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Coffee Consumption and Incident Tachyarrhythmias
Reported Behavior, Mendelian Randomization, and Their Interactions

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IMPORTANCE The notion that caffeine increases the risk of cardiac arrhythmias is common. However, evidence that the consumption of caffeinated products increases the risk of arrhythmias remains poorly substantiated.

OBJECTIVE To assess the association between consumption of common caffeinated products and the risk of arrhythmias.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study analyzed longitudinal data from the UK Biobank between January 1, 2006, and December 31, 2018. After exclusion criteria were applied, 386 258 individuals were available for analyses.

EXPOSURES Daily coffee intake and genetic polymorphisms that affect caffeine metabolism.

MAIN OUTCOMES AND MEASURES Any cardiac arrhythmia, including atrial fibrillation or flutter, supraventricular tachycardia, ventricular tachycardia, premature atrial complexes, and premature ventricular complexes.

RESULTS A total of 386 258 individuals (mean [SD] age, 56 [8] years; 52.3% female) were assessed. During a mean (SD) follow-up of 4.5 (3.1) years, 16 979 participants developed an incident arrhythmia. After adjustment for demographic characteristics, comorbid conditions, and lifestyle habits, each additional cup of habitual coffee consumed was associated with a 3% lower risk of incident arrhythmia (hazard ratio [HR], 0.97; 95% CI, 0.96-0.98; $P < .001$). In analyses of each arrhythmia alone, statistically significant associations exhibiting a similar magnitude were observed for atrial fibrillation and/or flutter (HR, 0.97; 95% CI, 0.96-0.98; $P < .001$) and supraventricular tachycardia (HR, 0.96; 95% CI, 0.94-0.99; $P = .002$). Two distinct interaction analyses, one using a caffeine metabolism–related polygenic score of 7 genetic polymorphisms and another restricted to CYP1A2 rs762551 alone, did not reveal any evidence of effect modification. A mendelian randomization study that used these same genetic variants revealed no significant association between underlying propensities to differing caffeine metabolism and the risk of incident arrhythmia.

CONCLUSIONS AND RELEVANCE In this prospective cohort study, greater amounts of habitual coffee consumption were inversely associated with a lower risk of arrhythmia, with no evidence that genetically mediated caffeine metabolism affected that association. Mendelian randomization failed to provide evidence that caffeine consumption was associated with arrhythmias.

Invited Commentary
Multimedia
Supplemental content

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Coffee is 1 of the most widely consumed beverages worldwide.[1] Although professional society guidelines that suggest avoiding caffeinated products to diminish the risk for arrhythmia[2,3] have relied on assumed mechanisms and a small observational study[4] from 1980, more recent investigations[5,6] have consistently not demonstrated an increased risk of tachyarrhythmia among coffee consumers.

Of importance, coffee consumption may have multiple beneficial properties, often attributed to antioxidant and anti-inflammatory effects,[7,8] and is associated with reduced risks of cancer,[9] diabetes,[10] Parkinson disease,[11] and overall mortality.[12] Indeed, the benefits appear to be most pronounced when caffeinated coffee is consumed.[13] When coffee avoidance is recommended,[14] we may withhold a beneficial substance that improves quality of life and longevity.[12,15] We investigated the association of coffee intake with the risk of tachyarrhythmias in a large, population-based cohort, using participant self-report, mendelian randomization, and an analysis of related interactions to elucidate these associations.

Key Points

Question Is moderate, habitual coffee intake associated with the risk of arrhythmia, and is that association modified by genetic variants that affect caffeine metabolism?

Findings In this large, prospective, population-based community cohort study of more than 300 000 participants, each additional daily cup of coffee was associated with a 3% reduced risk of developing an arrhythmia; these associations were not significantly modified by genetic variants that affect caffeine metabolism. A mendelian randomization study leveraging a polygenic score to capture inherited caffeine metabolism patterns did not reveal evidence that caffeine consumption increases the risk of incident arrhythmias.

Meaning Neither habitual coffee consumption nor genetically mediated differences in caffeine metabolism was associated with a heightened risk of cardiac arrhythmias.

