Nutrition, Metabolism & Cardiovascular Diseases (2019) **29**, 1185–1188

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

No association between coffee consumption and risk of atrial fibrillation: A Mendelian randomization study

Shuai Yuan [a,b], Susanna C. Larsson [a,b,*]

[a] Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[b] Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

Received 15 May 2019; received in revised form 18 July 2019; accepted 19 July 2019
Handling Editor: A. Siani
Available online 27 July 2019

KEYWORDS
Atrial fibrillation;
Coffee consumption;
Mendelian randomization

Abstract *Background and aims:* Some observational studies have found that habitual coffee and caffeine consumption might reduce the risk of atrial fibrillation (AF). We conducted a two-sample Mendelian randomization study to explore the potential association between coffee consumption and AF.

Methods and results: This study was based on summary-level data from the Atrial Fibrillation Consortium, including 588 190 individuals (65 446 cases and 522 744 non-cases). Nine single-nucleotide polymorphisms associated with coffee consumption at significance level of $P < 5 \times 10^{-8}$ were used as instrumental variables and were obtained from a genome-wide association study that included up to 375 833 individuals.

The odds ratio of AF per genetically-predicted 50% increase of coffee consumption was 0.98 (95% confidence interval, 0.88, 1.10; P = 0.80) in the standard inverse-variance weighted analysis. Results were consistent in sensitivity analyses using the weighted median and MR-Egger methods, and no directional pleiotropy ($P = 0.37$) was observed. Moreover, complementary analyses that separated the coffee-related single-nucleotide polymorphisms based on their association with blood levels of caffeine metabolites (lower, higher, unrelated or unknown association) revealed no association with AF.

Conclusions: This study does not support a causal association between habitual coffee consumption and risk of AF.

Background

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia of clinical significance. It has been shown to be a risk factor for stroke [1], myocardial infarction [2], heart failure [3], dementia [4] and thromboembolism [5]. A global burden of disease study estimated that around 33.5 million individuals worldwide had AF in 2010 [6]. The disability-adjusted life-years caused by AF increased by 18.8% from 1990 to 2010 [6].

Caffeine is a natural stimulant most commonly obtained from coffee, tea, chocolate, cocoa beverages, soft drinks, and energy drinks. Caffeine induces a transient increase in blood pressure [7] and has been postulated to be the main driving environmental factor for heart beat irregularities in clinical practice [8]. Thus, caffeine exposure may affect the risk of AF, but findings from observational studies of caffeine or coffee consumption in relation to risk of AF have

* Corresponding author. Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Nobelsväg 13, Stockholm, 17177, Sweden.
E-mail addresses: shuai.yuan@stud.ki.se (S. Yuan), susanna.larsson@ki.se (S.C. Larsson).

https://doi.org/10.1016/j.numecd.2019.07.015
0939-4753/

been inconsistent. No association between self-reported coffee consumption and risk of AF was observed in a meta-analysis of six prospective cohort studies [9]. However, a large Danish cohort study published since that meta-analysis found that coffee consumption was associated with a reduction in AF risk [10]. Moreover, caffeine consumption was found to be inversely associated with the risk of AF in a meta-analysis of four prospective cohort studies [11]. Given that available data on coffee consumption and AF risk come from observational studies, which may be biased by residual confounding and reverse causality, it remains unclear whether coffee consumption plays a causal role in the development of AF.

Mendelian randomization (MR) can strengthen casual inference on exposure-outcome relationship by using genetic variants as instrumental variables of an exposure. Genetic variants are less likely to be associated with confounding factors related with exposures and outcomes since they are randomly assorted at conception [12]. The MR design also diminishes reverse causality because allelic randomization precedes the development of disease [12]. We conducted a two-sample MR study to investigate the causal associations between coffee consumption and the risk of AF.

