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Association between Leukocyte Telomere Length and Atrial Fibrillation: A Mendelian Randomization Study

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide. The prevalence of AF increases significantly associated with increasing age, ranging from less than 0.5% of the population younger than 40 to 5% of those aged 65 and older and more than 10% of those surviving to the eighth decade of life. Therefore, AF is thought to be closely related to biological ageing. Telomeres (TL), repetitive DNA elements located at the ends of chromosomes, have been implicated as potential mediators of biological aging. TL is generally measured in leucocytes due to the easy accessibility of these cells in peripheral blood. Whether a causal effect of leucocytes TL (LTL) on AF is not clear. We used two-sample MR analysis model to evaluate the causal effect of LTL on AF. The summary statistics data for AF and LTL were derived from the recently published largest GWAS. Twenty SNPs at 17 genomic loci were discovered as genetic instruments for LTL. The MR analysis in the fixed-effect inverse-variance weighted models and MR Egger (bootstrap) method showed that LTL was associated with an increased risk of AF (odds ratio [OR], 1.145; 95% CI, 1.065-1.230, P<0.001; OR, 1.158; 95% CI, 1.007-1.331, P=0.021) based on 20 SNPs as the instrument variables. However, the opposite results were observed in other MR methods, which revealed LTL has no strong causal effect on AF at current evidence.

Keywords: Atrial fibrillation, Leukocyte telomere length, Mendelian randomization

Abbreviations: AF: Atrial Fibrillation; LTL: Leukocyte Telomere Length; MR: Mendelian Randomization; CI: Confidence Intervals

Short Communication

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide, the latest epidemiological studies show that North America (the prevalence is 2,364 per 100,000 population), Western Europe (the prevalence is 1,880 per 100,000 population), and Eastern Europe (the prevalence is 1,758 per 100,000 population) are the regions with the highest prevalence of AF in the world [1]. The prevalence of AF increases significantly associated with increasing age, ranging from less than 0.5% of the population younger than 40 to 5% of those aged 65 and older and more than 10% of those surviving to the eighth decade of life [2]. Therefore, AF is thought to be closely related to biological ageing, and age is the most important risk factor for atrial fibrillation.

Telomeres, repetitive DNA elements located at the ends of chromosomes, have been implicated as potential mediators of biological aging. Telomeres shorten progressively with each cell division and thus TL reflects the amount of cellular turnover within an individual. Accelerated telomere attrition might also occur due to increased exposure to oxidative stress and chronic low-grade inflammation, both of which are considered important drivers of biological ageing [3]. Telomere length (TL) varies considerably between subjects with heritability estimates between 44%-86% [4]. TL is generally measured in leucocytes due to the easy accessibility of these cells in peripheral blood.

Several observational studies have demonstrated positive associations between short leucocyte TL (LTL) and AF or long-term prognosis after catheter ablation [5,6]. However, some other studies revealed no evidence of a significant association between LTL and risk of incident AF and no evidence of relative atrial cell telomere shortening in AF [7,8]. Observational studies have many confounding factors that need to be

adjusted. Even for the same disease, different observational studies may reach different conclusions due to the adjustment of different confounding factors. Mendelian randomization (MR) is an epidemiological technique using genetic variants as instrumental variables for exposures such as TL. Because genotypes are randomly allocated at conception and are therefore not generally susceptible to reverse causation bias and confounding, in contrast to conventional epidemiological methods, MR can facilitate robust causal inference. Whether short TL is a cause or consequence of the AF remains unknown. We conducted a MR study to determine the association between genetically instrumented LTL and development of the AF.

