

Letter to the Editor

Longer Leukocyte Telomere Length Increases the Risk of Atrial Fibrillation: A Mendelian Randomization Study

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To the Editor,

Advanced age is the most critical driving factor for atrial fibrillation (AF) [1]. As a marker for biological aging, telomere shortening is implicated in numerous age-related diseases [2-5]. However, longer telomere length (TL) may also increase the risks of diseases [4, 5]. A few observational studies have investigated the association between TL and the risk of AF [6-9]. These studies provided inconsistent results and were unable to establish causality. Hence, we conducted the two-sample Mendelian randomization (MR) analysis to evaluate the causal role of leukocyte telomere length (LTL) in AF using summary statistics from large-scale genome-wide association studies (GWAS).

The GWAS data for LTL was from UK Biobank (UKB), involving 472,174 participants [5]. LTL was measured as the ratio of telomere repeat copy numbers relative to that of a single-copy gene. The genetic variants in the LTL GWAS have been adjusted for age and sex. Single-nucleotide polymorphisms (SNPs) associated with LTL at genome-wide significance ($P < 5 \times 10^{-8}$) were selected. These SNPs were clumped (linkage disequilibrium $R^2 = 0.01$, $> 10,000\text{kb}$) to ascertain independence. If a particular SNP is absent in the outcome GWAS, its proxy SNP ($R^2 > 0.8$) is considered as a substitution.

In the primary analysis, the GWAS data of AF was obtained from Nielsen's study [10], including 60,620 cases and 970,216 controls. Since the UKB individuals were also involved in the AF GWAS, this may have

produced weak instrumental bias due to sample overlap. We conducted the secondary analysis, and the latest FinnGen 2021 AF GWAS (22,068 cases and 116,926 controls) was used as the outcome data. The MR analyses were performed by Two-Sample MR and Mendelian Randomization packages [11, 12]. The study design was approved by the Institutional Committee on Human Research at the Second Xiangya Hospital. Ethical approval was obtained for all original studies.

In the main MR analysis (inverse-variance weighted method), longer genetically determined LTL increased risk of AF in Nielsen's study (odds ratio [OR], 1.083 [95% CI, 1.009-1.164]; $P = 0.028$) and in FinnGen consortium (OR, 1.182 [95% CI, 1.039-1.344]; $P = 0.011$). Sensitivity analyses (MR-Egger and weighted median method) provided less precise estimates but had consistent directions (Fig. 1). There is no directional pleiotropy (P -Egger intercept > 0.05) or reverse causality.

Heart enlargement has been implicated in the development of AF. The Framingham heart study [13] showed that LTL was positively associated with left ventricular mass. The causal relationship between LTL and heart volume was then investigated using the following GWAS summary data: indexed left ventricular end-diastolic volume (LVEDV, $n = 36,041$), indexed left ventricular end-systolic volume (LVESV, $n = 36,041$) [14], indexed left atrial maximum volume (LAm_{ax}, $n = 35,658$), and indexed left atrial minimum volume (LAm_{in}, $n = 35,658$) [15]. Our results confirmed that longer LTL had effect on

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increasing LVEDV (OR, 1.116 [95% CI, 1.053-1.182], $P = 0.00019$) and LVESV (OR, 1.073 [95% CI, 1.02-1.13], $P = 0.007$). No significant causality was detected between LTL and left atrial volume.