Methods

The UK Biobank study was approved by the National Information Governance Board for Health and Social Care and the National Health Service North West Multicenter Research Ethics Committee. Written consent was obtained from all participants.[16] The present analysis received certification from the University of California, San Francisco institutional review board to perform analyses of this deidentified data set. Race and/or ethnicity was self-reported at baseline surveys and obtained for the generalizability and applicability of the study results. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[17]

Population

We used the UK Biobank, a prospective study of participants in the UK National Health Services 40 to 69 years of age who resided within 40 km of 22 assessment centers. The UK Biobank study has been described previously.[16] In brief, 502 543 participants recruited between January 1, 2006, and December 31, 2010, completed questionnaires, underwent physical examinations, and provided biological samples. We excluded participants who were pregnant on study entry (because reported coffee consumption was less likely to reflect long-term habits), those who subsequently withdrew from the study, and those with missing data.

Coffee Consumption

Information regarding coffee consumption was obtained from participant questionnaires using a touch screen (eTable 1 in the Supplement). We grouped the participants into 8 categories corresponding to daily coffee intake: 0, less than 1, 1, 2, 3, 4, 5, and 6 or more cups daily. We excluded those who answered "do not know" or "prefer not to answer."

Outcome Ascertainment

The primary outcome of interest was incident tachyarrhythmia, ascertained between January 1, 2006, and December 31, 2018, using *International Classification of Diseases, Ninth Revision (ICD-9)* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes available from inpatient and outpatient records (eTable 2 in the Supplement). The presence of the first of the following diagnoses was used to define the presence of an incident tachyarrhythmia: atrial fibrillation or atrial flutter (AF), supraventricular tachycardia, ventricular tachycardia, premature atrial complexes, and premature ventricular complexes. Participants with preexisting diagnoses of any these arrhythmias based on the same *ICD-9* or *ICD-10* codes between January 1, 2000, and December 31, 2005, were excluded from the primary analyses. Secondary analyses examining the incidence of each tachyarrhythmia alone, excluding those with a prevalent diagnosis of that particular tachyarrhythmia, were also conducted.

Potential Mediators and Confounders

Race and ethnicity were self-identified and ascertained from the baseline survey. Educational level was categorized as middle school graduate, high school graduate, college degree, other professional degrees, and none of the above. Body mass index was derived from height and weight measurements obtained during the initial assessment and calculated as weight in kilograms divided by height in meters squared. Physical activity was categorized by tertiles from response to the question on the "number of days per week of moderate physical activity greater than 10 minutes." Hypertension, diabetes, hyperlipidemia, coronary heart disease, congestive heart failure, valvular heart disease, cerebrovascular disease, peripheral artery disease, chronic kidney disease, and cancer were determined by *ICD-9* and *ICD-10* codes from inpatient and/or outpatient visits between January 1, 2000, and December 31, 2005.

Genotyping and Validation for Mendelian Randomization

DNA was purified from biological samples obtained during the initial assessment, such as blood, urine, and saliva. The ini-

tial 49 950 participants were genotyped using the UK BiLEVE Axiom array (Affymetrix, later Thermo Fisher Scientific), and the remaining 438 427 participants were genotyped using the closely related UK Biobank Axiom array (Thermo Fisher Scientific). These 2 arrays share 95% common content covering approximately 800 000 single-nucleotide variations (SNVs) (formerly single-nucleotide polymorphisms) and insertion-deletion markers. Quality control and imputation were performed centrally by the Wellcome Trust Centre for Human Genetics.[18] More than 95% of caffeine is metabolized by CYP1A2, and the variability of its enzymatic activity is strongly associated with the variability of caffeine metabolism.[19-22] CYP1A2 rs762551 was directly genotyped with a call rate of 99.8% and a minor allele frequency of 0.27, and its distribution follows Hardy-Weinberg equilibrium (P = .75).[23] Previous population-based genome-wide association studies for caffeine metabolism revealed 8 loci associated with self-reported coffee and caffeine intake near the aryl hydrocarbon receptor and CYP1A2.[24,25] Among these, rs6968554 was in a moderate linkage disequilibrium (R^2 = 0.95). Therefore, we constructed a caffeine metabolism polygenic score by combining 7 genome-wide significant variants, including rs4410790, rs10275488, rs2892838, rs12909047, rs35107470, rs2470893, and rs2472297. The weighted genetic scores were derived by summing the number of alleles multiplied by their β coefficients (effect size for plasma paraxanthine to caffeine ratio) obtained from a previously reported genome-wide association study meta-analysis for caffeine metabolites.[20] A higher genetic score represents slower caffeine metabolism. CYP1A2 rs762551 was not included in the genetic score because it was in a moderate linkage disequilibrium with other CYP1A2 variants (R^2 = 0.05-0.29).[23] However, it was analyzed independently because this variant was studied extensively for the association of caffeine with disease outcomes in other studies.[23,26,27] To validate these SNVs as genetic markers of coffee consumption, we tested the hypothesis that faster metabolizers consumed more coffee by comparing self-reported coffee consumption to the polygenic score. The mendelian randomization analysis was performed only among those who self-identified as White British and had similar genetic ancestry based on a principal component analysis (UK Biobank data field 22006) and excluding related individuals so that no 2 individuals were a third-degree relative or closer.

