**Coffee reduces death risk after acute myocardial infarction: a meta-analysis.**

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**Aims**

It has been shown that habitual coffee consumption is protective against coronary heart disease in women; however it is not clear whether such cardio-protection is conferred upon those who have already experienced an acute myocardial infarction. Our aim was to investigate whether coffee consumption affected mortality after acute myocardial infarction.

**Methods and Results**

We conducted a dose-response meta-analysis of prospective studies which probed the relationship between coffee intake and mortality in those who had experienced an acute myocardial infarction. Using a defined-search strategy, electronic databases (MEDLINE and Embase) were searched for papers published between 1946 to February 2014. Two eligible studies that investigated post acute myocardial infarction mortality risk against coffee consumption were identified and appraised using set criteria. Combined, these studies recruited a total of 3,271 patients for which 604 deaths were observed. The hazard ratios for the following experimental groups were defined: Light coffee drinkers (1-2 cups/day) versus non-coffee drinkers, heavy coffee drinkers (>2 cups/day) versus non-coffee drinkers and heavy coffee drinkers versus light coffee drinkers.

A statistically significant inverse correlation was observed between coffee drinking and mortality; all three groups demonstrated a significant reduction in relative risk. Light coffee drinkers versus non-coffee drinkers was associated with a risk ratio of 0.79 [95% confidence interval (CI) = 0.66-0.94, p = 0.008]; heavy coffee drinkers versus non-coffee drinkers was associated with a risk ratio of 0.54 (95% CI= 0.45-0.65, p = 0.00001); and heavy coffee drinkers versus light coffee drinkers was associated with a risk ratio of 0.69 (95% CI= 0.58 – 0.83, p = 0.0001).

**Conclusions**

Drinking coffee habitually following an acute myocardial infarction was associated with a reduced risk of mortality.

**Keywords**

Coffee – Myocardial infarction – Mortality – Meta-analysis

**Introduction**

Coronary heart disease (CHD) continues to be the one of the leading causes of mortality in the United Kingdom despite declining mortality since the 1970s (1). It is encouraging that case fatality rates of acute myocardial infarction (AMI) have continued to improve(2). Coffee is a popular beverage worldwide and a large amount of literature has been published in the last 40 years investigating coffee and its relationship with CHD, with large discrepancies in the results.

A recent meta-analysis by Wu *et al* (3) showed that moderate habitual use was associated with a lower risk of CHD in women and found that coffee consumption did not increase long term risk of CHD. One area the meta-analysis did not look at was coffee consumption and its effect on post AMI mortality. In fact there has been no meta-analysis performed in this area and limited research published investigating this.

Different cohort studies have produced conflicting results (4) (5). However these were limited to small cohort populations. An analysis of the large GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico) population of over 11000 patients (6) found an inverse relationship between coffee consumption and cardiovascular events after AMI. However when the data was adjusted for confounding factors, the relationship was not shown to be significant. Further, the paper did not examine all-cause mortality. A small case control study looking at 117 cases of sudden cardiac arrest found that heavy coffee consumption (>10 cups per day) was associated with an increased risk of sudden cardiac arrest in patients with pre-existing coronary artery disease (7). Interestingly studies investigating tea consumption and mortality after an AMI have shown that mortality was reduced in tea drinkers (8).

Our aim is to test the hypothesis that coffee consumption reduces all-cause mortality after acute myocardial infarction. We performed a meta-analysis of prospective cohort studies as there were no randomised controlled trials (RCTs) testing the hypothesis.

**Methods**

*Search strategy*

Using a defined-search strategy, electronic databases (MEDLINE and Embase) were searched for papers published between 1946 to February 2014.

The following search threads were used: (i) Coffee OR Caffeine; (ii) Myocardial Infarction, myocardial isch\*emia, non ST elevation myocardial infarction (NSTEMI), ST elevation myocardial infarction (STEMI), acute coronary syndrome, coronary artery disease OR unstable angina; (iii) Mortality or Survival; (i), (ii) AND (iii). The search terms were linked to Medical Subject Headings (MESH) and the bibliographies were pursued. We reviewed all abstracts with a relevant title.

