Caffeine does not increase the risk of atrial fibrillation: a systematic review and meta-analysis of observational studies

Daniel Caldeira,[1,2] Cristina Martins,[2] Luís Brandão Alves,[2] Hélder Pereira,[2] Joaquim J Ferreira,[1,3] João Costa[1,4,5]

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[1]Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Lisboa, Portugal
[2]Cardiology Department, Hospital Garcia de Orta, Almada, Portugal
[3]Neurological Clinical Research Unit, Instituto de Medicina Molecular, Lisbon, Portugal
[4]Faculty of Medicine, Center for Evidence-Based Medicine, University of Lisbon, Lisbon, Portugal
[5]Faculty of Medicine, Portuguese Collaborating Center of the IberoAmerican Cochrane Network, University of Lisbon, Lisbon, Portugal

Correspondence to
Dr Daniel Caldeira, Laboratório de Farmacologia Clínica e Terapêutica, Faculdade de Medicina da Universidade de Lisboa, Av. Prof. Egas Moniz, Lisboa 1649-028, Portugal; dgcaldeira@hotmail.com

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ABSTRACT

Background Atrial fibrillation (AF) is the most prevalent sustained arrhythmia, and risk factors are well established. Caffeine exposure has been associated with increased risk of AF, but heterogeneous data exist in the literature.

Objective To evaluate the association between chronic exposure to caffeine and AF.

Design Systematic review and meta-analysis of observational studies.

Data sources PubMed, CENTRAL, ISI Web of Knowledge and LILACS to December 2012. Reviews and references of retrieved articles were comprehensively searched.

Study selection Two reviewers independently searched for studies and retrieved their characteristics and data estimates.

Data synthesis Random-effects meta-analysis was performed, and pooled estimates were expressed as OR and 95% CI. Heterogeneity was assessed with the I^2 test. Subgroup analyses were conducted according to caffeine dose and source (coffee).

Results Seven observational studies evaluating 115 993 individuals were included: six cohorts and one case–control study. Caffeine exposure was not associated with an increased risk of AF (OR 0.92, 95% CI 0.82 to 1.04, I^2=72%). Pooled results from high-quality studies showed a 13% odds reduction in AF risk with lower heterogeneity (OR 0.87; 95% CI 0.80 to 0.94; I^2=39%). Low-dose caffeine exposure showed OR 0.85 (95% CI 0.78 to 92, I^2=0%) without significant differences in other dosage strata. Caffeine exposure based solely on coffee consumption also did not influence AF risk.

Conclusions Caffeine exposure is not associated with increased AF risk. Low-dose caffeine may have a protective effect.

INTRODUCTION

Atrial fibrillation (AF) carries a significant burden for both patients and society because it is the most common sustained cardiac arrhythmia, and it is associated with increased cardiovascular morbidity and mortality, mainly due to the higher risk of thromboembolic events.[1–3] Classical risk factors include advanced age, congestive heart failure, valvular diseases, left ventricular hypertrophy, arterial hypertension, ischaemic heart disease, male gender, diabetes mellitus, endurance exercise and smoking.[4]

Caffeine is a major component of some of the most widely consumed beverages, such as coffee and tea.[5] The association between caffeine exposure and risk of heart disease has received extensive attention in the literature.[6–13] Inconsistencies between results have been attributed to differences in study design and presence of confounders, in particular tobacco smoking. Results from a recent meta-analysis of observational studies and from large cohort studies suggest a mild-to-moderate inverse association between coffee drinking and cardiovascular risk factors and diseases, including global mortality and death due to heart disease.[13]

The association between caffeine exposure and AF is currently unknown, although a positive association has been suggested in the literature.[14 15] To further evaluate this putative association, we performed a systematic review and meta-analysis of observational studies.

METHODS

This systematic review had PRISMA and MOOSE guidelines as standards for reporting data.[16 17]

Eligibility criteria

Randomised controlled trials, prospective or retrospective cohorts and case–control studies evaluating exposure to caffeine (whether as coffee, tea, chocolate or caffeinated beverages) and risk of AF (or atrial flutter) were eligible. Studies addressing the effects of short-term exposure to caffeine (ie, <6 months) as well as studies evaluating caffeine exposure in patients already in AF were excluded. Studies that met inclusion criteria were not excluded a priori on the basis of weakness of design or data quality.

