Title

Light to moderate coffee consumption is associated with lower risk of death: a UK Biobank study

Brief title

Regular coffee consumption reduces risk of death

Authors

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Abstract

Aims

To study the association of daily coffee consumption with all-cause and cardiovascular (CV) mortality and major CV outcomes. In a subgroup of participants who underwent cardiovascular magnetic resonance (CMR) imaging, we evaluated the association between regular coffee intake and cardiac structure and function.

Methods

UK Biobank participants without clinically manifested heart disease at the time of recruitment were included. Regular coffee intake was categorized into 3 groups: zero, light-to-moderate (0.5-3 cups/day) and high (>3 cups/day). In the multivariate analysis, we adjusted for the main CV risk factors.

Results

We included 468,629 individuals (56.2±8.1 years, 44.2% male), 22.1% did not consume coffee on a regular basis, 58.4% had 0.5-3 cups per day and 19.5% had >3 cups per day. Compared to non-coffee drinkers, light-to-moderate (0.5-3 cups per day) coffee drinking was associated with lower risk of all-cause mortality (multivariate HR=0.88, 95%CI:0.83-0.92; p<0.001) and CV mortality (multivariate HR=0.83, 95%CI:0.74-0.94; p=0.006), and incident stroke (multivariate HR=0.79, 95%CI:0.63-0.99 p=0.037) after a median follow-up of 11 years. CMR data were available in 30,650 participants. Both light-to-moderate and high coffee consuming categories were associated with dose-dependent increased left and right ventricular end-diastolic, end-systolic and stroke volumes, as well as greater left ventricular mass.

Conclusion

Coffee consumption of up to 3 cups per day was associated with favorable CV outcomes. Regular coffee consumption was also associated with a likely healthy pattern of CMR metrics in keeping with the reverse of age-related cardiac alterations.

Keywords

Cardiac magnetic resonance; Cardiovascular health; Coffee consumption

Introduction

Even though coffee is among the most consumed beverages in the world, little is known about the long-term impact of its regular consumption on cardiovascular (CV) health. Besides caffeine, it contains many bioactive components such as minerals and antioxidants (1, 2). Recent studies have shown that coffee plays a preventive role against cancer, obesity, type 2 diabetes mellitus, Parkinson's disease and dementia (3-7). However, there are inconsistent results regarding its CV effects. Although most studies have found no relationship between regular coffee intake and CV disease mortality, some have reported a moderate inverse association while others have found an increased risk (8-12).

Coffee is mainly consumed as ground or instant form, containing different chemical compounds. Instant coffee is reported to contain not only more caffeine and antioxidants as ground type coffee, but it also has twice as much acrylamide, which was shown to be neurotoxic and carcinogenic (13, 14). While several studies have investigated the relationship between coffee type and cancer, the association between coffee type and subclinical cardiac alterations are unclear (15-17).

We studied, in the UK Biobank, the association of regular coffee consumption with all-cause mortality, CV mortality, and cardiovascular magnetic resonance (CMR) phenotypes. We limited to participants without clinically manifested heart disease at the time of recruitment. In secondary analyses, we investigated the relationship between consumed coffee type and cardiac structural and functional alterations.

Methods

Study sample and outcomes

The UK Biobank is a prospective cohort study which collected questionnaire data, physical measurements and biological samples from over half a million 40-69 year-old individuals in the United Kingdom recruited between 2006 and 2010 (18). Baseline assessment of the participants included detailed assessment of medical history, lifestyle and nutritional habits, physical examination and blood sampling. Exclusion criteria of the current study were refusal to report coffee drinking habits, those who drink >25 cups of coffee per day, presence of heart failure, angina, prior myocardial infarction and stroke at the time of recruitment and refusal to consent. The endpoints of death, stroke and myocardial infarction were derived from Hospital Episode Statistics and death register data. CV mortality was defined as deaths where underlying (primary) causes were related to the circulatory system. Detailed list of causes with number of cases is reported in *Supplementary table 1*. This study was covered by the ethical approval for UK Biobank studies from the National Health Service (NHS) National Research Ethics Service on 17th June 2011 (Ref 11/NW/0382) and extended on 10th May 2016 (Ref 16/NW/0274).

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Cardiovascular measurements

Arterial stiffness index (ASI) was measured at the baseline visit with finger photoplethysmography with the PulseTrace PCA2 device (CareFusion, San Diego, CA, USA) while participants were seated. Readings were taken over 10-15 seconds. A detailed protocol has been described (https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/Pulsewave.pdf). ASI provides a measure of large artery stiffness, an indicator of arterial health and ischemic risk (19).

In total, 100,000 participants were recalled to undergo comprehensive imaging of the brain, heart, whole body, carotid artery, bone and joints. Imaging of the heart was performed by CMR (20). The UK Biobank CMR protocol has been described in detail previously (21, 22). Briefly, all examinations were performed on a 1.5 Tesla scanner (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany). For cardiac function, long-axis cines and a complete short-axis stack of balanced steady-state free precession (bSSFP) cines were acquired covering the left and right ventricle. The manual analysis dataset of 5,065 participants was used to develop an automated image analysis pipeline, which has been propagated to the first 32,000 CMR studies (23). Those with heart failure, prior myocardial infarction, stroke and angina at imaging visit were excluded from the CMR subanalysis. We examined left and right ventricular end-diastolic (LVEDV; RVEDV), end-systolic (LVESV; RVESV), and stroke volumes (LVSV; RVSV), left ventricular mass (LVM) and left and right ventricular ejection fractions (LVEF; RVEF).

