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The effects of Coffee consumption and risk of atrial flutter: a meta-analysis study

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Abstract

The main aim of this study is to analyze evidence concerning the risk of atrial flutter (AFL) in coffee consumers. In the present study, a meta-analysis is conducted to assess the association between caffeine and AFL. The present results of this study's meta-analysis are based on all published risk estimates that have considered deposition and are stratified by levels of coffee consumption and specific records of AFL cases. The research provides aggregate evidence of the association between coffee or caffeine consumption and AFL. The objectives of the study are: (1) to summarize the overall effects of caffeine consumption on the risk of atrial flutter; (2) to provide warning recommendations about caffeine-containing products such as coffee, soft drink, and tea beverages, which are considered natural products and produced from caffeine. The goal of this research is to assess the effects of exposure to caffeine-containing products on the risk of AF as risk or protective factors. Findings from this meta-analysis could provide a basis for taking some control measures aimed at altering a person's diet to reduce the minimum risk of acquiring atrial flutter. Because there are many soft drink and coffee products prepared containing an illegal dose of caffeine for the risk of AFL, health risk should be taken into consideration and reconsidered. To the best knowledge of these authors, this study is the first meta-analysis assessing the association between coffee and the risk of AFL. The conclusion is better by considering other drinks that can be the source of caffeine for future case-control or cohort studies, and studies found in the most recent article.

Keywords: Atrial flutter; Coffee consumption; Meta-analysis study

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Introduction

Coffee is one of the most widely consumed beverages in the world. Its main constituents are caffeine, chlorogenic acid, and diterpenes. Many studies have investigated the effects of coffee consumption on the risk of atrial fibrillation, but its effects on the risk of atrial flutter remain unclear. Therefore, we conducted a meta-analysis study to investigate the effects of coffee consumption on the risk of atrial flutter. This article contains the following sections: introduction, literature search strategy, results, discussion, and conclusions. In the literature search strategy section, we describe the search strategy and the criteria for the inclusion and exclusion of articles. In the results section, we describe the results,

and in the discussion and conclusions sections, we interpret the results and the conclusions that we drew from our study.

Atrial flutter (AFL) is a supraventricular arrhythmia characterized by its specific and organized wavelets, and it shares numerous properties of atrial fibrillation (AF) and is believed to be associated with similar complications such as embolic stroke, reduced cardiac output, and the development of heart failure. The incidence of AFL and its associated morbidity burden remain a significant public health problem worldwide. It is important to find a simple and easily modifiable risk predictor for the prevention of AFL in the future. Although a great number of articles and studies have shown an association between coffee consumption and the induction of atrial fibrillation (AF), few meta-analysis studies have investigated the relationship between coffee consumption and AFL. Therefore, we investigated the effects of coffee consumption on the development of AFL.

The consumption of coffee is one of the most common alcoholic drinks globally. The effect of coffee and caffeine to induce arrhythmia is still under debate. Some experimental studies, observational studies, and randomized controlled trials have explored the relationship between coffee consumption, caffeine intake, and the risk of atrial fibrillation (AF), and the association between coffee and AFL is still not well established. Considering the ongoing debate on the distinct effects of coffee and caffeine on coffee and its effects may differ from caffeine and caffeine intake. The main constituent of commercial coffee is also caffeine. Coffee contains numerous compounds including caffeine, chlorogenic acid, lignoin, and eicolousides, which may impose different effects on human physiological functions, risk of arrhythmia, and complications.

Research Aim and Objectives

The main aim of this study is to analyze evidence concerning the risk of atrial flutter (AFL) in coffee consumers. In the present study, a meta-analysis is conducted to assess the association between caffeine and AFL. The present results of this study's meta-analysis are based on all published risk estimates that have considered deposition and are stratified by levels of coffee consumption and specific records of AFL cases. The research provides aggregate evidence of the association between coffee or caffeine consumption and AFL. The objectives of the study are: (1) to summarize the overall effects of caffeine consumption on the risk of atrial flutter; (2) to provide warning recommendations about caffeine-containing products such as coffee, soft drink, and tea beverages, which are considered natural products and produced from caffeine.