Information sources and search process

Two investigators retrieved potential eligible studies through an electronic search in PubMed, CENTRAL, ISI Web of Knowledge and LILACS, from inception to December 2012. The search strategy for PubMed (in online supplementary information) included free-text words and MeSH (Medical Subject Headings) terms without language restrictions. In addition, we screened and cross-checked identified systematic reviews and meta-analyses evaluating caffeine exposure and heart diseases or cardiovascular risk factors, as well as reference lists of papers found for potential additional studies.

Data extraction, evaluation and synthesis

Titles and abstracts of obtained records were screened by two authors (DC and JC). Doubts and disagreements were solved by consensus. Selected

studies were assessed in full-text to determine their appropriateness for inclusion. Study characteristics and results were extracted independently by two authors (DC and JC) into a standardised form. We also extracted the following variables: population characteristics, region of study, study follow-up, caffeine exposure assessment, reference category, outcome assessment and outcome adjustments.

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

When different risk estimates for the same strata 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 caffeine intake, using these criteria sequentially.

The effect measurement estimate chosen was OR because relative estimates are more similar across studies with different designs, populations and lengths of follow-up than absolute effects.[18] Studies presenting risk ratio or HR adjusted estimates were considered as OR.

Reporting quality was independently evaluated by two investigators (DC and JC) using a qualitative classification according to risk of bias (high, unclear or low risk). We used a five-item classification system based on MOOSE, QATSO and STROBE adapted from previous published quality assessment instruments.[17 19–22] The following items were taken into consideration: (1) participants, if the population was adequate and the study reported appropriate inclusion and exclusion criteria; (2) exposure, if caffeine exposure use was adequately assessed through food questionnaires; (3) outcome, if AF was assessed by clinical, ECG methods or through database codes, and not exclusively based on self-report; (4) specific outcome adjustments, for both age and at least one of cardiovascular disease, alcohol intake or smoking; (5) other adjustments.

Data analysis

We used RevMan V.5.1.7 software for statistical analysis (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) and to derive forest plots showing the results of individual studies and pooled analysis. For primary analysis, we performed random-effects meta-analysis weighted by the inverse variance method to estimate pooled ORs and 95% CIs. For this purpose, in case studies that did not report a single estimate for consumers versus non-consumers, but expressed multiple levels of exposure, we pooled these estimates against the lowest quintile to derive an overall OR for that study, which was then used for pooled analysis.

We used a random-effects model independently of the existence of statistical heterogeneity because we combined studies with different designs and populations. We presented the results stratified according to study design (cohort and case–control) in order to explore differences in the outcome estimate. Statistical heterogeneity was assessed with the I^2 test, which measures the percentage of total variation between studies due to heterogeneity.[23] If significant heterogeneity was found, we planned to perform a sensitivity analysis excluding studies of poorer quality to explore the impact of the study quality on the results.

We planned to conduct three subgroup analyses: (1) to explore the effect of the level of caffeine exposure on AF risk; (2) to explore the effect of the source of caffeine on AF risk; (3) to explore the effect of the length of follow-up. For the first analysis, we considered three levels of caffeine intake: low, moderate and high. The highest category of exposure reported in each study was considered for the group of high caffeine intake, independently of the cut-off value used in that study. We considered low intake to be <350 mg, moderate intake 350–699 mg and high intake ≥700 mg. Many factors contribute to the caffeine content of beverages and food and differences exist in caffeine content of a given caffeine source (in particular coffee) between, and even within, countries.[24 25] For the purpose of this study, when cups of coffee were provided as a measure of caffeine intake, we considered each cup to have an amount of caffeine according to the geographic region of the study; UK/Northern Europe 140 mg; Southern Europe 50 mg; USA 85 mg.[25] When a study's interval for caffeine consumption crossed two of the above mentioned categories, we considered for analysis the mean value of caffeine intake.

For the second subgroup analysis, we considered only studies that took coffee consumption as the sole source of caffeine exposure because this beverage was the main source of caffeine.

In the third subgroup evaluation, we assessed pooled estimates according to follow-up, using the value of 10 years as the threshold (<10 vs ≥10 years).