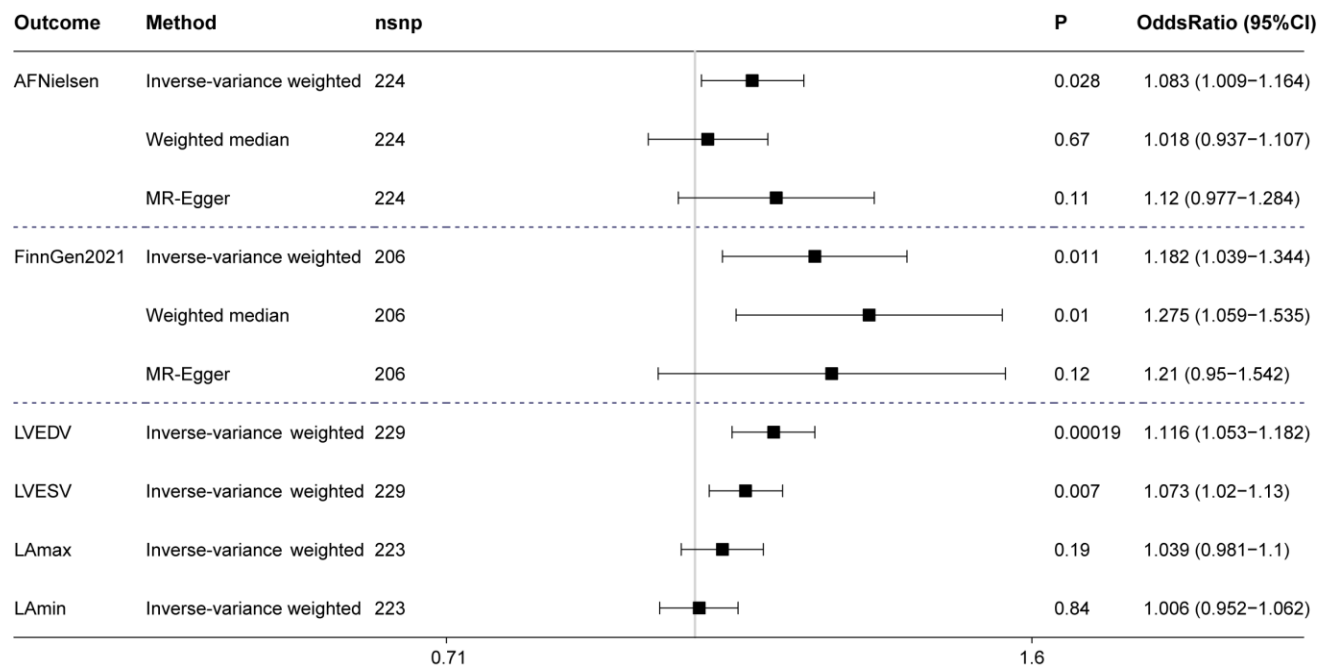


Figure 1. AF and heart volume associated with genetically determined LTL. Odds ratios are expressed per 1-SD increase in genetically determined LTL. AF, atrial fibrillation; LTL, leukocyte telomere length; LVEDV, indexed left ventricular end-diastolic volume; LVESV, indexed left ventricular end-systolic volume; LAmx, indexed left atrial maximum volume; LAmn, index left atrial minimum volume; CI, confidence interval.

Longer telomere length is generally considered a protective factor for cardiovascular diseases [3, 4]. However, we found that longer LTL increases the risk of AF. This finding could partly be attributed to the effect of longer LTL on increasing left ventricular volume[13]. Longer LTL probably promoted the proliferation of residual progenitor cells and then contributed to hypertrophy of the left ventricle. Likewise, this phenomenon was supposed to happen in the left atrium, despite the association between LTL and left atrial volume is not significant. Besides, a previous MR study [5] showed that longer LTL increased blood pressure, insulin-like growth factor-1 level, waist-hip ratio, and triglycerides level. These metabolic risk traits may mediate the effect of longer LTL on incident AF. Interestingly, our results could also explain why athletes are more vulnerable to AF since high-density physical activity could increase LTL. Further validation is required.

This study has some limitations. First, the results of the MR study could be disturbed by pleiotropy when genetic instruments affect the outcome through other exposure. However, no directional pleiotropy was detected, and sensitivity analyses yielded convincing results. Second, all participants of the GWASs were of European ancestry. Our finding may not apply to other

populations. Third, we can't investigate the non-linear relationship between LTL and AF because of lacking individual data of LTL.