Measurement of baseline covariates, potential confounders and coffee consumption

Data regarding coffee consumption were obtained from standardized and validated questionnaires filled in by the study participants at baseline visit. Participants were asked their average coffee intake in the last year: “how many cups of coffee do you drink each day”, as well as the most common type of consumed coffee (decaffeinated, ground, instant or other

type). We selected confounders and possible mediators of the relationship between coffee consumption with CV health. These covariates were determined from participant interview or touchscreen questionnaires. The following variables were recorded: age, sex, non-European ethnicities, Townsend deprivation index (a socio-economic measure based on area of residence), weight and height, cardiometabolic comorbidities such as hypertension or diabetes. Moreover, lifestyle factors such as physical activity (expressed as metabolic equivalent (MET) minutes/week), fresh and dried fruit, raw or cooked vegetable intake (portions per day), tea intake (cups per day), alcohol intake frequency (never, special occasions only, 1-3 times per month, 1-2 times per week, 3-4 times per week, and daily or almost daily), meat intake frequency (never, less than once per week, once per week, 2-4 times per week, 5-6 times per week, once or more daily) and smoking status (never smoker and previous or current smoker) were also ascertained. Detailed questions of the UK Biobank questionnaires can be found in UK Biobank Data Showcase (https://www.ukbiobank.ac.uk/data-showcase/). Total cholesterol levels were determined with blood biochemistry.

Data analysis and statistics

Summary statistics for independent variables were calculated as means and standard deviation (SD) for continuous variables. Categorical variables were expressed as frequencies and percentages. Consistent with previous studies, regular coffee consumption was categorized into 3 groups: zero, light-to-moderate (0.5–3 cups/day), and high (>3 cups per day) with the lowest group (zero coffee consumption) used as the reference in the analyses (24). The event-free survival rate was estimated using Kaplan-Meier method and log-rank test was applied for the comparisons between the various coffee intake groups. Cumulative event rates were calculated with event or censoring times measured from the date of baseline visit. For

participants without outcome, time-to-event measures were censored at the latest UK Biobank censor dates giving a follow-up duration of 10 to 15 years. To assess the relationship between the amount of coffee intake and CV morbidity and mortality, uni- and multivariable Cox proportional hazard regression models were executed.

We considered two approaches to covariate adjustment. Model 1 was created as a "true confounder model". In this model, we adjusted for covariates that were considered confounders of the associations of interest, selected based on biological plausibility and existing evidence. The purpose of Model 1 was to quantify the magnitude of the exposure-outcomes associations. Model 2 included adjustment of both true confounders (all covariates in Model 1) and potential mediators. Mediators were considered covariates that may lie on the causal pathway for the association between coffee and CV health. The expectation is that in the presence of significant mediating effect from these covariates, their addition to the model (as in Model 2) would attenuate the magnitude of exposure-outcome associations observed in the true confounder model. The purpose of Model 2 was to explore potential mediating effect from selected cardiometabolic morbidities. Model 1 included coffee consumption categories and the following potential confounders: age, sex, non-European ethnicity, weight and height, smoking status, physical activity, Townsend deprivation index, regular alcohol and meat consumption, tea, cooked and raw fruit and vegetable intake. Model 2 included parameters of Model 1 and the following potential mediators: hypertension, diabetes and cholesterol level.

Associations between regular coffee intake and structural and functional CMR parameters were analyzed using unadjusted and multivariable linear regression analyses using the same models. Definitions for these covariates were previously described (25, 26). In order to assess the association between most common type of consumed coffee and CMR parameters, we ran a subanalysis of decaffeinated, ground, instant or other coffee type. A p-value below 0.05 was

considered statistically significant. Statistical analysis was performed using R (version 4.0.2) Statistical Software (27).

Results

After exclusion, 468,629 individuals were included in this study. At the time of recruitment their mean age was 56.2±8.1 years and 44.2% of the participants were male. *Table 1* illustrates the characteristics of the study population. Among the 468,629 studied participants, 103,384 (22.1%) did not consume coffee on a regular basis, 274,088 (58.5%) consumed 0.5-3 cups per day and 91,157 (19.5%) >3 cups per day.

The association of regular coffee intake with cardiovascular outcomes and all-cause mortality

Median follow-up time was 11 (10-12) years. All-cause and CV mortality rates significantly differed among the various coffee consumption groups (all-cause mortality rate was 3.72%, 3.40% and 4.03% and CV mortality rate was 0.65%, 0.58% and 0.74% in zero, light-to-moderate and high coffee drinkers, respectively; both $p<0.001$). The univariate analysis showed that light-to-moderate coffee drinking was associated with decreased, while high coffee intake was linked with increased all-cause and CV mortality, as compared to zero coffee drinkers [HR of all-cause mortality 0.91 (95%CI=0.88-0.95) for light-to-moderate and 1.08 (95%CI=1.04-1.13) for high coffee drinkers and HR for CV mortality 0.89 (95%CI=0.82-0.98) for light-to-moderate and 1.14 (95%CI=1.03-1.27) for high coffee consumers, respectively; all $p<0.001$]. After adjustment for the potential confounders and mediators, 0.5-3 cups/day proved to be associated with decreased all-cause [HR=0.88 (95%CI=0.83-0.92), $p<0.001$] and CV mortality [HR=0.83 (95%CI=0.74-0.94) $p=0.006$] and lower stroke incidence [HR=0.79 (95%CI=0.63-0.99), $p=0.037$]. Moreover, drinking >3 cups per day was associated with increased risk of incident myocardial infarction [incidence of

myocardial infarction was 0.16% in zero and 0.22% in high coffee drinkers; univariable HR=1.31 (95%CI=1.07-1.61), p=0.009]. However, this association was not significant after adjustment for potential confounders. Detailed results of the uni- and multivariable Cox proportional hazard regression analyses are reported in *Table 2*. Kaplan-Meier curves of all-cause mortality by coffee consumption categories are shown in *Figure 1*.

