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FULL RESEARCH PAPER
Nutrition/obesity

The impact of coffee subtypes on incident cardiovascular disease, arrhythmias, and mortality: long-term outcomes from the UK Biobank

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Aims Epidemiological studies report the beneficial effects of habitual coffee consumption on incident arrhythmia, cardiovascular disease (CVD), and mortality. However, the impact of different coffee preparations on cardiovascular outcomes and survival is largely unknown. The aim of this study was to evaluate associations between coffee subtypes on incident outcomes, utilizing the UK Biobank.

Methods and results Coffee subtypes were defined as decaffeinated, ground, and instant, then divided into 0, <1, 1, 2–3, 4–5, and >5 cups/day, and compared with non-drinkers. Cardiovascular disease included coronary heart disease, cardiac failure, and ischaemic stroke. Cox regression modelling with hazard ratios (HRs) assessed associations with incident arrhythmia, CVD, and mortality. Outcomes were determined through ICD codes and death records. A total of 449 563 participants (median 58 years, 55.3% females) were followed over 12.5 ± 0.7 years. Ground and instant coffee consumption was associated with a significant reduction in arrhythmia at 1–5 cups/day but not for decaffeinated coffee. The lowest risk was 4–5 cups/day for ground coffee [HR 0.83, confidence interval (CI) 0.76–0.91, $P < 0.0001$] and 2–3 cups/day for instant coffee (HR 0.88, CI 0.85–0.92, $P < 0.0001$). All coffee subtypes were associated with a reduction in incident CVD (the lowest risk was 2–3 cups/day for decaffeinated, $P = 0.0093$; ground, $P < 0.0001$; and instant coffee, $P < 0.0001$) vs. non-drinkers. All-cause mortality was significantly reduced for all coffee subtypes, with the greatest risk reduction seen with 2–3 cups/day for decaffeinated (HR 0.86, CI 0.81–0.91, $P < 0.0001$); ground (HR 0.73, CI 0.69–0.78, $P < 0.0001$); and instant coffee (HR 0.89, CI 0.86–0.93, $P < 0.0001$).

Conclusion Decaffeinated, ground, and instant coffee, particularly at 2–3 cups/day, were associated with significant reductions in incident CVD and mortality. Ground and instant but not decaffeinated coffee was associated with reduced arrhythmia.

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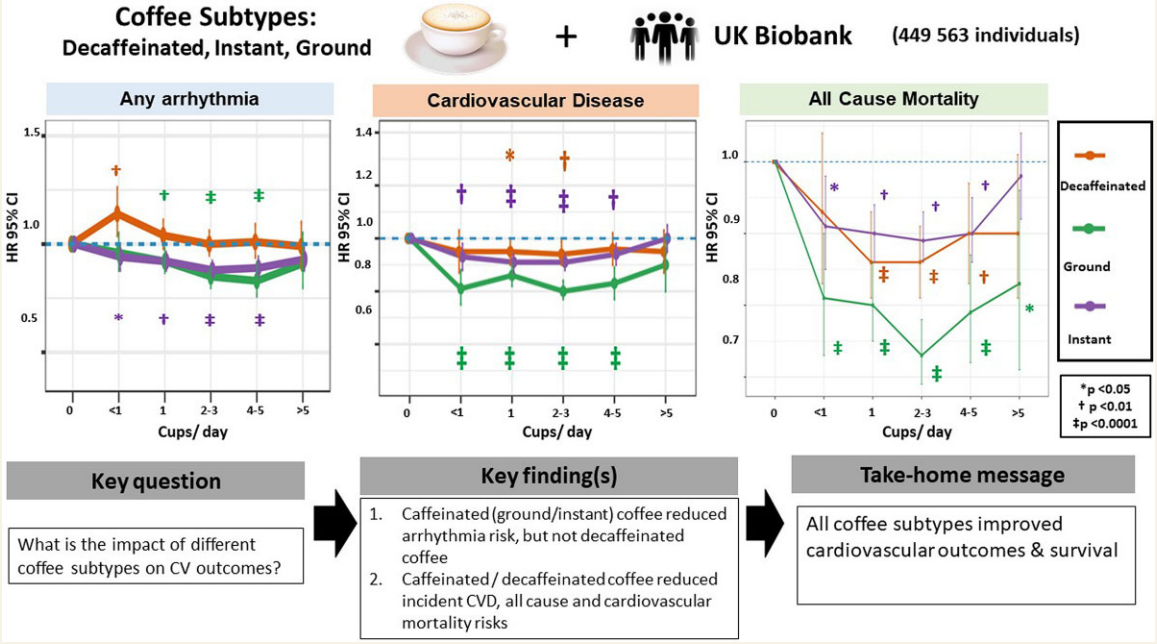
Graphical Abstract



Coffee subtypes and associations with incident arrhythmia, CVD, and mortality. Caffeinated (ground/instant) but not decaffeinated coffee reduced the risk of arrhythmia. Both caffeinated and decaffeinated coffee reduced incident CVD and all-cause and cardiovascular mortality risks. CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

Keywords Coffee • Decaffeinated • Instant • Ground • Arrhythmia • Cardiovascular disease • Coronary heart disease • Congestive cardiac failure • Stroke

Introduction

Coffee is ubiquitous in most societies, with its main constituent caffeine the most commonly consumed psychostimulant worldwide.[1] With increasing public awareness on cardiovascular disease (CVD) prevention, significant interest has focused on modifiable lifestyle risk factors, including the safety of coffee. Historically up to 80% of health practitioners recommend avoiding coffee in patients with CVD.[2] This misconception has been challenged by recent observational studies, which not only report the safety but a beneficial effect of coffee intake on incident arrhythmia and CVD prevention.[1,3,4] In fact, coffee consumption at 3–4 cups/day is described as moderately beneficial in the prevention of CVD in the 2021 European Society of Cardiology guidelines,[5] although no such recommendation was made in the 2019 AHA/ACC guidelines.[6]

Although observational studies support the beneficial health effects of coffee, there is a lack of dedicated studies aiming to address the impact of different coffee subtypes on hard clinical outcomes such as arrhythmia, CVD, and mortality.[4] Much attention is directed towards coffee's major constituent, caffeine; however, coffee is made up of more than 100 different biologic agents. The aim of this study was to provide some mechanistic insights into the role of caffeine on cardiovascular (CV) outcomes by comparing the impact of decaffeinated and caffeinated coffee.

