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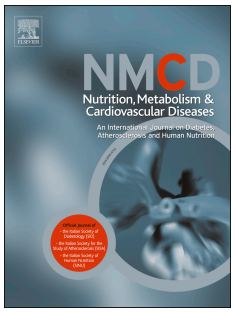


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# Safety of coffee consumption after myocardial infarction: A systematic review and meta-analysis

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# Abstract

**Background and Aims**

This systematic review aims to evaluate the impact of coffee consumption in patients with previous myocardial infarction (MI), in relation to all-cause and cardiovascular mortality, as well as other major cardiovascular events (MACE) such as stroke, heart failure, recurrent MI and sudden death.

**Methods and Results**

MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science Core Collection, SciELO Citation Database, Current Contents Connect®, KCI Korean Journal Database, African Index Medicus, and LILACS were searched for longitudinal studies evaluating the impact of coffee consumption in patients with previous myocardial infarction. We performed a random-effects meta-analysis to estimate the pooled hazard ratios (HR) with 95% confidence intervals (CI). The statistical heterogeneity was measured by $I^2$. A dose-response analysis was also conducted.

Six prospective cohort studies were included in the primary meta-analysis. Consumption of coffee was associated with lower risk of cardiovascular mortality (HR=0.70; 95% CI 0.54 to 0.91), $I^2$=0%; 2 studies) and was not associated with an increased risk of all-cause mortality (HR=0.85; 95% CI 0.63 to 1.13; $I^2$=50%; 3 studies), recurrent MI (HR=0.99; 95% CI 0.80 to 1.22; $I^2$=0%; 3 studies), stroke (HR=0.97; 95% CI 0.63 to 1.49; $I^2$=39%; 2 studies) and MACE (HR=0.96; 95% CI 0.86 to 1.07; $I^2$=0%; 2 studies). A significant non-linear inverse dose-response association was found for coffee consumption and all-cause mortality.

**Conclusions**

Consumption of coffee was not associated with an increased risk of all-cause mortality and cardiovascular events in patients with previous myocardial infarction.

**Keywords:** Coffee, caffeine, acute coronary syndrome, myocardial infarction, mortality, cardiovascular events, heart failure, angina

# Introduction

Ischemic heart disease is the leading cause of death in adults worldwide, according to the World Health Organization (WHO). Plaque rupture with thrombus formation in a coronary vessel results in an acute reduction of blood supply to myocardium, leading to myocardial infarction (MI) with irreversible damage [1].

Patients with previous myocardial infarction face a significant risk of further cardiovascular events, including recurrent MI, stroke, heart failure, arrhythmias and death [2]. Therefore, information regarding prognosis and management after myocardial infarction is of the utmost importance for clinical practice. Pharmacological measures, such as antiplatelet treatment and statins have an important prognostic role in the secondary prevention on patients with previous MI [3]. Concomitant non-pharmacological approaches, such as adopting healthy lifestyles (physical activity and diet) are desirable. Much is known and debated about how diet modulates cardiovascular risk factors (lipids and blood pressure) [4,5], but presently there are no recommendations about coffee consumption in this population. Despite the link of coffee consumption with myocardial infarction, there are studies, mostly based in disease-free populations, showing that coffee does not increase the MI risk [6,7].

Coffee is one of the most consumed beverages worldwide, and the understanding of the potential physiological effects of its consumption, either beneficial or harmful, may have meaningful implications for public health and patient care. Its consumption and association with cardiovascular disease has been studied extensively [6–8]. However, it is of critical importance to assess its clinical impact in the whole spectrum of potential consumers. Previous studies have focused on the effect of coffee in the development of acute myocardial infarction, but few have studied the impact of coffee consumption on prognosis in patients with previous MI.

Hereupon, we aimed to systematically study the risk of mortality and new cardiovascular events associated with coffee in patients with history of myocardial infarction.

# Methods

This systematic review was conducted and reported using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines [9,10]. It was registered in the International prospective register of systematic reviews – PROSPERO (https://www.crd.york.ac.uk/PROSPERO/) with the registration reference CRD42016032821.

## *Eligibility criteria*

### Study design and participants of interest

All longitudinal studies (clinical trials, cohort/nested case-control studies, case-control studies) were included, provided that they reported data or estimates about the coffee exposure and new cardiovascular events in patients that have or had myocardial infarction. History of myocardial infarction was defined according to clinical definitions [1], administrative codes, or autoreporting. Studies addressing the effects of short-term exposure to coffee (<1 year) as well as studies evaluating coffee exposure in patients who had not prior MI were excluded. Studies that met inclusion criteria were not excluded *a priori* on the basis of weakness of design or data quality.

### Intervention/exposure and control

Studies had to appraise the coffee consumption after the myocardial infarction and had to include a control group.

The control group had to include patients who were coffee abstainers, low-dose coffee drinkers or decaffeinated coffee consumers. We were flexible about the definition of low-dose coffee, accepting the definition of each study.

### Outcomes

The primary outcome of this review was all-cause (or overall) mortality. The secondary outcomes were cardiovascular (or cardiac) mortality, recurrent myocardial infarction, stroke, heart failure (incident or hospitalization) and sudden death. Studies that only reported information regarding secondary outcomes and that reported major cardiovascular events (MACE) as a single outcome were not excluded *a priori*.