The association between daily coffee intake and measures of arterial stiffness

ASI was measured in 139,727 participants at baseline visit. In the univariate analysis both light-to-moderate and high coffee consuming categories were associated with increased ASI [ß=0.06 (95%CI=0.01-0.11), p=0.017 in light-to-moderate and ß=0.26 (95%CI=0.20-0.33), p<0.001 in high coffee drinkers]. After adjustment for all potential confounders and mediators drinking 0.5-3 cups of coffee per day was linked with significantly decreased ASI [ß=-0.12 (95%CI=-0.18 to -0.06), p<0.001]. Data of the association between regular coffee intake and measured arterial stiffness can be seen in *Table 3.*

The association of regular coffee consumption with cardiac structure and function

In order to evaluate the possible underlying mechanisms of the observed association between regular coffee consumption and health outcomes, CMR data of 30,650 participants were analyzed after exclusion. Baseline characteristics of those with and without CMR examination can be seen in *Supplementary table 2*. In the univariable analysis significantly increased LVEDV, LVESV, LVSV, LVM, RVEDV, RVESV and RVSV were found both in light-to-moderate and high coffee intake categories as compared to zero coffee intake, while both LV and RV ejection fractions were reduced in high coffee consuming participants. After adjusting for potential confounders compared to non-coffee drinkers, both the light-to-moderate and high coffee consuming categories, were associated with dose-dependent increased LV and RV ventricular end-diastolic [β=2.21 (95%CI=1.35-3.08) and ß=3.28 (95%CI=2.18-4.37) for LV and ß=2.24 (95%CI=1.33-3.16) and ß=3.35 (95%CI=2.20-4.50) for RV in light-to-moderate

and high coffee drinkers, respectively; all p<0.001], end-systolic [β=0.91 (95%CI=0.39-1.42) and ß=1.64 (95%CI=0.99-2.30) for LV and ß=1.10 (95%CI=0.56-1.64) and ß=1.72 (95%CI=1.04-2.41) for RV; all p<0.001], and stroke volumes [β=1.31 (95%CI=0.77-1.85) and ß=1.64 (95%CI=0.95-2.32) for LV and ß=1.15 (95%CI=0.59-1.71) and ß=1.63 (95%CI=0.92-2.33) for RV; all p<0.001], as well as greater LV mass [β=0.78 (95%CI=0.30-1.26) and ß=1.64 (95%CI=1.03-2.25); both p<0.001]. Detailed data can be seen in *Table 4* and *Figure 2*.

The impact of coffee type on cardiovascular system

We additionally explored potential differential impact from different coffee type consumed. We compared the differences between the various coffee types, as compared to zero coffee consumption category. Among those who drank coffee regularly, 71,404 (19.5%) participants preferred decaffeinated coffee, 85,120 (23.3%) ground, 201,232 (55.1%) instant and 7,489 (2.1%) indicated other coffee type. After adjustment for all potential confounders and mediators, decaffeinated coffee was associated with decreased all-cause mortality [HR=0.84 (95%CI=0.75-0.94), p=0.001 for light-to-moderate and HR=0.83 (95%CI=0.70-0.97), p=0.022 for high decaffeinated coffee consumers], 0.5-3 cups of ground coffee per day was linked with decreased all-cause [HR=0.75 (95%CI=0.68-0.83), p<0.001] and CV mortality [HR=0.75 (95%CI=0.59-0.96), p=0.025], and high daily ground coffee intake was associated with lower CV mortality [HR=0.51 (95%CI=0.30-0.81), p=0.008]. When analyzing the underlying mechanisms in the CMR population, light-to-moderate decaffeinated coffee intake was linked with significantly higher LVEDV [ß=2.00 (95%CI=0.26-3.73), p=0.024], LVSV [ß=1.31 (95%CI=0.22-2.39), p=0.018], while high amount of daily decaffeinated coffee consumption was associated with significantly greater LVM [ß=1.49 (95%CI=0.09-2.89), p=0.037]. Ground coffee was associated with increased LVEDV [ß=3.99 (95%CI=2.36-5.62)

for light-to-moderate and ß=6.44 (95%CI=3.60-9.27) for high intake, both p<0.001], LVESV [ß=1.24 (95%CI=0.25-2.24), p=0.015 for light-to-moderate and ß=2.29 (95%CI=0.56-4.03), p=0.010 for high intake], LVSV [ß=2.75 (95%CI=1.76-3.74) for light-to-moderate and ß=4.14 (95%CI=2.41-5.87) for high intake, both p<0.001], RVEDV [ß=4.48 (95%CI=2.78-6.18) for light-to-moderate and ß=7.43 (95%CI=4.47-10.40) for high intake, both p<0.001], RVEDV [ß=1.88 (95%CI=0.86-2.91) for light-to-moderate and ß=3.80 (95%CI=2.01-5.59) for high intake, both p<0.001] and RVSV [ß=2.60 (95%CI=1.58-3.61) for light-to-moderate and ß=3.63 (95%CI=1.86-5.41) for high intake, both p<0.001] as well as with greater LVM [ß=1.74 (95%CI=0.86-2.63) for light-to-moderate and ß=3.33 (95%CI=1.79-4.88) for high intake, both p<0.001] as compared to zero coffee consumption in the fully adjusted model. Detailed data on the outcome and CMR parameters are reported in *Supplementary tables 3 and 4*.