Methods

Study design/setting

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.[7] A protocol for the study is available online.[8] Between 1 January 2006 and 31 December 2010, the study recruited UK participants aged between 40 and 69 years. Survey and questionnaire responses on lifestyle risk factors and physical examination findings were collected at baseline. Participants were followed up long term to assess health outcomes.

Analyses performed in this study had been conducted using the UK Biobank Resource under application number 55469 from the Baker Heart and Diabetes Institute, Melbourne, Australia. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Participant inclusion/exclusion criteria

The UK Biobank data set consisted of 502 521 participants. For this study, participants were excluded if they withdrew from the UK Biobank or did not provide ethnic background information (17 617). Furthermore, participants were excluded if responses were not provided for the following: coffee intake (1170, 0.2%), coffee type (8984, 1.8%), tea intake (665, 0.1%), and body mass index (BMI)/smoking/alcohol status (3764, 0.7%). Participants with self-reported atrial fibrillation (AF) at baseline were also excluded (389, 0.1%). Participants who already had

a diagnosis of CVD at the time of enrolment into the UK Biobank were considered prevalent cases and excluded (20 369, 4.0%).

The associations between coffee subtypes and incident CV outcomes were analysed in a cohort consisting of participants who developed a CV diagnosis during follow-up (incident cases), along with participants who did not receive any diagnosis of arrhythmia or CVD on follow-up ('healthy' cases).

Coffee consumption

Coffee consumption was self-reported by participants based on touchscreen questionnaire responses at the assessment centres. Participants were asked how many cups of coffee they drank each day. Coffee drinkers were also asked what type of coffee they usually drank including instant coffee, ground coffee (such as cappuccino or filtered coffee), and decaffeinated coffee. Those who reported drinking >10 drinks were asked to reconfirm the response. Participants were only able to select one type of coffee on the questionnaires, so the possibility that a proportion of participants may have consumed more than one type could not be excluded. For this study, participants were grouped into six daily intake categories, consisting of 0, <1, 1, 2–3, 4–5, and >5 cups/day. Those who answered 'do not know' or 'prefer not to answer' were excluded from the analysis.

Variables/outcome measurement

The primary outcome of interest was the relationship between coffee subtypes and incidence of arrhythmias, CVD, and mortality. The coffee subtypes that were examined in this study were decaffeinated coffee and caffeinated coffee (ground and instant). Cardiovascular disease was defined as a composite of coronary heart disease (CHD), congestive cardiac failure (CCF), and ischaemic stroke. Arrhythmia included ectopy, atrial fibrillation/atrial flutter (AF/flutter), supraventricular tachycardia (SVT), and ventricular tachycardia (VT)/ventricular fibrillation (VF). Mortality outcomes included all-cause mortality, CV mortality, and sudden cardiac death.

Other analyses include the relationship between coffee subtype consumption and the incidence of subcategories of arrhythmias, namely AF/flutter, SVT, and VT/VF; as well as the subcategories of CVD (CHD, CCF, and stroke). We also evaluated the associations between overall coffee intake and incident arrhythmia, CVD, CCF, CHD, stroke, and mortality outcomes.

Incident events were assessed between January 2006 and August 2021. For each endpoint, we considered participants with the respective disease incident cases and the 'healthy' cohort, and analysed the effects of differing coffee intake levels on the risk of developing the studied endpoint against non-coffee drinkers. Some participants may have two or more incident CV diagnoses which are not adjusted for in each endpoint evaluation.

Data sources/measurement

The outcomes of interest were ascertained using the International Classification of Diseases, Tenth Revision (ICD-10) codes available from medical records (see Supplementary material online, *Table S1*). Hospital inpatient and procedure data were identified through data linkage with the Hospital Episode Statistics database (England), Scottish Morbidity Records (Scotland), and Patient Episode Database for Wales Database (Wales). Data linkage with other providers is performed at the participant level using identifiers including National Health Service (NHS) number (England or Wales) or Community Health Index (CHI) number (Scotland) and name, date of birth, sex, residential address, and postcode.

Statistical methods

Continuous data were expressed as mean ± standard deviation when normally distributed, and medians ± interquartile range (IQR) when skewed. Categorical data were presented as numbers and percentages. Differences in variables were compared using the χ^2 test for categorical data, and the Student *t*-test or Mann–Whitney *U* test for normally distributed and skewed continuous data respectively. Cox proportional hazards regression models were used to assess coffee effects on endpoint events, adjusting for potential confounding covariates. Coffee consumption of 0 cup/day was used as reference for comparisons with other levels of intake.

Covariates adjusted for in regression modelling to account for potentially confounding effects included: age, gender (male, females), ethnicity (White or other ethnicity), BMI, comorbidities [hypertension, diabetes mellitus (DM), and obstructive sleep apnoea (OSA)], and lifestyle risk factors (smoking status, tea, and alcohol consumption). Alcohol intake was subcategorized as none, daily, weekly, and monthly. BMI was subdivided into ≤30 or >30 kg/m^2. Hypertension, diabetes, and OSA diagnoses were determined by ICD-10 codes (see Supplementary material online, *Table S1*). In adjusted models, age was inputted as a continuous variable, whereas other covariates were inputted as categorical variables. Participants' level of physical activity was not considered due to missing data in 17.4% of the cohort. We also did not include analysis of genetic variants/polygenic risk scores associated with caffeine metabolism as recent studies have not identified a significant effect modification on associations between coffee consumption and CV outcomes.[7,9]

Statistical significance was computed using Wald's statistic (corresponding to the ratio of each regression coefficient to its standard error). Proportional hazards assumptions were assessed using log–log survival plots.[7] Statistical significance was defined as a two-tailed *P*-value of <0.05. All analyses were performed using R (4.1.0) program's survival package.

The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed in reporting this study.

