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Causal relationship between leukocyte telomere length and two cardiomyopathies based on a bidirectional Mendelian randomization approach

Jun Li, PhD[a], Lanshuo Hu, PhD[b], Xuanchun Huang, PhD[a,*]

Abstract

This study aims to employ the Mendelian randomization (MR) approach to investigate the relationship between leukocyte telomere length (TL) and 2 prevalent forms of cardiomyopathies. Using R software (4.3.1) for MR study, independent genetic variants associated with leukocyte TL were extracted from the Integrative Epidemiology Unit database, while cardiomyopathies data were pooled from FinnGen and European Bioinformatics Institute databases. Analytical methodologies included inverse-variance weighting, MR-Egger regression, and weighted median methods. Further analyses involved MR-Egger intercept and MR-PRESSO for handling horizontal pleiotropy and Cochran *Q* test for study heterogeneity. Our forward Mendelian randomization study indicates a positive correlation between longer leukocyte TL and the risk of 2 forms of cardiomyopathies: the longer the leukocyte telomere, the higher is the risk of cardiomyopathies. Specifically, for hypertrophic obstructive cardiomyopathy the OR is 2.23 (95% CI: 1.19–4.14, $P = .01$), for hypertrophic cardiomyopathy the OR is 1.80 (95% CI: 1.14–2.85, $P = .01$), and for dilated cardiomyopathy the OR is 1.32 (95% CI: 1.01–1.71, $P = .04$). In contrast, our reverse Mendelian randomization showed that cardiomyopathies were not directly associated with TL, and the inverse-variance-weighted test was not statistically significant for any of the 3 ($P > .05$). The reliability tests for the forward Mendelian randomization, including both MR-Egger intercept and MR-PRESSO tests, show no evidence of horizontal pleiotropy, and Cochran *Q* test indicates no heterogeneity. The "leave-one-out" sensitivity analysis revealed no outlier genes. The reliability tests for the reverse Mendelian randomization, including both MR-Egger intercept and MR-PRESSO tests, also indicate no genetic pleiotropy. Despite the heterogeneity shown in our study between hypertrophic cardiomyopathy and leukocyte TL, the sensitivity analysis did not identify any anomalies. Our Mendelian randomization study suggests that longer leukocyte TL is associated with an increased risk of hypertrophic obstructive cardiomyopathy, hypertrophic cardiomyopathy, and dilated cardiomyopathy. However, the onset of these 2 kinds of disease does not directly lead to changes in leukocyte TL.

Abbreviations: DCM = dilated cardiomyopathy, GWAS = genome-wide association studies, HCM = hypertrophic cardiomyopathy, HOCM = hypertrophic obstructive cardiomyopathy, IVW = inverse-variance weighting, LTL = leukocyte telomere length, MR = Mendelian randomization, SNP = single nucleotide polymorphism, TL = telomere length.

Keywords: causal association, dilated cardiomyopathy, hypertrophic cardiomyopathy, hypertrophic obstructive cardiomyopathy, leukocyte telomere length, Mendelian randomization

1. Introduction

Hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) are the most common types of cardiomyopathies observed in clinical settings.[1] HCM is potentially stemming from genetic mutations tied to sarcomeric proteins or other unidentified causes.[2] Globally, it is estimated that around 20 million people are affected by HCM. According to current guidelines,[3] HCM is divided based on hemodynamic impact into 2 main categories: obstructive (HOCM) and non (HNOCM). It's noteworthy that HOCM accounts for roughly 70% of HCM. DCM, another prevalent cardiomyopathy type, is primarily characterized by ventricular dilation and compromised contractile function. It can be further classified into primary and secondary cardiomyopathies, though its exact origins

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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remain unclear. Existing theories propose that primary DCM may also be related to sarcomeric gene mutations.[4] While extensive research has been conducted, the precise pathogenesis of both HCM and DCM is yet to be fully understood. Current evidence points towards genetic mutations as potential culprits for both HCM and DCM. However, their clinical manifestations are results of an interplay of factors such as genotype, modifier elements, and environmental conditions. This complexity means that different external factors can lead to varied clinical outcomes.[5] As such, investigations into the deeper causes and pathological mechanisms of HCM and DCM persist.

Telomere length (TL) refers to the number of nucleotide sequences in telomeres within tissue cells.[6] The TL of leukocytes (leukocyte telomere length, LTL) is correlated with that of various tissue cells. Consequently, measurements often employ LTL as a surrogate for tissue cell TL in humans.[7,8] Numerous studies have already explored the relationship between peripheral blood LTL and coronary heart disease and atherosclerosis. As a result, using TL as a research tool in cardiovascular disease studies has garnered significant acknowledgments within the scientific community.[9,10]

HCM and DCM, the predominant forms of cardiomyopathies, present with a broad spectrum of clinical manifestations.[11] Some patients might be asymptomatic for long durations, while others, unfortunately, may experience sudden death as their first symptom.[12,13] However, much of the current research exploring the relationship between HCM, DCM, and LTL is limited to the end stages of cardiomyopathies,[14] with scant studies focusing on the disease's onset and progression phases. Thus, the relationship between TL and cardiomyopathies remains unclear. It is uncertain whether alterations in TL precipitate cardiomyopathies onset or if cardiomyopathies development affects TL. Given the inconclusive findings, there is a pressing need for additional experimental research to elucidate the relationship between TL and the initiation of cardiomyopathies.

