Cardiovascular symptoms affect the patterns of habitual coffee consumption

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ABSTRACT

Background: Excessive coffee consumption can lead to unpleasant sensations such as tachycardia and heart palpitations.

Objectives: Our aim was to investigate if cardiovascular symptoms can lead to alterations in habitual patterns of coffee consumption.

Methods: We used information from up to 390,435 European ancestry participants in the UK Biobank, aged 39–73 y. Habitual coffee consumption was self-reported, and systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate were measured at baseline. Cardiovascular symptoms at baseline were based on hospital diagnoses, primary care records, and/or self-report. Mendelian randomization (MR) was used to examine genetic evidence for a causal association between SBP, DBP, and heart rate with habitual coffee consumption.

Results: Participants with essential hypertension, angina, or heart arrhythmia were all more likely to drink less caffeinated coffee and to be non-habitual or decaffeinated coffee drinkers compared with those who did not report related symptoms ($P \leq 3.5 \times 10^{-8}$ for all comparisons). Higher SBP and DBP were associated with lower caffeinated coffee consumption at baseline, with consistent genetic evidence to support a causal explanation across all methods [MR-Egger regression (MR_{Eggr}) β: −0.21 cups/d (95% CI: −0.34, −0.07) per 10 mm Hg higher SBP and −0.33 (−0.61, −0.07) per 10 mm Hg higher DBP)]. In genetic analyses, higher resting heart rate was associated with a greater odds of being a decaffeinated coffee drinker (MR_{Eggr} OR: 1.71; 95% CI: 1.31, 2.21) per 10 beats/min).

Conclusions: We provide causal genetic evidence for cardiovascular system–driven influences on habitual coffee intakes, suggesting that people tend to naturally regulate their coffee consumption based on blood pressure levels and heart rate. These findings suggest that observational studies of habitual coffee intakes are prone to influences by reverse causation, and caution is required when inferred health benefits result from comparisons with coffee abstainers or decaffeinated coffee drinkers. *Am J Clin Nutr* 2021;114:214–219.

Keywords: coffee, habitual coffee intake, decaffeinated coffee, reverse causality, Mendelian randomization, cardiovascular symptoms, blood pressure, heart rate, UK Biobank

Introduction

Excessive coffee consumption will lead to cardiovascular symptoms such as tachycardia and heart palpitations. These types of unpleasant side effects are typically attributed to caffeine, which is a key constituent of coffee and known to cause a variety of physiological effects (1). In the short term, caffeine ingestion also increases blood pressure, and there are now in excess of 100 randomized controlled trials investigating related effects (2). Results are relatively consistent, and caffeine administration typically leads to modest to moderate elevations in blood pressure, depending on dosage (2). However, in observational studies, habitual coffee consumption has typically either no or an inverse association with blood pressure (1, 3). These differences in the observed associations for acute compared with habitual coffee consumption may be related to a development of tolerance to the stimulant effects of caffeine, which can explain why the blood pressure–increasing effects of coffee appear to be temporary. However, people also tend to self-regulate their patterns of coffee consumption, with experimental evidence showing how the number of cups consumed will decrease with increases in caffeine preload or concentration (4). Furthermore, there is evidence that coffee consumption is often one of the first behaviors to be altered when a

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Supplemental Methods, Supplemental Figures 1–3, and Supplemental Tables 1–3 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: DBP, diastolic blood pressure; GWAS, genome-wide association study; MR, Mendelian randomization; MR_{Eggr}, MR-Egger regression; SBP, systolic blood pressure; SNP, single nucleotide polymorphism; W_{median}, weighted median Mendelian randomization; W_{mode}, weighted mode Mendelian randomization.

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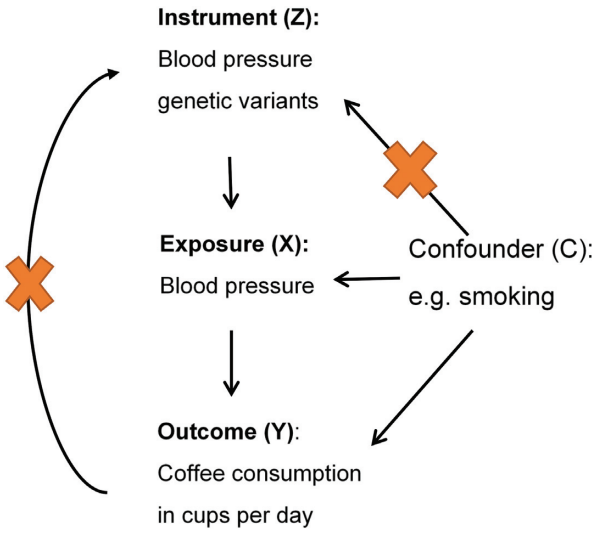