We used two-sample MR analysis model to evaluate the causal effect of LTL on AF (**Figure 1A**). We used published genetic variants associated with LTL from a recent published GWAS analysis in 78,592 individuals of European ancestry of LTL in a Network for Genetic and Genomic Epidemiology [4]. The outcome of this study was the lifetime risk of AF. The summary statistics data for AF were derived from the recently published largest GWAS [9]. Studies contributing data to these GWAS meta-analyses had received ethical approval from relevant institutional review boards. In this study, we only extracted the summarized data from these studies; thus, there was no additional ethics approval required. Twenty top SNPs were discovered as the genetic instruments for LTL. Twenty SNPs at 17 genomic loci were discovered as genetic instruments for LTL. There was no evidence that these SNPs were associated with the risk factors of AF (triglycerides, total cholesterol, Diabetes, hypertension and so on). Therefore, twenty SNPs were all included in the main MR analysis. We also performed sensitivity analysis to test the robustness of the final results. **Table 1** shows the characteristics of the 20 SNPs. Effect estimates were evaluated using inverse-variance weighted (IVW), simple mode, weighted mode, simple

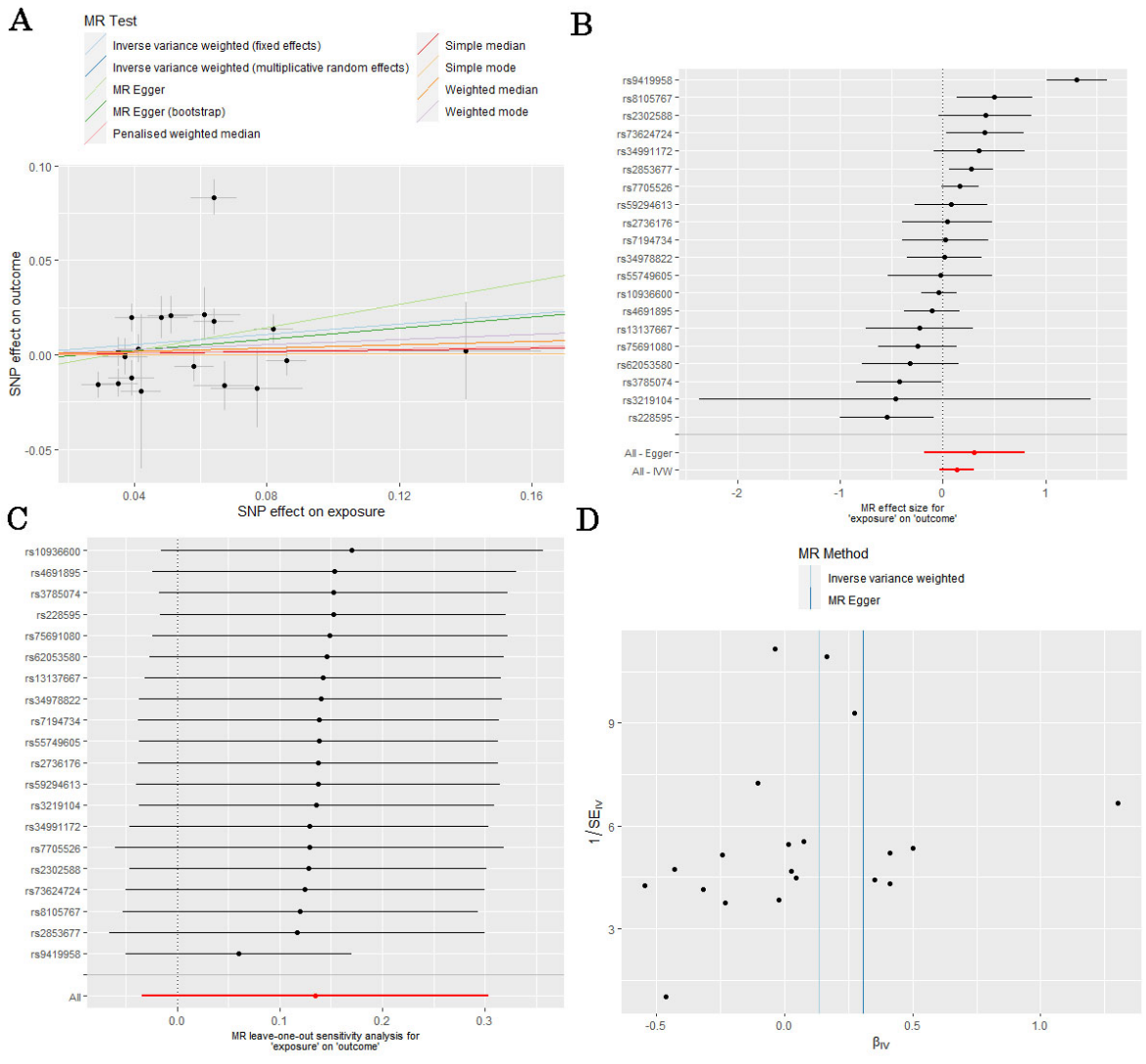

Figure 1.