Statistical Analysis

Normally distributed continuous variables are described as means (SDs) and compared using unpaired, 2-tailed t tests, and continuous variables without a normal distribution are described as medians (interquartile ranges [IQRs]). Categorical variables were compared using χ^2 tests. Kaplan-Meier curves were constructed to illustrate adjusted cumulative incidence rates. Unadjusted linear regression models were used to examine the association between coffee intake and the number of alleles among individual genetic variants and the polygenic score, respectively. Multivariate Cox proportional hazards regression models were used to assess factors associated with incident events, adjusting for covariates that were likely to confound or mediate examined associations based on the previous literature and biological plausibility. Genetic analyses were adjusted for the top 15 principal components and the specific genotyping array used, as recommended.[28] The main mendelian randomization analysis was performed using the inverse-variance weighted method in a fixed-effects model. We also performed sensitivity analyses to assess for pleiotropy using simple median, weighted median, mendelian randomization Egger, and mendelian randomization residual sum and outlier methods.[28,29] Analyses were executed on all variants as well as 2 subsets separately (chromosome 7 and chromosome 1) and were performed separately using coffee coefficient estimates from our UK Biobank sample as well as an independent sample.[20,23] A secondary analysis was performed without excluding related individuals and adjusted for the same covariates. The potential gene-coffee interaction was evaluated by assessing for effect modification using multivariate Cox proportional hazards regression time-dependent models for both the polygenic score and the genetic variant CYP1A2 (rs762551), including an interaction term between self-reported coffee consumed and the respective genetic variant covariate. Proportional hazards assumptions were checked with log-log survival plots rather than formal statistical tests for the association of time and Schoenfeld residuals, which are commonly oversensitive in very large data sets, signaling no violations of substantive importance.

The following sensitivity analyses were performed: analyses were performed again after excluding those who consumed decaffeinated coffee (to provide a comparison across varying amounts of caffeinated coffee, including no coffee), and all analyses were performed again after constraining outcome ascertainment to inpatient records alone and separately using outpatient records alone. We repeated the main analyses comparing those with and without prevalent arrhythmias using logistic regression. In addition, the analyses were performed again after restricting the cohort to the youngest quartile, and interaction testing to evaluate age as an effect modifier of the coffee-arrhythmia association was conducted. Analyses were performed again after stratifying by biological sex, and interaction testing by sex was performed. We performed multivariate Cox proportional hazards regression analysis as a positive control to assess smoking status as a factor associated with incident arrhythmia based on its established association with arrhythmia risk.[30]

A 2-tailed P < .05 was considered to be statistically significant. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc); Stata software, version 14.2 (StataCorp LLC); and R software, version 3.5.1[31] with R package Mendelian Randomization, version 0.3.0.[32]

Results

Among 502 543 UK Biobank participants, a median of 2 cups (IQR, 1-4 cups) of coffee were consumed per day, and 111 218 participants (22.1%) did not drink coffee. Among coffee drinkers, 310 061 (61.7%) were caffeinated and 74 371 (14.8%) were noncaffeinated drinkers (eTable 1 in the Supplement). After exclusion criteria were applied, 386 258 participants (mean [SD]

Table 1. Baseline Characteristics of the Study Participants[a]