Methods

Data sources and SNP selection

This study is based on summary-level data from published genome-wide association studies (Supplementary table 1). Single-nucleotide polymorphisms (SNPs) robustly associated with coffee consumption were obtained from the hitherto largest genome-wide association study on coffee consumption [13] (Supplementary table 2). That study included 375 833 individuals of European ancestry from the UK Biobank and identified 15 SNPs at the level of genome-wide significance ($P < 5 \times 10^{-8}$) [13]. These SNPs explained 0.48% of the variation in coffee consumption [13]. We evaluated whether the 15 SNPs were uncorrelated, that is, not in linkage disequilibrium (defined as $R^2 < 0.1$) and searched the PhenoScanner database (on June 19, 2019) [14] for pleiotropic associations of the SNPs with potential confounders. Six of the 15 SNPs were excluded due to linkage disequilibrium (rs4719497 was in linkage disequilibrium with rs4410790 in the *AHR* gene ($R^2 = 0.2$; $P < 0.0001$)) or associated with potential risk factors for AF (rs1260326 in the *GCKR* gene is associated with multiple phenotypes such as alcohol consumption, fat-free mass, height, resting heart rate, etc.; rs574367, rs10865548, and rs66723169 in the *SEC16B*, *TMEM18*, *MC4R* gene regions are strongly associated with body mass index; rs34060476 in the *MLXIPL* gene is associated with serum lipids and fat-free mass) at genome-wide significance. The remaining 9 SNPs were used as instrumental variables for coffee consumption. Among the selected SNPs, the coffee-raising allele has been reported to be associated with lower blood levels of caffeine metabolites (reflecting faster caffeine metabolism) for three SNPs, higher blood levels of caffeine metabolites for one SNP, and unrelated to caffeine metabolites for two SNPs; for three SNPs, the association with blood levels of caffeine metabolites was unknown (Supplementary table 2) [15,16].

Summary-level data for the associations of the coffee-associated SNPs with AF were available from the Atrial Fibrillation Consortium, which includes data from over 50 studies with a total of 588 190 individuals (65 446 AF cases and 522 744 non-cases) of mainly (91%) European ancestry [17]. AF was defined as paroxysmal or permanent AF or atrial flutter.

Statistical analysis

We calculated an instrumental variable ratio estimate for each SNP by dividing the beta-coefficients of AF by the beta-coefficients of coffee consumption. The main analyses were conducted using the inverse-variance weighted method in fixed-effects model. Several sensitivity analyses were carried out, including the inverse-variance weighted method in random-effects model, the weighted median method [18] and the MR-Egger regression method [19]. The MR pleiotropy residual sum and outlier (MR-PRESSO) method was used to detect potential outlier SNPs [20]. In a complementary analysis, we grouped the coffee-associated SNPs based on their association with blood levels of caffeine metabolites [15,16], and performed separate inverse-variance weighted MR analyses for each set of SNPs. We scaled the odds ratio estimates of AF per 50% increase in coffee consumption. All statistical analyses were two-sided and considered statistically significant at P values < 0.05. The mrrobust package [21] in Stata (StataCorp, College Station, TX, USA) and the MR-PRESSO package [20] in R (R Foundation) were used to conduct the MR analyses. Statistical power was calculated using a web-based application [22].

Results

We had over 90% statistical power to detect an OR of 0.8 (or 1.2) and 100% statistical power to detect an OR of 0.7 (or 1.3). Genetically predicted coffee consumption was not associated with AF (Fig. 1). In the standard MR analysis, the odds ratio of AF per genetically-predicted 50% increase of coffee consumption was 0.98 (95% confidence interval (CI), 0.88, 1.10; $P = 0.80$), with moderate heterogeneity between individual SNPs ($I^2 = 45\%$, $P = 0.07$). Results of sensitivity analyses were consistent (Fig. 1). The odds ratios of AF per genetically predicted 50% increment of coffee consumption were 0.98 (95% CI, 0.84, 1.14; $P = 0.80$), 1.01 (95% CI, 0.86, 1.18; $P = 0.92$), and 1.10 (95% CI, 0.82, 1.47; $P = 0.52$) in analyses based on the random-effects inverse-variance weighted, weighted median, and MR-Egger approaches, respectively (Fig. 1). The MR-Egger analysis detected no directional pleiotropy ($P = 0.37$). No outlier SNPs were detected in the MR-PRESSO analysis.

When the coffee-related SNPs were separated based on their association with blood levels of caffeine metabolites, the odds ratios of AF were 1.02 (95% CI, 0.90, 1.16; $P = 0.73$) for the three SNPs associated with lower caffeine