Results

Overall coffee intake and incident cardiac arrhythmias

There were 449 563 participants in the final study cohort. The participants had a median age of 58 years (IQR 50–63), with 55.3% females. The median follow-up was 12.5 years (IQR 11.7–13.2). There were 100 510 (22.4%) non-coffee drinkers who served as controls. An arrhythmia was diagnosed in 30 100 (6.7%) participants during long-term follow-up which included AF/flutter in 15 302 (3.4%), SVT in 3023 (0.7%), and VT/VF in 2008 (0.4%). Compared with non-drinkers, a U-shaped relationship was seen between increasing levels of coffee consumption and incidence of any arrhythmia (*Figure 1*). After adjustment for covariables age, gender, alcohol intake, tea intake, obesity, DM, hypertension, OSA, and smoking status, the lowest risk for arrhythmias was seen in those who consumed 2–3 coffee cups/day, with a hazard ratio (HR) of 0.91 [confidence interval (CI) 0.88–0.94, $P < 0.0001$; see Supplementary material online, *Table S2*]. A similar relationship was observed for AF/flutter and SVT. For AF/flutter, significant risk reductions were seen in those who consumed between 1 and 5 cups/day, with the peak risk reduction seen in 4–5 cups/day (HR 0.88, CI 0.83–0.94, $P < 0.0001$).

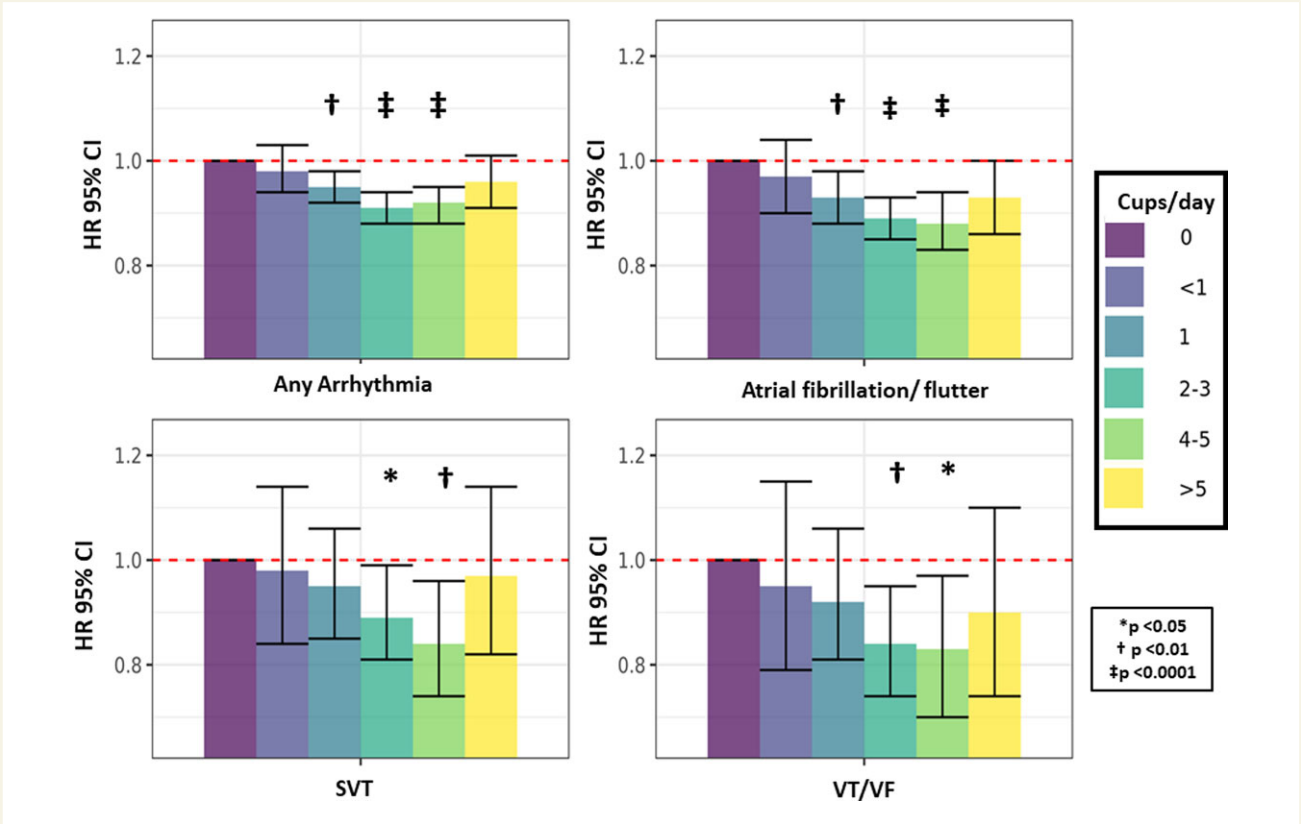


Figure 1 Coffee intake and incident cardiac arrhythmias. 'U-shaped' relationship between coffee cups/day and incident arrhythmias, atrial fibrillation/flutter, supraventricular tachycardia, and ventricular tachycardia/ventricular fibrillation. Model adjusted for the covariables of age, gender, alcohol intake, tea intake, obesity, diabetes mellitus, hypertension, obstructive sleep apnoea, and smoking status. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.0001$.

For VT/VF, increasing coffee intake was associated with lower risk of incident arrhythmia, with the lowest risk seen in 4–5 cups/day (HR 0.83, CI 0.70–0.97, $P = 0.0201$; see Supplementary material online, *Table S3*).

Overall coffee intake and incident cardiovascular disease

Cardiovascular disease was diagnosed in 43 173 (9.6%) participants during follow-up. A total of 34 677 (7.7%) participants were diagnosed with incident CHD, 12 966 (2.8%) with incident CCF, and 6767 (1.5%) with incident stroke. Habitual coffee intake of up to 5 cups/day was associated with significant reductions in the risk of incident CVD, when compared with non-drinkers. Significant reductions in the risk of incident CHD were associated with habitual coffee intake of up to 5 cups/day, with the lowest risk for CHD observed in those who consumed 2–3 cups/day (HR 0.89, CI 0.86–0.91, $P < 0.0001$). Coffee consumption at all levels was associated with significant reduction in the risk of CCF and ischaemic stroke (*Figure 2*). The lowest risks were observed in those who consumed 2–3 cups/day, with HR 0.83 for CCF (CI 0.79–0.87, $P < 0.0001$), and HR 0.84 for ischaemic stroke (CI 0.78–0.90, $P < 0.0001$; see Supplementary material online, *Table S2*).

