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ORIGINAL ARTICLE

Sweetened Beverages, Genetic Susceptibility, and Incident Atrial Fibrillation: A Prospective Cohort Study

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BACKGROUND: An association between sweetened beverages and several cardiometabolic diseases has been reported, but their association with atrial fibrillation (AF) is unclear. We aimed to investigate the associations between consumption of sugar-sweetened beverages (SSB), artificially sweetened beverages (ASB), and pure fruit juice (PJ) and risk of consumption with AF risk and further evaluate whether genetic susceptibility modifies these associations.

METHODS: A total of 201 856 participants who were free of baseline AF, had genetic data available, and completed a 24-hour diet questionnaire were included. Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% CIs.

RESULTS: During a median follow-up of 9.9 years, 9362 incident AF cases were documented. Compared with nonconsumers, individuals who consumed >2 L/wk of SSB or ASB had an increased risk of AF (HR, 1.10 [95% CI, 1.01–1.20] and HR, 1.20 [95% CI, 1.10–1.31]) in the multivariable-adjusted model. A negative association was observed between the consumption of ≤1 L/wk of PJ and the risk of AF (HR, 0.92 [95% CI, 0.87–0.97]). The highest HRs (95% CIs) of AF were observed for participants at high genetic risk who consumed >2 L/wk of ASB (HR, 3.51 [95% CI, 2.94–4.19]), and the lowest HR were observed for those at low genetic risk who consumed ≤1 L/wk of PJ (HR, 0.77 [95% CI, 0.65–0.92]). No significant interactions were observed between the consumption of SSB, ASB, or PJ and genetic predisposition to AF.

CONCLUSIONS: Consumption of SSB and ASB at >2 L/wk was associated with an increased risk for AF. PJ consumption ≤1 L/wk was associated with a modestly lower risk for AF. The association between sweetened beverages and AF risk persisted after adjustment for genetic susceptibility to AF. This study does not demonstrate that consumption of SSB and ASB alters AF risk but rather that the consumption of SSB and ASB may predict AF risk beyond traditional risk factors.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: artificially sweetened beverages ■ atrial fibrillation ■ genetic risk ■ pure fruit juice ■ sugar-sweetened beverages

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Atrial fibrillation (AF) has high morbidity and mortality worldwide, and it has been estimated that 17.9 million people will suffer from AF in Europe by 2060, making it a major public health burden.[1] For the early prevention of AF, increasing attention has been given to lifestyle-related risk factors.[2] The latest American Heart

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WHAT IS KNOWN?

- Associations of sugar-sweetened beverages, artificially sweetened beverages, and pure fruit juice consumption with the risk of cardiometabolic diseases have been revealed, but little is known about the association of these sweetened beverages with atrial fibrillation (AF).

WHAT THE STUDY ADDS

- Consumption of sugar-sweetened beverages and artificially sweetened beverages at >2 L/wk was associated with an increased risk for AF, whereas pure fruit juice consumption ≤1 L/wk was associated with a modest lower risk for AF.
- The association between sweetened beverages and AF risk persisted with adjustment for genetic susceptibility for AF.
- This study does not demonstrate that consumption of sugar-sweetened beverages and artificially sweetened beverages alters AF risk but rather that the consumption of sugar-sweetened beverages and artificially sweetened beverages may predict AF risk.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
ASB	artificially sweetened beverages
BMI	body mass index
HF	heart failure
HR	hazard ratio
PJ	pure fruit juice
PRS	polygenic risk score
SSB	sugar-sweetened beverages

Association guidelines and European Society of Cardiology guidelines for the management of AF point out the role of alcohol as an important trigger,[3,4] but other types of drinks are not mentioned.[5]

Sugar-sweetened beverages (SSB) are one of the largest sources of added sugar in the diet. They include energy-containing sweeteners, such as sucrose, high-fructose corn syrup, or fruit juice concentrates.[6] High consumption of SSB is associated with a high risk of obesity,[7] type 2 diabetes,[8] cardiovascular diseases, and even all-cause mortality.[9] Therefore, the World Health Organization recommends reducing sugar intake to <10% of total energy intake.[10] Moreover, as an alternative to SSB, ASB have gained popularity over the past decades, owing to their low calories.[11] In the National Health and Nutrition Examination Survey study, ≈31.9% of adults reported consuming low-calorie beverages,[12] and similar results were found among UK Biobank participants.[13] Pure fruit juice (PJ) is not blended with added sweeteners and is often considered separately from SSB and ASB. Previous studies have found the positive association of SSB and ASB consumption and the inverse association of PJ consumption with the risk of cardiometabolic multimorbidity, heart failure (HF), nonalcoholic fatty liver disease, visceral adipose tissue mass, and diabetes but have not evaluated the risk of AF.[14–17] Although dietary modifications, including reductions in alcohol consumption and moderate coffee consumption, have been considered for AF prevention,[18,19] little is known about the effect of different types of sweetened beverages on AF risk.

In addition to lifestyle factors, genetic risk plays an important role in AF risk. Evidence from a population-based cohort revealed that lifestyle factors, including cardiorespiratory fitness, grip strength, and long-term night shift work, were associated with the risk of AF within and across genetic risk groups,[20,21] but whether there is a potential interaction between genetic predisposition and the consumption of different beverages on AF risk is still unclear. The polygenic risk score (PRS) is the weighted sum of the effect of an allele associated with a particular disease as an indicator of genetic risk and has been used to estimate an individual's risk of certain diseases, including AF.[22]

In this population-based cohort study including 201 856 participants, we aimed to investigate the associations of SSB, ASB, and PJ consumption with the risk of incident AF. We further evaluated whether there was a modification effect of genetic susceptibility on the relationship between the consumption of sweetened beverages and AF risk.