### *Information sources and search strategy*

Electronic identification of studies was conducted by two authors (DC and ER), searching in MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science Core Collection, SciELO Citation Database, Current Contents Connect®, KCI Korean Journal Database, African Index Medicus, and LILACS, lastly updated in April 2020. Reference lists and systematic reviews evaluating coffee/caffeine exposure and cardiovascular diseases or cardiovascular risk factors were comprehensively assessed to ensure the sensitivity of the search.

### *Study records*

Data extraction, selection and collection: two reviewers (DC and ER) screened all articles resulting from the database search. Titles and abstracts were first screened independently in accordance with eligibility criteria and any doubts or disagreements were discussed and solved by consensus. Afterwards, the selected studies were evaluated in detail to determine if they fit the eligibility criteria.

For primary analysis, we evaluated the exposure to coffee at baseline compared with a reference group of non-consumers or with the lowest quantile of intake. Data from different estimates evaluating different levels of exposure compared with a reference were abstracted.

When different risk estimates for the same levels were available in the same publication, we considered for analysis those reflecting the greatest degree of control for potential confounders, or the most comprehensive assessment of coffee intake, using these criteria sequentially. We aimed to retrieve and use hazard ratio (HR) as estimate measure for the outcome. When this estimate was not available, we attempted to calculate it through the analysis of Kaplan-Meier/actuarial curves, otherwise the other relative measures estimates (risk ratio or odds ratio) were retrieved.

### *Risk of bias assessment*

The risk of bias of individual studies was evaluated using the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) tool [11], using the following domains: confounding, selection of participants into study, classification of

intervention, deviations from intended intervention, missing data, measurement of outcome and selection of reported results. These domains were qualitatively classified as serious, moderate or low risk of bias.

Disagreements were solved by consensus.

## *Data synthesis*

In the quantitative analysis, there were 2 phases:

Firstly, a random-effects meta-analysis using the Mantel-Haenszel method was performed comparing the highest vs. lowest category coffee consumption [12], which included "consumers vs. abstainers", if the data were not stratified. Statistical heterogeneity was defined as p-value<0.10 in the Chi-square test and it was measured through the $I^2$ metric [13], which measures the percentage of total variation between studies due to heterogeneity.

Secondly, we performed a dose-response analysis using the methods of Greenland and Longnecker exemplified by Orsini [14,15]. The analysis was undertaken for each outcome if three or more studies reported data and they had to discriminate three or more levels of consumption, otherwise no dose-response analysis was performed. The classes of coffee consumption and their respective hazard ratios (HR) and 95% confidence intervals (CI) for clinical events were retrieved. If the lower class was an interval that included the absence of coffee consumption, we assumed it as the reference for the class. For the remainder classes, the mid of each quantile was assigned to the respective HR. For classes with the highest consumption, if these were open-ended, we assumed that the range of category was the same as the closest category and we also assigned the mid-point of the case to the estimate for the meta-analysis [16]. A potential non-linear relationship between coffee consumption and the risk of clinical events was evaluated through restricted cubic splines with three knots at 10, 50, and 90% of the distribution [17]. A Wald-type test was performed to assess non-linearity. If the data were suggestive of a linear relationship, we reported the HR and 95% CI associated with consumption of each cup of coffee derived from an iterative generalized least-squares regression and the goodness-of-fit chi-square test p-value. If the data had a non-linear dispersion, an informative graph with the HR and 95% CI along with the amount of coffee cups taken was plotted.

We provided funnel plots for the evaluation of publication bias but formal tests for funnel plot asymmetry were only planned if at least 10 studies were included in the pooled analysis.

### *Assessment of confidence in cumulative evidence*

The Grading of Recommendation, Assessment, Development and Evaluation (GRADE) criteria was used to grade the quality of the pooled evidence for each outcome. The GRADE approach was independently assessed by two investigators (DC and ER) in the following domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. Discrepancies were solved by consensus. The confidence on the pooled evidence accounted for all the factors and was graded as very low, low, moderate or high [18]. The pooled risk difference with coffee and the confidence on the pooled evidence were reported in the Summary of findings table.