Overall coffee intake and all-cause/ cardiovascular mortality

A total of 27 809 (6.2%) participants died during long-term follow-up, including 4402 (1.0%) from CV causes. A significant reduction in all-cause mortality was associated with coffee consumption up to 5 cups/day, with the greatest effect seen with 2–3 cups/day (HR 0.86, CI 0.83–0.89, $P < 0.0001$). A significant reduction in CV mortality was observed in coffee drinkers of 1–5 cups/day (lowest risk 1 cup/day; HR 0.82, CI 0.74–0.90, $P < 0.0001$; see Supplementary material online, *Figure S1*). Coffee intake was not associated with a risk of sudden cardiac death (see Supplementary material online, *Figure S2*).

Coffee subtype analysis

Coffee subtype analyses were undertaken in the same 449 536 participant cohort who did not have a prevalent diagnosis of CVD at baseline. The coffee type was instant in 198 062 (44.1%), ground in 82 575 (18.4%), and decaffeinated in 68 416 (15.2%). The overall characteristics of the cohort are summarized in *Table 1*.

Ground coffee

Of the 82 575 ground coffee drinkers, an arrhythmia was diagnosed in 5872 (7.0%) which was predominantly AF/flutter (3269, 3.9%);

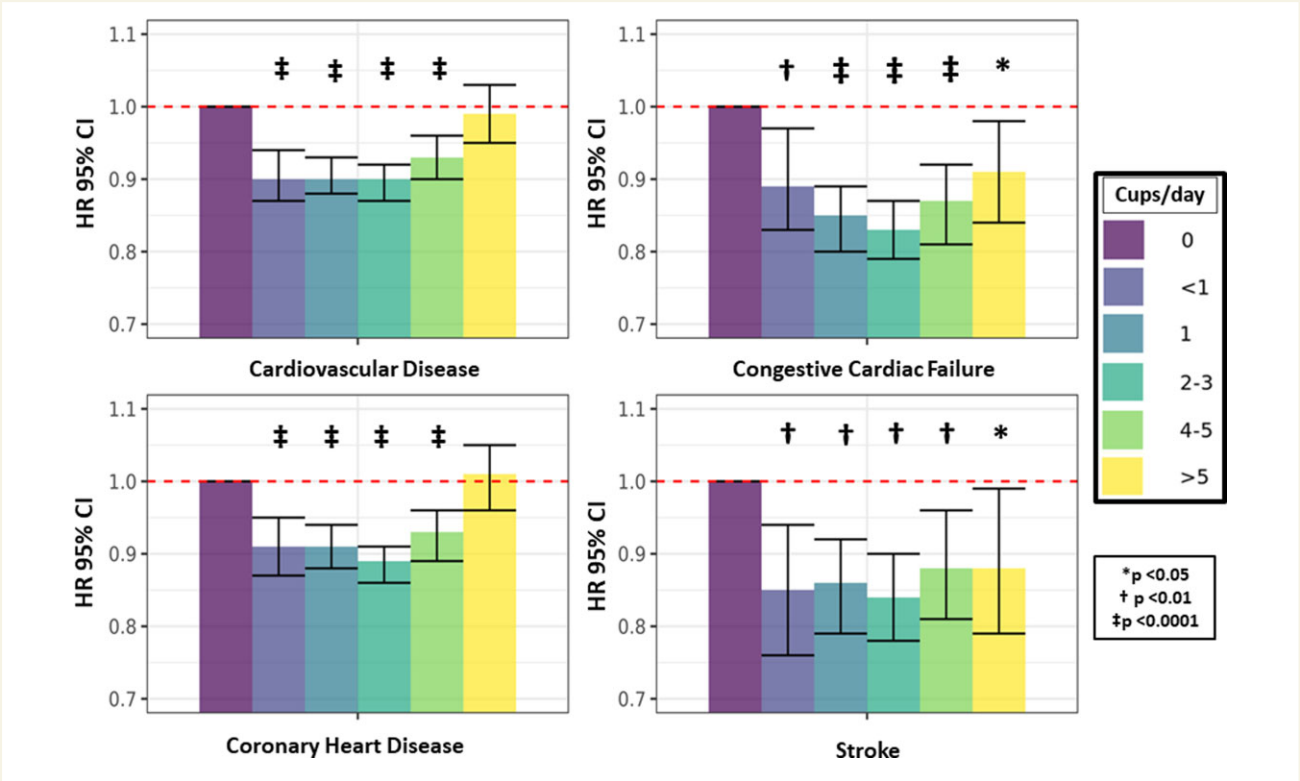


Figure 2 Coffee intake and incident cardiovascular disease. Coffee consumption up to 5 cups/day was associated with reduced risk of cardiovascular disease and coronary heart disease. All levels of coffee consumption reduced risk of congestive cardiac failure and stroke. Model adjusted for covariables age, gender, alcohol intake, tea intake, obesity, diabetes mellitus, hypertension, obstructive sleep apnoea, smoking status. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.0001$.

CVD in 8670 (10.5%), CHD in 7154 (8.6%), CCF in 1976 (2.3%), and stroke in 1114 (1.3%). Total mortality was 5.5% (4511) at a median follow-up of 12.5 years (IQR 11.7–13.2). Ground coffee intake between 1 and 5 cups/day was associated with a significant reduction in the incidence of any arrhythmia, and specifically AF/flutter (*Figure 3A*, Supplementary material online, *Table S4*). A reduction in SVT and VT/VF risk was seen with 2–5 cups/day (*Figure 3B*). Ground coffee consumption at up to 5 cups/day was associated with a significant reduction in the risk of CVD, CHD, and CCF (*Figure 4*). Ground coffee consumption at all levels significantly reduced the risk of all-cause and CV mortality (*Figure 5*). All-cause mortality was lowest at 2–3 cups/day (HR 0.73, CI 0.69–0.78, $P <$ 0.0001), whereas CV mortality was lowest at 4–5 cups/day (HR 0.65, CI 0.51–0.83, $P < 0.0001$; see Supplementary material online, *Table S5*).