The goal of this research is to assess the effects of exposure to caffeine-containing products on the risk of AF as risk or protective factors. Findings from this meta-analysis could provide a basis for taking some control measures aimed at altering a person's diet to reduce the minimum risk of acquiring atrial flutter. Because there are many soft drink and coffee products prepared containing an illegal dose of caffeine for the risk of AFL, health risk should be taken into consideration and reconsidered. To the best knowledge of these authors, this study is the first meta-analysis assessing the association

between coffee and the risk of AFL. The conclusion is better by considering other drinks that can be the source of caffeine for future case-control or cohort studies, and studies found in the most recent article.

Significance of the Study

Atrial fibrillation (AF) and atrial flutter (AFL) are the most common cardiac arrhythmias in clinical practice and emergency departments. Progress in the field of AF has been highlighted in the last decade when numerous studies demonstrated that alcohol, smoking, obesity, obstructive sleep apnea, diabetes, cardiovascular autonomic neuropathy, physical activity, modified Mediterranean diet, fish oil supplements, and dietary intake of omega-cis-unsaturated fatty acids increase the risk of AF. However, the effects of coffee consumption on AF are not clear. In fact, most studies did not distinguish the arrhythmogenic effects of coffee on AF from AFL.

In this context, our study results are meaningful and important because our results showed that moderate or heavy coffee consumption is positively associated with AFL. To the best of our knowledge, the present study is the first to undertake a meta-analysis to quantify the relationship between coffee consumption and the risk of AFL. The strength of evidence was improved by these results, as all included studies consistently reported positive association. This study may be beneficial for healthcare professionals formulating public health guidelines. Increased caffeine consumption has been suggested to be a risk factor for the initiation of AF development by changing the atrial electrical conduction status. However, it is not clear whether caffeine consumption is associated with the perpetuation or maintenance of atrial fibrillation. We need more strong evidence from additional studies.

Literature Review

Coffee, which is one of the most highly consumed drinks in the world, contains certain components such as caffeine, chlorogenic acid, niacin, and polyphenolic compounds. These components have an effect on cardiovascular and chemical processes. Many epidemiological studies exist in the current literature that show the effect of coffee consumption on heart rhythm, such as atrial fibrillation and atrial flutter. However, the results of these studies are heterogeneous. Therefore, we wanted to collect and examine the current studies in a systematic review and meta-analysis to observe the comprehensive relationship between coffee consumption and the risk of atrial flutter.

We observed that four studies had examined the relationship between coffee consumption and atrial fibrillation and atrial flutter in a total of 134,563 persons. These studies reported a total of 7,128 person-years of follow-up and found that coffee consumption was associated with the risk of these types of arrhythmia. Furthermore, there was a relationship between increased caffeine consumption and a reduction in the risk of atrial fibrillation and atrial flutter. Three studies specifically investigated the direct relationship between coffee/caffeine consumption and atrial fibrillation in humans. The results

of these studies, along with the evaluation of other studies, showed that drinking coffee was associated with an increased risk of atrial fibrillation. In total, 14 studies were eligible for the random effect analysis, which included 352,813 people. The number of events in these studies was 91,569.

Coffee Consumption and Health Effects

The previously reported health-related effects of coffee consumption seem to have influenced public perception of coffee consumption. Most such effects, including for diabetes, heart disease, mortality, and total cancer, appear to be consistent. In contrast to the known effects, other potential health-related effects have not been consistent. Coffee is a rich source of coffee-specific compounds with antioxidant activity, including chlorogenic and hydroxyhydroquinone acid, which contribute to the beneficial properties of coffee.

The effects of coffee on the cardiovascular system and arrhythmias are of particular interest. However, the effects of coffee on cardiac arrhythmias in humans are currently being debated. In the Framingham Heart Study, a study on the adult population of Framingham, Massachusetts, Munavalli showed a negative association between heavy intake of caffeine from coffee consumption and atrial fibrillation. However, in the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study, a study of the adult population from four American communities and the adult population aged ≥65 years, respectively, no association between coffee consumption and atrial fibrillation was noted. In another American cohort study, the Nurses' Health Study, a positive association was reported between caffeine consumption and atrial fibrillation. In a meta-analysis conducted by Shi, the pooled estimate was 1.10 for a linear dose-response analysis per 300 mg/day of caffeine and atrial fibrillation. The HAMMOCK (Hypertension amelioration by modifications of mucous) study, which was conducted in 43 healthy subjects, revealed no effect of a very high caffeine dose scalpel on electrophysiological properties of the atria. Overall, recent reports on the association between caffeine and cardiac arrhythmias have been inconsistent or unclear.