# Results

## *Study selection*

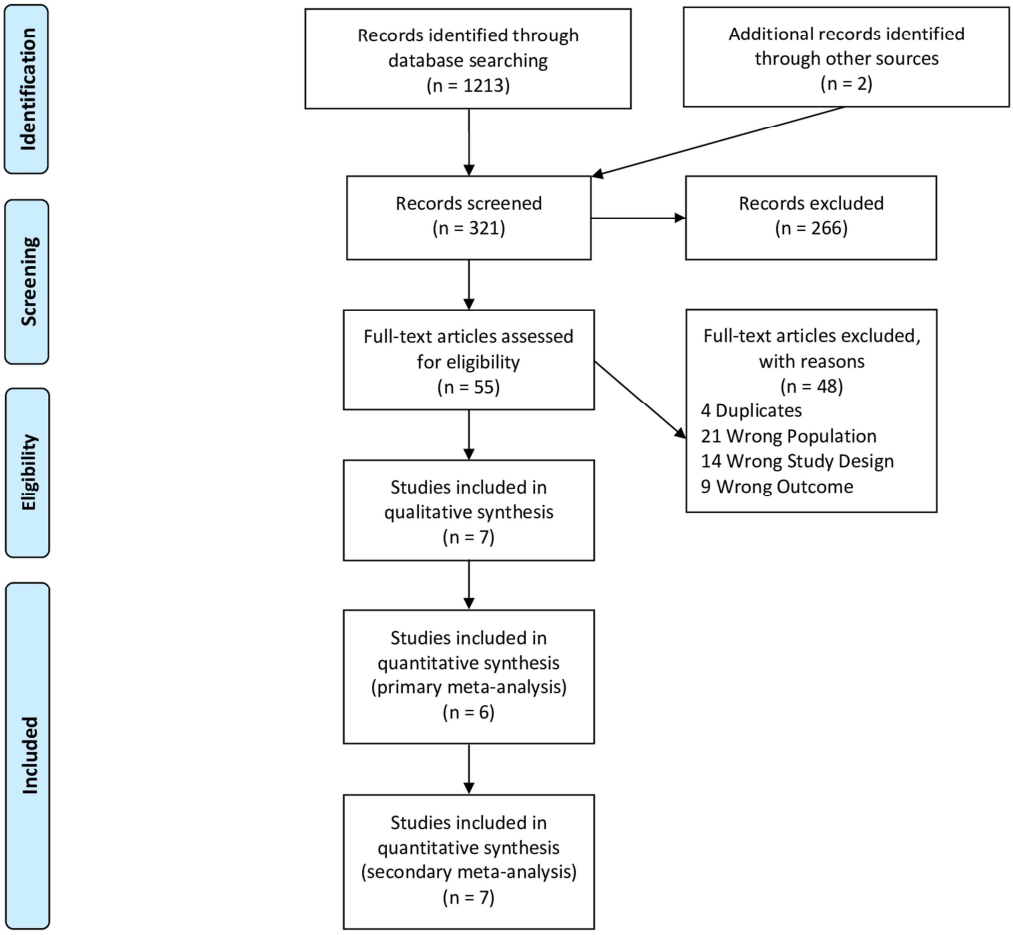


**Figure 1.** Flow chart of study selection

The electronic database search yielded 341 references. Two additional records were identified through other sources (references handsearch). After removal of duplicates, screening of title and abstract and evaluation for full-text eligibility, seven studies remained for inclusion [19–25]. Six of the studies evaluated coffee consumption [19–23,25] and one of the studies evaluated caffeine consumption [24]. We divided our quantitative synthesis in a primary meta-analysis with only the studies that accounted for coffee consumption and a secondary meta-analysis adding the data from the study that assessed for caffeine consumption rather than coffee, accounting for all the seven studies.

### *Study characteristics*

All studies ultimately included in the review were prospective cohort studies. Five studies were conducted in Europe (Netherlands [21], Sweden [20], Italy [22,25] and Greece [23]) and two in the United States [19,24]. Overall, 21890 patients with previous myocardial infarction were included in these studies (ranging from 112 to 11231 patients). The mean age of participants at baseline varied between 41 and 69 years old. The duration of follow-up varied from 3.5 years to 10 years. All-cause mortality was evaluated by four studies [19–21,24]. Of the secondary outcomes, three studies reported cardiovascular mortality [20,21,24] four studies evaluated recurrent acute myocardial infarction [20,22–24], three studies evaluated stroke [20,22,24] and two studies evaluated MACE as a single outcome [22,25]. All studies had a multivariable outcome adjustment for major potential confounders, including age, smoking, alcohol consumption, body mass index, socioeconomic status and education, physical activity and history of diabetes and hypertension [19–25].

Van Dongen et al. assessed both caffeinated coffee and decaffeinated coffee consumption. In this study, the fully adjusted HRs in separate categories of caffeinated and decaffeinated coffee were essentially of the same magnitude when comparing to those for total coffee consumption [21]. Two studies assessed caffeinated coffee consumption only [19,20], and three studies did not specify whether they included decaffeinated coffee [22,23,25]. Fornengo et al. quantified coffee in cups per day but did not specify categories of coffee consumption. They evaluated coffee as a binary covariate, using a multivariate analysis based on Cox proportional regression model [25]. Suri et al assessed caffeinated coffee consumption, but portions were not defined. Therefore, their primary analysis consisted of caffeine consumption, in which they included caffeinated coffee and other beverages but not nutrients obtained from nutritional supplements or medications. For data analysis, they divided caffeine intake into equivalent of 150-mg of coffee cups [24].

All studies had an assessment of coffee consumption through a dietary questionnaire/interview at baseline. Three of the studies assessed weekly coffee consumption during the previous year [19,20,23], one of the studies assessed coffee consumption in the past month [21] and one of the studies assessed caffeine consumption in the past 24 hours [24]. Beyond the baseline assessment, Silletta et al.

also assessed at the 6th, 18th, and 42nd month of follow-up [22] and Fornengo et al. also assessed at the end of follow-up [25].

All studies provided a clear definition for MI. Also, all studies that assessed mortality, did it through the respective National Death Index/Register death certificate records, and used WHO-ICD (International Classification of Diseases) coding to identify cause of death.