Instant coffee

Of the 198 062 instant coffee drinkers, an arrhythmia was diagnosed in 16 696 (8.4%) which was predominantly AF/flutter (9273, 4.7%), CVD in 29 751 (15.0%), CHD in 25 051 (12.6%), CCF in 7029 (3.5%), and stroke in 3707 (1.8%). Total mortality was 7.7% (15 365) at a median follow-up of 12.5 years (IQR 11.7–13.2). In general, a U-shaped relationship was observed between instant coffee intake and the various CVD endpoints. In particular, 2–3 cups of instant coffee/day was associated with the lowest risk for any arrhythmia (HR 0.88, CI 0.85–0.92, $P < 0.001$), CVD (HR 0.91, CI 0.88–0.94, $P < 0.0001$), CHD (HR 0.91, CI 0.88–0.94, $P < 0.0001$), stroke (HR 0.83, CI 0.76–0.90, $P < 0.0001$), and all-cause mortality (HR 0.89, CI 0.86–0.93, $P < 0.0001$; *Figures 4* and *5*). Amongst the arrhythmia subtypes incident risks were lowest at 4–5 cups/day for AF/flutter (HR 0.85, CI 0.79–0.91, $P < 0.0001$; *Figure 3A*), and SVT (HR 0.75, CI 0.63–0.88, $P = 0.0005$; *Figure 3B*, Supplementary material online, *Table S4*).

Decaffeinated coffee

Of the 68 416 decaffeinated coffee drinkers, an arrhythmia was diagnosed in 6737 (9.8%) with (AF/flutter in 3889), CVD in 9904 (14.5%), CCF in 2263 (3.3%), and ischaemic stroke in 1224 (1.7%). Total mortality was 10.9% (7434) at a median follow-up of 12.5 years (IQR 11.7–13.2). The risk of CVD, CHD, and CCF were reduced particularly with an intake of 2–3 cups/day, with hazard ratios of 0.94 (CI 0.90–0.99, $P = 0.0093$), 0.94 (CI 0.89–0.99, $P = 0.0127$), and 0.86 (CI 0.79–0.94, $P = 0.0004$), respectively (*Graphical Abstract*). A U-shaped relationship was demonstrated between decaffeinated coffee intake and all-cause mortality, with the lowest risk seen with 2–3 cups/day (HR 0.86, CI 0.80–0.91, $P < 0.0001$). Cardiovascular mortality was also reduced at a coffee intake between 1 and 3 cups/day (lowest risk 1 cup/day: HR 0.74, CI 0.61–0.89, $P = 0.0012$; *Graphical Abstract*). Decaffeinated coffee intake was generally associated with a neutral effect against any arrhythmias (*Figure 3A*, Supplementary material online, *Table S4*).

Table 1 Cohort characteristics for coffee subtype analysis

	None ($n = 100\,510$)	Decaffeinated ($n = 68\,416$)	Ground ($n = 82\,575$)	Instant ($n = 198\,062$)
Demographic				
Age (years), median (IQR)	56 (49–62)	59 (52–64)	57 (50–63)	58 (51–64)
White ethnicity	90 973 (90.5%)	65 954 (96.4%)	79 828 (96.7%)	190 317 (96.1%)
Female, *n* (%)	59 803 (59.5%)	43 996 (64.3%)	43 213 (52.3%)	101 958 (51.5%)
BMI >30 kg/m^2, *n* (%)	24 926 (24.8%)	16 178 (23.6%)	15 269 (18.5%)	49 382 (24.9%)
Cardiovascular risk factors, n (%)				
Hypertension	28 041 (27.9%)	19 327 (28.2%)	18 104 (21.9%)	55 152 (27.8%)
Diabetes mellitus	7960 (7.9%)	5548 (8.1%)	4585 (5.6%)	17 363 (8.8%)
Obstructive sleep apnoea	1804 (1.7%)	482 (0.7%)	1271 (1.5%)	3525 (1.8%)
Smoking				
Previous	30 910 (30.7%)	22 442 (32.8%)	30 484 (36.9%)	69 742 (35.2%)
Current	9619 (9.5%)	4570 (6.7%)	7656 (9.3%)	24 831 (12.5%)
Never	59 981 (59.7%)	41 404 (60.5%)	44 435 (53.8%)	103 489 (52.3%)
Alcohol				
Monthly	28 596 (28.5%)	17 983 (26.3%)	11 542 (13.9%)	42 517 (21.5%)
Weekly	14 112 (14.0%)	5397 (7.9%)	3208 (3.9%)	11 270 (5.7%)
Daily	43 100 (42.8%)	34 534 (50.5%)	42 234 (51.1%)	102 212 (51.6%)
Never	33 273 (33.1%)	10 502 (15.4%)	25 591 (30.9%)	42 063 (21.2%)
Deaths				
Total	6309 (6.2%)	4076 (5.9%)	4084 (4.9%)	13 340 (6.7%)
Cardiovascular death	1035 (1.0%)	600 (0.9%)	581 (0.7%)	2186 (1.1%)
Sudden cardiac death	57 (0.06%)	25 (0.03%)	41 (0.04%)	135 (0.06%)
Coffee cups/day *n* (%)				
<1	0 (0%)	1949 (2.9%)	3567 (4.3%)	6694 (3.4%)
1	0 (0%)	5156 (7.5%)	8838 (10.7%)	17 124 (8.6%)
2–3	0 (0%)	20 624 (30.1%)	28 054 (33.9%)	60 131 (30.4%)
4–5	0 (0%)	17 700 (25.9%)	19 972 (24.2%)	47 642 (24.1%)
>5	0 (0%)	11 172 (16.3%)	11 546 (13.9%)	30 636 (15.5%)

Sensitivity analyses

A sensitivity analysis was conducted among coffee drinkers only. Using 1 cup/day as the reference category, we found no significant difference in the incidence of CVD at all intake categories and across all coffee subtypes (see Supplementary material online, *Figure S3*). We also considered subgroups with/without the following comorbidities: in those with prevalent hypertension, coffee drinking was associated with a reduction in incident CVD when compared with non-drinkers (HR 0.91, CI 0.89–0.94, $P < 0.0001$). In those without prevalent hypertension, coffee drinking was associated with a reduction in incident CVD (HR 0.90, CI 0.86–0.94, $P < 0.0001$). Similarly, coffee drinking, when compared with non-drinkers, was also associated with reduced incidence of CVD in those with prevalent DM (HR 0.92, CI 0.88–0.97, $P = 0.001$), those without prevalent DM (HR 0.91, CI 0.88–0.93, $P < 0.0001$), those with prevalent OSA (HR 0.87, CI 0.78–0.96, $P = 0.008$), and those without prevalent OSA (HR 0.91, CI 0.89–0.94, $P < 0.0001$).