METHODS

Data Availability

The data set used and analyzed during the current study is available from the UK Biobank (www.ukbiobank.ac.uk). This research was conducted using the UK Biobank Resource under Application Number 77740.

Study Design and Sample

From 2006 to 2010, >500 000 participants aged 37 to 73 years were enrolled in the UK Biobank, a nationwide cohort that was recruited from the general population at 22 assessment centers throughout the United Kingdom. The study design has been described in detail previously.[23] In brief, information on lifestyle factors, physical measurements, medical records, and biological samples was collected. Blood samples were collected for genotyping. The UK Biobank study was approved by the North West Multicenter Research Ethics Committee. All participants gave written informed consent before enrollment in the study and were not involved in the design, conduct, reporting, or dissemination plans of our research.

Of a total of 502 414 participants with available data, 291 459 were excluded from the current study because of missing information from the online 24-hour dietary recall questionnaire. Among the 210 955 participants who completed at

least 1 dietary questionnaire, 4331 with a history of AF before completing the last dietary questionnaire and 4768 without genetic data were further excluded. Thus, 201 856 participants were included in the main analyses. Furthermore, we excluded 56 992 individuals with any kinship to other individuals in the UK Biobank, leaving 144 864 participants for the genetic interaction analysis (Figure S1).

Assessment of Beverage Consumption

Participants were asked to provide information on the types and quantities of various foods, including different beverages, consumed during the past 24 hours through a dietary recall questionnaire (Oxford Web-Q).[24] As previously done, fizzy drinks and squash were defined as SSB, low-calorie drinks were defined as ASB, and pure orange juice, pure grapefruit juice and other pure fruit or vegetable juice were defined as PJ.[25] Other drinks, such as milk, tea, and coffee, were not included as sweetened beverages in the current study, as they are usually evaluated separately for their specific nutritional value or composition, not only sugar. Participants were asked how many cups (glasses/cans/250 mL/cartons) of beverages they drank the previous day; 4 cups were equal to 1 L. We calculated the mean consumption of beverages if the participant completed >1 questionnaire on 5 repeated occasions between April 2009 and June 2012, and we multiplied the mean value (liters) by 7 days to determine weekly consumption. Of the current study population, 39.9%, 22.8%, 20.1%, 14.5%, and 2.7% of subjects answered the 24-hour dietary recall 1, 2, 3, 4 and 5×, respectively. We classified the participants into 4 groups: nonconsumers with 0 L per week and consumers with ≤1, 1 to 2, and >2 L/wk of SSB, ASB, and PJ, respectively.

Ascertainment of Atrial Fibrillation

The outcome of interest in the present study was AF, which was defined as *International Classification of Diseases-Tenth Revision* code I48 (field ID 131351 in the UK Biobank). The diagnosis of AF was obtained by linkage from primary care, hospital inpatient, and death register records up to March 8, 2022. Detailed information on the date and cause of AF was obtained from Health Episode Statistics (England and Wales) and Scottish Morbidity Records (Scotland).

Assessment of Covariates

A wide range of potential confounders related to the exposure and outcome were included in the current analyses: age, sex, ethnicity (White/others), education level (university or college degree/others), the Townsend deprivation index (reflecting socioeconomic status), current smoking (yes/no), alcohol consumption (g/wk), ideal physical activity level (yes/no), sleep duration (hours/day), body mass index (BMI, kg/m^2), level of triglycerides (mmol/L), systolic blood pressure (mm Hg), estimated glomerular filtration rate (mL/min), obstructive sleep apnea (*International Classification of Diseases-Tenth Revision code* G47.3)/snoring (self-reported snoring without obstructive sleep apnea)/others, coronary heart disease (yes/no), HF (yes/no), diabetes (yes/no), the use of cholesterol-lowering medication (yes/no), and the use of blood pressure medication (yes/no). According to the International Physical Activity Questionnaire, an ideal physical activity level was defined as 150 minutes of moderate activity per week or 75 minutes of vigorous activity per week or an equivalent combination. The estimated glomerular filtration rate was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation.[26] If information on the above covariates was missing, mean values were imputed for normally distributed continuous variables, median values were imputed for estimated glomerular filtration rate, and a missing-indicator approach was used for categorical variables. From the 24-hour dietary recall questionnaire, the following variables were collected: the consumption of fruits (servings/day), vegetables (servings/day), red meat (servings/day), processed meat (servings/day), coffee (servings/day), total fat (g/day), total energy (kj/day), and total sugar (g/day). The overall healthy diet score, ranging from 0 to 50, was calculated by combining the scores for fruit, vegetable, red meat, processed meat and fat consumption based on the Alternative Healthy Eating Index..[27] Total fat, total sugar, and total energy intake were estimated based on the answers to the dietary questionnaire with the nutrient calculation described in a previous study.[28]

Assessment of Genetic Risk of AF

The genetic risk of AF was based on the standard PRS (field 26212 in the UK Biobank). The PRS was obtained from a combination of external genome-wide association studies, which were conducted by Genomics PLC under UK Biobank project 9659.[29] We classified participants into 3 categories of genetic risk for AF: high (the highest PRS quartile), intermediate (the middle 2 PRS quartiles), and low (the lowest PRS quartile).