FIGURE 1 The principle of Mendelian randomization for testing reverse causality in the association between blood pressure and coffee consumption. This model gains its strength from the property that patterns of coffee consumption (Y) cannot alter inherited genetic variants affecting blood pressure (Z). The approach relies on the assumption that blood pressure genetic variants (Z) are robustly associated with blood pressure (X) but not with confounders (C), and there is no path from Z to coffee consumption (Y) other than through X.

person becomes acutely ill (5). Understanding of the disease-related drivers determining the patterns of coffee consumption is essential for enabling appropriate interpretation of observational evidence relating to habitual coffee consumption. In this study, we examine the evidence for cardiovascular symptom–led self-regulation of coffee intake and test for underlying causality using a genetic approach called Mendelian randomization (MR) (6) (**Figure 1**). In our MR analyses, we used genetic variants reflecting higher blood pressures and higher resting heart rate to instrument cardiovascular symptoms, with an aim to establish causal evidence for the role of reverse causation in determining patterns of habitual coffee intake.

Methods

The UK Biobank cohort includes >500,000 participants aged 37–73 y at recruitment (2006–2010) from throughout the United Kingdom (7). All participants underwent genome-wide genotyping and participated in clinical assessments and questionnaire surveys. In this study, the sample was restricted to white British Caucasians based on self-report and genetic profiling (8). We allow for a maximum of 2 members from each family and exclude participants with mismatch between self-reported and genetic sex (8). Final analyses were conducted among individuals with complete information on coffee intake, coffee type, and relevant covariates (n up to 390,435; **Supplemental Figure 1**). All participants provided an informed consent to participate, and the UK Biobank study was approved by the National Information Governance Board for Health and Social Care and North West Multi-centre Research Ethics Committee (11/NW/0382).

Information on coffee consumption was recorded as cups per day and obtained by the question, "How many cups of coffee do you drink each day? (include decaffeinated coffee)." Among the coffee drinkers, a further question was asked about the types of coffee. Our primary outcome is caffeinated coffee consumption as cups per day. We also coded the participants according to whether they typically drank caffeinated compared with decaffeinated coffee and into nonhabitual compared with habitual caffeinated coffee drinkers (0 cups/d compared with >0 cups/d). For the caffeinated coffee consumption (cups/d), individuals who reported drinking <1 cup/d were coded as 0.5 cup/d, and those who reported drinking an infeasible amount of coffee (>15 cups/d, $n = 285$) were excluded from the analysis. Because 80% of coffee drinkers in the cohort identify as caffeinated coffee drinkers, we coded participants who did not specify the type of coffee ($n = 1469$) as caffeinated coffee drinkers.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated as an average of the 2 measurements, and medication use was accounted for by adding 15 and 10 mm Hg to SBP and DBP (9), respectively. Heart rate was measured during the automated BP readings. Information on essential hypertension, angina, and heart arrhythmia was derived based on hospital admissions and primary care records, and it was supplemented with self-reported information (**Supplemental Methods**). Information on poor self-rated health and the presence of long-standing illness was obtained by a questionnaire as part of the baseline assessment. As covariates, we included age, sex, BMI, assessment center location, Townsend deprivation index, smoking [nonsmokers, ex-smokers, current smokers with no information on the type of tobacco that they smoke, cigar/pipe smokers, cigarette smokers (<1–5 cigarettes/d, 6–10 cigarettes/d, 11–15 cigarettes/d, 16–20 cigarettes/d, 21–25 cigarettes/d, >25 cigarettes/d)], alcohol intake (never, special occasion only, 1–3 times/mo, 1 or 2 times/wk, 3–4 times/wk, ≥5 times/wk), tea intake (<1 cup/d, 1–2 cups/d, 3–4 cups/d, >4 cups/d), intensity of physical activity (light, moderate, vigorous), and education (none or National Vocational Qualification/Certificate of Secondary Education/A-levels, or degree/professional). Townsend deprivation index (10) reflects socioeconomic area deprivation, and each participant was assigned a score corresponding to socioeconomic data attributed to their postcode.