Characteristic	Non-coffee drinker (n = 83 228)	Daily coffee intake		P value
		<2 Cups per day (n = 105 187)	≥2 Cups per day (n = 195 555)	
Age, mean (SD), y	55.2 (8.2)	56.7 (8.1)	56.5 (8.0)	<.001
Sex				
Female	47 115 (57)	57 435 (55)	96 705 (49)	<.001
Male	36 113 (43)	47 752 45)	98 850 (51)	
White	75 702 (91)	99 275 (94)	190 244 (97)	<.001
BMI, mean (SD)	27.4 (4.9)	26.9 (4.6)	27.4 (4.6)	<.001
Educational level				
Middle school graduate	27 653 (33)	35 072 (33)	64 445 (33)	<.001
High school graduate	11 344 (14)	11 400 (11)	22 489 (12)	
College degree	24 518 (29)	38 553 (37)	72 455 (37)	
Other professional	4172 (5)	5352 (5)	10 091 (5)	
None of the above	15 541 (19)	14 810 (14)	26 075 (13)	
Hypertension	5495 (6.6)	6826 (6.5)	12 100 (6.2)	<.001
Diabetes	1505 (1.8)	1696 (1.6)	3209 (1.6)	.002
Hyperlipidemia	1679 (2.0)	2202 (2.1)	4185 (2.1)	.12
Coronary heart disease	1349 (1.6)	1464 (1.4)	2832 (1.5)	<.001
Congestive heart failure	232 (0.3)	242 (0.2)	517 (0.3)	.09
Valvular heart disease	216 (0.3)	273 (0.3)	548 (0.3)	.47
Cerebrovascular disease	103 (0.1)	104 (0.1)	240 (0.1)	.15
Peripheral artery disease	112 (0.1)	104 (0.1)	277 (0.14)	.007
Chronic kidney disease	244 (0.3)	291 (0.3)	4357 (0.2)	<.001
Cancer	902 (1.1)	1286 (1.2)	2294 (1.2)	.02
Smoking				
Never	49 047 (59)	60 891 (58)	100 663 (51)	<.001
Former	26 463 (32)	36 534 (35)	71 372 (37)	
Current	7718 (9)	7762 (7)	23 520 (12)	
Alcohol, mean (SD), drinks per wk	2.7 (1.6)	3.2 (1.5)	3.3 (1.4)	<.001
Tea intake, mean (SD), cups per d	3.6 (1.5)	3.5 (1.3)	2.6 (1.6)	<.001
Physical activity				
Light	36 259 (44)	40 925 (39)	78 881 (40)	<.001
Moderate	19 805 (24)	28 807 (27)	51 719 (26)	
High	27 164 (33)	35 455 (34)	64 955 (33)	

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Data are presented as number (percentage) of study participants unless otherwise indicated.

age, 56 [8] years; 52.3% female) were eligible for the current analyses (eFigure in the Supplement). A total of 208 810 participants had only inpatient records available, and the remaining population had both inpatient and outpatient records available for analyses. Baseline characteristics of the cohort are given in **Table 1**. Those who consumed more than the daily median amount of coffee were more likely to be older, White, and male, have peripheral artery disease, have cancer, be a current smoker, or drink alcohol and less likely to have hypertension, diabetes, and chronic kidney disease and to drink tea.

During a mean (SD) of 4.5 (3.1) years of follow-up, 16 369 incident arrhythmias occurred: 12 811 AFs, 1920 supraventricular tachycardias, 909 ventricular tachycardias, 97 premature atrial complexes,632 premature ventricular complexes, and 610 unspecified arrhythmias. After adjustment for basic age, sex, race, ethnicity, hypertension, diabetes, hyperlipidemia, coronary heart disease, congestive heart failure, valvular heart disease, cerebrovascular disease, peripheral artery disease, chronic kidney disease, cancer, educational level, smoking, alcohol and tea consumption, and physical activity, each additional cup of coffee intake was associated with a 3% lower risk of incident arrhythmia (hazard ratio [HR], 0.97; CI, 0.96-0.98; $P < .001$) (**Figure 1** and **Figure 2**). In analyses of each arrhythmia alone, statistically significant associations exhibiting a similar magnitude were observed for AF (HR, 0.97; 95% CI, 0.96-0.98; $P < .001$) and supraventricular tachycardia (HR, 0.96; 95% CI, 0.94-0.99; $P = .002$) (Figure 2). Although the point estimates were similar for ventricular tachycardia and premature atrial complexes, those associations did not achieve statistical significance. In the positive control analysis using the same outcome ascertainment for arrhythmias and adjusting for the same covariates as were used in the coffee analy-