Discussion

In this large prospective cohort study, we investigated the associations between habitual coffee intake, more specifically the impact of coffee subtype including decaffeinated coffee, and major CV endpoints. The main findings from the study are:

(1) Ground, instant, and decaffeinated coffee were associated with equivalent reductions in the incidence of CVD and CV/all-cause mortality.
(2) Two to three cups/day of all coffee subtypes was consistently associated with the largest risk reduction in CVD, CHD, CCF, and all-cause mortality.
(3) Ground and instant coffee but *not* decaffeinated were associated with a reduction in arrhythmias including AF.
(4) A 'U-shaped' relationship exists between caffeinated coffee intake and incidence of any arrhythmia, including AF. The largest risk reduction was present at 4–5 cups/day.

Coffee subtypes and cardiovascular outcomes

Coffee is a complex compound composed of >100 biologically active components, with caffeine the most well recognized.[10] Acute caffeine intake results in sympathetic activation, mediated by phosphodiesterase inhibition, cytosolic calcium increase, and stimulation of noradrenaline/adrenaline release.[4] Coffee is the most common cognitive enhancer increasing mental alertness and concentration.

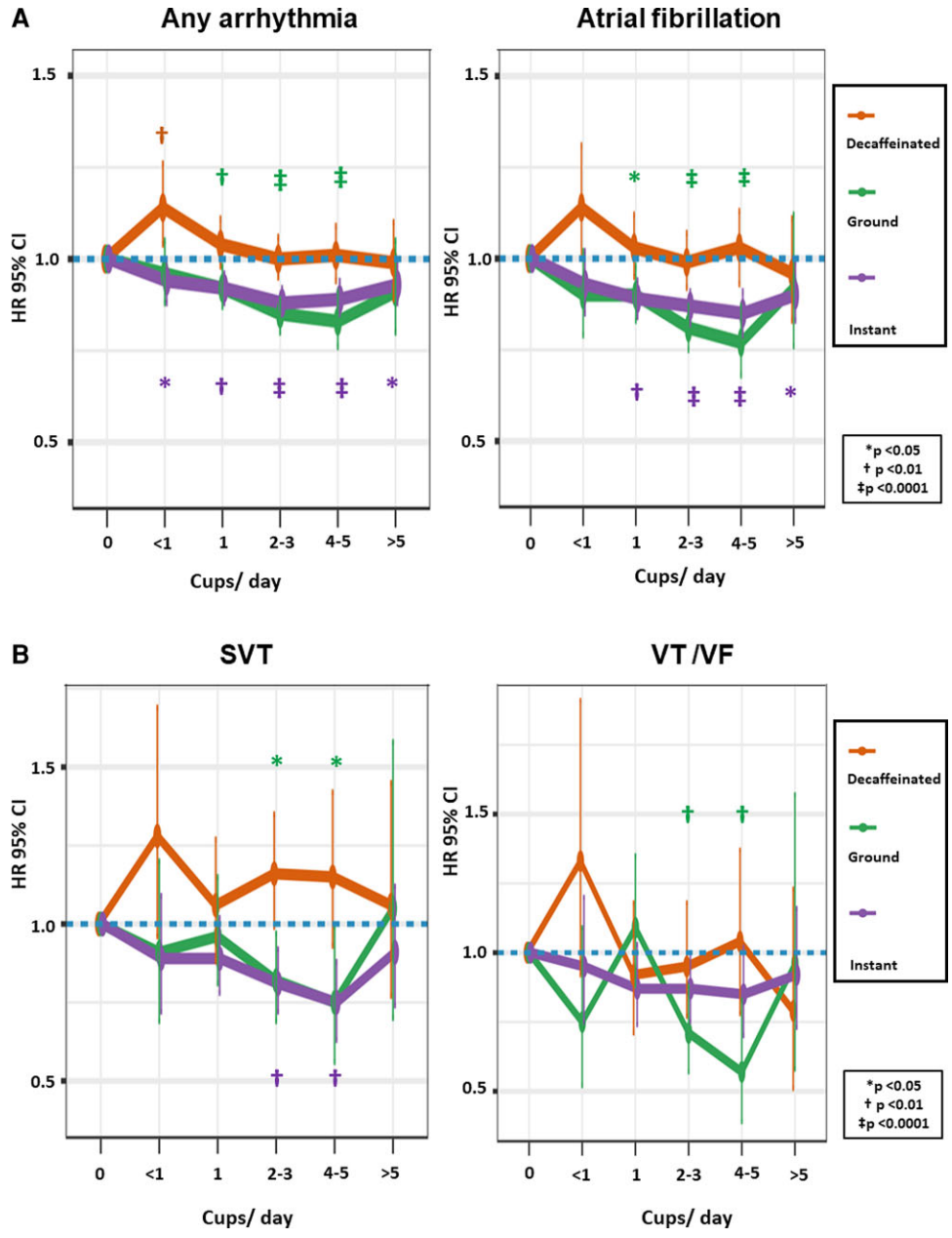


Figure 3 (*A*) Coffee subtype intake and incident any arrhythmia and atrial fibrillation. Ground and instant coffee intake at 1–5 cups/day were consistently associated with reduced risk of any arrhythmia, and atrial fibrillation/flutter. Model adjusted for covariables age, gender, alcohol intake, tea intake, obesity, diabetes mellitus, hypertension, obstructive sleep apnoea, smoking status. (*B*) Coffee subtype intake and incident supraventricular tachycardia and ventricular tachycardia/ventricular fibrillation. Ground and instant coffee intake at 2–5 cups/day were consistently associated with reduced risk of supraventricular tachycardia. Ventricular tachycardia/ventricular fibrillation risk was reduced with 2–5 cups/day or ground coffee. Model adjusted for covariables age, gender, alcohol intake, tea intake, obesity, diabetes mellitus, hypertension, obstructive sleep apnoea, smoking status. $^{*}P < 0.05$; $^{\dagger}P < 0.01$; $^{\ddagger}P < 0.0001$.