We used genome-wide information from the UK Biobank to create genetic instruments for SBP (9), DBP (9), and resting heart rate (11). Variants were selected as the top hits in the most recent genome-wide association study (GWAS) on the trait, which did not include the UK Biobank (**Supplemental Table 1**). We removed 1 variant (rs936226, *CYP1A1–ULK3*) which was identified for both SBP and DBP and which was in strong linkage with variants affecting caffeine metabolism in the liver (Supplemental Methods). All genetic instruments for SBP [53 single nucleotide polymorphisms (SNPs)], DBP (52 SNPs), and resting heart rate (20 SNPs) used in the analyses were confirmed to be independent from loci related to habitual coffee intake (all with $r^2 < 0.05$) (12). We coded variants to approximate higher SBP (per 10 mm Hg), DBP (per 10 mm Hg), and resting heart rate (per 10 beats/min higher).

Statistical analyses

We tested for the differences in the number of cups of coffee consumed by differences in SBP, DBP, and heart rate using linear regression and the likelihood of being a decaffeinated

TABLE 1 Patterns of coffee drinking by sex, age, cardiovascular disease, and general health factors in the UK Biobank[1]

	Caffeinated coffee, % (*n*)	Decaffeinated, % (*n*)	None, % (*n*)	Caffeinated, cups/d, β (95% CI)	Decaffeinated vs. caffeinated, OR (95% CI)	None vs. caffeinated, OR (95% CI)
Sex						
Men	68.5 (122,289)	12.6 (22,574)	18.9 (33,693)	Ref.	Ref.	Ref.
Women	59.4 (125,217)	18.3 (38,462)	22.3 (47,086)	−0.22 (−0.23, −0.21)	1.50 (1.47, 1.53)	1.21 (1.18, 1.23)
P			$<1.0 \times 10^{-300}$	1.8×10^{-220}	$<1.0 \times 10^{-300}$	2.9×10^{-96}
Age, y						
<65	63.3 (197,681)	15.2 (47,352)	21.5 (67,089)	Ref.	Ref.	Ref.
≥65	64.5 (49,825)	17.7 (13,684)	17.7 (13,690)	−0.14 (−0.16, −0.13)	1.13 (1.11, 1.16)	0.71 (0.70, 0.73)
P			2.3×10^{-151}	4.0×10^{-66}	1.3×10^{-26}	1.7×10^{-189}
Essential hypertension, %						
No	64.2 (216,182)	15.4 (51,763)	20.5 (68,934)	Ref.	Ref.	Ref.
Yes	60.5 (23,303)	16.8 (6472)	22.7 (8742)	−0.14 (−0.17, −0.12)	1.16 (1.13, 1.20)	1.22 (1.18, 1.25)
P			1.1×10^{-44}	6.6×10^{-32}	1.8×10^{-21}	1.3×10^{-38}
Angina, %						
No	64.2 (216,182)	15.4 (51,763)	20.5 (68,934)	Ref.	Ref.	Ref.
Yes	59.5 (8939)	17.1 (2561)	23.5 (3522)	−0.11 (−0.15, −0.07)	1.28 (1.22, 1.34)	1.29 (1.23, 1.35)
P			1.4×10^{-30}	3.5×10^{-8}	2.6×10^{-24}	4.1×10^{-29}
Heart arrhythmia, %						
No	64.2 (216,182)	15.4 (51,763)	20.5 (68,934)	Ref.	Ref.	Ref.
Yes	54.4 (5254)	22.7 (2188)	22.9 (2212)	−0.27 (−0.31, −0.22)	1.85 (1.75, 1.95)	1.53 (1.45, 1.62)
P			1.0×10^{-106}	5.8×10^{-32}	2.2×10^{-114}	4.6×10^{-51}
Poor self-rated health, %						
No	63.8 (238,558)	15.8 (58,929)	20.5 (76,480)	Ref.	Ref.	Ref.
Yes	57.8 (8196)	13.8 (1961)	28.4 (4020)	−0.06 (−0.10, −0.01)	1.04 (0.99, 1.10)	1.21 (1.16, 1.27)
P			8.9×10^{-114}	0.02	0.12	3.1×10^{-17}
Longstanding illness, %						
No	64.9 (168,815)	15.2 (39,517)	19.9 (51,749)	Ref.	Ref.	Ref.
Yes	60.8 (73,384)	16.7 (20,175)	22.6 (27,241)	−0.021 (−0.04, −0.01)	1.19 (1.17, 1.21)	1.15 (1.13, 1.17)
P			3.1×10^{-136}	0.007	3.7×10^{-63}	1.3×10^{-45}