Statistical Analyses

Demographic characteristics and potential covariates are summarized as the mean (SD) or median (lower to upper quartiles) for continuous variables and numbers (percentages) for categorical variables according to the consumption of SSB, ASB, and PJ. Linear regression models and logistic regression models were used to assess the associations of SSB, ASB, and PJ (independent variables) with baseline characteristics (dependent variables). Characteristic information about participants with and without dietary questionnaire data is presented in the Table S1. We further described the individuals included and excluded for the genetic interaction analysis and diet consumption analysis, and the standardized mean difference was also calculated (Tables S2 and S3). Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% CIs for incident AF associated with SSB, ASB, and PJ consumption. The proportional hazards assumption was checked using the Schoenfeld test, and the results showed that the association of SSB, ASB, and PJ intake with AF did not change over time. Model 1 was adjusted for age and sex and was mutually adjusted for 2 additional beverages when 1 of the 3 sweetened beverages was tested as the exposure factor of interest. Model 2 was further adjusted for ethnicity (white/others), education level (university or college degree/others), the Townsend deprivation index, current smoking (yes/no), alcohol consumption, ideal physical activity level (yes/no), sleep duration, BMI, TC, systolic blood pressure, estimated glomerular filtration rate, obstructive sleep apnea/snoring, coronary heart disease, HF, diabetes, and the PRS (as a continuous variable). Model 3 was

further adjusted for the consumption of fruits, vegetables, red meat, processed meat, and coffee and total fat, total sugar, and total energy. The follow-up time was calculated from the response date of the last dietary questionnaire through the time of incident AF, death, or censoring (March 8, 2022), whichever came first. The ordered categories of beverages consumption as a 1 degree-of-freedom linear term were used to test the *P* for trend of the regression analyses. A multicollinearity test was performed to evaluate the intake of drinks, foods, and nutrients in Model 3 for AF risk.

To examine whether genetic susceptibility to AF modified the association of the consumption of SSB, ASB, and PJ with AF risk, we performed joint analysis of beverages consumption and the PRS in relation to AF risk. Participants who did not consume each beverage and were at low genetic risk (the lowest PRS quartile) were set as the reference group. The likelihood ratio test was used to examine the significance of interactions by comparing models with and without the cross-product term between the consumption of beverages (0, ≤1, 1–2, >2 L/wk) and the groups of genetic predisposition (high, intermediate, and low).

Moreover, stratified analyses were performed by sex, age (<60 or ≥60 years), ideal physical activity level, current smoking, sleep duration (<7 or ≥7 h/day), BMI (<25 or ≥25 kg/m^2), and systolic blood pressure (<140 or ≥140 mm Hg). The *P values* for the product terms between the consumption of different beverages and the stratification variables were used to estimate the significance of interactions.

A series of sensitivity analyses were conducted to test the robustness of our findings. First, we restricted the follow-up time to >2 years to minimize potential reverse causality. Second, we reran the regression models only in participants with at least 2 dietary assessments. Third, we did not adjust total energy intake to avoid overadjustment, as it was partly derived from sugar intake. Fourth, we additionally adjusted for the use of cholesterol-lowering medication and blood pressure medication in the model. Fifth, we used the first questionnaire completed to evaluate beverages intake, as it was most proximal to baseline. Sixth, we used the healthy diet score instead of individual dietary confounders to represent the overall diet quality.

All statistical analyses were performed using IBM SPSS Statistics, Version 26 (IBM Corporation, Armonk, NY). All tests of significance were 2-sided, and a *P*<0.05 was considered significant.

RESULTS

The baseline characteristics of the study population according to the consumption of SSB, ASB, and PJ are shown in Table 1. Of the 201 856 participants (45.1% men; mean age, 55.9±7.9 years), the percentages of the population consuming 0, ≤1, 1 to 2, and >2 L/wk were 67.5%, 15.3%, 10.5%, and 6.6% for SSB; 79.4%, 8.2%, 6.9%, and 5.5% for ASB; and 48.4%, 22.2%, 22.3%, and 7.0% for PJ, respectively. Participants who consumed more SSB were more likely to be younger, be male, have a lower socioeconomic status, have a higher BMI and have a higher prevalence of coronary heart disease. Similarly, participants who had higher consumption of ASB were younger, more often female, had a higher BMI and had a higher prevalence of diabetes. Both SSB and PJ consumers tended to have a higher intake of total sugar and energy, but ASB consumers did not (Tables S4 and S10). The characteristics of the population were comparable between the participants with and without information on diet, those included and excluded for genetic interaction analysis, and those with data across the 5 dietary questionnaires (Tables S1-S3).

During a median follow-up of 9.9 years (>2.0 million person-years), we documented 9362 incident AF cases. The associations between the consumption of SSB, ASB, and PJ and the risk of AF are shown in Table 2 and Figure 1. Higher consumption of ASB was associated with a higher risk of AF after adjustment for age and sex (*P* for trend <0.001). Compared with nonconsumers, individuals who consumed >2 L/wk of ASB had a significantly increased risk of AF (HR, 1.20 [95% CI, 1.10–1.31]) after adjustment for potential confounders, including demographic factors, cardiometabolic indicators, the PRS of AF, and other dietary components in Model 3. The HR for consumers of >2 L SSB/wk was 1.10 (95% CI, 1.01–1.20). However, the consumption of <2 L/wk of SSB or ASB did not present a significant association with AF risk. An inverse association was observed between the consumption of ≤1 liter/wk of PJ and the risk of incident AF (HR, 0.92 [95% CI, 0.87–0.97]), but the association was not significant for the consumption of 1 to 2 l/wk or >2 l/wk. Table S5 shows that there was no multicollinearity between the consumption of sweetened beverages, other foods and nutrients and the AF risk.