As for cardiovascular events, in three studies [20,23,24] they were recorded and identified by WHO-ICD coding. In one study [22], its assessment was validated by a committee of experts [26,27]. Another study [25] used case definitions for acute coronary heart disease in epidemiology and clinical research studies by the American Heart Association (AHA) [28].

A summary of the main characteristics of the included studies can be found on Table 1.

The hazard ratios and 95% confidence intervals of the different outcomes according to category of coffee consumption, for each study can also be found on Supplementary Table 2.

### *Risk of bias within studies*

According to the ROBINS-I tool (Supplementary Table 3), the overall risk of bias was serious, with only two studies being considered as having moderate risk of bias [22,25]. The key element for downgrading the evidence was the bias in the classification of intervention/exposure, because just a baseline assessment is clearly insufficient to retrieve a reliable estimate of coffee exposure overtime. The studies that evaluated at least twice overtime were considered with moderate risk of bias [22,25].

**Table 1.** Main characteristics of included studies

| Study Year | Design | Region | Population | Follow-up | Mean age/% female | Type of Coffee | Coffee Exposure | Outcomes | Outcome adjustments |
|---|---|---|---|---|---|---|---|---|---|
| **Mukamal 2004** [18] | Prospective cohort | USA | 1902 hospitalized with a confirmed AMI between 1989 and 1994 at 45 community hospitals and tertiary care centers in the United States, as part of the Determinants of Myocardial Infarction Onset Study | Median of 3.8 years | 56-65 years/32% | Caffeinated coffee only | Standardized questionnaire by trained interviewers | All-cause Mortality | Age, sex, previous MI, previous angina, hypertension, diabetes mellitus, BMI, current smoking, former smoking, educational attainment, race, household income, usual frequency of exertion, usual alcohol consumption, use of thrombolytic therapy, use of cardiac medications (aspirin, β blockers, calcium channel blockers, ACEi, digoxin diuretics, lipid-lowering agents), congestive heart failure or ventricular tachycardia during hospitalization |
| **Silletta 2007** [20] | Prospective cohort | Italy | 11231 participants in the GISSI-Prevenzione trial - a prospective study investigating the relationship between coffee intake and cardiovascular events in a cohort of patients who survived myocardial infarction | 3.5 years | 52.3-63.6 years/14.7% | Coffee only (not specified) | Dietary questionnaire administered by cardiologists/ nurses during clinical visits at the baseline examination and at the 6th, 18th, and 42nd month of follow-up | Recurrent AMI<br>Stroke<br>Sudden Death | Age, gender, smoking, time from MI to enrollment, prior MI previous to index MI, BMI, history of hypertension, history of diabetes mellitus, peripheral vascular disease, electrical instability, results of exercise stress testing, left ventricular ejection fraction, New York Heart Association class, Canadian Cardiovascular Society angina symptoms, revascularization procedures, n-3 PUFA use, vitamin E use, antiplatelet agent use, angiotensinconverting enzyme inhibitor use, lipid-lowering medication use, β-blocker use and intake of cooked vegetables, raw vegetables, fruit, fish, olive oil, other oil, butter, cheese, and wine |
| **Mukamal 2009** [19] | Prospective cohort | Sweden | 1369 hospitalized with a confirmed first acute myocardial infarction between 1992 and 1994 in Stockholm County, Sweden, as part of the Stockholm Heart Epidemiology Program | 6.9 to 9.9 years | 59.5 years/30% | Caffeinated coffee only | Standardized questionnaire distributed during hospitalization | All-cause Mortality<br>CV Mortality<br>Recurrent AMI<br>Stroke<br>Heart Failure | Age, sex, diabetes, smoking, obesity, physical inactivity, alcohol consumption, tea consumption, education, intake of boiled coffee, hypertension and systolic blood pressure |
| **Fornengo 2010** [24] | Prospective cohort | Italy | 112 patients with ≤45 years admitted to the Coronary Care Unit with acute MI | 5.3 years | 41 years/10% | Coffee (not specified) | Standardized questionnaire at baseline and end of follow-up | MACE (defined as cardiac death, recurrent MI, heart failure needing hospitalization stroke and angina pectoris needing re-vascularization procedure) | Age, gender, current smoking, hypercholesterolemia, hypertriglyceridemia, family history, previous CV events, hypertension, heart rate, diabetes mellitus, BMI, obesity, diet, physical activity, alcohol consumption, end-diastolic and end-systolic ventricular diameter and LV ejection fraction |
| **Notara 2015** [21] | Prospective cohort | Greece | 2172 ACS consecutive patients hospitalized in the cardiology clinics or | 10 years | 65 ± 13 years/24% | Coffee only (not specified) | Validated semiquantitative Food Frequency Questionnaire | Recurrent AMI | Sex, age, physical activity, years of school, MedDietScore, current smoking, body mass index, CES-depression, family history of CV disease, hypertension, hypercholesterolemia and diabetes mellitus |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | the emergency units of six major General Hospitals in Greece | | | | | | |
| **Suri 2015** [23] | Prospective cohort | USA | 739 survivors of AMI | 9.0 ± 5.2 years | 69 ± 17 years/41% | Caffeine intake divided into equivalent of 150-mg of coffee cups | Dietary interviews by trained dietary interviewers | All-cause Mortality<br>Fatal stroke<br>Fatal recurrent AMI<br>Fatal cardiovascular disease (CV mortality) | Age, sex, race/ethnicity, socioeconomic status group, smoking status, alcohol, history of diabetes mellitus, history of hyperlipidemia and history of hypertension |
| **van Dongen 2017** [22] | Prospective cohort | Netherlands | 4365 Dutch patients from the Alpha Omega Cohort between 60 and 80 years and that had experienced an MI less than 10 years before study enrollment | Median of 7.1 years | 69.0 ± 5.6 years/21% | Caffeinated and decaffeinated coffee (total) | 203-item validated food-frequency questionnaire by trained dietitians | All-cause Mortality<br>CV Mortality | Age, sex, and type of intervention during the initial Alpha Omega Trial phase, prevalent diabetes, BMI, physical activity, educational level, smoking status, and alcohol use |