[1] *P* values for the distribution of coffee intakes are from Pearson's chi-square test. *P* values for β and OR are from linear and logistic regression, respectively, adjusted for age, assessment center, sex, BMI, Townsend deprivation index, smoking, alcohol intake, tea intake, physical activity, and education and accounted for relatedness.

coffee or nonhabitual coffee drinker using multiple logistic regression adjusting for age, sex, BMI, assessment center location, Townsend deprivation index, smoking, alcohol intake, tea intake, physical activity, general health, long-standing illness, and education. We tested for curvature by including the relevant squared term (e.g., SBP^2) in the model. Models including genetic variants were adjusted for age, sex, genotyping array, birth location, assessment center location, and top 40 genetic principal components accounting for population structure. All models for phenotypic and genetic analyses were weighed by 1 – kinship coefficient to account for relatedness.

MR was used to examine genetic evidence for a causal association between higher SBP, DBP, and heart rate with the habitual patterns of caffeinated coffee consumption (cups/d), and the odds of being a decaffeinated coffee (decaffeinated compared with caffeinated) or nonhabitual coffee (none compared with caffeinated) drinker. We computed MR estimates using 4 approaches —inverse-variance-weighted (IVW), weighted median (W_{median}), weighted mode (W_{mode}), and MR-Egger regression (MR_{Eggr}), because these models rely on different assumptions of pleiotropy and will provide valid evidence under different conditions (13) (Supplemental Methods). We conducted sensitivity analysis by removing genetic variants associated with potential confounders and by restricting the sample to unrelated individuals (Supplemental Methods). All phenotypic analyses were performed using Stata version 14.1 (StataCorp). MR analyses were run with R version 4.0.2 (R Foundation for Statistical Computing) using TwoSampleMR (version 0.5.5) and MR PRESSO (version 1.0) packages.

Results

Men were more likely to drink caffeinated coffee compared with women (68.5% compared with 59.4%, respectively), whereas women were more likely to choose decaffeinated coffee or to abstain from coffee (**Table 1**). There was also some variation in coffee drinking habits by age. Participants with essential hypertension, angina, or heart arrhythmia were all more likely to drink less coffee, and to be nonhabitual coffee or decaffeinated coffee drinkers, compared with participants without related symptoms. The strongest associations were between heart arrhythmia and patterns of coffee intake, and those who had experienced related symptoms were 85% more likely to drink decaffeinated coffee and 53% more likely not to drink any coffee than to drink caffeinated coffee (Table 1). Self-reported poor health and a history of long-standing illness at baseline were also associated with coffee intake, with participants reporting related concerns more likely to choose decaffeinated coffee or not to drink any coffee than to drink caffeinated coffee.

In phenotypic association analyses, higher SBP and DBP were associated with lower caffeinated coffee intakes