Discussion

In this large cross-sectional population study of 468,629 individuals free from clinical cardiovascular disease, light-to-moderate coffee consumption was associated with decreased all-cause and CV mortality, and incident stroke. In comparison to zero coffee intake, light-moderate and high coffee consumption was also associated with favorable cardiovascular phenotypes, both in terms of cardiac and arterial health. Importantly, these associations remained robust to adjustment for cardiometabolic morbidities (hypertension, high cholesterol, diabetes).

Comparison with other studies

Coffee is among the most widely consumed pharmacologically active beverages in the world. In our study population, 77.9% consumed coffee daily. The CV effects of coffee consumption are a combination of favorable and unfavorable effects of caffeine and other drink components. Caffeine is by far the most studied compound of coffee. While caffeine has inotropic effect on the heart, induces high blood pressure, increases cholesterol level in Nordic countries but not in other populations, regular coffee intake was also associated with lower risk of type 2 diabetes mellitus, lower body weight and decreased platelet aggregation, inhibition of inflammation (28-33). While coffee consumption has been associated with an acute increase in blood pressure in caffeine-naive individuals, this effect is negligible in habitual coffee drinkers, and many further studies came to the conclusion that long-term coffee consumption has no clinical importance on the risk of hypertension (34-36). In line with these findings, the prevalence of hypertension was not higher in those drinking >3 cups of coffee per day as compared to zero coffee drinkers in the present study. Moreover, in a subpopulation of 139,727 participants who underwent arterial stiffness measurement at baseline visit, light-to-moderate coffee consumption was associated with lower ASI, an

indicator of arterial health and strong correlate of hypertension and ischemic cardiovascular risk.

Antioxidants in coffee have been reported to improve glucose metabolism and insulin sensitivity (37). Another study concluded that consumption of more than 5 cups of coffee per day increases adiponectin levels, and decrease insulin resistance (38). In our study population prevalence of diabetes mellitus was significantly lower in light-to-moderate coffee drinkers as compared to zero coffee intake, and similar in high and zero coffee consuming categories. Interestingly, we did not observe a significant attenuation of associations with additional adjustment for diabetes, suggesting that associations reported in the present studies are mediated by alternative processes.

Several previous studies aimed to investigate the effect of regular coffee consumption on CV health. In a prospective study of two Spanish cohorts, 1-7 cups of caffeinated coffee per week was associated with lower risk of atrial fibrillation (39). Moreover, in an umbrella review of 201 meta-analyses, coffee consumption was more often linked with beneficial than harmful health outcomes including lower all-cause and CV mortality with the largest relative risk reduction for those consuming 3 to 4 cups/day versus zero (40). Consistent with these findings, in our study light-to-moderate coffee consumption defined as 0.5-3 cups per day was associated with lower risk of all-cause and CV mortality, as compared to zero coffee drinkers. This favorable effect might be partly explained by lower arterial stiffness measures as well as by significantly increased stroke volume in both cardiac ventricles.

Clinical competencies and translational outlook

The UK Biobank offers a unique opportunity for the assessment of the potential differences between consumed coffee types. In our study population, ground and instant coffee were the two most commonly taken types. While ground coffee was associated with decreased all-cause and CV mortality, we did not find statistically significant association between regular

instant coffee consumption and health outcomes.. The difference among the various coffee types may be explained by the differences in their production process, as they contain different chemicals. In a recent study of 508,747 participants in the Norwegian cardiovascular surveys, unfiltered brew was linked with higher mortality than filtered brew. Filtered brew was associated with lower mortality than no coffee consumption (41). Interestingly, in our study population regularly consuming decaffeinated coffee was significantly linked with lower all-cause mortality as compared to zero coffee drinkers, suggesting that the observed associations can be explained only partly by caffeine itself. However, further studies with more detailed information on consumed coffee type and preparation are needed to explain the underlying mechanisms.

Strengths and limitations of this study

The main strengths of our study are firstly, the large cohort of asymptomatic population with no prevalent CV disease where prospectively collected data, physical measurements and biological samples are available. Secondly, we used CMR which provides the most accurate and reproducible imaging modality in the assessment of cardiac structure and function. Our study's limitations are important to be acknowledged. First, data regarding coffee consumption was assessed by questionnaires, therefore recall bias may lead to inaccuracy. Furthermore, the single snapshot of coffee consumption habits registered by UK Biobank might not accurately reflect the total lifetime coffee consumption, especially in older people. The observed dose-response relationship between the amount of regular coffee consumption and cardiac changes indicates favorable effects on an epidemiological level despite the observed small effect sizes. Moreover, data regarding strength or size of the consumed coffee were not obtained from the participants, as questionnaire contained only data on cups of daily coffee intake and type of usually consumed coffee. Therefore, we could not calculate the caffeine content. In our study population, there were significant differences between the

coffee consuming categories in many dietary, sociological and lifestyle aspects, therefore the possibility that coffee consumption may be acting as a surrogate marker of some other CV risk factor cannot be fully excluded.