Publication bias was assessed through visual inspection of funnel plot asymmetry and the Peters regression test.[26]

RESULTS

An electronic database search performed in December of 2012 yielded a total of 266 published references. Following our inclusion and exclusion criteria, we were able to include seven studies for analysis. Online supplementary figure S1 shows the detailed results of the search strategy. The main reasons for excluding studies were the type of publication (eg, basic science studies and case reports) and failure to report exposure to caffeine or caffeine-containing products. Eleven studies were excluded in the late stages of the selection process. These included patients already in AF (n=3), studies assessing acute effects of caffeine mostly within 72 h (n=3), abscence of AF incidence data (n=1), and review papers (n=4). Reviews were analysed to retrieve any missing study not identified by the electronic search.[27–30]

Description of studies

Seven studies fulfilled the inclusion criteria. One study had a case–control design[31] and six were cohort studies.[32–37] The case–control study had a retrospective design, five cohort studies were prospective, and the remaining one was unclear.[32] Four studies reported data exclusively for coffee,[31 32 34 37] whereas the other three referred to overall caffeine-containing beverages/food.[33 35 36] Three studies were conducted in the USA and four in Europe (three in Scandinavia and one in Italy). The lengths of the studies were considered to be reasonable, with a mean follow-up ranging from 4 to 25 years in the cohort studies.

Overall, 115 993 patients were included in these seven studies (ranging from 232 to 57 053 patients). The mean age of participants at baseline varied between 51 and 62 years-old. Table 1 shows the main study characteristics.

The reporting quality of the included studies was globally acceptable (see online supplementary figure S2). All studies showed correct reporting of participants' inclusion/exclusion criteria and correctly fulfilled the outcome assessment criterion. The method of caffeine exposure ascertainment was unclear in the study of Wilhelmsen and colleagues.[32] Neither the Wilhelmsen nor the Mattioli study reported their estimates adjusted for several potential confounders.[31 32] Wilhelmsen

Table 1 Main characteristics of included studies

Study/year	Design	Region	Population	Follow-up (years)	Age (years)/ male %	Caffeine exposure	Comparator/ reference category	Outcome assessment	Outcome adjustments
Mattioli 2005[31]	Case–control study	Italy	116 patients hospitalised for an acute episode of lone AF 116 healthy outpatient age- and sex-matched control subjects.	N/A	54/74%	Self-administered questionnaire	Non-coffee drinkers: 0 cups per day	ECG evaluation	None (crude OR)
Wilhelmsen 2001[32] Multifactor Primary Prevention Study	Cohort	Sweden	7495 male individuals who participated in Multifactor Primary Prevention Study	25.2	47–55/ 100%	Not defined	Non-coffee drinkers: 0 cups per day	ECG, hospital records and AF ICD-9 codes	Age
Frost and Vestergaard 2006[33] Danish diet, cancer, and health study	Prospective cohort	Denmark	57 053 individuals aged between 50 and 64 years	5.7	56/47%	Food frequency questionnaire was applied and quantity of caffeine was derived with FOODCALC software	First quintile: mean caffeine intake 248 mg/ day (SD 91)	ICD-8 and ICD-10 codes	Age, sex, body height, BMI, smoking, consumption of alcohol, systolic blood pressure, treatment for hypertension, total serum cholesterol, and level of education
Mukamal 2009[34] Stockholm Heart Epidemiology Program (SHEEP)	Prospective cohort	Sweden	1369 survivors of myocardial infarction and included in SHEEP	6.9–9.9 in patients free from events	59.8/ 70.2%	Cups of coffee per day assessed through questionnaire	0 to <1 cup of coffee per day	ICD-10 codes	Age, sex, diabetes, smoking, obesity, physical inactivity, alcohol consumption, tea consumption, education, and intake of boiled coffee
Conen 2010[35] Women's Health Study (WHS)	Prospective cohort	USA	33 638 women older than 45 and free from CV disease	~10	53/0%	Food frequency questionnaire was applied in order to determine specific amount of coffee, tea, cola and chocolate	First quintile: median caffeine intake 22 mg/day (IQR 9–44)	AF reporting by individuals prompted medical record review to retrieve ECG evidence of AF or a clear medical report indicating a personal history of AF	Age, systolic blood pressure, BMI, hypertension, diabetes, hypercholesterolaemia, smoking, exercise, alcohol consumption, parental history of myocardial infarction, treatment group, fish intake, and race/ethnicity
Shen 2010[36] Framingham Heart Study	Prospective cohort	USA	4526 adults from Framingham Heart Study original and offspring cohort	4	62/44%	126-item semiquantitative food frequency questionnaire	First quintile: mean caffeine intake 23 mg/day (minimum 0; maximum 82)	AF was ascertained and recorded from interim medical evaluations. Afterwards it was validated by cardiologists who reviewed and classified all available ECG and clinical records	Age, sex, BMI, systolic blood pressure, hypertension treatment, ECG, PR interval, significant heart murmur, and heart failure
Klatsky 2011[37]	Prospective cohort	USA	11 679 individuals who voluntarily underwent a health examination before subscribing to a healthcare plan and supplied information about coffee	17.6	43.4% >60 y 47.2%	Questionnaire that included coffee and tea consumption patterns	Non-coffee drinkers	ICD-9 codes	Age, sex, ethnicity, BMI, education, cigarette smoking, alcohol intake and a cardiorespiratory composite covariate