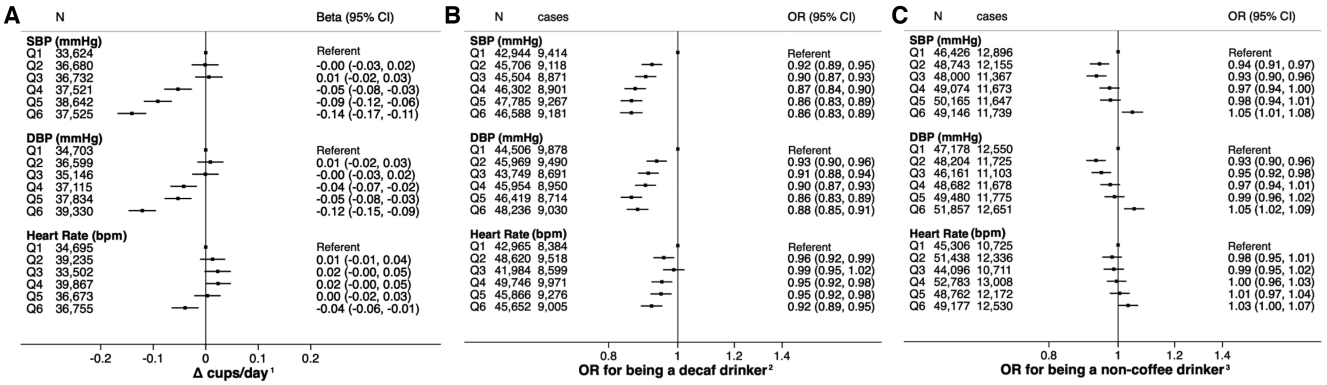

FIGURE 2 Patterns of habitual coffee consumption by sextiles of SBP, DBP, and heart rate. Analyses were conducted using linear or logistic regression and models adjusted for age, sex, BMI, smoking, alcohol intake, tea intake, physical activity, education, Townsend deprivation index, education, general health, long-standing illnesses, and assessment center and accounted for relatedness. bpm, beats per minute; DBP, diastolic blood pressure; Q1–Q6, sextiles; SBP, systolic blood pressure; [1]caffeinated coffee; [2]decaffeinated coffee compared with caffeinated coffee; [3]none compared with caffeinated coffee.

($P_{trend} < 1.1 \times 10^{-28}$) and lower odds of being a decaffeinated coffee drinker ($P_{trend} \leq 3.2 \times 10^{-14}$). The odds of being a nonhabitual coffee drinker were higher both for individuals with the lowest and those with the highest levels of SBP and DBP ($P_{curvature} \leq 2.2 \times 10^{-15}$) (**Figure 2**). Heart rate had a nonlinear association with caffeinated coffee intake ($P_{curvature} = 3.1 \times 10^{-7}$), but with only small differences between the groups. Participants with the highest heart rates were the least likely to be decaffeinated coffee drinkers ($P_{trend} < 1.5 \times 10^{-7}$) (Figure 2).

Genetic scores reflecting higher SBP, DBP, and heart rate demonstrated expected associations with their respective cardiovascular traits in the UK Biobank (**Supplemental Figure 2**). In MR analyses, both higher SBP and higher DBP were associated with a consistently lower amount of habitual coffee consumption (**Table 2**). For SBP, we identified evidence for pleiotropy ($P_{pleiotropy} = 0.02$), but consistent with a true effect, the strongest associations were seen with pleiotropy robust methods including W_{median} and MR_{Eggr}. We observed genetic evidence for an association between higher heart rate and the odds of drinking decaffeinated coffee, and for each 10 beats per minute higher rate, the odds of choosing decaffeinated coffee were 71% higher (MR_{Eggr} OR: 1.71; 95% CI: 1.31, 2.21). There was evidence for pleiotropy also in the analyses investigating the associations between resting heart rate and decaffeinated coffee intake ($P_{pleiotropy} = 0.001$), but again, the strongest evidence was obtained with pleiotropy robust methods including W_{median} and MR_{Eggr} (Table 2). Sensitivity analyses excluding identified pleiotropic variants provided support for all associations identified in the main analyses, and they also suggested associations for SBP and DBP with higher odds of being a non-coffee drinker [OR per 10 mm Hg: 1.06 (95% CI: 1.0, 1.12) and 1.10 (1.01, 1.19), respectively] (**Supplemental Table 2**).

Sensitivity analyses restricting phenotypic and genetic analyses to unrelated individuals provided similar results (**Supplemental Figure 3**, **Supplemental Table 3**).

Discussion

Coffee is one of the most consumed beverages in the world, and as such it has important implications for public health. Yet, the evidence relating to the health effects of coffee remains elusive, and some promote beneficial effects and the safety of even very high intakes (14, 15). In this study, we show that people who experience cardiovascular symptoms, such as hypertension, angina, and arrhythmias, or who report poor health tend to drink less coffee compared with others, to choose decaffeinated coffee, and to be more commonly non-coffee drinkers. We also show causal genetic evidence that a higher blood pressure will lead to lower coffee consumption and that those with higher heart rates are more likely to choose decaffeinated coffee. It is well known that observational studies are prone to bias from reverse causation, and this study clearly shows that caution is required when inferring health benefits for coffee intakes that result from comparisons with coffee abstainers, whose behavior may in part be determined by their cardiovascular symptoms.