Conclusions

To our knowledge, this is the biggest study to systematically assess the CV effects of regular coffee consumption in a large asymptomatic population. Our results suggest that regular coffee consumption is safe, as even high daily coffee intake was not associated with adverse cardiovascular outcomes and all-cause mortality after a follow-up duration of 10 to 15 years. Moreover, 0.5-3 cups of coffee per day was independently associated with lower risk of all-cause and CV mortality, and incident stroke. This favorable impact might be partly explained by lower ASI and subclinical beneficial alterations in cardiac structure and function.

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Authors' contribution

JS, KF, ZRE, NA, SEP and PMH contributed to the conception or design of the work. JS contributed to the acquisition, analysis, or interpretation of data for the work. JS drafted the manuscript. KF, ZRE, NA, SEP and PMH critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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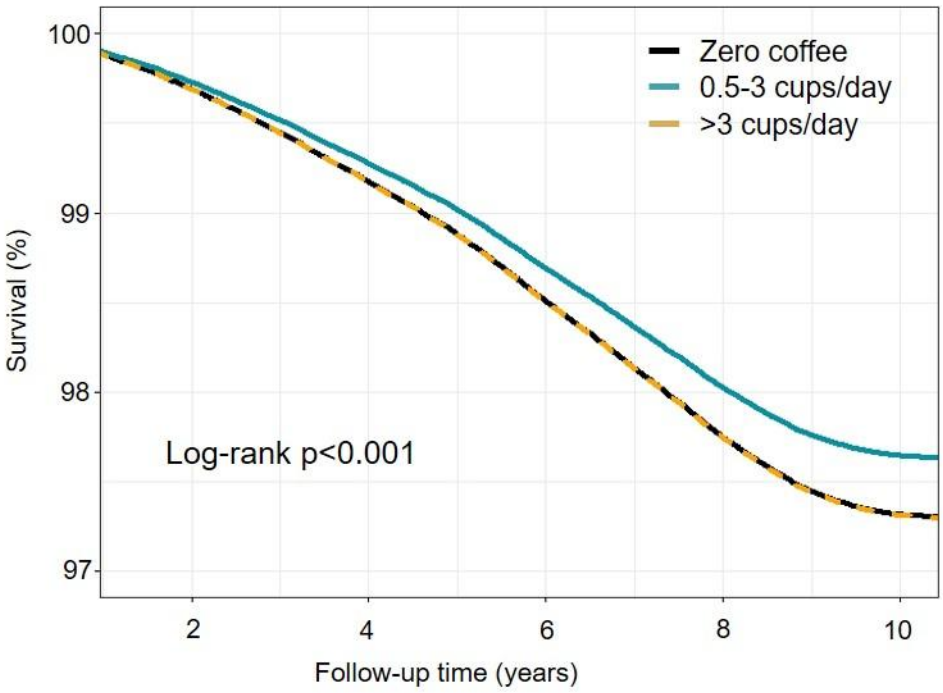
Figure legends

Central illustration



	2	4	6	8	10	All events
zero coffee (n=103,384)	464	1,249	2,151	3,203	3,814	3,844
0.5-3 cups (n=274,088)	1,092	2,921	5,173	7,782	9,250	9,333
>3 cups (n=91,157)	417	1,089	1,988	3,024	3,634	3,671

Figure 1. Kaplan-Meier curve of all-cause mortality as stratified by coffee consumption categories