AF, atrial fibrillation; BMI, body mass index; CV, cardiovascular; ICD, International Classification of Diseases; N/A, not available.

et al only reported the age-adjusted estimate.[32] For the Mattioli study, we had to derive the crude OR from the raw data.[31]

Risk of AF

There was no significant association between caffeine exposure and AF risk (OR 0.92; 95% CI 0.82 to 1.04; I^2 72%). We found similar results when considering pooled results from cohort studies (OR 0.91; 95% CI 0.81 to 1.02; I^2 73%) and from the single case–control study (OR 1.36; 95% CI 0.84 to 2.19), which had a small weight in the overall pooled analysis (4.7%). Figure 1 shows the forest plot with individual study results and pooled analysis.

Significant heterogeneity existed between the results of the studies (I^2=72%). Sensitivity analysis after exclusion of studies of poorer quality (studies in which the caffeine exposure assessment method was unclear[32] and/or that failed to report AF risk estimates adjusted for multiple counfounders[31 32]) explained about half the heterogeneity among results (decrease of I^2 from 72% to 39%). Moreover, the pooled estimate became significant with a 13% reduction in the odds of AF among caffeine consumers (OR 0.87; 95% CI 0.80 to 0.94; I^2=39%).

Subgroup analysis

Analysis according to the level of caffeine exposure, showed that people with a low intake may be at lower risk of AF (OR 0.85; 95% CI 0.78 to 0.92; I^2 0%). No differences existed for the other categories (figure 2).

Four studies (three cohort studies and one case–control study) reported caffeine exposure based on coffee consumption estimates (figure 3).[31 32 34 37] Results were similar to overall caffeine exposure (OR 0.94; 95% CI 0.72 to 1.22; I^2=85%).

We performed an aggregation of studies according to mean/median follow-up, taking 10 years as the threshold. We found a statistically significant association between caffeine exposure and AF protection (OR 0.88; 95% CI 0.78 to 0.98; I^2=49%) in the subgroup of studies with <10 years of follow-up. The pooled estimate of the two studies with ≥10 years of follow-up did not show any significant association with increased or decreased risk of incident AF (OR 0.99; 95% CI 0.71 to 1.36; I^2=92%).[32 37] There were no differences between the estimates of the group with <10 years follow-up and the group with ≥10 years of follow-up (p=0.51).

Publication bias

Visual inspection of funnel plots shows symmetry, suggesting that publication bias was not a major drawback of our review (see online supplementary figure S3). However, direct interpretation of funnel plots with a small number of studies is not recommended and often inconclusive.[38] A funnel plot is shown in online supplementary figure S3. The Peters regression test did not show any significant publication bias (p=0.134).

DISCUSSION

The main finding of this systematic review is that the best evidence available does not support the hypothesis that caffeine exposure increases the risk of AF.

Our study had the merit of overviewing studies and giving an estimate with increased statistical power through meta-analysis. Heterogeneity was significant, and many factors could have contributed to this result. We included both cohort and case–control studies, and follow-up was different among the studies. Nevertheless, the most important source of heterogeneity can be attributed to differences in the estimates reference category and outcome adjustments to confounders. In fact, sensitivity analysis after exclusion of studies of poorer quality showed significantly reduced heterogeneity and suggests an inverse association between caffeine exposure and AF risk. Three of the seven studies reported estimates of caffeine/coffee consumption compared with the first quintile. The mean/median caffeine intake in these cases was about 22–23 mg/day, but the Danish Diet, Cancer, and Health Study first quintile of caffeine consumption was 10 times higher (248 mg/day) because of the high average daily caffeine intake in Northern Europe.[33] The Mattioli and Wilhelmsen studies did not report either minimum or other adjustments in outcome estimates.[31 32]

Myers has previously reviewed the clinical data on the association between caffeine exposure and risk of cardiac arrhythmias. He found no increase in the frequency or severity of cardiac arrhythmias in healthy subjects, or in patients with ischaemic heart disease or known ventricular arrhythmias.[30] Klatsky *et al*[37] also failed to detect any increased risk of global