The adjusted HRs (95% CIs) for participants with intermediate and high genetic risk for AF were 1.74 (1.61–1.88) and 3.16 (2.93–3.41), respectively (*P* for linear trend <0.001; Table S6). Figure 2 shows the combined categories of beverages consumption and genetic risk for AF. Compared with participants who were at low genetic risk and did not consume these beverages, those at high genetic risk who consumed >2 L/wk of ASB (3.51, 2.94–4.19) had the highest HRs (95% CIs) of AF. Participants who were at low genetic risk and consumed ≤1 L/wk of PJ had the lowest risk of AF (HR, 0.77 [95% CI, 0.65–0.92]). However, no significant interactions were observed among these groups (*P* for interaction=0.698, 0.536, and 0.489, respectively).

In the stratified analyses, we found a significant interaction between SSB consumption and smoking for AF risk (*p* for interaction=0.013; Table S7). The association between SSB consumption and AF risk was stronger in current smokers than in nonsmokers (HR, 1.31 [95% CI, 1.00–1.72 versus 1.08, 0.99–1.19 for >2 L/wk). In addition, the associations of the consumption of SSB, ASB, and PJ with AF risk did not differ by age, sex, physical activity level, sleep duration, BMI, or systolic blood pressure (all *p* for interaction >0.05).

Table 1. Baseline Characteristics of the Participants by Consumption of Sugar-Sweetened Beverages, Artificially Sweetened Beverages, and Pure Fruit Juice

	Nonconsumers	Beverage consumers			
	0 L/wk	≤1 L/wk	1–2 L/wk	>2 L/wk	*P* for trend
Sugar-sweetened beverages					
No. of participants (%)	136 229 (67.5)	30 942 (15.3)	21 274 (10.5)	13 411 (6.6)	
Age, y	56.4±7.8	56.1±7.9	55.0±8.2	53.4±8.2	<0.001
Men, n (%)	58 408 (42.9)	13 753 (44.4)	10 410 (48.9)	7385 (55.1)	<0.001
Ethnicity, White (%)	130 572 (95.8)	29 568 (95.6)	19 988 (94.0)	12 450 (92.8)	<0.001
Townsend deprivation index	−1.6±2.9	−1.7±2.8	−1.5±2.9	−1.2±3.1	<0.001
University or college degree, n (%)	58 889 (43.2)	13 893 (44.9)	8387 (39.4)	4894 (36.5)	<0.001
Current smoking, n (%)	10 717 (7.9)	2138 (6.9)	1696 (8.0)	1375 (10.3)	<0.001
Alcohol drinking, g/wk	154.0±262.1	149.1±239.7	144.5±250.1	149.8±309.4	<0.001
Ideal physical activity, n (%)	62 388 (45.8)	13 985 (45.2)	9696 (45.6)	6183 (46.1)	0.463
Sleep duration, h/d	7.2±1.0	7.2±1.0	7.1±1.0	7.1±1.1	<0.001
Obstructive sleep apnea/snoring, n (%)	527 (0.4)/82 170 (60.3)	107 (0.3)/18 466 (59.7)	97 (0.5)/12 250 (57.6)	92 (0.7)/7364 (54.9)	<0.001/<0.001
Coronary heart disease, n (%)	7473 (5.5)	1678 (5.4)	1204 (5.7)	813 (6.1)	0.014
Heart failure, n (%)	313 (0.2)	69 (0.2)	58 (0.3)	40 (0.2)	0.088
Diabetes, n (%)	5592 (4.1)	994 (3.2)	718 (3.4)	481 (3.6)	<0.001
Body mass index, kg/m^2	26.8±4.6	26.8±4.5	27.3±4.7	27.9±5.1	<0.001
Systolic blood pressure, mm Hg	139±19	139±19	139±19	138±18	<0.001
Total cholesterol, mmol/L	5.7±1.1	5.7±1.1	5.7±1.1	5.6±1.1	<0.001
Estimated glomerular filtration rate, mL/min	87.8 (73.3–96.4)	87.7 (71.4–95.9)	87.7 (69.9–96.1)	87.7 (69.6–96.5)	<0.001
Cholesterol-lowering medication, n (%)	20 347 (14.9)	4447 (14.4)	3084 (14.5)	1954 (14.6)	0.025
Blood pressure medication, n (%)	24 047 (17.7)	5283 (17.1)	3848 (18.1)	2388 (17.8)	0.503
Polygenic risk score of atrial fibrillation	0.08±0.91	0.09±0.91	0.08±0.92	0.09±0.92	0.989
Artificially sweetened beverages					
No. of participants (%)	160 240 (79.4)	16 622 (8.2)	13 972 (6.9)	11 022 (5.5)	
Age, y	56.4±7.9	55.2±7.9	54.1±8.0	53.2±8.0	<0.001
Men, n (%)	72 793 (45.4)	7035 (42.3)	5629 (40.3)	4499 (40.8)	<0.001
Ethnicity, White (%)	152 759 (95.3)	15 920 (95.4)	13 324 (95.4)	10 575 (95.9)	0.004
Townsend deprivation index	−1.6±2.9	−1.7±2.8	−1.6±2.9	−1.4±3.0	<0.001
University or college degree, n (%)	69 956 (43.7)	6910 (41.6)	5185 (37.1)	4012 (36.4)	<0.001
Current smoking, n (%)	12 686 (7.9)	1158 (7.0)	1080 (7.7)	1002 (9.1)	0.050
Alcohol drinking, g/wk	149.0±253.3	158.8±254.9	156.8±262.5	178.9±359.1	<0.001
Ideal physical activity, n (%)	73 660 (46.0)	7547 (45.4)	6284 (45.0)	4761 (43.2)	<0.001
Sleep duration, h/day	7.2±1.0	7.2±1.0	7.1±1.0	7.1±1.1	<0.001
Obstructive sleep apnea/snoring, n (%)	600 (0.4)/96 094 (60.0)	73 (0.4)/9861 (59.3)	53 (0.4)/8073 (57.8)	97 (0.9)/6222 (56.5)	<0.001/<0.001
Coronary heart disease, n (%)	8810 (5.5)	896 (5.4)	787 (5.6)	675 (6.1)	0.020
Heart failure, n (%)	349 (0.2)	45 (0.3)	48 (0.3)	38 (0.3)	<0.001
Diabetes, n (%)	5060 (3.2)	805 (4.8)	908 (6.5)	1012 (9.2)	<0.001
Body mass index, kg/m^2	26.5±4.4	28.0±4.7	28.4±5.1	29.6±5.7	<0.001
Systolic blood pressure, mm Hg	139±19	139±19	138±18	138±18	<0.001
Total cholesterol, mmol/L	5.7±1.1	5.7±1.1	5.6±1.1	5.5±1.1	<0.001
Estimated glomerular filtration rate, mL/min	87.8 (71.6–95.9)	87.7 (73.0–96.7)	88.8 (75.0–98.2)	89.6 (76.1–99.0)	<0.001