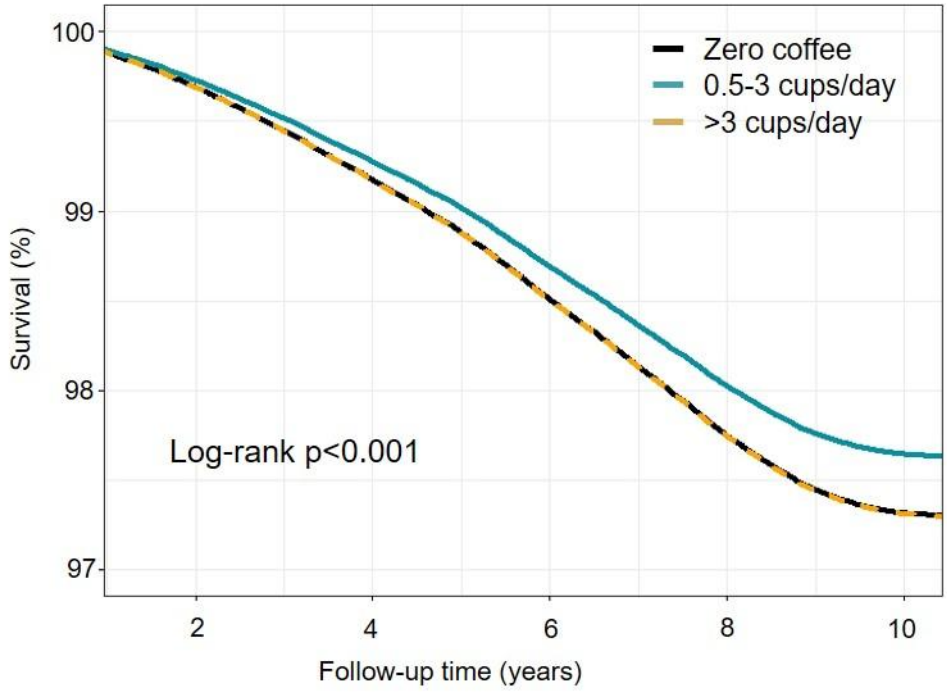


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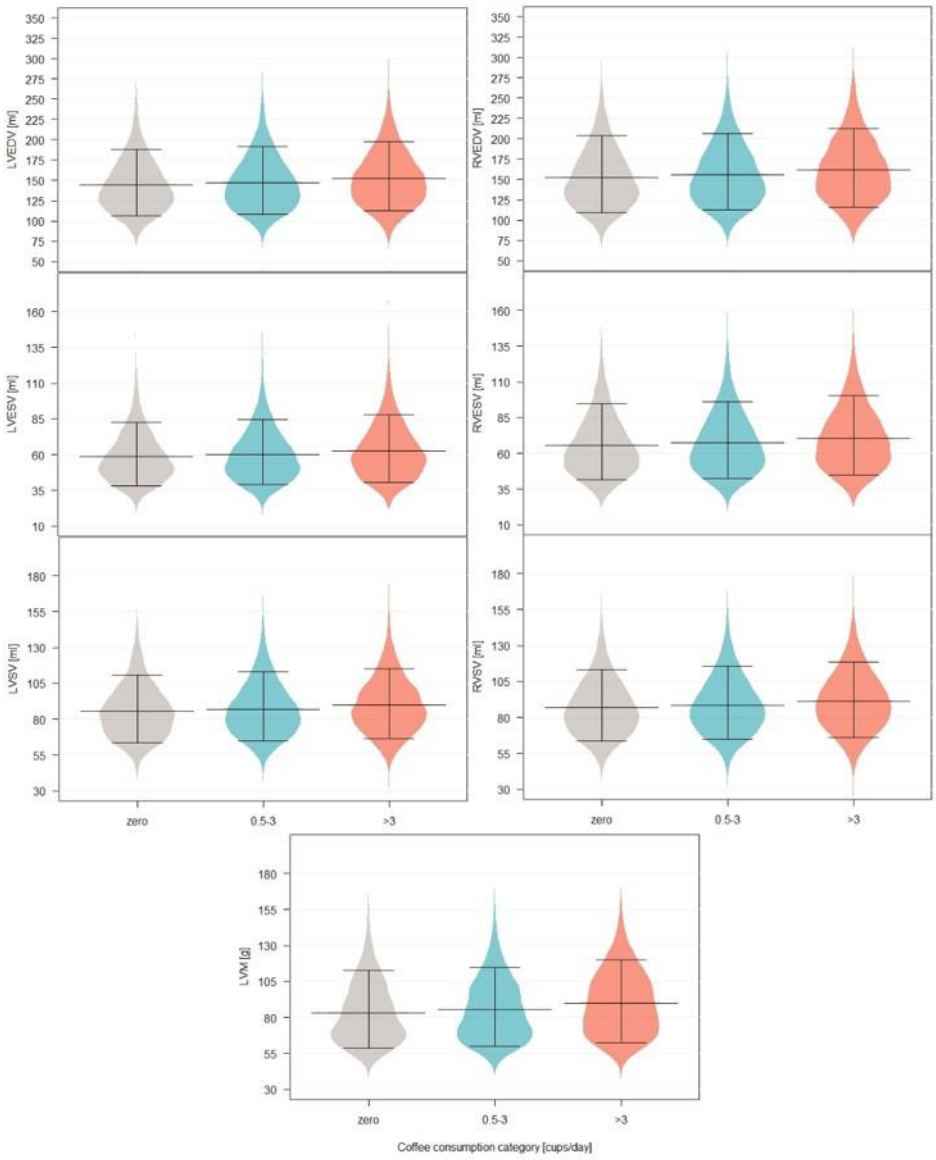
Figure 2. Distribution of left and right ventricular structural and functional parameters with light-to-moderate (turquoise) and high (orange) daily coffee consumption as compared to no coffee consumption (gray).



Abbreviations: LVEDV=Left ventricular end-diastolic volume; LVESV= Left ventricular end-systolic volume; LVM=Left ventricular mass; LVSV=Left ventricular stroke volume; RVEDV=Right ventricular end-diastolic volume; RVESV=Right ventricular end-systolic volume; RVSV=Right ventricular stroke volume.