AMI, acute myocardial infarction; MI, myocardial infarction; BMI, body mass index; ACEi, ACE-inhibitor; PUFA, polyunsaturated fatty acids; CV, cardiovascular; MACE, major cardiovascular events; LV, left ventricular; ACS, acute coronary syndrome; CES, center for epidemiologic studies

## *Synthesis of results*

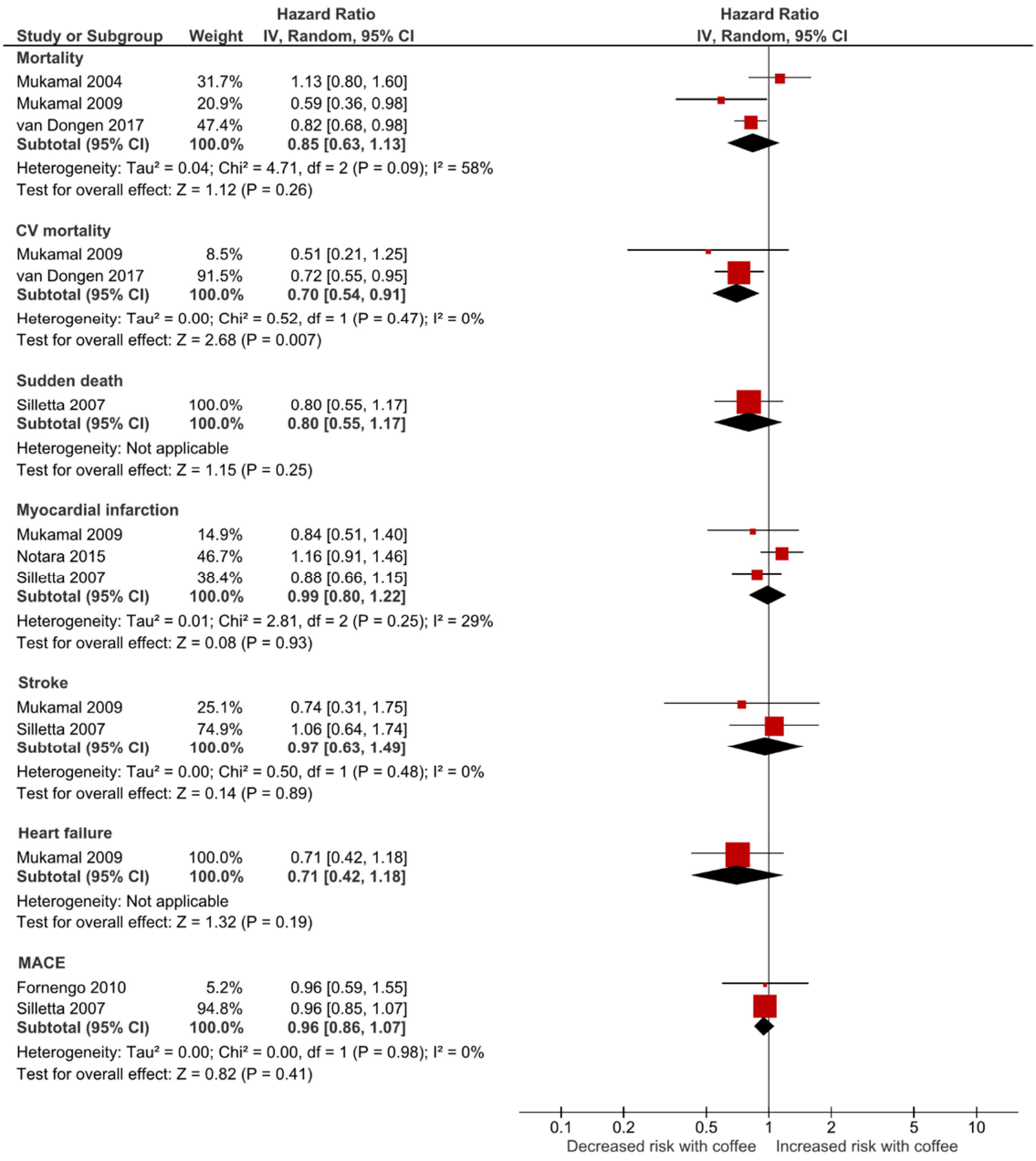


**Figure 2.** Forest plot of the primary analysis (random-effects model) of the effect of coffee consumption/exposure (highest vs lowest category) on mortality and cardiovascular events after myocardial infarction. IV, inverse variance; CI, confidence interval, CV, mortality; MACE, major cardiovascular events.