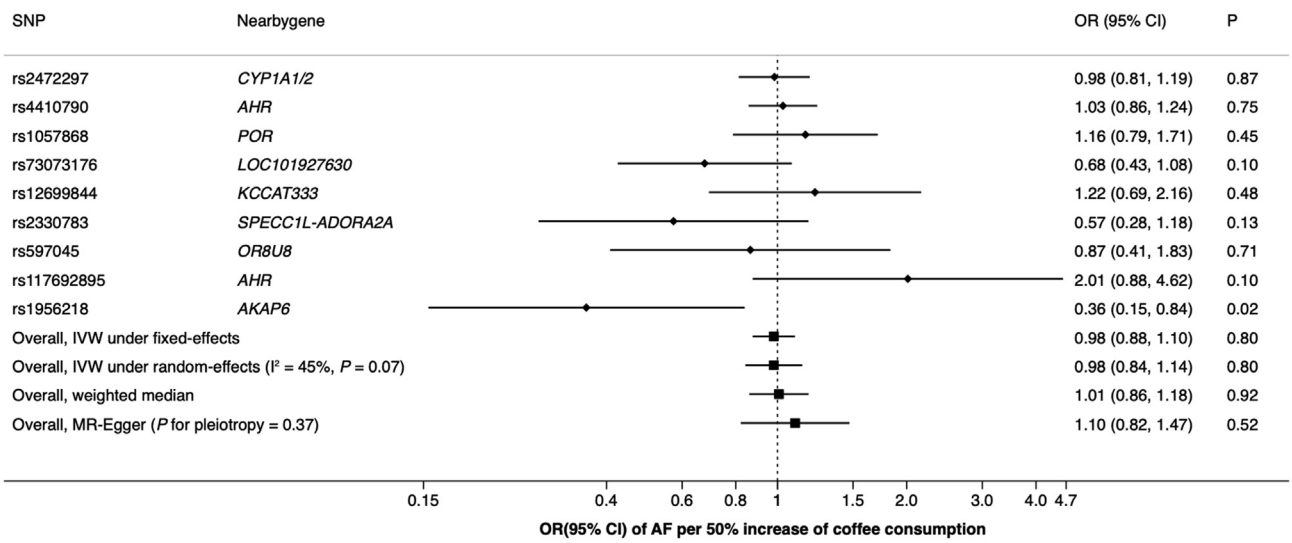

Figure 1 Association of genetically predicted coffee consumption with AF. AF indicates atrial fibrillation; CI, confidence interval; IVW, inverse-variance weighted; OR, odds ratio; SNP, single-nucleotide polymorphism.

metabolite levels, 0.57 (95% CI, 0.28, 1.18; $P = 0.13$) for the SNP associated with higher caffeine metabolite levels, 0.59 (95% CI, 0.34, 1.03; $P = 0.06$) for the two SNPs unrelated to caffeine metabolites, and 0.98 (95% CI, 0.71, 1.37; $P = 0.92$) for the three SNPs with unknown association with caffeine metabolites.

Discussion

This study found no association between genetically-predicted habitual coffee consumption and risk of AF. Results were robust in sensitivity analyses and no pleiotropy or outlier SNPs were identified. Furthermore, coffee-related SNPs that are associated with lower or higher blood levels of caffeine metabolites, reflecting faster and slower caffeine metabolism, respectively, or unrelated to caffeine metabolites were not significantly associated with AF.

Previous studies based on self-reported coffee or caffeine intake in relation to risk of AF have produced inconsistent results [9–11]. However, those studies may be limited by their observational design and cannot rule out that misclassification of life-long coffee consumption, residual confounding, and reverse causality affected the results. Specifically, most observational studies did not fully adjust for dietary factors, such as magnesium and anti-oxidative nutrients [23,24], which have been found to be inversely associated with risk of AF [23–27]. In addition, the measurement of long-term coffee consumption in observational studies may be inaccurate [11].

A major strength of this study is the MR study design, which mitigated unobserved confounding and reverse causality by exploiting genetic variants as proxies of life-long coffee consumption. A limitation is that the standard MR method assumes a linear association between exposure and outcome. If a nonlinear relationship between habitual coffee consumption and AF or a threshold effect exists, we were unable to detect such association. We also cannot entirely rule out that population stratification affected our results. However, this bias is unlikely to have had a major impact on the results because around 91% of included individuals were of European decent. Finally, in the complementary analyses, we may have had insufficient power to detect weak associations of different levels of caffeine metabolites with AF risk. Thus, further studies of the causal nature of the association between caffeine metabolite exposure and AF are needed to verify our findings.

Conclusion

This MR study does not support a causal association between coffee consumption and risk of AF.

Author contributions

SY analyzed the data and wrote the manuscript. SCL designed the study, managed and analyzed the data and reviewed the manuscript.

Funding

This study was supported by the Swedish Research Council (Vetenskapsrådet).

Conflicts of interest

All authors declare no competing interest.

Acknowledgements

The authors thank the Atrial Fibrillation Consortium for providing summary-level data for atrial fibrillation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.07.015.