Table 1. Participant characteristics

	All participants (n=468,629)	Zero cup of coffee/day (n=103,384)	0.5-3 cups of coffee/day (n=274,088)	>3 cups of coffee/day (n=91,157)	p
Age (years)	**56.2±8.1**	**55.1±8.2**	**56.8±8.0**	**55.9±8.0**	**<0.001**
Male, n (%)	**207,137 (44.2)**	**41,504 (40.1)**	**119,767 (43.7)**	**45,866 (50.3)**	**<0.001**
Non-European ethnicities, n (%)	**24,923 (5.3)**	**10,156 (9.9)**	**12,901 (4.7)**	**1866 (2.1)**	**<0.001**
Townsend deprivation index	**-1.24±3.06**	**-0.92±3.24**	**-1.50±2.98**	**-1.39±3.03**	**<0.001**
BMI (kg/m^2)	**27.3±4.8**	**27.4±5.0**	**27.1±4.6**	**27.9±4.8**	**<0.001**
Hypertension, n (%)	**119,129 (25.4)**	**27,083 (26.2)**	**69,776 (25.5)**	**22,270 (24.4)**	**<0.001**
Diabetes mellitus, n (%)	**21,084 (4.5)**	**5,077 (4.9)**	**11,640 (4.3)**	**4,367 (4.8)**	**<0.001**
Total cholesterol level (mmol/L)	**5.8±1.1**	**5.7±1.1**	**5.8±1.1**	**5.7±1.1**	**<0.001**
IPAQ (METs/week)	**1,382 (655-2,586)**	**1,386 (622-2,755)**	**1,384 (685-2,550)**	**1,351 (610-2,622)**	**<0.001**
Regular fruit intake (portions/day)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	0.856
Regular raw vegetable intake (portions/day)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	0.763
Regular cooked vegetable intake (portions/day)	3 (2-3)	2 (2-3)	3 (2-3)	3 (2-3)	0.468
Regular tea intake (cups/day)	**3 (1-5)**	**4 (2-6)**	**3 (2-5)**	**1 (0-3)**	**<0.001**
Eating meat at least once a week, n (%)	**280,023 (59.8)**	**58,979 (57.2)**	**163,028 (59.6)**	**58,016 (63.8)**	**<0.001**
Drinking alcohol at least once a month, n (%)	378,593 (80.8)	72,282 (70.0)	230,828 (84.3)	75,483 (82.9)	
Previous or	**206,535**	**41,192**	**117,099**	**48,244**	**<0.001**

current smoker, n (%)	**(44.1)**	**(40.0)**	**(42.9)**	**(43.1)**	
Types of most commonly consumed coffee					**<0.001**
Decaffeinated, n (%)	**71,404 (19.5)**	**-**	**53,173 (19.4)**	**18,231 (20.0)**	
Ground, n (%)	**85,120 (23.3)**	**-**	**71,811 (26.2)**	**13,309 (14.6)**	
Instant, n (%)	**201,232 (55.1)**	**-**	**143,074 (52.2)**	**58,158 (63.8)**	
Other, n (%)	**7,489 (2.1)**	**-**	**6,030 (2.2)**	**1,459 (1.6)**	

Summary statistics for independent variables were calculated as means and standard deviation (SD) or median and interquartile range (IQR) for continuous variables or case numbers and percentages for categorical variables

Abbreviations: BMI=body mass index; IPAQ=international physical activity questionnaire; METs=metabolic equivalents

Table 2. Association of regular coffee consumption with all-cause and CV mortality, and CV disease incidence as compared with non-coffee drinkers

	Univariable		Confounders (Model 1)		Confounders + mediators (Model 2)	
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
All-cause mortality						
0.5-3 cups	**0.91 (0.88-0.95)**	**<0.001**	**0.87 (0.83-0.91)**	**<0.001**	**0.88 (0.83-0.92)**	**<0.001**
>3 cups	**1.08 (1.04-1.13)**	**<0.001**	0.99 (0.93-1.05)	0.641	1.00 (0.94-1.07)	0.955
CV mortality						
0.5-3 cups	**0.89 (0.82-0.98)**	**0.014**	**0.85 (0.76-0.95)**	**0.005**	**0.83 (0.74-0.94)**	**0.006**
>3 cups	**1.14 (1.03-1.27)**	**0.015**	0.98 (0.85-1.13)	0.768	0.98 (0.85-1.13)	0.786
Incidental stroke						
0.5-3 cups	0.91 (0.76-1.08)	0.277	0.82 (0.66-1.02)	0.071	**0.79 (0.63-0.99)**	**0.037**
>3 cups	1.03 (0.84-1.28)	0.763	0.97 (0.74-1.27)	0.797	0.98 (0.74-1.29)	0.873
Incidental heart attack						
0.5-3 cups	1.01 (0.85-1.20)	0.938	0.99 (0.79-1.22)	0.897	0.96 (0.77-1.20)	0.733
>3 cups	**1.31 (1.07-1.61)**	**0.009**	1.15 (0.89-1.49)	0.274	1.10 (0.85-1.43)	0.466

Abbreviations: CI=Confidence interval; CV=Cardiovascular; HR=Hazard ratio.

Confounders: (baseline) age, sex, non-European ethnicities, body mass index, smoking, physical activity, Townsend deprivation index, alcohol, meat, tea, fruit and vegetable intake.

Mediators: (baseline) hypertension, diabetes mellitus, cholesterol level.

Table 3. Association between regular coffee consumption and ASI as compared to non-coffee drinkers

	Mean ± SD	**Univariate**		**Confounders**		**Confounders + mediators**	
		ß (95%CI)	**p**	**ß (95%CI)**	**p**	**ß (95%CI)**	**p**
ASI							
0.5-3 cups	9.27± 3.65	**0.06 (0.01-0.11)**	**0.017**	**-0.10 (-0.16-0.00)**	**<0.001**	**-0.12 (-0.18 to -0.06)**	**<0.001**
>3 cups	9.48± 3.50	**0.26 (0.20-0.33)**	**<0.001**	0.01 (-0.07-0.09)	0.775	-0.01 (-0.07-0.09)	0.821

Confounders: (baseline) age, sex, non-European ethnicities, body mass index, smoking, physical activity, Townsend deprivation index, alcohol, meat, tea, fruit and vegetable intake.

Mediators: (baseline) hypertension, diabetes mellitus, cholesterol level.

Abbreviations: ASI=Arterial stiffness index.