Our MR study found that longer LTL may increase the risk of AF, suggesting that longer LTL should be regarded as a risk factor of AF instead of a protective one. Further studies are still required to confirm our findings. It would be necessary to determine whether the LTL is associated with the severity of AF.

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References

- [1] Kornej J, Borschel CS, Benjamin EJ, Schnabel RB (2020). Epidemiology of Atrial Fibrillation in the 21st Century: Novel Methods and New Insights. *Circ Res*, 127:4-20.
- [2] Aubert G, Lansdorp PM (2008). Telomeres and aging.

- Physiol Rev, 88:557-579.
- [3] Haycock PC, Heydon EE, Kaptoge S, Butterworth AS, Thompson A, Willeit P (2014). Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ*, 349:g4227.
- [4] Telomeres Mendelian Randomization C, Haycock PC, Burgess S, Nounu A, Zheng J, Okoli GN, et al. (2017). Association Between Telomere Length and Risk of Cancer and Non-Neoplastic Diseases: A Mendelian Randomization Study. *JAMA Oncol*, 3:636-651.
- [5] Codd V, Wang Q, Allara E, Musicha C, Kaptoge S, Stoma S, et al. (2021). Polygenic basis and biomedical consequences of telomere length variation. *Nat Genet*, 53:1425-1433.
- [6] Roberts JD, Dewland TA, Longoria J, Fitzpatrick AL, Ziv E, Hu D, et al. (2014). Telomere length and the risk of atrial fibrillation: insights into the role of biological versus chronological aging. *Circ Arrhythm Electrophysiol*, 7:1026-1032.
- [7] Carlquist JF, Knight S, Cawthon RM, Le VT, Jared Bunch T, Horne BD, et al. (2016). Shortened telomere length is associated with paroxysmal atrial fibrillation among cardiovascular patients enrolled in the Intermountain Heart Collaborative Study. *Heart Rhythm*, 13:21-27.
- [8] Staerk L, Wang B, Lunetta KL, Helm RH, Ko D, Sherer JA, et al. (2017). Association Between Leukocyte Telomere Length and the Risk of Incident Atrial Fibrillation: The Framingham Heart Study. *J Am Heart Assoc*, 6.
- [9] Siland JE, Geelhoed B, van Gelder IC, van der Harst P, Rienstra M (2017). Telomere length and incident atrial fibrillation - data of the PREVEND cohort. *PLoS One*, 12:e0171545.
- [10] Nielsen JB, Thorolfsson RB, Fritsche LG, Zhou W, Skov MW, Graham SE, et al. (2018). Biobank-driven genomic discovery yields new insight into atrial fibrillation biology. *Nat Genet*, 50:1234-1239.
- [11] Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, et al. (2018). The MR-Base platform supports systematic causal inference across the human phenome. *Elife*, 7.
- [12] Yavorska OO, Burgess S (2017). MendelianRandomization: an R package for performing Mendelian randomization analyses using summarized data. *Int J Epidemiol*, 46:1734-1739.
- [13] Vasani RS, Demissie S, Kimura M, Cupples LA, White C, Gardner JP, et al. (2009). Association of leukocyte telomere length with echocardiographic left ventricular mass: the Framingham heart study. *Circulation*, 120:1195-1202.
- [14] Pirruccello JP, Bick A, Wang M, Chaffin M, Friedman S, Yao J, et al. (2020). Analysis of cardiac magnetic resonance imaging in 36,000 individuals yields genetic insights into dilated cardiomyopathy. *Nat Commun*, 11:2254.
- [15] Ahlberg G, Andreassen L, Ghouse J, Bertelsen L, Bundgaard H, Haunso S, et al. (2021). Genome-wide association study identifies 18 novel loci associated with left atrial volume and function. *Eur Heart J*, 42:4523-4534.