Excessive caffeine intake is known to cause acute increases in blood pressure, elevate heart rate, and lead to palpitations (1); hence, it is very intuitive that the presence of cardiovascular symptoms could alter the patterns of habitual coffee intakes. Individuals tend to be aware of their individual tolerance to coffee, and it is known that average coffee intakes are in part determined by genetic factors (12). However, what is not always appreciated is how symptom-driven influences on coffee consumption ("reverse causality") can affect the associations between habitual coffee intake and cardiovascular risk in standard observational studies. As for other exposures such as adiposity and alcohol consumption, observational studies on coffee intake have often reported nonlinear associations with health outcomes, where both those who are in the lowest group and those who are in the highest group are at an elevated risk compared with moderate consumers (3, 16–18). In terms of interpretation, these types of associations are open to ambiguity because the same data can be used to infer "beneficial effects by moderate intakes" simply by using the coffee-avoiding (and possibly disease-affected) lowest category as the comparison group. We have shown this as part of our previous work by re-examining data from a meta-analysis of 36 prospective studies examining the association between coffee consumption and cardiovascular disease (CVD) risk. The original study showed a U-shaped association, which was used to infer lower risk of CVD for moderate coffee consumers compared with nondrinkers, and no increases in risk for heavy drinkers (16).

TABLE 2 Mendelian randomization analyses to estimate a causal role of cardiovascular symptoms on coffee drinking patterns[1]

	MR IVW		W_{median}		W_{mode}		MR PRESSO[2]				MR_{Egger}		
	β/OR (95% CI)	*P*	β/OR (95% CI)	*P*	β/OR (95% CI)	*P*	β/OR (95% CI)	*P*	$P_{distortion}$[3]	Outliers	β/OR (95% CI)	*P*	$P_{intercept}$
SBP, per 10 mm Hg increase													
Caffeinated coffee (cups/d)	−0.05 (−0.096, −0.008)	0.02	−0.09 (−0.14, −0.03)	0.002	−0.12 (−0.23, −0.005)	0.05	−0.05 (−0.097, −0.007)	0.03	NA		−0.21 (−0.34, −0.07)	0.004	0.02
Decaffeinated coffee drinker[4]	1.04 (0.97, 1.12)	0.29	1.04 (0.98, 1.11)	0.20	1.00 (0.89, 1.13)	1.00	1.07 (1.01, 1.13)	0.02	0.5	rs13107325	0.90 (0.72, 1.12)	0.35	0.19
Non-coffee drinker[5]	1.04 (0.99, 1.09)	0.09	1.01 (0.96, 1.07)	0.69	0.96 (0.84, 1.10)	0.58	1.04 (0.99, 1.09)	0.10	NA		1.02 (0.88, 1.18)	0.83	0.74
DBP, per 10 mm Hg increase													
Caffeinated coffee (cups/d)	−0.13 (−0.22, −0.04)	0.003	−0.13 (−0.22, −0.04)	0.004	−0.17 (−0.34, −0.003)	0.05	−0.11 (−0.18, −0.029)	0.008	0.5	rs2187668	−0.33 (−0.61, −0.07)	0.02	0.12
Decaffeinated coffee drinker[4]	1.04 (0.93, 1.16)	0.51	1.03 (0.93, 1.14)	0.61	0.98 (0.81, 1.18)	0.84	1.10 (1.01, 1.19)	0.02	0.5	rs13107325	0.69 (0.49, 0.98)	0.04	0.02
Non-coffee drinker[5]	1.06 (0.98, 1.14)	0.14	1.0 (0.91, 1.10)	0.98	0.94 (0.75, 1.18)	0.59	1.06 (0.98, 1.14)	0.15	NA		0.93 (0.73, 1.19)	0.56	0.28
Resting heart rate, per 10 bpm increase													
Caffeinated coffee (cups/d)	0.005 (−0.07, 0.08)	0.90	0.002 (−0.10, 0.11)	0.97	0.04 (−0.12, 0.20)	0.61	0.001 (−0.08, 0.08)	0.98	NA		0.11 (−0.13, 0.35)	0.38	0.38
Decaffeinated coffee drinker[4]	1.03 (0.92, 1.15)	0.58	1.20 (1.07, 1.35)	0.001	1.20 (1.03, 1.39)	0.03	1.02 (0.91, 1.15)	0.70	NA		1.71 (1.31, 2.21)	0.001	0.001
Non-coffee drinker[5]	0.97 (0.88, 1.06)	0.46	0.97 (0.88, 1.09)	0.63	0.96 (0.82, 1.12)	0.63	0.96 (0.87, 1.05)	0.33	NA		1.01 (0.76, 1.35)	0.93	0.74