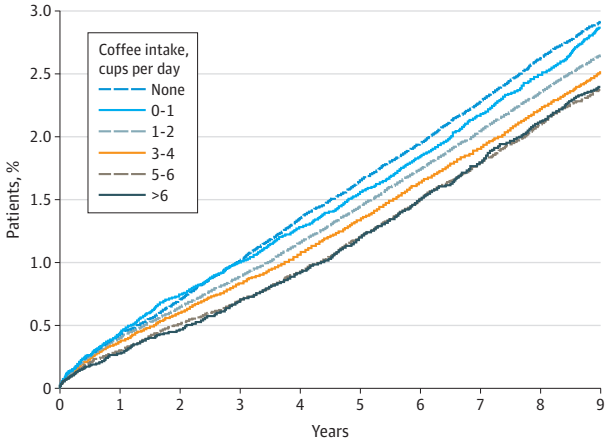
ses, smokers experienced a significantly higher risk of incident arrhythmia (HR, 1.09; 95% CI, 0.03-1.15; P = .002).

Consistent with previous reports,[20,23,26,33] those with genetic variants associated with slower caffeine metabolism consumed less coffee (eTables 3 and 4 in the Supplement). In models to assess possible modification by polygenic score or the CYP1A2 rS762551 variant on the association between coffee intake and arrhythmia risk, we found no meaningful differences in the point estimates among those with different genetic variants or any statistically significant interactions (eTable 5 in the Supplement).

In genetic analysis, higher weighted polygenic score (slower caffeine metabolism, separately associated with lower coffee consumption) did not reveal any significant association with arrhythmia risk (**Table 2**). Adjustment for the same covariates listed above without excluding related individuals did not alter this finding (eTable 6 in the Supplement). Analyses of the association between the CYP1A2 variant alone and incident arrhythmias revealed similar findings in both pruned and multivariable adjusted analyses (**Table 3**; eTable 7 in the Supplement). No meaningful differences in these results were observed in any of the mendelian randomization sensitivity analyses, with no evidence of directional pleiotropy (eTable 8 in the Supplement).

Additional sensitivity analyses examining prevalent arrhythmias similarly found a statistically significant 7% decreased odds (95% CI, 0.90-0.96; P < .001) of prevalent arrhythmia per each additional daily cup of coffee, and, as in the incident analyses, neither the polygenic score nor differences in the CYP1A2 variant revealed evidence of heightened risks of prevalent arrhythmias (eTable 9 in the Supplement). Results remained consistent whether restricting to the youngest quartile of the cohort, women only, or men only. No interactions by age or sex were observed (eTables 10 and 11 in the Supplement).

Figure 1. Cumulative Incidence of Any Arrhythmia by Coffee Consumption



Kaplan-Meier curves for the cumulative incidence of any arrhythmia according to daily coffee intake after adjusting for basic demographic characteristics (age, sex, and ethnicity), body mass index, educational level, other comorbid conditions (hypertension, diabetes, hyperlipidemia, coronary heart disease, congestive heart failure, valvular heart disease, cerebrovascular disease, peripheral artery disease, chronic kidney disease, and cancer), smoking habits, alcohol consumption, tea consumption, and physical activity.