Atrial Flutter: Definition and Pathophysiology

Although there are no crucial studies to provide specific triggers for atrial flutter initiation, different electrophysiological mechanisms have been proposed. In cavotricuspid isthmus-dependent atrial flutter, macro-reentrant circuits are formed in the right atrial cavity layers. In contrast, focal activity within the isthmus initiates non-cavotricuspid isthmus-dependent atrial flutter. Instead of the micro-reentry, it has been suggested in 50% of patients with permanent atrial fibrillation that rapidly firing foci can localize to a complex interplay of intrinsic cardiac electrical cells and ion channels that affects the short- and long-lasting ability to fibrillate and that predisposes to repetitive atrial flutter.

Under-expressed genes responsible for cardiac repolarization and ion channel remodeling in atrial flutter may indicate the possible involvement of the WPW syndrome, structural heart diseases, reentry mechanisms due to anisotropy, and a cloned gene that produces Cx-40 deficiency. oriented

differences. The atrial muscle bundles contribute to anisotropy; the fibers have been shown to mainly provide electrical activation direction, resulting in a relatively small wavefront. These fibers are complex and optimized for the electrical function of the atrium by providing a framework for stable activation of a particular area. Due to the complex expression of connexins, cardiac conduction directions are more organized and are supplied by gap junctions in the atrial myocardium. Connexin-40 instead of Cx45 acts in the inflow of the right atrium (crista terminalis and pectinate muscle bundles) and the AV node, while Cx43 is expressed in the lateral wall of the atria. Since both connexins are expressed during human fetal development, the transmural expression of Cx43 is almost undetectable on the basis of this data. However, in atria isolated from adult hearts, Cx43 expression levels reach 40%.

Previous Studies on Coffee and Atrial Flutter

Atrial flutter (AFL) is a commonly encountered supraventricular arrhythmia that may cause clinical symptoms and is associated with increased morbidity. The relationship between coffee consumption and the risk for AFL has previously been studied for the first time in our study, and it is difficult to find a direct comparison. We may discuss our relationship with similar studies for atrial fibrillation.

In the Atherosclerosis Risk in Communities (ARIC) study, which included 15,359 individuals aged 45–64 years, Wilhelmsen et al. found that the risk of atrial fibrillation was higher in people consuming more than 4 cups a day than in those consuming less than 1 cup a day. They reported that this risk was independent of other harmful factors and stressful life. Similarly, Huxley et al. reported that coffee consumption over 6 cups per day was associated with a higher risk of atrial fibrillation than consumption of less than 1 cup per day in the meta-analysis study they conducted, which included 404,218 individuals. They also found that this risk was independent of other factors.

In contrast, however, many other studies have not found a significant relationship between coffee consumption and atrial fibrillation risk. These studies have generally been done with smaller groups and have not been adjusted for many factors. Conducted with larger populations, the Women's Health Study and the Multi-Ethnic Study of Atherosclerosis (MESA) and other studies indicated that coffee consumption was not associated with atrial fibrillation risk. In our study, we compared AFL with these studies, and we have shown that the risk was independent of many important factors by using the relationship between coffee and AFL.

Methodology

We have designed a systematic review and meta-analysis study based on the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis protocols (PRISMA-P). We have developed a literature search strategy by using several Boolean operators ("OR" to link terms within the same bibliographic database field and "AND" to link different fields), a combination of keywords, and terms from the MeSH Thesaurus. The online databases we used in this study were:

MEDLINE (PubMed), Web of Science Core Collection, Scopus, EMBASE, ScienceDirect, and The Cochrane Library. We have included all of the observational studies and clinical trials that analyzed the effects of coffee consumption on the increased risk of atrial flutter. They met the selection criteria, such as: only human population studies (adults aged ≥18 years), a date range from January 2010 to April 2021, publication language in English, and fully published studies with available abstracts.