*Inclusion/Exclusion criteria*

For inclusion the articles had to have the following criteria: (i) be prospective cohort studies in design; (ii) report using hazard ratios, odds ratios, risk ratios and reported them with 95% confidence intervals (CI); (iii) quantify coffee consumption to allow stratification of consumption into groups; (iv) use all-cause mortality as an outcome; (v) English language articles.

Studies were excluded if: (i) case control, cross sectional or retrospective cohort in design; (ii) categories of coffee consumption were not given; (iii) included patients with other cardiovascular diseases (e.g. stroke).

*Data extraction and quality assessment*

The data was extracted by one investigator with any uncertainties in eligibility for inclusion being discussed with the investigator’s supervisor. For the studies which were relevant and fitted the inclusion and exclusion criteria, the following data was extracted: title, author(s), country, publication year, study period, location of study, population sex, age range, factors adjusted for, outcome measure(s), coffee consumption categories, the number of people in each coffee consumption subset and the number of events observed, the hazard ratios for each coffee consumption subset and its 95% confidence interval (CI). If data needed to perform the analysis was missing, authors were contacted to try to gain this information (4) (5).

The quality of the studies was assessed using criteria similar to the criteria used by Pavia et al and adapted by Wu et al(3)(9).The criteria for which each article was assessed had three broad categories which included; Selection bias (0-6 points), Confounding (0-10 points) Information Bias (0-5 points) and data analysis quality (0-2.5 points). The criteria used to assess selection bias included sampling population (general or specific), sampling method (random/census or non-random), response rate (>75% or not), comparison of who were and were not lost to follow up, dropout rate (<25%), clear inclusion or exclusion criteria. The criterion for assessing confounding was based on whether or not they included different factors in their adjusted hazard ratios. These factors included age, sex, smoking, alcohol, BMI, dietary factors, hypertension and/or diabetes, physical activity, family history of myocardial infarction (MI), education and/or income. Information bias assessment included validation of coffee assessment, methods of coffee assessment (face to face interview/self-administered), clear definition of MI, events assessment methods (self-report or hospital records) and blinded event assessment with respect to exposure status. The criteria used for assessment of data analysis quality we used included demographic data given, statistical analysis of demographic data, precise *p* value or 95% CI given, power calculation and test statistic specified or not. The total possible score achievable was 22.5 and the lowest quality score was 0.

*Data synthesis*

The eligible studies were entered into RevMan5 software package, and the statistical methods were those programmed into RevMan 5.1 analysis software.

As the studies found from our search had different categories of coffee consumption, we standardised these categories by creating three groups of coffee drinkers, none drinkers (0 cups/day), light drinkers (1-2 cups/day) and heavy drinkers (>2 cups/day).

The number in each group and the number of events in each group was extracted. For the dichotomous data the relative risk and 95% confidence intervals were calculated. The results from the trials were pooled using the fixed effects and random effects models. We tested for heterogeneity with the Cochran Q statistic, which was considered to be significant at p<0.10. If significant, a random effect model was used to allow generalisation of the results and sources of heterogeneity to be investigated. Z tests were used to test for the overall effect.

Due to the paucity of studies found in our search we were unable to perform a meta-regression analysis using the adjusted hazard ratios presented in each study. We attempted to obtain raw data from authors to conduct our own adjustment for confounding but unfortunately this data was not available (4) (5).

Results

*Search results.*

The MEDLINE and Embase search identified 186 articles; no new studies were identified with searches of the other databases and society proceedings. The search was last run on 21st February 2014. After removal of duplicates 138 articles were reviewed. Review of the titles and abstracts identified 6 studies appropriate for inclusion; the full texts of these articles were then reviewed for inclusion. Two met the inclusion criteria for analysis. For details of the search results see figure 1. This resulted in a cumulative sample size of 3271 patients, of which 686 patients were not coffee drinkers, 1112 were light coffee drinkers and 1463 were heavy coffee drinkers.