References

[1] Lip GY, Lane DA. Stroke prevention in atrial fibrillation: a systematic review. Jama 2015;313:1950–62.
[2] Violi F, Soliman EZ, Pignatelli P, Pastori D. Atrial fibrillation and myocardial infarction: a systematic review and appraisal of pathophysiologic mechanisms. J Am Heart Assoc 2016;5.
[3] Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. Circulation 2016;133:484–92.
[4] Singh-Manoux A, Fayosse A, Sabia S, Canonico M, Bobak M, Elbaz A, et al. Atrial fibrillation as a risk factor for cognitive decline and dementia. Eur Heart J 2017;38:2612–8.
[5] Ganesan AN, Chew DP, Hartshorne T, Selvanayagam JB, Aylward PE, Sanders P, et al. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. Eur Heart J 2016;37:1591–602.
[6] Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. Circulation 2014;129:837–47.
[7] Mesas AE, Leon-Munoz LM, Rodriguez-Artalejo F, Lopez-Garcia E. The effect of coffee on blood pressure and cardiovascular disease in hypertensive individuals: a systematic review and meta-analysis. Am J Clin Nutr 2011;94(4):1113–26.
[8] Mattioli AV. Link between coffee and atrial fibrillation debunked? Expert Rev Cardiovasc Ther 2019;17(2):75–7.
[9] Larsson SC, Drca N, Jensen-Urstad M, Wolk A. Coffee consumption is not associated with increased risk of atrial fibrillation: results from two prospective cohorts and a meta-analysis. BMC Med 2015;13(1):207.
[10] Mostofsky E, Johansen MB, Lundbye-Christensen S, Tjønneland A, Mittleman MA, Overvad K. Risk of atrial fibrillation associated with coffee intake: findings from the Danish Diet, Cancer, and Health study. Eur J Prev Cardiol 2016;23(9):922–30.
[11] Cheng M, Hu Z, Lu X, Huang J, Gu D. Caffeine intake and atrial fibrillation incidence: dose response meta-analysis of prospective cohort studies. Can J Cardiol 2014;30(4):448–54.
[12] Bennett DA, Holmes MV. Mendelian randomisation in cardiovascular research: an introduction for clinicians. Heart 2017;103:1400–7.
[13] Zhong VW, Kuang A, Danning RD, Kraft P, van Dam RM, Chasman DI, et al. A genome-wide association study of bitter and sweet beverage consumption. Hum Mol Genet 2019. https://doi.org/10.1093/hmg/ddz061.
[14] Staley JR, Blackshaw J, Kamat MA, Ellis S, Surendran P, Sun BB, et al. PhenoScanner: a database of human genotype-phenotype associations. Bioinformatics 2016;32(20):3207–9.
[15] Cornelis MC, Munafo M. Mendelian randomization studies of coffee and caffeine consumption. Nutrients 2018;10(10).
[16] Cornelis MC, Kacprowski T, Menni C, Gustafsson S, Pivin E, Adamski J, et al. Genome-wide association study of caffeine metabolites provides new insights to caffeine metabolism and dietary caffeine-consumption behavior. Hum Mol Genet 2016;25(24):5472–82.
[17] Roselli C, Chaffin MD, Weng LC, Aeschbacher S, Ahlberg G, Albert CM, et al. Multi-ethnic genome-wide association study for atrial fibrillation. Nat Genet 2018;50:1225–33.
[18] Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity analyses for robust causal inference from Mendelian randomization analyses with multiple genetic variants. Epidemiology 2017;28:30–42.
[19] Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. Eur J Epidemiol 2017;32:377–89.
[20] Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet 2018;50(5):693–8.
[21] Spiller W, Davies NM, Palmer TM. Software application profile: mrrobust—a tool for performing two-sample summary Mendelian randomization analyses. Int J Epidemiol 2018:1–7.
[22] Brion MJ, Shakhbazov K, Visscher PM. Calculating statistical power in Mendelian randomization studies. Int J Epidemiol 2013;42:1497–501.
[23] Mattioli AV, Miloro C, Pennella S, Pedrazzi P, Farinetti A. Adherence to Mediterranean diet and intake of antioxidants influence spontaneous conversion of atrial fibrillation. Nutr Metab Cardiovasc Dis 2013;23:115–21.
[24] Rodrigo R, Korantzopoulos P, Cereceda M, Asenjo R, Zamorano J, Villalabeitia E, et al. A randomized controlled trial to prevent post-operative atrial fibrillation by antioxidant reinforcement. J Am Coll Cardiol 2013;62:1457–65.
[25] Khan AM, Lubitz SA, Sullivan LM, Sun JX, Levy D, Vasan RS, et al. Low serum magnesium and the development of atrial fibrillation in the community: the Framingham Heart Study. Circulation 2013;127:33–8.
[26] Kotecha D. Magnesium for atrial fibrillation, myth or magic? Circ Arrhythm Electrophysiol 2016;9.
[27] Larsson SC, Drca N, Michaëlsson K. Serum magnesium and calcium levels and risk of atrial fibrillation. Circ Genom Precis Med 2019;12(1):e002349.