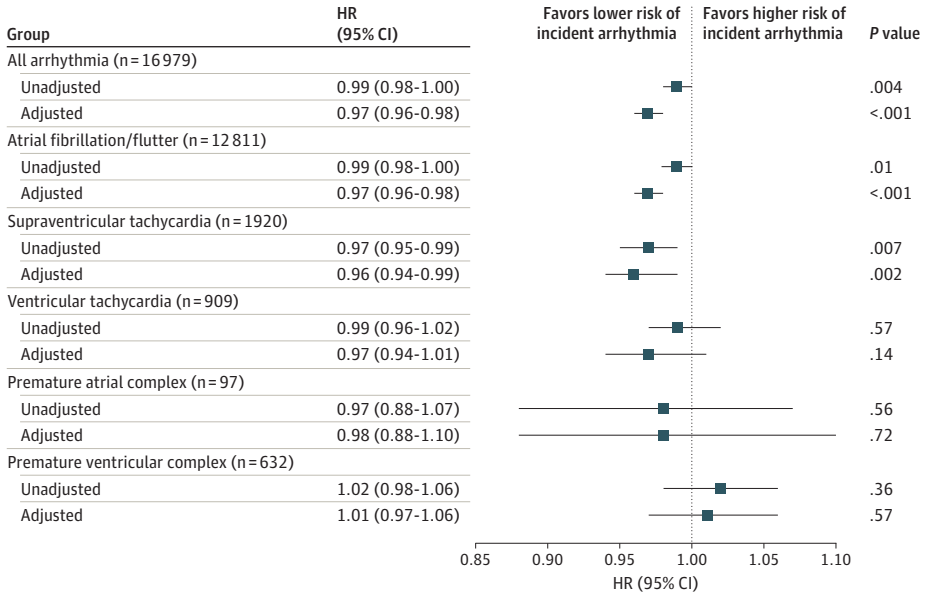
Discussion

In this large, prospective, population-based cohort study, consuming more habitual coffee was associated with a lower risk of developing an arrhythmia. There was no evidence that the association between coffee intake and arrhythmia risk was affected by genetic variants associated with caffeine metabolism. The mendelian randomization analyses failed to provide evidence that caffeine consumption leads to a greater risk of arrhythmias.

Coffee serves as the primary source of caffeine for most individuals,[34] and it has a reputation for causing or exacerbating arrhythmias.[2,3] Caffeine as a proarrhythmic drug has biological plausibility given factors associated with the increase in serum catecholamine levels[35,36] and the calcium release from the sarcoplasmic reticulum in a fashion that may lead to delayed afterdepolarizations.[36] Early, small observational studies[4,37] supported the concept that caffeine was associated with a higher arrhythmia risk. The Physician's Health Study, limited to only male physicians, then suggested a U-shaped association between coffee consumption and arrhythmia risk, with the lowest risk of AF among those who consumed 1 to 3 cups daily.[6] However, another study[5] failed to replicate similar findings. A meta-analysis[38] of 7 observational studies of 115 993 participants found that caffeine exposure based on coffee consumption did not affect AF risk. In a more recent Danish study,[39] coffee consumption in general (compared with no consumption) was inversely associated with AF incidence. Furthermore, possible health benefits of caffeine and coffee in particular have emerged, such as reduction in cancer, diabetes, cardiovascular disease, and overall mortality.[9-12] A review[15] of 201 meta-analyses found that moderate consumption of coffee is likely more beneficial than harmful to health. However, the predominant perception among the public and health care professionals is that caffeine commonly triggers arrhythmias.[4,14,40]

Most research exploring the associations between coffee and arrhythmias has relied on self-reported coffee consumption. In addition, because most of these studies are observational rather than randomized trials, decisions to drink coffee and the amounts regularly consumed are likely associated with other variables that may confound observed associations. Mendelian randomization is a tool that may help mitigate these limitations: by identifying alleles in common genetic variants that are associated with the factor studied (in this case, coffee consumption) without inherent associations with the outcome (in this case, tachyarrhythmias), the random properties of meiosis in assigning genotype can be used to infer causality.[41,42] Because other behaviors or circumstances during life cannot affect the genotype, confounding by such factors should not be operative. Such methods have been used in alcohol research, leveraging the observation that those who metabolize alcohol more quickly tend to drink more

Figure 2. Risks of Incident Arrhythmias for Each Category Increase in Daily Coffee Intake



The relative hazard of each incident arrhythmia for each increasing category of coffee consumption (0-1, 2-3, 4-5, or ≥6 cups per day) is shown. Hazard ratios (HRs) are adjusted for basic demographic characteristics (age, sex, and ethnicity), body mass index, educational level, other comorbid conditions (hypertension, diabetes, hyperlipidemia, coronary heart disease, congestive heart failure, valvular heart disease, cerebrovascular disease, peripheral artery disease, chronic kidney disease, and cancer), smoking habits, alcohol consumption, tea consumption, and physical activity. Error bars indicate 95% CIs.

alcohol,[43,44] and the technique has recently been applied to understanding caffeine metabolism.[26,45]