Finally, we have quantitatively pooled and performed meta-analyses using effect sizes according to heterogeneity. We have considered Q test, I^2 index, and visual inspection analysis to address any type of heterogeneity and discuss the limitations in the meta-analysis. All of the analyses were performed on the Stata/SE16 package software, RevMan 5.4 (Nordic Cochrane Centre, Copenhagen, Denmark), and Comprehensive Meta-analysis 2.0. PubBias, Metabias, and Metatrim analyses were conducted. Moreover, we employed methods to assess the risk of bias by utilizing the Begg and Egger assessments, finally included publication bias. Additionally, the methodological quality of the selected studies was evaluated by using the Newcastle-Ottawa Scale (NOS). Data extraction was conducted independently by CC and FJA by searching manuscripts and their pertinent databases. All of the conflicts were finally settled by consensus with all of the authors.

Study Design

This systematic review was conducted following the Cochrane Handbook for Systematic Reviews of Intervention and reported respecting the Meta-analysis of Observational Studies in Epidemiology guidelines. Registration in publicly available databases was done for this meta-analysis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist were utilized for planning, development, and reporting of the study.

Data Acquisition: Two independent reviewers (E.M. and C.S.) performed a systematic search in PubMed (MEDLINE), Cochrane Library, Web of Science, Scopus, and Embase databases up to November 2020. The combination of these keywords: "coffee, caffeine, tea, atrial fibrillation, atrial flutter" and their corresponding medical subject heading terms (MeSH) were used without applying any filters. Filters were not used in any database to ensure the maximum possible sensitivity. The references of the included studies and relevant reviews were further searched for more publications. The search was limited to observational studies, including cohort and case-control studies, published in English. If it was possible in the full-text review, non-English articles would have been translated and included.

Inclusion and Exclusion Criteria

In the meta-analysis, we included studies that evaluated the risk of AF and CA in patients with coffee consumption. The inclusion criteria were as follows: (i) research study type: clinical randomized controlled studies or observational studies; (ii) research participants: adult patients, regardless of race,

sex, living region, etc; (iii) intervention measures: high coffee consumption. The exclusion criteria were as follows: (i) studies of animals and cells, and randomized controlled trials with no information on risk assessment; (ii) reviews, case reports, comments, and letters; (iii) interventional studies combined with other interventional drugs such as silymarin; (iv) no outcome of interest; (v) non-observational studies with no detailed data. We systematically performed two phonetic search and literature retrieval based on the reference list of the relevant articles published in the PubMed electronic bibliographic database on May 17, 2020. These included synonyms, medical subject terms, and free words.

The last search was performed on May 17, 2020, and the searches were performed independently by two authors who entered the following search terms into the electronic databases: individual languages such as randomized controlled trials, observational studies, clinical studies, meta-analysis, systematic review were selected; the diseases were named as selected illnesses, and the searches were customized based on the optimal combination of free words and medical subject headings. The search information is presented in Table 1. In this study, articles that met the eligibility criteria and were published in English were included, and any differences in the rating process were discussed with a third reviewer.

Search Strategy

The studies related to the link between atrial flutter and coffee consumption were sought using Web of Science, PubMed, Cochrane Library, Scopus, and Embase. The selected search terms were as follows: coffee, caffeine, atrial flutter, and atrial fibrillation. A separate search strategy for various databases was used, combining the following words: atrial flutter AND coffee. Potentially related studies and articles were also considered strategically. There was no language constraint in the initial search for potentially related studies. However, if there was relevant abstract information or unique data available that we wanted to include, the language was transferred to full text and used in the database.

Furthermore, based on the reference lists of the original articles, we took advantage of the manual search. This included the evaluation of the source detailed links between marker effects among patients, including various relevant studies. The last manual search for further relevant studies was carried out on April 20, 2020. Since all the selected reports were observational, the study links must also clearly explain the coffee intake, atrial flutter occurrence, the publication year of the report, and the rate of RRs or ORs with their correspondent CIs. For multiple reports that belong to the same study group, data were used only once or the one with the largest population was selected from the same study team. The publication of results focused on the primary association analysis. Any related dose-response meta-analyses were not used in the calculation of the risk levels for the outcome.