However, higher intake levels can result in feelings of anxiety, restlessness, insomnia, and psychomotor agitation, with toxic effects estimated to occur with intakes of ≥1.2 g.[11] Intracellular calcium elevation may increase atrial pacemaker cell automaticity and after depolarization-induced triggered activity, which may increase arrhythmia risk particularly in high doses.[12] Coffee may acutely elevate blood pressure through sympathetic activation,[13] although tolerance develops quickly and there is minimal effect on long-term blood pressure control. Caffeine can adversely impact the effects of antihypertensive medications including beta-blockers and calcium-channel blockers like felodipine.[14] Caffeine has near 100% bioavailability with metabolism determined by cytochrome CYP1A2 enzyme

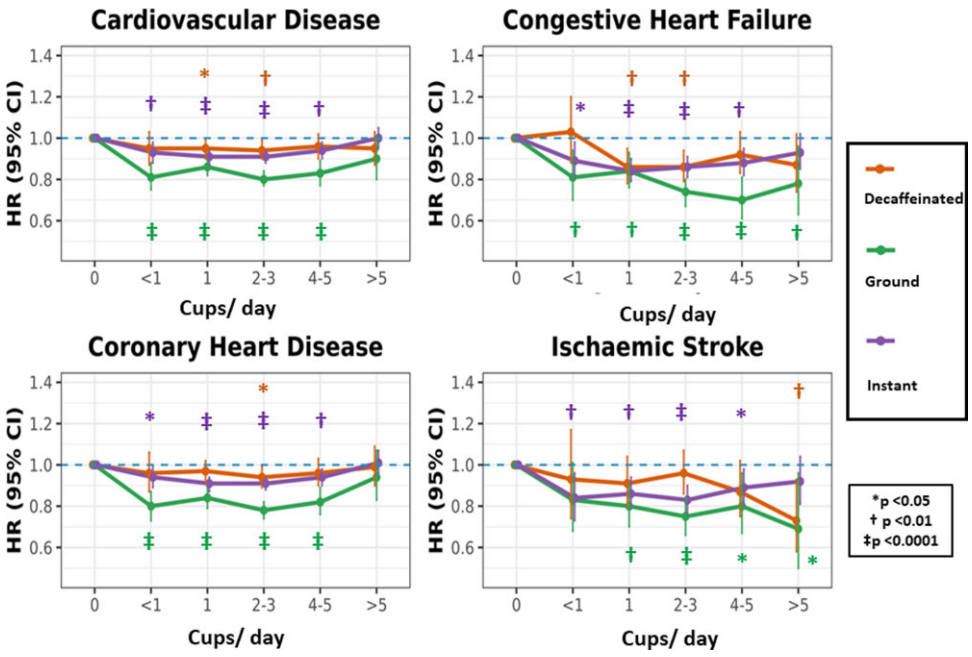


Figure 4 Coffee subtype intake and incident cardiovascular disease. Decaffeinated coffee intake was associated with reduced incidence of cardiovascular disease/congestive cardiac failure at an intake of 1–3 cups/day. Ground and instant coffee intake up to 5 cups/day were consistently associated with reduced risk of cardiovascular disease, coronary heart disease, congestive cardiac failure, and stroke. Model adjusted for covariables age, gender, alcohol intake, tea intake, obesity, diabetes mellitus, hypertension, obstructive sleep apnoea, and smoking status. $^{*}P < 0.05$; $^{\dagger}P < 0.01$; $^{\ddagger}P < 0.0001$.

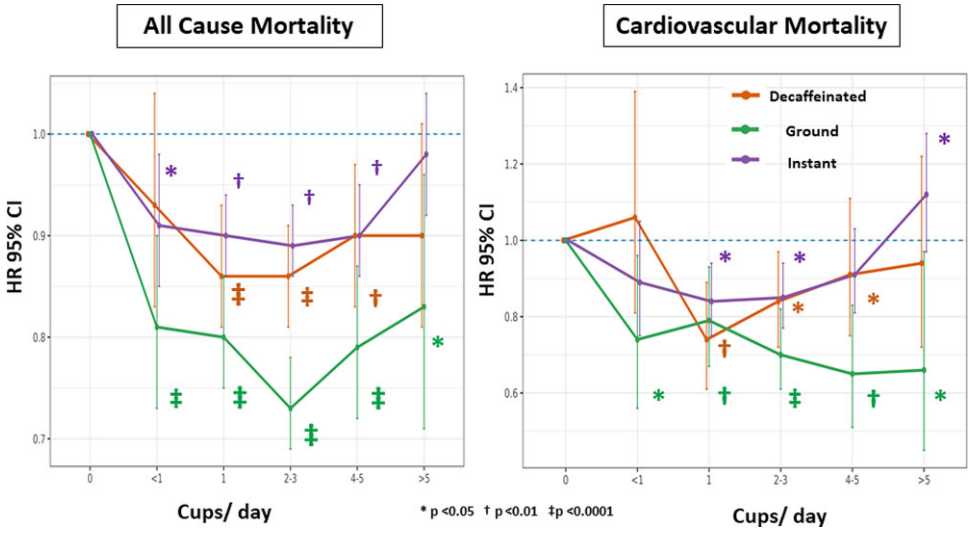


Figure 5 Coffee subtype intake and mortality outcomes. U-shaped relationships were seen between decaffeinated, ground, and instant coffee intake and all-cause mortality, with the lowest risk seen in 2–3 cups/day across all three coffee subtypes. Cardiovascular mortality reduction was seen 1–3 cups/day for decaffeinated coffee, 1–3 cups/day for instant coffee, and all levels of consumption for ground coffee. Model adjusted for covariables age, gender, alcohol intake, tea intake, obesity, diabetes mellitus, hypertension, obstructive sleep apnoea, and smoking status. $^{*}P < 0.05$; $^{\dagger}P < 0.01$; $^{\ddagger}P < 0.0001$.