In our primary analysis, we performed the meta-analysis for all-cause mortality using data from three studies, which included a total of 7636 patients with previous myocardial infarction. The pooled analysis showed that coffee consumption was not associated with an increased risk of all-cause mortality with HR=0.85 (95% CI 0.63 to 1.13), with statistically significant heterogeneity (p-value for heterogeneity chi-square = 0.09) and $I^2$=58%.

Regarding cardiovascular mortality, the pooled analysis with a total of 5734 patients demonstrated that coffee consumption was associated with a statistically significant lower risk of CV mortality with HR=0.70 (95% CI 0.54 to 0.91). The analyses on recurrent MI (HR=0.99; 95% CI 0.80 to 1.22), stroke (HR=0.97; 95% CI 0.63 to 1.49) and MACE (HR=0.96; 95% CI 0.86 to 1.07) were also not associated with an increased risk with coffee consumption. None of these analyses were remarkable for statistical heterogeneity and all had $I^2$=0%.

The other secondary outcomes (sudden death and heart failure) were only reported by one study each, rendering any pooled analysis impossible.

All individual estimates are depicted in Supplementary Table 3.

## *Dose-Response Meta-Analysis*

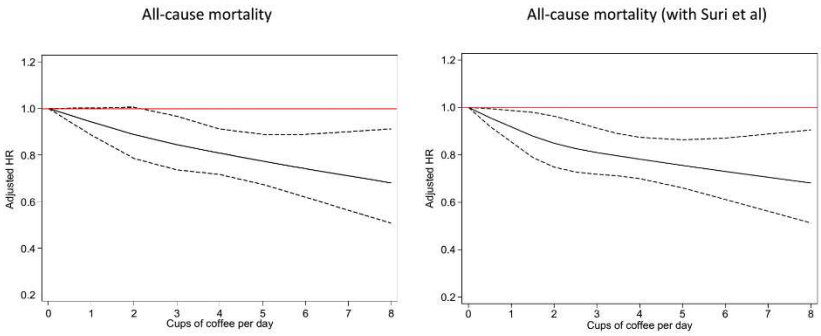


**Figure 3.** The pooled relative risk of all-cause mortality associated to the different coffee consumption strata.Note: The solid line represents the non-linear trend. Black dashed lines represent the 95% confidence intervals. Red dashed line represents HR=1. HR, hazard ratio;

A dose-response meta-analysis was undertaken for outcomes with reported data in three or more studies and that discriminated three or more levels of consumption. The only outcomes in our primary analysis which met these criteria were all-cause mortality [19–21] and recurrent MI [20,22,23].

For all-cause mortality, we found a significant non-linear dose-response inverse relationship (p-value for non-linearity = 0.001) (Figure 3). Regarding recurrent MI the data fitted a non-significant linear dose-response model with HR 1.01 (95%CI 0.92-1.11) for each cup of coffee consumed.

## *Publication bias and secondary analysis*

Due to the small number of studies, the publication bias analysis was not formally assessed. Supplementary Figure 1 shows the funnel plot for the outcomes with 3 or more studies and overall, there was not a clear asymmetry in the estimates.

We carried out a secondary analysis (Supplementary Figure 2) by including data from one study (Suri et al.) which analysis accounted for caffeine consumption rather than coffee [24].

The inclusion of data from this study yielded similar results in the pooled analysis for every outcome that the study assessed: all-cause mortality (HR=0.81; 95% CI 0.65 to 1.00; p-value for heterogeneity=0.11; $I^2$=50%), CV mortality (HR=0.70; 95% CI 0.57 to 0.86; $I^2$=0%), recurrent myocardial infarction (HR=1.01; 95% CI 0.85 to 1.19; $I^2$=0%), and stroke (HR=0.77; 95% CI 0.42 to 1.43; $I^2$=39%) (Figure 3; Supplementary Figure 2).

We also carried out the dose-response analysis for all-cause mortality (Figure 3), cardiovascular mortality [20,21,24] and stroke [20,22,24] the latter possible as these outcomes now met the criteria of reported data in three or more studies. The all-cause mortality data overlapped the primary analysis. CV mortality was associated to a non-linear inverse relationship (p-value for non-linearity < 0.001) (Supplementary Figure 3) while stroke, there was not a significant change in the risk for each cup of coffee consumed.

