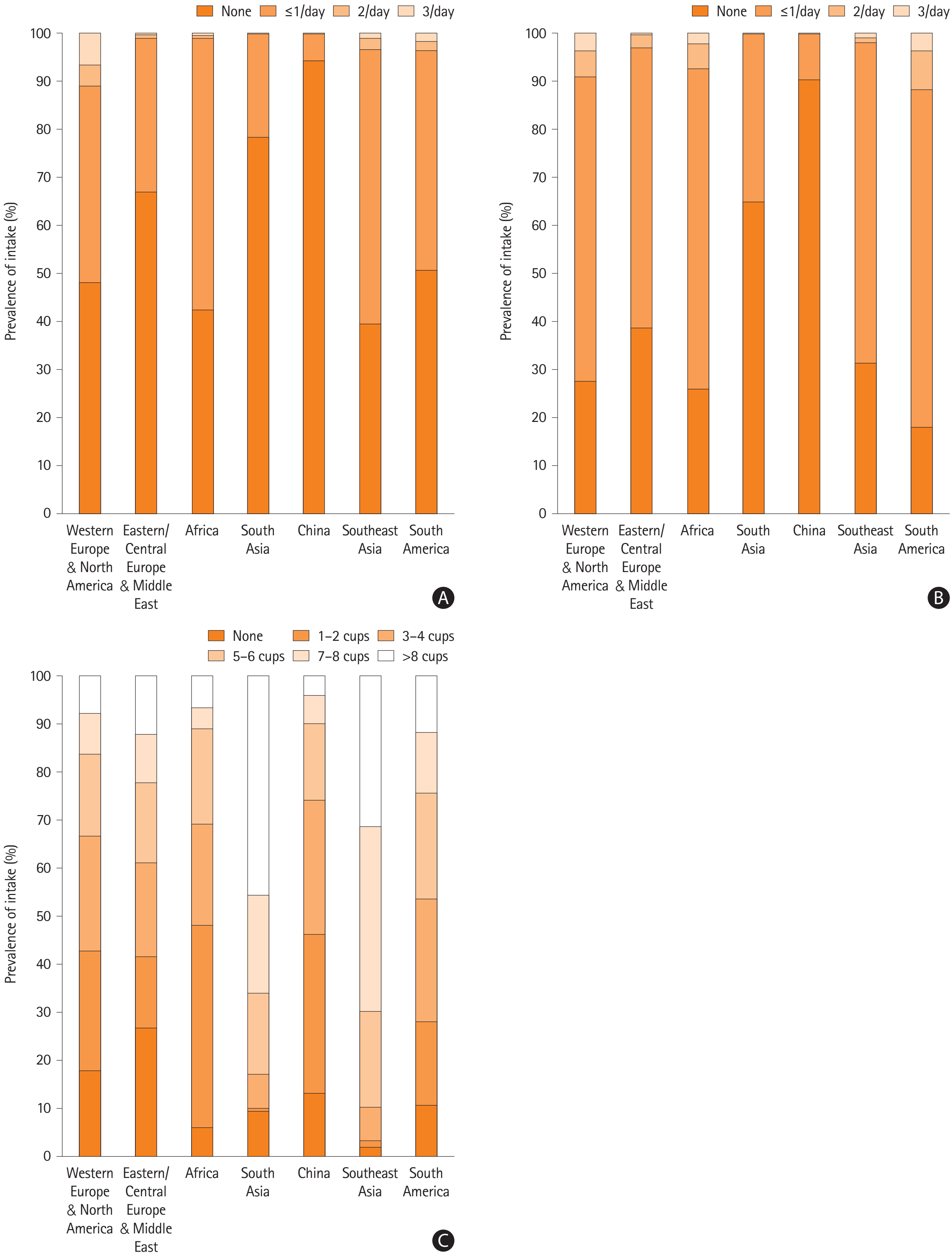
Carbonated drink	None	≤1/day		2/day		>2/day	P_{int}
Overall	1.00 (Ref)	1.22 (1.10–1.34)		1.76 (1.25–2.48)		2.29 (1.62–3.24)	-
No hypertension	1.00 (Ref)	1.08 (0.83–1.41)		0.76 (0.30–1.88)		2.57 (0.81–8.09)	0.458
Hypertension	1.00 (Ref)	1.28 (1.11–1.48)		1.68 (0.99–2.84)		2.00 (1.19–3.37)	
Fruit juice/drink	**None**	**≤1/day**		**2/day**		**>2/day**	P_{int}
Overall	1.00 (Ref)	1.08 (0.98–1.19)		1.26 (0.99–1.58)		1.13 (0.83–1.55)	-
No hypertension	1.00 (Ref)	1.11 (0.85–1.45)		1.72 (0.85–3.45)		0.72 (0.31–1.65)	0.044
Hypertension	1.00 (Ref)	1.08 (0.93–1.24)		1.45 (1.04–2.02)		1.07 (0.66–1.74)	
Water	**None**	**1–2 cups**	**3–4 cups**	**5–6 cups**	**7–8 cups**	**>8 cups**	P_{int}
Overall	1.00 (Ref)	1.07 (0.94–1.23)	1.07 (0.93–1.23)	0.92 (0.79–1.07)	0.84 (0.71–0.99)	0.77 (0.65–0.91)	-
No hypertension	1.00 (Ref)	1.17 (0.82–1.68)	1.34 (0.91–1.96)	0.95 (0.63–1.43)	1.01 (0.65–1.56)	0.69 (0.44–1.09)	<0.001
Hypertension	1.00 (Ref)	1.09 (0.90–1.32)	1.04 (0.85–1.27)	0.90 (0.72–1.12)	0.80 (0.63–1.02)	0.88 (0.68–1.13)	