(*Continued*)

Table 1. Continued

	Nonconsumers	Beverage consumers			
	0 L/wk	≤1 L/wk	1–2 L/wk	>2 L/wk	*P* for trend
Cholesterol-lowering medication, n (%)	22 804 (14.2)	2633(15.8)	2331 (16.7)	2064 (18.7)	<0.001
Blood pressure medication, n (%)	27 197 (17.0)	3072 (18.5)	2792 (20.0)	2505 (22.7)	<0.001
Polygenic risk score of atrial fibrillation	0.08±0.91	0.09±0.91	0.11±0.91	0.11±0.91	<0.001
Pure fruit juice					
No. of participants (%)	97 754 (48.4)	44 801 (22.2)	45 085 (22.3)	14 216 (7.0)	
Age, y	55.7±8.0	56.4±7.8	56.3±7.9	55.5±8.0	<0.001
Men, n (%)	41 350 (42.3)	19 875 (44.4)	21 420 (47.5)	7311 (51.4)	<0.001
Ethnicity, White (%)	92 896 (95.0)	43 051 (96.1)	43 429 (96.3)	13 202 (92.9)	0.518
Townsend deprivation index	−1.4±2.9	−1.7±2.8	−1.8±2.8	−1.4±3.0	<0.001
University or college degree, n (%)	35 816 (36.6)	20 557 (45.9)	22 040 (48.9)	7650 (53.8)	<0.001
Current smoking, n (%)	9224 (9.4)	2934 (6.5)	2718 (6.0)	1050 (7.4)	<0.001
Alcohol drinking, g/wk	148.7±273.4	151.8±237.8	157.9±249.5	155.7±279.2	<0.001
Ideal physical activity, n (%)	43 545 (44.5)	20 658 (46.1)	21 107 (46.8)	6942 (48.8)	<0.001
Sleep duration, h/day	7.1±1.0	7.2±1.0	7.2±1.0	7.1±1.0	0.026
Obstructive sleep apnea/Snoring, n (%)	416 (0.4)/ 57 425 (58.7)	152 (0.3)/ 27 044 (60.4)	178 (0.4)/ 27 231 (60.4)	77 (0.5)/ 8550 (60.1)	0.217/ <0.001
Coronary heart disease, n (%)	5720 (5.9)	2319 (5.2)	2358 (5.2)	771 (5.4)	<0.001
Heart failure, n (%)	252 (0.3)	94 (0.2)	102 (0.2)	32 (0.2)	0.189
Diabetes, n (%)	4585 (4.7)	1578 (3.5)	1236 (2.7)	386 (2.7)	<0.001
Body mass index, kg/m²	27.2±4.8	26.7±4.5	26.5±4.4	26.7±4.5	<0.001
Systolic blood pressure, mm Hg	138±19	139±19	140±19	139±19	<0.001
Total cholesterol, mmol/L	5.7±1.1	5.7±1.1	5.7±1.1	5.7±1.1	<0.001
Estimated glomerular filtration rate, mL/min	87.7 (72.5–96.6)	87.7 (72.3–95.9)	87.7 (71.6–96.0)	87.7 (71.4–96.2)	<0.001
Cholesterol-lowering medication, n (%)	15 103 (15.5)	6392 (14.3)	6368 (14.1)	1969(13.9)	<0.001
Blood pressure medication, n (%)	17 773 (18.2)	7646 (17.1)	7746 (17.2)	2401 (16.9)	<0.001
Polygenic risk score of atrial fibrillation	0.09±0.91	0.08±0.91	0.08±0.91	0.08±0.92	0.005

Data are mean±SD or median (lower to upper quartile) for continuous variables and number (percentage) for categorical variables. Linear regression models and logistic regression models were used to assess the associations of sugar-sweetened beverages, artificially sweetened beverages, and pure fruit juice consumption (independent variable) with baseline characteristics (dependent variable).

Sensitivity analyses showed that the results remained similar when restricting the follow-up time to >2 years or analyzing only those with at least 2 dietary assessments (Tables S7 and S9). We reran the models without adjusting for total energy intake and without further adjusting for cholesterol-lowering medication or blood pressure medication use, and the results did not materially change (Tables S10 and S11). Moreover, these associations did not change appreciably when using the first questionnaire to calculate beverages intake or using the healthy diet score instead of individual dietary confounders (Tables S12 and S13).