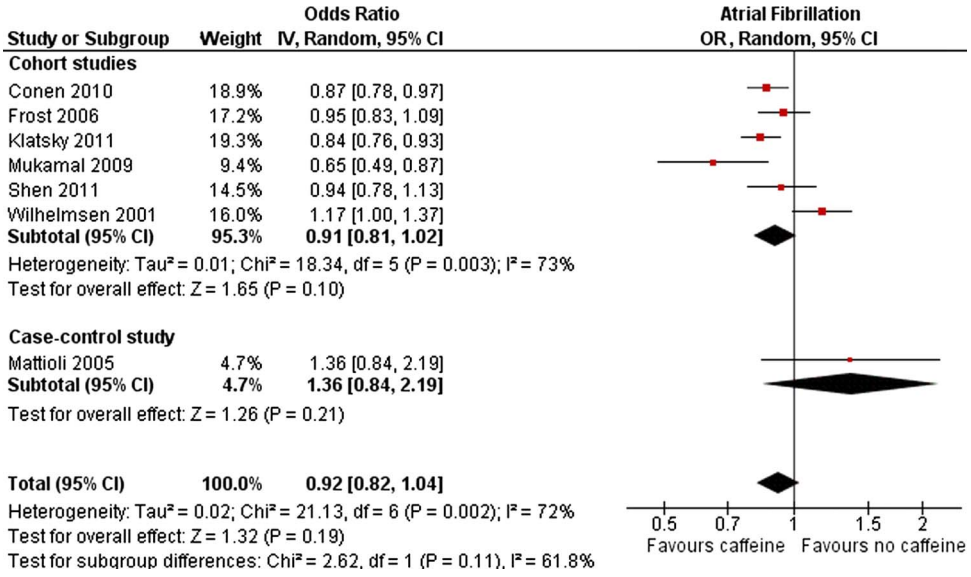

Figure 1 Caffeine intake and risk of atrial fibrillation.

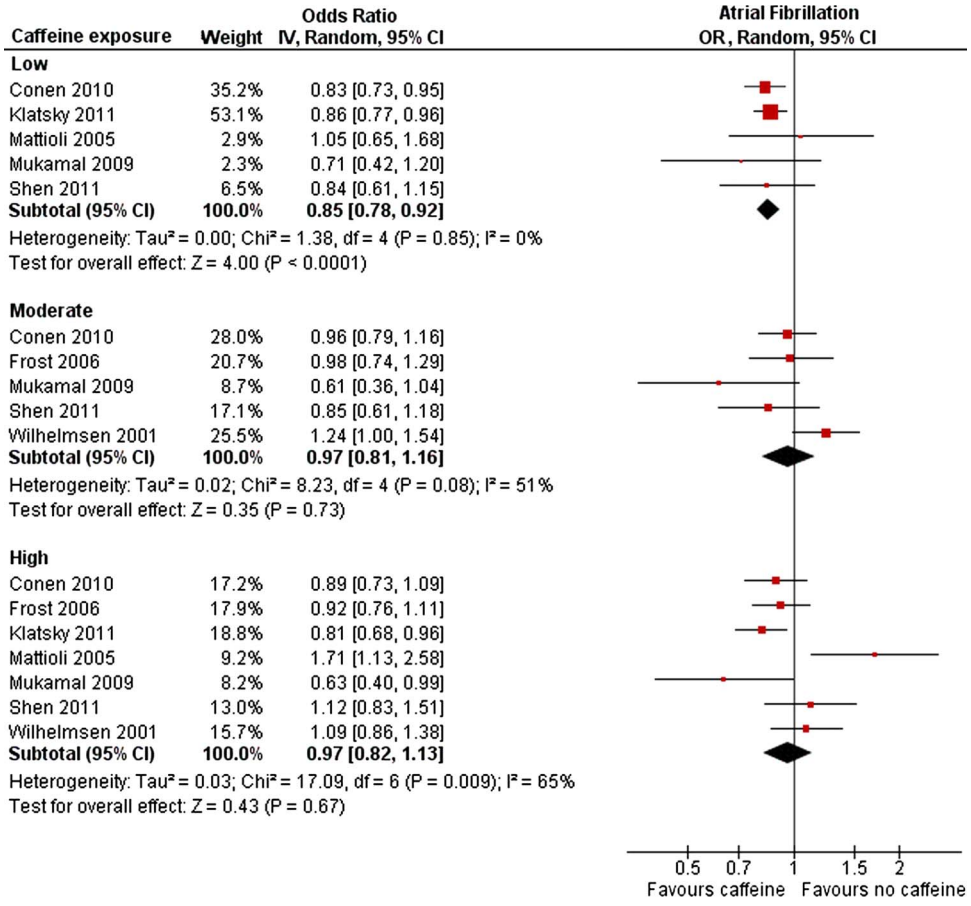

Figure 2 Risk of atrial fibrillation according to caffeine exposure.