Table 1. The characteristics of 20 SNPs and their genetic associations with leukocyte telomere length and AF.

SNP	Gene	Chr: Bp	EAF	Effect	Reference	Leukocyte Telomere Length			AF		
				allele	allele	Beta	SE	P	Beta	SE	P
rs3219104	PARP1	Chr1:226562621	0.83	C	A	0.042	0.006	9.60E-11	0.0195	0.0408	0.6327
rs55749605	SENP7	Chr3:101232093	0.58	A	C	-0.037	0.007	2.45E-08	-0.0009	0.0096	0.9244
rs10936600	TERC	Chr3:169514585	0.24	T	A	-0.086	0.006	7.18E-51	0.0033	0.0077	0.6668
rs13137667	MOB1B	Chr4:71774347	0.96	C	T	0.077	0.014	2.43E-08	-0.0179	0.0205	0.3818
rs4691895	NAF1	Chr4:164048199	0.78	C	G	0.058	0.006	1.58E-21	0.006	0.008	0.4519
rs7705526	TERT	Chr5:1285974	0.33	A	C	0.082	0.006	5.34E-45	-0.0136	0.0075	0.06948
rs2853677	TERT	Chr5:1287194	0.59	A	G	-0.064	0.006	3.35E-31	0.0175	0.0069	0.01189
rs34991172	CARMIL1	Chr6:25480328	0.07	G	T	-0.061	0.011	6.19E-09	-0.0215	0.0138	0.1205
rs2736176	PRRC2A	Chr6:31587561	0.31	C	G	0.035	0.006	3.53E-10	-0.0015	0.0078	0.8426
rs59294613	POT1	Chr7:124554267	0.29	A	C	-0.041	0.006	1.17E-13	0.0031	0.0074	0.6784
rs9419958	STN1	Chr10:105675946	0.86	C	T	-0.064	0.007	5.05E-19	-0.0834	0.0096	5.36E-18
rs228595	ATM	Chr11:108105593	0.42	A	G	-0.029	0.005	1.43E-08	-0.0158	0.0068	0.01983
rs2302588	DCAF4	Chr14:73404752	0.1	C	G	0.048	0.008	1.68E-08	-0.0198	0.0111	0.07389
rs3785074	TERF2	Chr16:69406986	0.26	G	A	0.035	0.006	4.64E-10	-0.015	0.0074	0.04383
rs62053580	RFWD3	Chr16:74680074	0.17	G	A	-0.039	0.007	4.08E-08	0.0124	0.0094	0.1834
rs7194734	MPHOSPH6	Chr16:82199980	0.78	T	C	-0.037	0.006	6.94E-10	0.0009	0.0079	0.9068
rs8105767	ZNF208	Chr19:22215441	0.3	G	A	0.039	0.005	5.42E-13	0.0196	0.0073	0.007308
rs75691080	RTEL1	Chr20:62269750	0.09	T	C	-0.067	0.009	5.99E-14	-0.0164	0.013	0.2086
rs34978822	RTEL1	Chr20:62291599	0.02	G	C	-0.14	0.023	7.26E-10	-0.002	0.0257	0.9377
rs73624724	RTEL1/ZB	Chr20:62436398	0.13	C	T	0.051	0.007	6.33E-10	-0.0209	0.0098	0.03313

median, weighted median, Penalised weighted median and MR-Egger method, as shown in **Figure 1A**. In the sensitivity analysis, the heterogeneity and pleiotropy of individual SNPs were evaluated using IVW method with Cochran's Q statistics and MR Egger intercept, respectively. Also, a leave-one-out analysis was performed to evaluate the robustness of MR analysis results through any outlier SNPs. All statistical analyses were undertaken using the "TwoSampleMR" package in R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and a two-tailed p value <0.05 was considered statistically significant.