activity, which vary by as much as 24%. Furthermore, CYP1A2 activity can be affected by medications and dietary factors.[15] This may explain the considerable variation in the effects and tolerability of coffee between individuals. Few studies have explored the relationship between the habitual intake of different coffee subtypes, and more specifically the impact of caffeinated vs. decaffeinated coffee, on CV

endpoints and mortality. In the present study, ground and instant but not decaffeinated coffee consumption were associated with a significantly lower risk of incident arrhythmias. Habitual coffee consumption has not been shown to result in changes in heart rate, electrocardiogram parameters, or heart rate variability.[1] Caffeine also has antiarrhythmic properties particularly through the inhibition of adenosine A1 and A2A receptors. Endogenous adenosine shortens refractory periods in both the atrium and ventricle and consequently increases the risk of arrhythmias.[16,17] By blocking adenosine receptors, caffeinated coffee may mitigate the effects of endogenous adenosine and protect against arrhythmias. This may explain the differing effects of caffeinated vs. decaffeinated coffee on the incidence of arrhythmias reported in the present study.

In the UK Biobank cohort, all three coffee subtypes were associated with a significant reduction in CVD, CCF, CHD, stroke, and CV/all-cause mortality. Caffeine increases endothelial nitric oxide release, down-regulates lipogenesis, reduces insulin sensitivity, and has antioxidant properties which may all in part reduce CVD.[4,18,19] However, coffee also contains polyphenols such as chlorogenic acid, antioxidant ferulic acid, and microelements such as magnesium. These constituents have been shown to reduce oxidative stress, modulate metabolism through stimulation of insulin-mediated cellular glucose uptake through GLUT4 and insulin receptor activation, reduce leptin production, and improve the gut microbiome.[11,18,20,21] A meta-analysis of 28 prospective studies also demonstrated that increasing coffee intake was associated with a progressive reduction in T2DM risk compared with non-drinkers, regardless of whether caffeinated or decaffeinated coffee was consumed.[22] Caffeinated and decaffeinated coffee have a neutral effect on the incidence of hypertension.[17,23]

In the NIH–AARP Diet and Health Study, 229 119 men and 173 141 women were followed from 1995 to 2008.[24] The study reported a significant reduction in total and cause specific mortality in coffee drinkers, with the greatest benefit at 4–5 cups/day among both men (HR 0.88, 95% CI 0.84–0.93) and women (HR 0.84, 95% CI 0.79–0.90). Importantly, the beneficial effects on mortality reduction was observed in both caffeinated and decaffeinated coffee drinkers.[24] Lopez-Garcia *et al.*[25] reported an inverse relationship between consumption of both caffeinated and decaffeinated coffee and all-cause and CV mortality. The relative importance of the non-caffeinated constituents of coffee in reducing mortality is supported by genomics. Genetic variants which determine the rate of caffeine metabolism did not affect the relationship between coffee consumption and all-cause mortality.[9,24] In concert with the findings from the present study, non-caffeinated compounds are likely responsible for the beneficial effects of coffee consumption on CVD and survival.

Overall coffee intake and incident arrhythmia and cardiovascular disease outcomes

Our findings from the UK Biobank further corroborate the beneficial associations of habitual coffee intake as reported in recent population studies.[22,26–32] Coffee intake at mild–moderate levels (1–7 cups/week) was shown to significantly reduce the incidence of AF.[28] Kim *et al.*[7] reported an incremental 3% risk reduction in incident arrhythmia with each additional cup of coffee/day in the UK Biobank cohort but did not report on coffee subtypes. In keeping with the findings of the present study, a meta-analysis showed an inverse association between coffee intake and CVD/CHD risk, with the lowest risk seen at 3–5 cups/day.[26] Another meta-analysis reported a U-shaped dose–response relationship between coffee and CCF, with the strongest risk reduction seen in those who consumed 4 cups/day of coffee.[29] Coffee consumption between 3 and 6 cups/day was also shown to reduce stroke risk.[33] In addition, several smaller studies reported reductions in all-cause and CV mortality in habitual coffee drinkers,[9,24,34,35] with the greatest benefit seen at between 3 and 5 cups/day.[30,36]

Strengths and limitations

The study provides insights into the associations between coffee and coffee subtypes and important CV outcomes in a very large prospective cohort followed for more than 10 years. This may provide some mechanistic insights particularly into the putative role of caffeine as the predominant component of coffee. Sensitivity analyses were performed to adjust for potential confounders on the associations between coffee and outcomes, including demographic, risk factors, and comorbid conditions.

There are several limitations to consider when interpreting the study findings. A number of participants were excluded for missing data. Coffee intake was based on participant self-reporting, with the attendant risk of reporting bias. However, as the data were collected before incident conditions had developed, the occurrence of recall bias was extremely unlikely. Coffee consumption at baseline was assumed to remain unchanged throughout the participants' follow-up. This is supported by previous studies, which have shown that the assessment of nutrient intake has a high degree of reproducibility over time.[37] It is possible that some participants consumed more than one subtype of coffee over time. Outcome assessment relied on ICD-10 codes, which may be subject to measurement/reporting errors. The detection of certain arrhythmias may be missed, in particular atrial/ventricular ectopy, in the absence of routine monitoring. However, false negatives would be expected to reduce the power to detect an association. The UK Biobank is a predominantly Caucasian population and the findings may not be entirely applicable to the populations of other ethnicities. Lastly, residual/unaccounted confounding including dietary factors may have occurred despite the multivariate adjustment.

Conclusions

In this large prospective cohort study, consumption of instant, ground, and decaffeinated coffee subtypes, particularly at 2–3 cups/day, was associated with significant reductions in incident CVD and mortality. Arrhythmia reduction was seen with caffeinated but not decaffeinated coffee. Mild–moderate coffee intake of all types should not be discouraged but rather considered part of a healthy lifestyle.

Author contributions

D.C. wrote the first draft with inputs from P.M.K. and R.C. R.C. conducted all statistical analyses. D.C., P.M.K., and R.C. had full access to

the data. All authors commented on multiple drafts and supported the decision of D.C. and P.M.K to submit the final draft.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

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