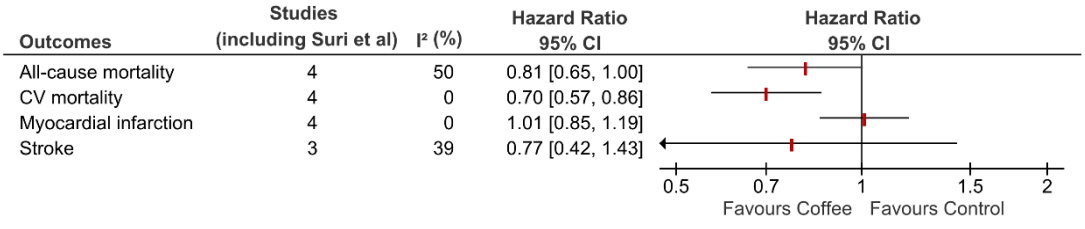

**Figure 4.** Pooled analysis (random-effects model) of the effect of coffee consumption/exposure (highest vs lowest category) in the outcomes where Suri et al. was added (secondary analysis; Supplementary Figure 2)

## *Assessment of confidence in cumulative evidence*

Table 2 presents a summary of findings table which summarizes the results obtained according to certainty of the evidence (GRADE). Results on most of the outcomes present very low certainty, however on cardiovascular mortality presents low certainty and, according to our estimates, coffee may be associated with reduced risk of cardiovascular mortality in 5 for each 1000 patients, or in the worst case-scenario 2 for each 1000. More importantly, this seems to exclude harm regarding cardiovascular mortality.

**Table 2.** Summary of findings according to the GRADE criteria, depicting the primary and the secondary outcomes

| Outcomes | Number and type of studies | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated yearly absolute effects** | |
|---|---|---|---|---|---|
| | | | | Risk with no coffee*** | Risk difference with coffee |
| All-cause mortality | 3 observational studies | ⊕◯◯◯ VERY LOW [a,b,c] | **0.85** (0.63 to 1.13) | 43 per 1000 | **6 fewer per 1000** (16 fewer to 6 fewer) |
| CV mortality | 2 observational studies | ⊕⊕◯◯ LOW [a] | **0.70** (0.54 to 0.91) | 18 per 1000 | **5 fewer per 1000** (8 fewer to 2 fewer) |
| Sudden death | 1 observational study | ⊕◯◯◯ VERY LOW [d,e,f] | **0.80** (0.55 to 1.17) | 10 per 1000 | **2 fewer per 1000** (5 fewer to 2 more) |
| Myocardial infarction | 3 observational studies | ⊕◯◯◯ VERY LOW [a,f] | **0.99** (0.80 to 1.22) | 16 per 1000 | **0 fewer per 1000** (3 fewer to 3 more) |
| Stroke | 2 observational studies | ⊕◯◯◯ VERY LOW [a,f] | **0.77** (0.42 to 1.43) | 5 per 1000 | **0 fewer per 1000** (2 fewer to 3 more) |
| Heart failure | 1 observational study | ⊕◯◯◯ VERY LOW [a,f,g] | **0.71** (0.42 to 1.18) | 40 per 1000 | **12 fewer per 1000** (23 fewer to 7 more) |
| MACE | 2 observational studies | ⊕◯◯◯ VERY LOW [a,c] | **0.96** (0.86 to 1.07) | 39 per 1000 | **2 fewer per 1000** (6 fewer to 3 more) |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** The anticipated yearly absolute risks were calculated assuming a constant risk of events overtime.
*** Data calculated from the control group in the largest study in each outcome: All-cause mortality and CV mortality (Van Dongen 2017); Sudden death, myocardial infarction, stroke and MACE (Silletta 2007); Heart failure (Mukamal 2009).

*Explanations*

**a.** The risk of bias strata of most studies corresponds to very serious; **b.** Statistical heterogeneity was substantial with $I^2$ statistic of 50%; **c.** The confidence interval overlaps the HR 1.0. However, it excludes substantial harm; **d.** The risk of bias of the study was moderate**; e.** Only one study (Silletta et al.); **f.** The confidence interval overlaps the HR 1.0; **g.** Only one study (Mukamal et al. 2009)

## Discussion

The main finding of this systematic review is that the best evidence available suggests that coffee consumption in patients with previous myocardial infarction is safe, without increasing the risks of all-cause mortality and cardiovascular events.

It is known that patients with a previous myocardial infarction face a significant risk of further cardiovascular events, including recurrent MI, stroke, heart failure, arrhythmias and death [2]. Concomitantly, it has been shown that coffee exposure has not been associated with an increased incidence of multiple cardiovascular events considered to be the main cardiovascular mortality risk factors. Furthermore, in disease-free population, coffee intake does not appear to be associated with coronary heart disease [6,7,29]. Likewise, in the dose-response meta-analysis by Larsson et al., it was shown that moderate coffee consumption may be weakly inversely associated with risk of stroke [30]. In another dose-response meta-analysis by Zhang et al., coffee intake of >3 cups/day did not show an increased risk of arterial hypertension. However, a slightly elevated risk appeared to be associated with light to moderate consumption, as an inverse "J-shaped" relation was found [31]. Coffee consumption has also not been associated with an increased frequency or severity of cardiac arrhythmias [32,33].

The consumption of coffee and its association with cardiovascular disease and mortality has been studied extensively but few studies have studied its impact on high-risk patients with cardiovascular disease. In the meta-analysis by Brown et al., which only assessed all-cause mortality and two cohort studies [19,20] that were also included in this review, drinking coffee habitually following an acute myocardial infarction (AMI) was associated with a reduced risk of mortality. Furthermore, the overall results indicated that there was a statistically significant inverse association between coffee consumption and mortality after an AMI. Compared with noncoffee drinkers, light (1–2 cups/day) and heavy (>2 cups/day) coffee drinkers had a decreased risk of mortality, with the greatest benefit being shown with heavy consumption [34].