DISCUSSION

In this large prospective cohort study, we found that consumption of SSB, ASB, and PJ were all related to the risk of AF, independent of traditional risk factors. Among the 3 types of beverages, the consumption of >2 L/wk of ASB was associated with the highest risk of AF, followed by the consumption of >2 L/wk of SSB. In contrast, consuming ≤1 L/wk of PJ was associated with a decreased risk of AF. Moreover, the associations between the consumption of these beverages and AF risk persisted after adjustment for genetic susceptibility for AF.

To the best of our knowledge, this is the first study to estimate the associations of the consumption of different sweetened beverages with the risk of AF in a large prospective cohort. Previous studies have suggested that both diabetes and obesity are strong risk factors for AF, which may be due to atrial dilatation and remodeling.[30] In this and other cohorts, a higher BMI was observed for participants who had higher consumption of SSB or

Table 2. Associations Between the Consumption of Sugar-Sweetened Beverages, Artificially Sweetened Beverages, and Pure Fruit Juice and the Risk of Incident Atrial Fibrillation

	Nonconsumers	Beverage consumers			
	0 L/wk	≤1 L/wk	1–2 L/wk	>2 L/wk	*P* for trend
Sugar-sweetened beverages					
Case	6415	1392	929	626	
N	136 229	30 942	21 274	13 411	
Model 1	1.00 (Ref)	1.03 (0.97–1.09)	0.99 (0.93–1.06)	1.18 (1.09–1.29)	0.008
Model 2	1.00 (Ref)	1.03 (0.97–1.09)	0.98 (0.92–1.05)	1.12 (1.03–1.21)	0.110
Model 3	1.00 (Ref)	1.03 (0.97–1.09)	0.98 (0.91–1.05)	1.10 (1.01–1.20)	0.329
Artificially sweetened beverages					
Case	7513	688	593	568	
N	160 240	16 622	13 972	11 022	
Model 1	1.00 (Ref)	1.06 (0.98–1.15)	1.17 (1.07–1.27)	1.54 (1.42–1.68)	<0.001
Model 2	1.00 (Ref)	0.99 (0.91–1.07)	1.01 (0.93–1.10)	1.20 (1.10–1.31)	0.002
Model 3	1.00 (Ref)	0.99 (0.91–1.07)	1.02 (0.93–1.11)	1.20 (1.10–1.31)	0.002
Pure fruit juice					
Case	4662	1928	2069	703	
N	97 754	44 801	45 085	14 216	
Model 1	1.00 (Ref)	0.86 (0.82–0.91)	0.90 (0.86–0.95)	1.02 (0.94–1.10)	0.007
Model 2	1.00 (Ref)	0.92 (0.88–0.98)	0.96 (0.91–1.01)	1.07 (0.98–1.16)	0.843
Model 3	1.00 (Ref)	0.92 (0.87–0.97)	0.95 (0.90–1.01)	1.05 (0.96–1.14)	0.441

Data are shown as hazard ratio (95% CI).

Model 1 was adjusted for age and sex and mutually adjusted for 2 additional beverages.

Model 2 was further adjusted for ethnicity (white/others), education level (university or college degree/others), the Townsend deprivation index, alcohol consumption, current smoking, ideal physical activity level, sleep duration, body mass index, systolic blood pressure, total cholesterol, estimated glomerular filtration rate, obstructive sleep apnea/snoring, coronary heart disease, heart failure, diabetes, and the polygenic risk score for atrial fibrillation.

Model 3 was further adjusted for the consumption of vegetables, fruits, red meat, processed meat, and coffee and total fat, total sugar and total energy intake.

ASB. However, we also found a lower prevalence of diabetes among SSB consumers and a higher prevalence of diabetes among ASB consumers. We suspected that this may be because people with diabetes at baseline paid more attention to having a healthy diet and so consumed more ASB than SSB.[31,32] In the present study, the increased risk of AF was still significant for the consumption of >2 L/wk of SSB or ASB after adjustment for BMI, diabetes at baseline, numerous confounding factors, and other food intake, which implied that both SSB and ASB were associated with AF risk independently. Unexpectedly, we observed a 20% increased risk of AF from the consumption of >2 L/wk of ASB, much higher than the 10% risk from similar SSB consumption. Findings from a prospective cohort in Sweden showed no significant associations between the consumption of SSB and incident AF.[33] Although the evidence was limited, 1 study of 200 cardiac patients showed that 16% of the participants experienced changes in their heart rate or rhythm after consuming aspartame, which is the main artificial sweetener today.[34] Intervention studies on SSB and ASB consumption are warranted to confirm whether the observed associations with AF risk are causal.

We also found that the consumption of ≤1 L/wk of PJ was related to a decreased risk of AF. A small, randomized study with 40 healthy subjects suggested that grapefruit juice at a large dose (>2 liters) could have arrhythmogenic actions, especially in patients with congenital long-QT syndrome.[35] However, the effects of daily consumption of smaller quantities of grapefruit juice could not be determined in the above trial, and it is relatively rare for the general population to consume large amounts of PJ in the United Kingdom.[36] Our study quantified the amount of overall pure fruit and vegetable juice, not only pure grapefruit juice but also orange juice, other fruit juice, and vegetable juice. Similar to previous research, the consumption of fruit and vegetable juice was associated with a decreased risk of cardiovascular diseases possibly based on their effects on blood pressure and blood lipid level reductions, antiinflammatory action, and antioxidant activity.[37]

For the first time, we examined the joint association of SSB, ASB, and PJ consumption with the genetic risk of AF and tested whether genetic susceptibility may modify the relationship between sweetened beverages consumption and AF incidence. As expected, a high