[1] Data are from two-sample MR analyses with genetic variant SBP (9), DBP (9), and heart rate (11) associations taken from consortia meta-analyses. Genetic variant coffee intake associations are from the UK Biobank, with models adjusted for age, sex, genotyping array, birth location, assessment center location, and top 40 genetic principal components and accounted for relatedness. bpm, beats per minute; DBP, diastolic blood pressure; MR, Mendelian randomization; MR IVW, inverse-variance-weighted MR; MR_{Egger}, MR-Egger regression; W_{median}, weighted median MR; W_{mode}, weighted mode MR; SBP, systolic blood pressure.

[2] MR PRESSO estimates are presented excluding outlying variants where detected.

[3] *P* value for distortion test conducted only where outliers are detected, and it denotes the difference between estimates before and after exclusion of outlying variants.

[4] Decaffeinated compared with caffeinated.

[5] None compared with caffeinated.

However, changing the reference group to light drinkers suggests that the greatest CVD risk is with non-coffee drinkers and that participants in the highest intake group may be at an increased risk compared with those drinking in moderation (3). MR studies of coffee consumption on CVD risk or mortality have not provided evidence for an effect (19–21), with reverse causality or confounding a likely explanation for the observed benefits with moderate consumption (21). This also aligns with the current interpretation of the U-shaped associations with adiposity and alcohol, where reverse causality robust methods have challenged both the proposed health benefits for being overweight rather than slim (22) [with a possible exception for smokers (23)] and the benefit of moderate alcohol consumption rather than alcohol abstinence (24–26).

Findings from our study need to be interpreted in the context of its strengths and limitations. The strengths of our study arise from the large sample available for our analyses and the use of a genetic approach for testing the effects of SBP, DBP, and heart rate on coffee consumption patterns, which allowed us to overcome some of the limitations with observational studies, including confounding and reverse causation. However, we only tested for linear associations between blood pressure and heart rate with coffee intake in the MR analyses. Because it is likely that people at the extremes of the distribution, such as people diagnosed with hypertension or arrhythmias, are likely to make stronger alterations to their lifestyles compared with people with minor symptoms, the strength of the association estimated by our analyses may have been underestimated. It is also a limitation that information on coffee consumption was available only from 1 time point, although for the purposes of cross-sectional analyses to illustrate associations with concurrent cardiovascular symptoms, this is likely to be sufficient.

Pleiotropy is an important issue in all MR studies of coffee intake on CVD risk given the strong genetic link between blood pressure and coffee intake. Indeed, the strongest variant affecting habitual coffee intakes (*CYP1A1/2*) (12) has also been identified as a variant affecting both SBP and DBP in GWAS (9). To avoid misleading conclusions due to possible pleiotropic effects, we excluded this variant from all analyses and ascertained that all variants used as instruments in this study were not correlated with any variants identified in the coffee GWAS (12). We also conducted analyses using multiple complementary approaches, including several pleiotropy robust MR methods, and obtained consistent evidence regardless of the approach used for all associations identified. To ensure that the findings were robust, we conducted further sensitivity analyses excluding all variants associated with potential confounders. Findings from these sensitivity analyses supported all associations seen in the main analyses, and they provided further support for the strong observational associations between cardiovascular symptoms and coffee abstinence.

In conclusion, we provide causal genetic evidence that the way people's cardiovascular symptoms functions, as reflected by blood pressure and heart rate, can affect the patterns of coffee intake. This suggests that people tend to naturally regulate their coffee intakes based on blood pressure levels and heart rate, which at an individual level may help avoid potential harm that could arise from excessive coffee intakes. At the same time, this suggests that general promotion of high coffee intakes as safe or beneficial is likely to be misguided and that

a more personalized approach that accounts for the individual characteristics is required.

The authors' responsibilities were as follows—EH: designed the study, wrote the manuscript, and provided final content; AZ: analyzed the data and revised the manuscript; and both authors: interpreted the data and read and approved the final manuscript. The authors report no conflicts of interest.

Data Availability

Data described in the manuscript and analytic code are available to registered users of the UK Biobank upon application (https://www.ukbiobank.ac.uk/register-apply).

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