Although much attention is paid to caffeine – and rightfully so, as it is coffee's major active ingredient and may have short-term harmful effects, such as the stimulation of the release of adrenaline, an inhibitor of insulin activity, and the acute increase in blood pressure and homocysteine concentrations [35] –, there are several other biologically active substances in coffee that may have beneficial effects on the cardiovascular system and their understanding is essential to further comprehend the

potential effects of coffee on health. Several studies have found an inverse association between coffee consumption and blood concentrations of some inflammatory markers, such as C-reactive protein and E-selectin, decreasing inflammation and endothelial dysfunction.[36–39] Some phenolic compounds in coffee (specially chlorogenic acid), magnesium, trigonelline and quinides also seem to have a strong antioxidant activity which reduces chronic inflammation and oxidative stress and may reduce the oxidation of low-density lipoprotein cholesterol, contributing to lessen the atherosclerotic process [40,41].

The presence of a dose-response non-linear association between coffee consumption and overall mortality suggests that coffee consumption is safe in patients with previous MI. As the results of our analysis for other cardiovascular events did not show a significantly reduced risk with coffee consumption, further investigation is required to better understand the association between coffee consumption and cardiovascular risk in patients with previous MI. The inclusion of more studies with larger sample sizes and higher quality might lead to firmer conclusions and, consequently, meaningful implications for public health and patient care in this high-risk population.

### *Limitations*

The first limitation of this review is the small number of studies included in the single meta-analysis. There are also limitations inherent to the included studies themselves - given their observational nature, the possibility of residual or unmeasured confounding cannot be excluded, even though all studies had a multivariable outcome adjustment. Also, the control group was heterogeneous as included abstainer, low quantity drinkers or decaffeinated coffee drinker.

Regarding coffee exposure, all studies had equivalent assessment of coffee consumption - through a standardized dietary questionnaire/interview. However, the categories and classification regarding coffee doses were heterogeneous, as was the period of time in which coffee consumption was measured. The reference of coffee exposure was also heterogeneous among studies and studies with estimates referring to intervals were considered as abstainers in the dose-response analysis, which limits the robustness of the method.

The overall risk of bias regarding the studies included in this meta-analysis was serious. One of the main elements for downgrading the evidence was the bias in the classification of intervention/exposure. There was only one study that accounted for updated information on coffee consumption during follow-up [22]. As for the others, they only assessed coffee consumption at baseline. Therefore, eventual behavioural changes were not accounted for, which may not reflect changes in dose during the follow-up period. Evaluating the study of Silletta et al [22], which may be less prone to bias, the results also supported the safety of coffee in patients with previous myocardial infarction.

The pooled evidence, as per GRADE assessment, had a very low to low certainty, which disables claims for considering coffee as intervention that improves the prognosis. Nonetheless, we consider that these data favour the safety of coffee use in patients with previous history of myocardial infarction.

# Conclusions

Consumption of coffee was not associated with an increased risk of all-cause mortality and cardiovascular events in patients with previous myocardial infarction.

The presence of a significant dose-response non-linear association between coffee consumption and risk of mortality in this population emphasise the relevancy for further observational studies to confirm our findings and to better elucidate the possible underlying mechanism of the impact of the consumption of coffee on mortality and other cardiovascular events in patients with previous myocardial infarction.

## Author Contributions

DC contributed to the concept and design. DC and ER contributed to data acquisition, data analysis, and interpretation of the data; wrote the first draft of the manuscript; critically revised the manuscript; and gave final approval of the submitted manuscript. MA contributed to data analysis, interpretation of data, critically revised the manuscript, and gave final approval of the submitted manuscript. JC, JJF and FJP contributed to interpretation of data, critically revised the manuscript, and gave final approval of the submitted manuscript.

## Declaration of conflicting interests

DC has participated in educational meetings and/or attended a conferences or symposia (including travel, accommodation and/or hospitality) with Roche, Daiichi-Sankyo, and Menarini, Merck-Serono, in the last 3 years. MA reported participation in conferences with Boehringer-Ingelheim, AstraZeneca, Bayer, Bristol-Myers-Squibb, Grünenthal, Tecnimede, Merck Sharp & Dohme. JJF had speaker and consultant fees with Grünenthal, Fundação MSD (Portugal), TEVA, MSD, Allergan, Medtronic, GlaxoSmithKline, Novartis, Lundbeck, Solvay, BIAL, Merck-Serono, Merz, Ipsen, Biogen, Acadia, Allergan, Abbvie, Sunovion-Pharmaceuticals. FJP had consultant and speaker fees with Astra Zeneca, Bayer, BMS, Boehringer Ingelheim and Daiichi Sankyo.



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# Highlights

- We aimed to assess whether there is an association between coffee consumption and mortality and cardiovascular risk in patients with previous myocardial infarction
- Higher coffee consumption was associated with lower risk of all-cause mortality and cardiovascular mortality
- Long-term coffee consumption is safe after myocardial infarction and may be associated with reduced risk of cardiovascular mortality