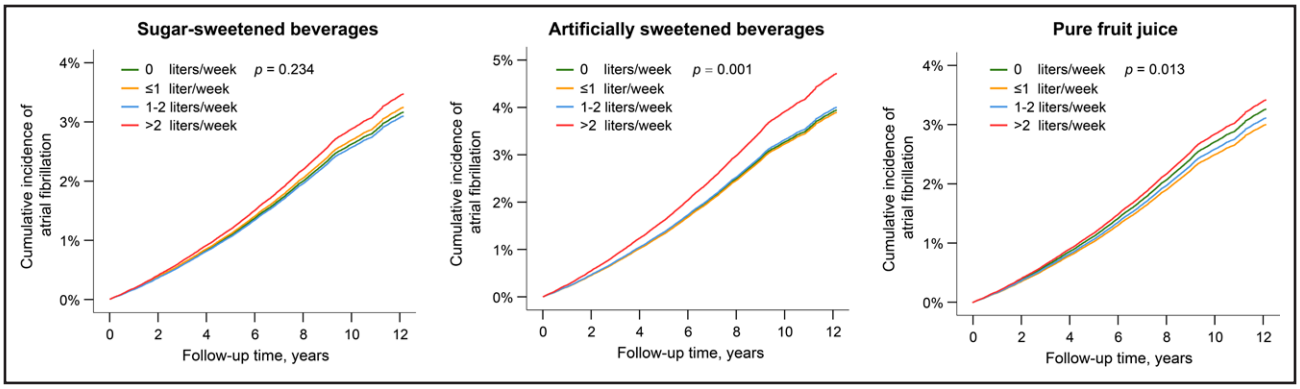

Figure 1. Multivariable-adjusted cumulative incidence of atrial fibrillation according to consumption of sugar-sweetened beverages, artificially sweetened beverages, and pure fruit juice. The unit of beverages consumption is liter per week.
Model was adjusted for age, sex, ethnicity (White/others), education level (university or college degree/others), the Townsend deprivation index, alcohol consumption, current smoking, ideal physical activity level, sleep duration, body mass index, systolic blood pressure, total cholesterol, estimated glomerular filtration rate, obstructive sleep apnea/snoring, coronary heart disease, heart failure, diabetes, the polygenic risk score for atrial fibrillation, the consumption of vegetables, fruits, red meat, processed meat, coffee, total fat, total sugar, total energy, and mutually adjusted for 2 additional beverages. *P* value was for Log-rank test.

PRS was significantly associated with an increased risk of AF. That associations between sweetened beverages and AF risk were weaker but still significant after adjustment for the PRS of AF and other covariates could also mean that the association was independent of genetic risk. Consistent with previous findings,[20] environmental factors could have an additive effect with genetic susceptibility on AF risk even though the interaction was not significant: populations with excessive intake of ASB and high genetic risk for AF had the highest AF risk.

In stratified analyses, a significant interaction was found between smoking status and SSB consumption for the risk of AF. A greater risk of AF was observed among current smokers who consumed SSB than among nonsmokers. Previous findings showed that there was a >2-fold increase in the incidence of AF for current smokers.[38] We suspect that the adverse association of SSB consumption with incident AF might be aggravated by smoking. Although participants with higher BMI were more likely to choose and consume greater amounts of ASB, it is interesting to note that BMI did not modify the association between the consumption of ASB and AF risk, indicating that even among those with normal weight who consume ASB as an alternative to SSB, the consumption of more than 2 l/wk of ASB was also associated with an increased risk of AF.

Although the mechanisms linking the consumption of sweetened beverages and AF risk are still unclear, there are several possibilities. First, insulin resistance might play a mediating role. Fructose absorbed from SSB promotes hepatic de novo lipogenesis that drives metabolic complications, including hepatic insulin resistance.[39] Subjects who consumed >350 mL/day of high-fructose SSB had a 52% increased risk of insulin resistance.[40] A recent animal study revealed that insulin resistance engendered both abnormal intracellular calcium homeostasis and atrial structural remodeling, contributing to increased AF susceptibility.[41] However, diet-stimulated changes in vagal tone should not be ignored.[42] Recent evidence highlighted that the vagus nerve can respond to sugars and artificial sweeteners.[43] Duodenal neuropod cells differentiate and transduce luminal stimulation from sweeteners and sugar to the vagus nerve by sweet taste receptors and sodium glucose transporters. Based on the role of sympathetic/parasympathetic nervous system imbalance in AF incidence,[44] mechanisms related to the parasympathetic nerve deserve further exploration.

The strengths of this study include its prospective design, its large sample size of over 200 000 participants, and its detailed data on dietary consumption, which enabled us to analyze the association of beverages subtypes with AF risk and further stratify the patients by potential risk factors. Moreover, our study is the first prospective study to assess the association between joint exposure to different sweetened beverages and genetic risk for AF. The novel findings on the relationship between SSB, ASB, and PJ consumption and AF risk might prompt the development of new prevention strategies for AF.