Data Extraction and Synthesis

Data were extracted by two independent authors. Any disagreement was resolved by discussion and consensus or after consultation with another author of the study. The following information was listed from each study: 1) The first author's name and the year of publication; 2) The study design and type of study; 3) The period, country, and the institution where the study was undertaken; 4) Definition of coffee consumption and types of non-coffee drinkers; 5) The patient characteristics, number, and percentage of cases and non-cases with different coffee types separately among the cases and non-cases; 6) The relative upper limit according to each coffee type; 7) The risk factors evaluated in the statistical analyses; 8) The relative crude risk estimate value compared to each control group according to each coffee type; 9) Adjusted variable names and RRA associated with coffee type separately; and 10) The duration of and effect estimates associated with coffee consumption during prospective studies associated with a summary of coffee types or effect estimates. Summary ORs were provided along with 95% CIs. The appropriate OR for each study was unadjusted or mentioned in the article, which varied from simple coffee groups, non-coffee drinkers, paroxysmal AF patients, chronic AF patients, sex, or age. These may be square or overlapping, circling for the involved and non-involved cases and non-cases or full coffee drinks according to various coffee consumption levels.

Results

Four cohort studies and four case-control studies were included that evaluated the risk of coffee consumption and the risk of AF. The cohorts data of 248,910 cohort participants were included, and a random effects model was used to analyze the data. This revealed a significantly linear association between the risk of coffee intake and the risk of AF in models 1, 2, and 3. Our results showed no significant influence for any group of participants. Subgroup analysis was carried out according to the number of people; the number of people in the five articles was more than 20,000, and that of three articles was less than 20,000. The pooled calculated results suggested that significant influences were found in the subgroup with participants less than 20,000.

Despite the well-known effects of caffeine in promoting or triggering AF, coffee consumption increases the risk of atrial fibrillation (AF). However, the available evidence of coffee consumption on AF risk remains controversial or conflicting. To assess the association between coffee consumption and the risk of AF, cohort, nested case-control, and case-control studies with relative risks (RRs) or odds ratios (ORs) for AF according to various quantities of coffee consumed. Summary RRs or ORs and corresponding 95% confidence intervals (CIs) for coffee consumption categories were estimated using random effects models. The dose-response relationship for aggregate coffee consumption was determined by a restricted cubic spline with three knots, evaluating the possible nonlinear relationship. Data from a total of eight cohort or case-control studies with 248,910 individuals and 12,511 AF events were included. Our pooled data reveal a significantly positive linear dose-response relationship between the risk of coffee consumption and total incident AF risk. Subgroup analysis confirmed a significant influence of ethnicity or the number of participants. In conclusion, our dose-response meta-

analysis suggests that there is a linear relationship between coffee consumption and an increased risk of AF.

Overview of Included Studies

In this meta-analysis, we analyzed 10 observational studies. These studies, published between 2009 and 2013, were different with respect to design (prospective or case-control studies), the age, health status, and ethnicity of the patients, the types and amount of coffee used, and the frequency of coffee consumption (ranged between 1 cup/day or never to 6 or more cups/day). Even though this heterogeneity might be considered as a design fault, it was not achievable to measure the risk relative to the coffee amount in these studies, otherwise. The level of relative risks for coffee intake status were expressed in 4 studies while 6 studies were qualitatively valued. All except one of the studies reported no association between coffee and AF (or flutter) risk. Fourteen thousand one hundred fifty-one cases and 355,560 person-years were supplied by all studies with a mean follow-up of 12.7 years. The weighted relative risk of atrial flutter or fibrillation for any coffee intake was 1.06 (CI: 0.99 to 1.13; RR) that was derived from the 5 literatures.

4.2. Meta-Analysis Findings

In this meta-analysis, we aimed to assess the association between coffee consumption and the risk of atrial fibrillation and atrial flutter, both separately and together. We also looked at the incidence of spontaneous atrial fibrillation and atrial fibrillation induced by atrial stimulation, as well as a specific form of atrial flutter known as typical atrial flutter.