Values are presented as odds ratios (95% confidence intervals).
P_{int}, *P* for interaction.
*Conditional logistic regression models adjusted for age, ethnicity, education, occupation, body mass index, alcohol, smoking, diet (tertile), apolipoprotein B:A ratio (apoB:apoA), diabetes, hypertension, cardiac risk factors, global stress, and other beverage types.

Supplementary Table 11. Association* between beverage intake and all stroke excluding proxy assistance

Carbonated drink	None	≤1/day		2/day		>2/day
All participants	1.00 (Ref)	1.22 (1.10–1.34)		1.76 (1.25–2.48)		2.29 (1.62–3.24)
Excluding proxy assistance	1.00 (Ref)	1.19 (1.04–1.37)		1.88 (1.25–2.82)		2.47 (1.64–3.73)
Fruit juice/drink	**None**	**≤1/day**		**2/day**		**>2/day**
All participants	1.00 (Ref)	1.08 (0.98–1.19)		1.26 (0.99–1.58)		1.13 (0.83–1.55)
Excluding proxy assistance	1.00 (Ref)	1.00 (0.88–1.15)		1.23 (0.91–1.68)		0.89 (0.59–1.34)
Water	**None**	**1–2 cups**	**3–4 cups**	**5–6 cups**	**7–8 cups**	**>8 cups**
All participants	1.00 (Ref)	1.07 (0.94–1.23)	1.07 (0.93–1.23)	0.92 (0.79–1.07)	0.84 (0.71–0.99)	0.77 (0.65–0.91)
Excluding proxy assistance	1.00 (Ref)	1.00 (0.83–1.20)	1.08 (0.90–1.31)	0.82 (0.68–1.01)	0.87 (0.68–1.11)	0.84 (0.65–1.08)

Values are presented as odds ratios (95% confidence intervals).
P_{int}, *P* for interaction.
*Conditional logistic regression models adjusted for age, ethnicity, education, occupation, body mass index, physical activity, alcohol, smoking, diet (tertile), apolipoprotein B:A ratio (apoB:apoA), diabetes, hypertension, cardiac risk factors, global stress, and other beverage types.



Supplementary Figure 1. Level of beverage intake by region. (A) Carbonated beverages. (B) Fruit juice/drink. (C) Water.

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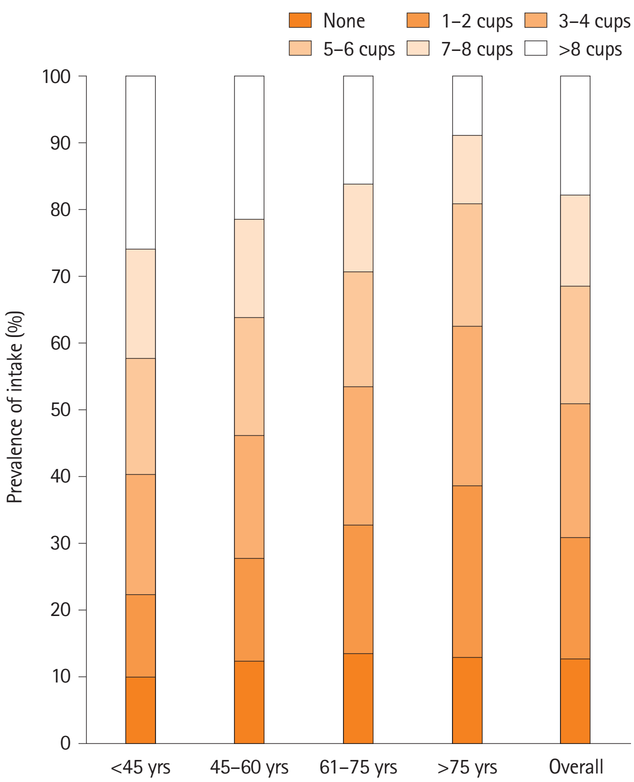

Supplementary Figure 2. Daily water consumption categorized by age group (cups/day). *P*<0.001.