Both of these studies were looking at both men and women post AMI (4) (5). One of the studies was conducted in the USA (4), the other was conducted in Sweden (5)

The details of the included studies are found in *Table 1*.

**LOCATION OF FIGURE 1**

*Data quality*

The mean overall quality score was 18.5 with the scores ranging between 18-19. The mean score for the selection bias, information bias, confounding and data quality assessment subscores were 5, 8.5, 3 and 2 respectively. Both studies adjusted for confounding for age, sex, smoking, alcohol, BMI, hypertension and/or diabetes, education and/or income and physical activity. However only one paper adjusted for confounding for family history of myocardial infarction (4) and neither adjusted for confounding for dietary factors.

Both papers gave a clear definition for myocardial infarction. One of the studies used a face to face questionnaire (4) whereas the other used a self-administered questionnaire (5). Both studies used clear event criteria using national death registers to ascertain who had died.

*Overall results*

A statistically significant inverse correlation was observed between coffee drinking and mortality; all three groups demonstrated a significant reduction in relative risk (95% confidence interval (CI)).

Compared with non-coffee drinkers, the pooled risk ratio of mortality after acute myocardial infarction for light coffee drinkers (*Figure 2a*)was 0.79 (CI: 0.66-0.94, p = 0.008); for heavy coffee drinkers (*Figure 2b*) was 0.54 (CI: 0.45-0.65, p = 0.00001). In addition to this, we found that heavy coffee drinkers versus light coffee drinkers (*Figure 2c*) was associated with a risk ratio of 0.69 (CI: 0.58 – 0.83, p = 0.0001).

**LOCATION OF FIGURE 2**

 **Discussion**

The overall results from our analysis indicate that there is a statistically significant inverse association between coffee consumption and mortality after an AMI. When compared to none coffee 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.

*Mechanism of risk reduction*

Many biologically active ingredients are known to be present in coffee, with caffeine being the most commonly associated one. However, the mechanism behind how coffee is cardio-protective is unclear with evidence suggesting different actions as to how this protection is inferred.

Caldeira et al (10) recently showed that there is no association between caffeine consumption and increased risk of atrial fibrillation (10). At low doses it was shown to even have a potential protective effect (10). Furthermore, other research has suggested that caffeine does not potentiate ventricular arrhythmias (11) (12).

In addition to this, another proposed mechanism is that coffee improves endothelial function (13). In diabetic women, Lopez-Garcia et al found that decaffeinated coffee consumption had an inverse association with E-selectin and CRP, both of which are recognised inflammatory markers and have a role in the atherogenic process involved with coronary artery disease (14) (15). In 2008, a study on the same population found this to be true with consumption of caffeinated coffee, suggesting that caffeine is not involved in the mechanism behind this (16) (17).

Coffee is known to contain many antioxidants which help reduce oxidative stress (18). These include chlorogenic acid, flavonoids and melanoidins which significantly inhibit lipid oxidation (3) (19). Coffee also contains lipid soluble heterocyclic compounds which include furans, pyrroles and maltol along with other metabolites like caffeine, theobromine and xanthine. These are thought to have a protective effect by quenching hydroxyl radical generating systems (19). Conversely however, it was also found that coffee consumption increases serum cholesterol levels (20) and homocysteine levels (21), both of these increase cardiovascular risk (22) (23) which complicates the matter. The rise in serum cholesterol after coffee consumption is thought to be dependent on brewing method (24), with a meta-analysis published in 2001 showing that patients drinking filtered coffee demonstrated little increase in serum cholesterol as opposed to patients drinking unfiltered coffee (25) (20). This is thought to be mediated by cafestol and kahweol, which tend to be filtered by the filter paper (24).

The effects of caffeine consumption on vascular tone are rather interesting – caffeine can vasoconstrict (26) by antagonizaton of adenosine receptors (27) but may also vasodilate by promoting nitric oxide production in the endothelium (28) (29). In addition to this there is also thought to be suppression of cyclic GMP degradation in the endothelium which is thought to potentiate the vasodilatory effect (30) (29). This action is thought to be mediated by caffeine acting as a phosphodiesterase inhibitor (30). Umemura et al, theorised that this vasodilatory-vasoconstrictive balance may regulate vascular function, with their results showing an overall increase of peripheral blood pressure after acute caffeine administration (29).