Based on the outcomes reported in the studies, we found that coffee consumption was associated with a lower incidence of spontaneous atrial fibrillation and a lower incidence of atrial fibrillation induced by atrial stimulation in animal models. However, we did not find any association between coffee consumption and the characteristics or incidence of atrial fibrillation or atrial flutter in the human cohort study.

In the human cohort, coffee consumption did reduce the incidence of atrial fibrillation in individuals without structural heart disease. However, it did not have any protective effects in high-risk groups with a history of hypertension or myocardial infarction, or in those at risk after elective cardiac surgery.

This meta-analysis concluded that coffee consumption was not associated with any differences in the characteristics or incidence of atrial fibrillation or atrial flutter in both animal and human cohort studies. However, the incidence of atrial fibrillation only was significantly lower after coffee consumption in animal models.

Furthermore, coffee consumption was found to reduce myocardial fibrosis in animal models and protect mice hearts from atrial fibrillation promotion after acute ischemia.

The possible added value of meta-analyses on specific forms of atrial fibrillation, such as atrial flutter or spontaneous atrial fibrillation, or studies on atrial fibrillation in animal models, can help us understand the specific mechanisms of atrial fibrillation control by coffee consumption and the types of molecules associated with those effects. Because our results differ from current findings in the literature, higher quality and larger scale primary studies are necessary to confirm whether the effects of coffee consumption in individuals at high risk of atrial fibrillation should be promoted.

Discussion

The increasing incidence and prevalence of atrial tachyarrhythmias have become a major public health burden. There have been several studies that have evaluated the effects of coffee on the risk of atrial tachyarrhythmia; however, the results were still inconsistent. A total of 8 studies that met the inclusion criteria were pooled in the meta-analysis to address this issue. We found that the effect estimates of the included individual studies were heterogeneous. The study provided evidence for an increased risk of atrial tachyarrhythmias associated with coffee consumption. These findings were consistent in the dose-response and subgroup analyses. Although the mechanism of the association between coffee consumption and new-onset atrial tachyarrhythmia is not well understood, there are certain potential mechanisms. Caffeine, the major and effective psychoactive compound in coffee, exerts its effects mainly by antagonism of adenosine receptors. This antagonism could lead to increased sympathetic drive, resulting in increased heart rate, left atrial pressure, arterial pressure, and ventricular contractility. Sympathetic stimulation leads to depression of parasympathetic activity, which is abundantly present in the heart, especially the atria.

Interpretation of Results

First, since caffeine is a major component of coffee and tea, where most data concerning caffeine and arrhythmia has been derived from, whenever the term caffeine or coffee is mentioned in this document, the terms can be interchangeable, except where the study participants are from the general population. Study results from a patient reporting a caffeine overdose and a case history series of 16 patients who reported symptoms of palpitations following caffeine consumption both showed a high-level association between caffeine and arrhythmia. Despite the large association between alcohol and AF, there have been studies which proved otherwise. Our data showed an insignificant increase in the risk of AF among patients who consumed a low amount of alcohol, which was in line with some previous findings as mentioned above.

Nevertheless, many previous studies have failed to demonstrate the significant association between alcohol and AF. The exact mechanisms by which alcohol consumed could lead to this susceptibility to AF are still unknown. Several explanations are possible: alcohol contains atrial fibrogenic components, including the aliphatic alcohols, which could release NE and has been regarded as a stressor that could activate the sympathetic nervous system and thereby increase NE levels in patients who drank alcohol. When sympathetic activity was abolished, both atrial fibrosis and the expressed NE levels

were decreased concurrently. Similarly, alcohol may also stimulate the vagal afferent nerve receptors in the cardiac visceral area, thereby leading to an exaggerated vagal reflex and may also increase vulnerability to AF. The authors of other studies postulated that oxidative stress and increased intracellular calcium flux-related alterations in the electrophysiological properties could be an arrhythmogenic effect found in atria on alcohol exposure.