The findings of this study failed to provide any evidence that coffee consumption heightens the risk of developing arrhythmias. Instead, on the basis of self-report of coffee consumption, the results suggest that coffee intake may in fact reduce the risk of arrhythmias, with the strongest evidence pertaining to developing atrial arrhythmias and supraventricular tachycardia. These findings are consistent with previous studies[6,38,46,47] that found no significant association with or a reduced risk of AF. Several possible mechanisms may be involved in the association between antiarrhythmic factors and caffeine. For example, AF is more likely to occur in the setting of a shorter atrial effective refractory period, whereas caffeine appears to prolong left atrial effective refractory periods.[48] Caffeine is known to block adenosine receptors, high doses of adenosine are known to trigger AF, and reduced AF attributed to inhibiting adenosine receptors has been observed in animal models.[49,50] Coffee's antioxidant and anti-inflammatory properties may also play a role[1,7,8,51] given that inflammation can be a sufficient substrate for cardiac arrhythmias via multiple mechanistic pathways.[52,53] Finally, even the catecholaminergic properties of caffeine could be protective against some arrhythmias, such as some premature ventricular complexes,[54] as well as some arrhythmias triggered by enhanced vagal tone.[55]

It is also possible that the reduced risk of arrhythmia among those who consumed more coffee in the present study occurred because of underascertainment of prevalent arrhythmias, particularly if this underascertainment led to abstention from caffeine among those with previous arrhythmias before study enrollment, leading to misclassification of prevalent cases as incident ones. It would appear unlikely, however, that such misclassification would explain a graded reduction in arrhythmia risk with more habitual coffee consumption among large numbers of coffee drinkers. In addition, this limitation cannot explain the mendelian randomization findings because these findings do not rely on self-reported coffee consumption but instead on inherited and static (within an individual) genetic polymorphisms.

It is plausible that some individuals experience coffee or caffeine-induced arrhythmias, whereas others do not. This study was unable to identify any modification of the association between coffee consumption and arrhythmia risk by different genetic determinants of coffee metabolism. However, there may be other genes, such as those related to arrhythmia risk, that may yet modify this association.

Mendelian randomization evaluating the association between genetic polymorphisms that affect caffeine metabolism and incident arrhythmia revealed neutral, nonsignificant associations, again supporting the absence of an association between caffeine consumption and arrhythmia risk. This approach was validated by our observation that those participants expected to metabolize caffeine more quickly did indeed consume more coffee. Multiple sensitivity analyses and multivariable adjustment of the analyses for polygenic score or CYP1A2 variant did not alter the association. Although it may be a true phenomenon, the results of mendelian randomization studies warrant a cautious interpretation. Mendelian randomization is considered a powerful tool to infer causality from nature's randomization, but it is not completely protected from bias and confounders.[42] For example, CYP1A2 activity is strongly affected by smoking status, sex, and ethnicity.[21] However, confounding could not have resulted in the genetic variant, and it is possible that attenuation of a protective effect against arrhythmias may have been caused by adjusting for mediators that are actually along the causal pathway or associated with collider bias.[45] In addition, the polygenic score ex-

Table 2. Polygenic Score of Caffeine Metabolism and Risk of Incident Arrhythmia[a]

Arrhythmia type	Hazard ratio (95% CI)[b]	*P* value
All arrhythmia	1.00 (0.99-1.00)	.75
Atrial fibrillation or flutter	1.00 (0.99-1.00)	.96
Supraventricular tachycardia	1.01 (0.998-1.00)	.38
Ventricular tachycardia	1.00 (0.996-1.00)	.94
Premature atrial complex	1.00 (0.99-1.02)	.76
Premature ventricular complex	1.00 (0.99-1.00)	.39

[a] The polygenic score was calculated by multiplying the number of slower caffeine-metabolizing alleles by their β coefficients (effect size for plasma paraxanthine to caffeine ratio).[20] A higher polygenic score represents slower caffeine metabolism and was associated with lower coffee consumption. Analyses exclude all family members up to third-degree relatives and are adjusted for age, sex, top 15 principal components, and genotyping array.

[b] Hazard ratios are reported for each increasing unit of polygenic score and the risk of incident arrhythmia.