arrhythmias. In fact, a small yet significant risk reduction was found in this study for arrhythmias among coffee drinkers (HR 0.97 per cup per day; 95% CI 0.95 to 0.99). The acute effect of caffeine on heart rate has been studied in randomised controlled trials, and the results point towards a decreased heart rate, particularly in the subset of individuals who are not caffeine-naïve.[39 40] Previous ECG studies showed that caffeine exposure (by means of coffee consumption) had no effect on the analysis of the signal-averaged P-wave from atrial ECG.[41 42]

Previous systematic reviews have addressed the question whether caffeine exposure (mainly based on coffee) increase the incidence of conditions considered to be AF risk factors. Zhang and colleagues showed that coffee intake did not increase the risk of arterial hypertension.[43] Similarly, coffee intake does not appear to be associated with coronary heart disease, another

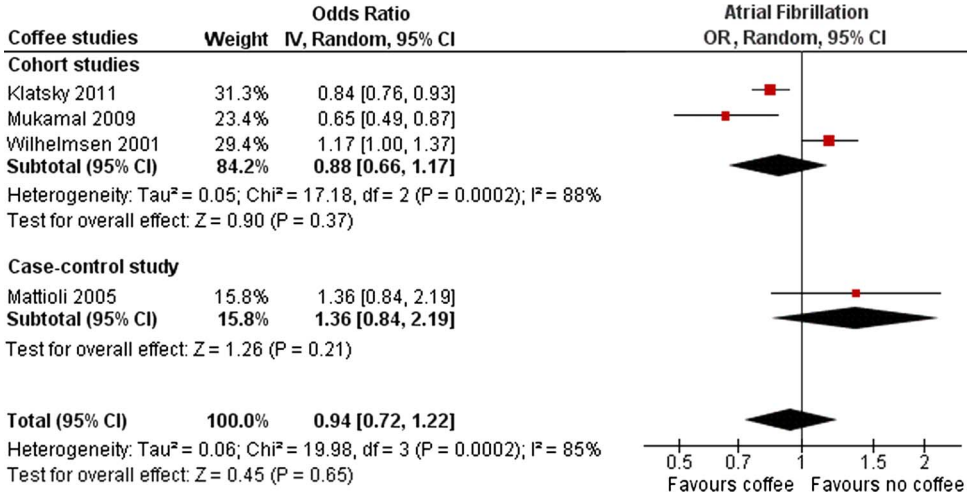

Figure 3 Coffee intake and risk of atrial fibrillation.

important risk factor for AF.[9] Evidence exists for a reduced risk of heart failure among coffee consumers.[11]

In this study, we found that subjects in the low-dose caffeine exposure category may benefit from a reduction in AF risk. We can only speculate whether this finding is a sketch of a J-shape curve, a well-known epidemiological phenomenon,[44 45] because of the relatively small number of studies included. This putative dose–response effect was in fact documented in a previous meta-analysis for coffee intake and heart failure incidence.[11]

Limitations

Our review has limitations inherent to the included studies themselves and to meta-analytical methodology.

Pooling data of studies with different designs that evaluated different populations should also be considered a potential limitation. Nevertheless, it increases the power and external validity of the data obtained. Furthermore, pooled results of studies of acceptable quality provided estimates with low heterogeneity and suggestive of a protective effect.

In most studies, caffeine exposure is estimated on the basis of coffee consumption. Although caffeine is one of the major components of coffee, other substances such as chlorogenic acid, cafestol, kahweol, flavonoids, melanoidins and quinide can contribute to the pleiotropic effects of coffee.[46 47] The association in such studies may have been biased.

CONCLUSIONS

There are no data to support the hypothesis that long-term caffeine exposure is associated with an increased risk of AF. Conversely, the exposure to low doses of caffeine may offer a small protective effect against AF.

Contributors DC and JC contributed to the concept and design of the study and acquisition, 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. JJF contributed to the concept and design of the study and interpretation of the data, critically revised the manuscript, and gave final approval of the submitted manuscript. CM, HP and LBA contributed to interpretation of data, critically revised the manuscript, and gave final approval of the submitted manuscript.

Competing interests None.

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