The MR analysis in the fixed-effect inverse-variance weighted models and MR Egger (bootstrap) method showed that LTL was associated with an increased risk of AF (odds ratio [OR], 1.145; 95% CI, 1.065-1.230, P<0.001; OR, 1.158; 95% CI, 1.007-1.331, P=0.021) based on 20 SNPs as the instrument variables, as shown in **Figure 1B**. However, the opposite results were observed in the method of simple mode (OR, 1.002; 95% CI, 0.802-1.253, P=0.986), weighted mode (OR, 1.069; 95% CI, 0.929-1.229, P=0.365), simple median (OR, 1.019; 95% CI, 0.892-1.165, P=0.777), weighted median (OR, 1.046; 95% CI, 0.932-1.173, P=0.448), Penalised weighted median (OR, 1.026; 95% CI, 0.910-1.158, P=0.671), MR-Egger method (OR, 1.360; 95% CI, 0.835-2.215, P=0.233), and random-effect inverse-variance weighted models (OR, 1.145; 95% CI, 0.967-1.355, P=0.117), as shown in **Table 2**. Therefore, we did not believe that there is a significant causal relationship between LTL and AF. The leave-one-out sensitivity analysis showed that the association between LTL and AF was not substantially driven by any individual SNP (**Figure 1C**). Asymmetry in the funnel plot indicates directional horizontal pleiotropy, which can bias MR methods; however, the funnel plot and MR Egger regression test showed no evidence of asymmetry (**Figure 1D**).

LTL measurement was increasingly recognized as a clinical gauge for age-related disease risk. However, our study did not demonstrate a strong causal effect of LTL on AF through MR analysis. The results of this study supported the conclusions of previous observational studies (the Framingham Heart Study). Our study is based on two GWAS analyses which were all derived from the cross-sectional study, the TL at a single time point cannot reflect the dynamic changes of biological age. Additionally, the TL at a single time point not only reflects the aging effect but also integrates the cumulative lifetime burdens of genetic, epigenetic, environmental, and lifestyle exposures. The considerable inter-individual variation in TL makes it difficult to fully appreciate TL dynamics in relation to age without knowing other unmeasured confounding factors. Roberts et al. tested the strength of telomere shortening and chronological age, and they also concluded that chronological aging was a stronger predictor of AF than telomere length as a biomarker for biological aging [10]. Overall, LTL measurement is a dynamic marker of biological health and well-being that together with genetically defined telomere lengths can provide insights into improved healthcare for the individual, but LTL has no strong causal effect on AF at current evidence.

Table 2. The Association of leukocyte telomere length with AF risk using various methods.

Method	Beta	SE	OR	95% CI	P value
IVW (random effects)	0.135	0.086	1.145	0.967-1.355	0.117
IVW (fixed effects)	0.135	0.037	1.145	1.065-1.230	<0.001
Simple mode	0.002	0.114	1.002	0.802-1.253	0.986
Weighted mode	0.066	0.071	1.069	0.929-1.229	0.365
Simple median	0.019	0.068	1.019	0.892-1.165	0.777
Weighted median	0.044	0.059	1.046	0.932-1.173	0.448
Penalized weighted median	0.026	0.062	1.026	0.910-1.158	0.671
MR Egger	0.307	0.249	1.360	0.835-2.215	0.233
MR Egger (bootstrap)	0.146	0.071	1.158	1.007-1.331	0.021

IVW: Inverse-Variance Weighted; MR: Mendelian Randomization

Declarations

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None.

Competing interests

All other authors have no conflicts of interests.

Authors' contributions

CJ conceived and designed the research; CJ collected the data and conducted the research; CJ analyzed and interpreted the data; LJM wrote the initial paper; CJ revised the paper; CJ approved the final version to be submitted. CJ had primary responsibility for the final content. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Ethics approval and consent to participate

Not applicable.

Consent for publication

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