Several limitations warrant mention. First, by the nature of observational studies, the associations do not necessarily imply causation. Second, the consumption of beverages was self-reported, so bias was inevitable, and changes in or a long-term pattern of beverages consumption could not be captured. Even so, we calculated the mean value of 5 dietary questionnaires on food intake and only included participants with at least 2 assessments in the sensitivity analysis to minimize possible bias. Third, limited by the questionnaires, we could not tell whether the SSB and ASB were caffeinated, and we cannot rule out residual confounding by

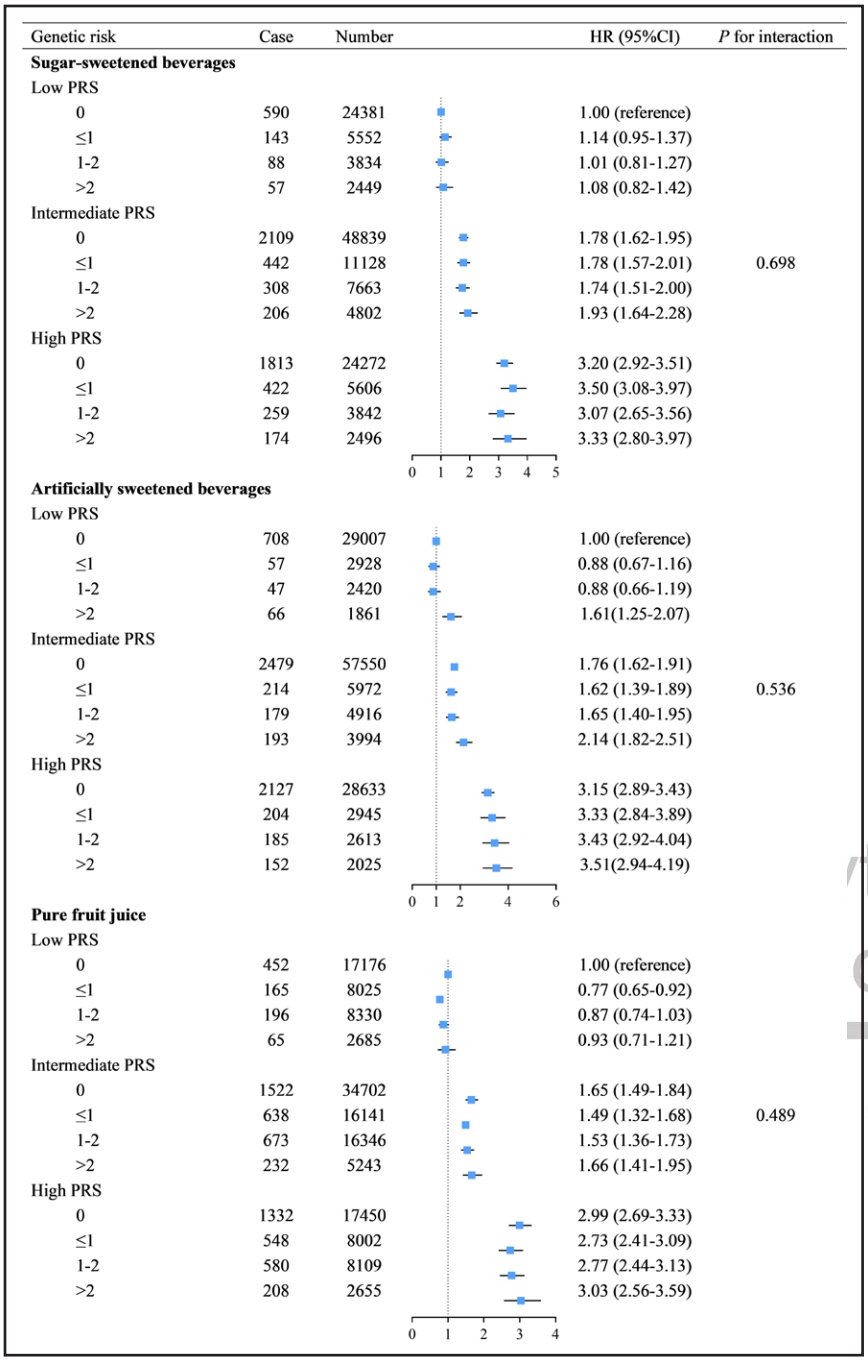

Figure 2. Hazard ratios (HRs) of atrial fibrillation according to the combination of sugar-sweetened beverages, artificially sweetened beverages, or pure fruit juice consumption with genetic risk for atrial fibrillation.
The sample included participants without any kinship to other individuals in UK Biobank (n=144 864). The unit of beverages consumption is liters per week. The vertical line indicates the reference value of 1. The model was adjusted for age, sex, ethnicity (White/others), education level (university or college degree/others), the Townsend deprivation index, alcohol consumption, current smoking, ideal physical activity level, sleep duration, body mass index, systolic blood pressure, total cholesterol, estimated glomerular filtration rate, obstructive sleep apnea/snoring, coronary heart disease, heart failure, diabetes, the consumption of vegetables, fruits, red meat, processed meat, and coffee and total fat, total sugar, and total energy intake and was mutually adjusted for 2 additional beverages. PRS indicates polygenic risk score.

other unmeasured or unknown factors. That said, we did adjust for coffee intake in the model and additionally adjusted for medicine usage in the sensitivity analysis, and the results did not change materially. Fourth, there could have been reverse causation. To address this issue, we excluded AF cases that occurred within the first 2 years of follow-up, and the results were largely unchanged. Finally, we acknowledge that the UK Biobank includes a relatively healthy population of mostly white British individuals. Therefore, generalizing our findings to other wider populations should be done with caution.

CONCLUSIONS

Our study newly demonstrated that consumption of SSB and ASB >2 L/wk was associated with an increased risk of AF, which was even more prominent for individuals with consumption of ASB >2 L/wk. PJ consumption ≤1 L/wk was associated with a modestly lower risk for AF. The association between sweetened beverages and AF risk persisted after adjustment for genetic susceptibility to AF. Intervention studies and basic research are warranted to confirm whether the observed associations are causal. This study does not demonstrate that

consumption of SSB and ASB alters AF risk but rather that the consumption of SSB and ASB may predict AF risk beyond traditional risk factors.

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Disclosures

None.

Supplemental Material

Tables S1–S13
Figures S1
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