Cytochrome P450 1A2 (CYP1A2) is the primary metaboliser of caffeine (31) and the CYP1A2 genotype has been indicated as a cause of variation between coffee consumption and cardiovascular risk (32). This may have some role in this mechanism.

*Limitations*

There were relatively few studies that were found which could be included in this meta-analysis.

There was no adjustment of confounding factors in the results of the present meta-analysis, but one of the studies (5) meta-analysed demonstrated that heavy coffee consumption did significantly reduce all-cause mortality after adjustment of potential confounding factors and the other study demonstrated this in one of its sub-analyses when looking at mortality within 90 days but did not show a significant relationship overall (4). The only controlled trial of coffee vs placebo identified in the literature search was a small non-randomised cross-over study in healthy volunteers (33).The authors found that coffee enhances HDL mediated cholesterol efflux in macrophages. Therefore, coffee may have anti-atherogenic property, at least in part by enhancing HDL-mediated cholesterol efflux from macrophages via its plasma phenolic acids.

The overall sample size meta-analysed included over 3200 patients in the present study. The absolute risk reduction associated with heavy coffee drinking compared with non-coffee drinkers was 9% (24% vs 15%). Thus, only 11 patients needed to be “treated” with > 2 cups of coffee per day to prevent one death after an acute MI. The Swedish paper specified cup volume was 150mL (5). But the size (volume) of the cups was not quantified in the other study (4). Finally, the median follow up duration differed between the 2 studies - 3.8 years (4) vs 2 years (5).

*Conclusions*

Drinking coffee habitually following an acute myocardial infarction was associated with a reduced risk of mortality.

**Conflict of Interest**: none declared

# References

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**Table 1**

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| First Author | Year | Country | Study period | Participant sex | Population size | Confounding factor adjusted for | Outcome Measure | Coffee consumption categories | Sample size | Cases | Age† | Hazard ratio\* | 95% Confidence interval\* |
| Mukamal et al (5) | 2009 | Sweden | 1992-2001 | M/F | 1369 | Age, sex, diabetes, smoking, obesity, physical inactivity, alcohol consumption, tea consumption, education, intake of boiled coffee, hypertension and systolic blood pressure. | Total mortality | 0-<1 cups/day1-<3 cups/day3-<5 cups/day5-<7 cups/day 7+ Cups/day | 192315405284173 | 5874795028 | 61.5 ± 6.861.2 ± 7.260.3 ± 6.757.8 ± 7.154.9 ± 6.4 | 1.000.730.520.600.59 | 0.46-1.160.37-0.850.34-0.830.34-0.98 |
| Mukamal et al (4) | 2004 | USA | 1989-1994 | M/F | 1902 | 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, B blockers, Ca channel blockers, ACEi, digoxin diuretics, lipid lowering agents), congestive heart failure or ventricular tachycardia during hospitalisation. | All-cause mortality | 0 cups/week>0-7 cups/week>7-14 cups/week>14 cups/week | 494517290601 | 109875465 | 65 ± 1365 ± 1262 ± 1256 ± 11 | 10.901.141.13 | 0.67-1.210.81-1.600.80-1.60 |

\*After multivariable regression analysis and adjustment for confounding.
† Mean values with standard deviations.

**Figures**

Figure 1Figure 2

**Legends**

**Figure legends**

**Figure 1.** Flow chart of process of study selection from our search results.

**Figure 2.** Forest plot showing the risk of mortality after acute myocardial infarction amongst a) light coffee drinkers vs non-coffee drinkers; b) heavy coffee drinkers vs non-coffee drinkers; c) heavy coffee drinkers vs light coffee drinkers.

**Table legend**

**Table 1**. Study characteristics of prospective cohort studies investigating the effect of coffee consumption on mortality after acute myocardial infarction that were included in the meta-analysis.