Table 3. Caffeine Metabolism Determined by the CYP1A2 Variant and Risk of Incident Arrhythmia[a]

Arrhythmia type	Hazard ratio (95% CI)[b]	*P* value
All arrhythmia	1.00 (0.96-1.03)	.89
Atrial fibrillation or flutter	0.98 (0.94-1.02)	.22
Supraventricular tachycardia	1.01 (0.91-1.12)	.86
Ventricular tachycardia	0.99 (0.85-1.15)	.91
Premature atrial complex	0.95 (0.59-1.53)	.82
Premature ventricular complex	1.11 (0.92-1.32)	.27

[a] Analyses exclude all family members up to third-degree relatives and are adjusted for age, sex, top 15 principal components, and genotyping array.

[b] Hazard ratios are reported for each increasing number of the allele associated with slower caffeine metabolism.

plains only a relatively small proportion of the variation in coffee consumption.[33] Finally, the use of caffeine metabolism variants as proxies for caffeine intake has inherent limitations because of opposing effects on coffee intake vs resultant circulating caffeine levels, including biological exposure to caffeine.[20,25,34,45] In the end, however, this study found no consistent evidence from these genetic analyses that a greater propensity to consume caffeinated beverages increased the risk of arrhythmia.

Strengths and Limitations

Our study has multiple strengths. The study was a community-based prospective cohort study with an unprecedented sample size to investigate the association between coffee intake and incident arrhythmias, including the first such analyses of genetic interactions or a related mendelian randomization analysis. The data were carefully collected for potential confounders and mediators, including demographic characteristics, health, and lifestyle factors.

It is important to acknowledge several limitations of the study. Similar to nearly every epidemiologic study on the subject, coffee intake data were obtained from self-report. However, that information was obtained before the subsequent development of the outcomes of interest, so recall bias could not have been operative. The mendelian randomization analyses, despite the limitations already described, should also help to mitigate that limitation. The detailed information regarding the type of coffee, such as espresso or not, or other caffeinated products was not available. The analyses were performed with an assumption that the coffee consumption reported at baseline was sufficiently indicative of consumption that persisted during the study. Although this assumption is a limitation, previous studies[56,57] have demonstrated consistent answers regarding coffee consumption over time, suggesting that a baseline assessment accurately captures long-term consumption patterns. Multiple studies[56,58] evaluating different types of nutrient questionnaires revealed a high degree of reproducibility of nutrient intake over time. The effect of coffee intake on arrhythmia risk was assumed to be constant over time, which is challenging to prove. Although the risk of arrhythmias associated with caffeine is generally considered to be immediate (rather than a long-term event that only manifests over many years),[54] the mean follow-up of just more than 4 years does not allow comments on the longer-term association. A substantial number of participants needed to be excluded because of missing data. Although constraining our study cohort to those with complete data available should help mitigate against threats to internal validity, these exclusions could limit generalizability. This study relied on *ICD-9* and *ICD-10* codes to ascertain the incident arrhythmia outcomes. Although these codes yield high sensitivities and specificities when compared with adjudication by detailed medical record review,[59,60] they likely present a lack of sensitivity for certain arrhythmias, particularly premature atrial complexes (which would potentially require continuous electrocardiographic monitoring in all participants to achieve maximum accuracy). This lack of sensitivity may explain why significant differences in more common and more clinically evident arrhythmias, such as AF and supraventricular tachycardia, were observed. Of note, this limitation would be expected to reduce power to detect an association (therefore we cannot exclude a false-negative result in regard to less common arrhythmias) but should not have led to type I errors or spurious false-positive results. Although exhaustive adjustment was performed in the multivariable analyses, residual or unmeasured confounding cannot be excluded. Although mendelian randomization is purported to provide a methodologic approach wherein causality may be inferred from observational data, such conclusions should be cautioned against. Despite the sensitivity analyses, there may yet be pleiotropic effects, important variants in linkage disequilibrium with the SNVs that were studied, or insufficient power that explains the observations. Ultimately, only a randomized clinical trial can definitively demonstrate clear effects of coffee or caffeine consumption.

Conclusions

In this prospective cohort study, increasing amounts of habitual coffee intake were associated with a lower risk of arrhythmia, particularly for AF and supraventricular tachycardia, with no evidence that genetically determined differences

in caffeine metabolism modified these associations. Mendelian randomization similarly failed to reveal any evidence that expected increases in coffee consumption would be associated with a higher risk of arrhythmia. These data suggest that common prohibitions against caffeine to reduce arrhythmia risk are likely unwarranted.

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