Table 4. Association between regular coffee consumption and cardiac structural and functional parameters

	Mean±SD	Univariable		Confounders		Confounders + mediators	
		β (95% CI)	**p**	**β (95% CI)**	**p**	**β (95% CI)**	**p**
LVEDV (ml)							
zero coffee	144.3±33.0	Ref		Ref		Ref	
0.5-3 cups/day	147.3±33.3	**3.01 (2.04-3.97)**	**<0.001**	**2.13 (1.28-2.97)**	**<0.001**	**2.21 (1.35-3.08)**	**<0.001**
>3 cups/day	152.5±34.2	**8.22 (7.04-9.39)**	**<0.001**	**3.08 (2.02-4.15)**	**<0.001**	**3.28 (2.18-4.37)**	**<0.001**
LVESV (ml)							
zero coffee	58.6±18.7	Ref		Ref		Ref	
0.5-3 cups/day	60.0±18.8	**1.44 (0.90-1.98)**	**<0.001**	**0.85 (0.35-1.35)**	**<0.001**	**0.91 (0.39-1.42)**	**<0.001**
>3 cups/day	62.8±19.5	**4.17 (3.51-4.84)**	**<0.001**	**1.56 (0.93-2.20)**	**<0.001**	**1.64 (0.99-2.30)**	**<0.001**
LVSV (ml)							
zero coffee	85.7±18.9	Ref		Ref		Ref	
0.5-3 cups/day	87.2±19.1	**1.57 (1.01-2.12)**	**<0.001**	**1.27 (0.74-1.80)**	**<0.001**	**1.31 (0.77-1.85)**	**<0.001**
>3 cups/day	89.7±19.5	**4.04 (3.37-4.72)**	**<0.001**	**1.52 (8.54-2.19)**	**<0.001**	**1.64 (0.95-2.32)**	**<0.001**
LVEF (%)							
zero coffee	59.8±5.9	Ref		Ref		Ref	
0.5-3 cups/day	59.5±6.0	-0.16 (-0.33-0.01)	0.070	-0.03 (-0.21-0.16)	0.795	-0.03 (-0.23-0.16)	0.705
>3 cups/day	59.2±6.1	**-0.55 (-0.76 to -0.33)**	**<0.001**	-0.20 (-0.43-0.04)	0.108	-0.21 (-0.45-0.04)	0.100
LVM (g)							
zero coffee	83.5±21.9	Ref		Ref		Ref	
0.5-3 cups/day	85.7±22.0	**2.20 (1.56-2.84)**	**<0.001**	**0.77 (0.30-1.24)**	**0.001**	**0.78 (0.30-1.26)**	**0.001**
>3	90.3±23.3	**6.84 (6.06-**	**<0.001**	**1.57 (0.98-2.16)**	**<0.001**	**1.64 (1.03-**	**<0.001**

cups/day		**7.62)**				**2.25)**	
RVEDV (ml)							
zero coffee	152.4±36.8	Ref		Ref		Ref	
0.5-3 cups/day	155.9±36.8	**3.48 (2.41-4.55)**	**<0.001**	**2.19 (1.30-3.08)**	**<0.001**	**2.24 (1.33-3.16)**	**<0.001**
>3 cups/day	161.7±38.2	**9.23 (7.93-10.54)**	**<0.001**	**3.17 (2.04-4.29)**	**<0.001**	**3.35 (2.20-4.50)**	**<0.001**
RVESV (ml)							
zero coffee	65.6±21.1	Ref		Ref		Ref	
0.5-3 cups/day	67.3±21.2	**1.71 (1.10-2.32)**	**<0.001**	**1.06 (0.54-1.59)**	**0.001**	**1.10 (0.56-1.64)**	**<0.001**
>3 cups/day	70.4±21.8	**4.83 (4.08-5.57)**	**<0.001**	**1.63 (0.97-2.30)**	**<0.001**	**1.72 (1.04-2.41)**	**<0.001**
RVSV (ml)							
zero coffee	86.8±19.8	Ref		Ref		Ref	
0.5-3 cups/day	88.6±20.0	**1.78 (1.20-2.36)**	**<0.001**	**1.13 (0.58-1.67)**	**<0.001**	**1.15 (0.59-1.71)**	**<0.001**
>3 cups/day	91.3±20.8	**4.41 (3.70-5.12)**	**<0.001**	**1.53 (0.84-2.23)**	**<0.001**	**1.63 (0.92-2.33)**	**<0.001**
RVEF (%)							
zero coffee	57.4±6.1	Ref		Ref		Ref	
0.5-3 cups/day	57.3±6.2	-0.16 (-0.33-0.02)	0.082	-0.08 (-0.27-0.10)	0.376	-0.10 (-0.29-0.10)	0.330
>3 cups/day	56.9±6.1	**-0.58 (-0.79 to -0.36)**	**<0.001**	-0.17 (-0.41-0.07)	0.164	-0.19 (-0.43-0.06)	0.135

Abbreviations: CI=Confidence interval; LVEDV= Left ventricular end-diastolic volume; LVEF=Left ventricular ejection fraction; LVESV= Left ventricular end-systolic volume; LVM=Left ventricular mass; LVSV=Left ventricular stroke volume; RVEDV=Right ventricular end-diastolic volume; RVEF=Right ventricular ejection fraction; RVESV=Right ventricular end-systolic volume; RVSV=Right ventricular stroke volume.

Confounders: (baseline) age, sex, non-European ethnicities, body mass index, smoking, physical activity, Townsend deprivation index, alcohol, meat, tea, fruit and vegetable intake.

Mediators: (baseline) hypertension, diabetes mellitus, cholesterol level.