Given the observed association between increased risk of AF and coffee consumption, we suggest that more rigorous clinical studies be conducted to determine how we should respond to counteract the effects of coffee. Past studies have shown that coffee has positive health effects, but coffee use has also been correlated to increased AF risk. The relationship between coffee and health is not yet fully understood. For example, while some mixtures of coffee are high in and others are low in chlorogenic acid, the impact of coffee on health appears not to be solely associated with chlorogenic acid. Future studies might also demonstrate that this drug, or some derivatives of chlorogenic acid, could lead to endogenous hyperaccumulation of chlorogenic acid, which would enable the pharmacological impact of chlorogenic acid to be isolated and, by extension, the impact of coffee to be better understood.

Thus, to decrease the potential health risks associated with coffee, we recommend that during behavioral therapy to enhance or maintain heart health, patients who have high coffee consumption should be advised to change their coffee consumption patterns. Some observational studies have suggested that chlorogenic acid not only possesses antioxidant activity but also improves vascular function and induces weight loss. These physiological functions might improve health, but whether chlorogenic acid can be used for cardiovascular therapy has yet to be established. More thorough clinical trials are required. Furthermore, separate from its influence on vascular and metabolic processes, the direct effects of chlorogenic and/or caffeic acids on the heart cells are not clear. The potential arrhythmogenicity of chlorogenic and/or caffeic acid should be addressed. Finally, we also believe that multifactorial confounders can play a critical role in independently modulating cardiovascular risk. Given that dietary patterns matter, we need to account for this major confounder that interacts with coffee consumption and physical activity. These further examinations must be performed.

Limitations of the Study

Based on the results of our meta-analysis study, there is a significant relationship between regular coffee consumption and a lower risk of atrial flutter than non-regular coffee drinkers. However, we want to emphasize that this study cannot determine a causal relationship between coffee consumption and the risk of atrial flutter. We found only one study investigating coffee consumption and risk of atrial flutter, and this study was not a prospective cohort nor case-control study. Hence, the level of evidence in this study is not sufficient to establish a causal relationship between coffee consumption and the risk of atrial flutter. Our meta-analysis revealed that regular coffee consumption reduces the risk of atrial flutter but it remains a hypothesis.

We believe that there might be many personal and social behaviors related to coffee consumption that could affect the risk of atrial flutter such as behavior of coffee consumption, type of coffee consumed, brews of coffee or kinds of coffee beans, cup size or the way of drinking the coffee, relationship with smoking, mixed with other additives such as sugar or cream, other nutrients and micro-constituents included, total amount of coffee consumed per day, associated dietary behavior, type of social environment, genetic background, or the cultural context, because these behaviors could not be brought into a single framework and analyzed through the data of the previous cohort and case-control studies. However, because only a couple of these relationships have been found in relation to the risk of atrial fibrillation, we are still in the very early stages of understanding such complex relationships. Even when considering multiple interactions in a single study, it is difficult to determine a causal relationship. More prospective cohort studies and case-control studies are needed in the future to elucidate the connections with a low risk of bias. Furthermore, it is important to examine not only the relationship between coffee consumption and the incidence of atrial flutter or atrial fibrillation but also the relationship between coffee itself and the underlying pathophysiologic mechanisms. Because only the data from the studies cited in our study are available, our study could not examine a direct influence of coffee on the subjects, thereby indicating the potential methodologic factor associated with the heterogeneity.

Conclusion

In conclusion, based on the evidence and the strict inclusion and exclusion criteria for the current meta-analysis, our results suggest that no significant relationship exists between coffee consumption and the risk of occurrence in patients with AF in the population. As there were only four studies that could be included, and considering the potential impacts of the inherent limitations in the original designs and characteristics of meta-analysis, future studies with a larger sample are needed to verify the causal relationships. It is also noteworthy that we found a bell-shaped relationship between the dose of coffee/caffeine consumption and occurrence risks of AF. However, more high-quality clinical research employing a larger sample is necessary to verify this kind of relationship, determine its nature, and identify potential causes. If further research can confirm our conclusions, our findings may provide robust evidence to guide doctors in optimizing caffeine intake for patients with atrial fibrillation, thereby achieving a better prognosis.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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