In recent years, given the advent of genome-wide association studies (GWAS) and the availability of various data resources,[15] employing Mendelian randomization (MR) analyses has become a convenient approach for analyzing the causal relationships between different exposures and outcomes. Therefore, this study plans to utilize MR analyses to eliminate the influence of various confounders and mixed factors, aiming to explore the bidirectional causal relationship between LTL and HCM and DCM, as well as to estimate the magnitude of their effects.

2. Analytical methods and data sources

2.1. Study design

In MR analyses, the instrumental variables (IVs) must satisfy 3 assumptions[16]: the IVs must be strongly associated with the exposure; the IVs should not be associated with any confounders; the IVs should not be directly related to the outcome, and its influence on the outcome should only be mediated through the exposure, as illustrated in Figure 1.

2.2. Date source

In this study, we employed a bidirectional MR analyses approach to analyze the data on LTL, HOCM, HCM, and DCM. The data of LTL were sourced from the IEU database (https://gwas.mrcieu.ac.uk/datasets/),[17] data of HOCM (ICD-10:I42.1) and HCM (ICD-10:I42.1, I42.2) was obtained from the Finn database (https://r5.finngen.fi/), and data of on DCM (ICD-10:I42.0) was derived from the EBI database (https://www.ebi.ac.uk/gwas/).[18] Our selection criteria for pertinent SNPs from these databases were: They must reach genome-wide significance, with P-values < 5×10^{-8} and 1×10^{-5}; 2. SNPs in linkage disequilibrium (LD) were excluded. We set the LD coefficient R^2 at 0.001 and defined the LD window as 10,000 kb. For missing SNPs, those in high LD were used as substitutes, and SNPs without alternative loci were discarded (details are shown in Table 1).

Two-sample MR analyses requires the independence of 2 samples, originating from different populations but share similar characteristics in terms of gender, age, and ethnicity. Therefore, both sample populations in our study consisted of European ancestry and were analyzed using distinct datasets. As the data utilized in this article are from publicly available GWAS publications, no ethical controversies arise from this research.

2.3. Single nucleotide polymorphism collation and proofreading

If weak IVs are used in Mendelian analyses, they may cause bias in the results, so the strength of association between IVs and exposure factors was assessed by calculating the F statistical value, which was calculated by the formula as follows[19]:

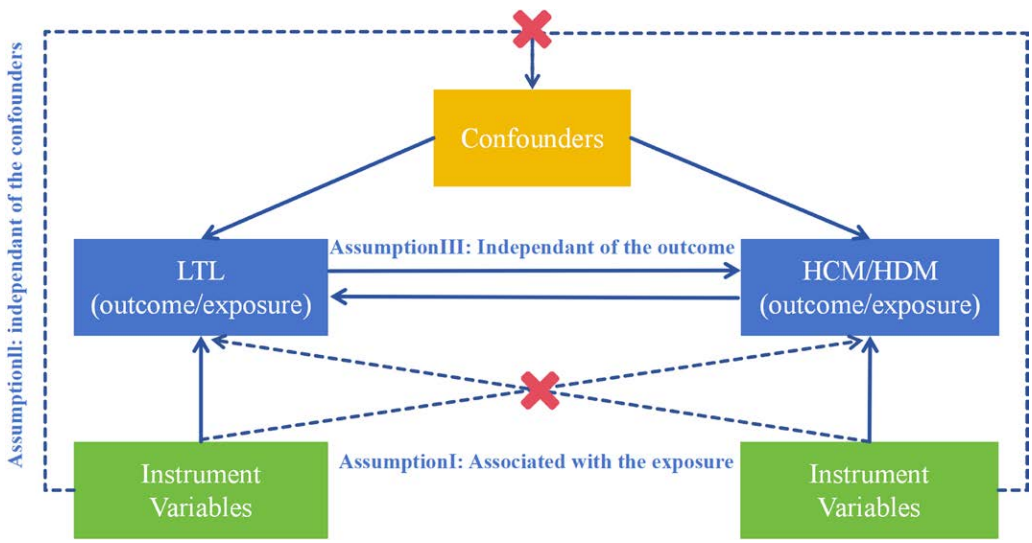

Figure 1. Mendelian randomization study assuming that genetic variation is associated only with LTL and not with confounders or other causal pathways and that instrumental variables (IVs) directly affect the risk of cardiomyopathies only through LTL and, conversely, that genetic variation is associated only with HCM/DCM and not with but not with confounders or other causal pathways and that IVs alter LTL only through HCM/DCM.

Table 1

Information status of SNPs sources and basic details.

Phenotype	Consortium of study	Sample size	Number of SNPs	Ethnicity	Year
HOCM	FinnGen (FINN)	157,024	16,380,164	European	2021
HCM	FinnGen (FINN)	218,792	16,380,466	European	2021
DCM	European Bioinformatics Institute (EBI)	355,381	19,080,278	European	2021
LTL	Integrative Epidemiology Unit (IEU)	472,174	20,134,421	European	2021

DCM = dilated cardiomyopathy, HCM = hypertrophic cardiomyopathy, HOCM = hypertrophic obstructive cardiomyopathy, LTL = leukocyte telomere length.

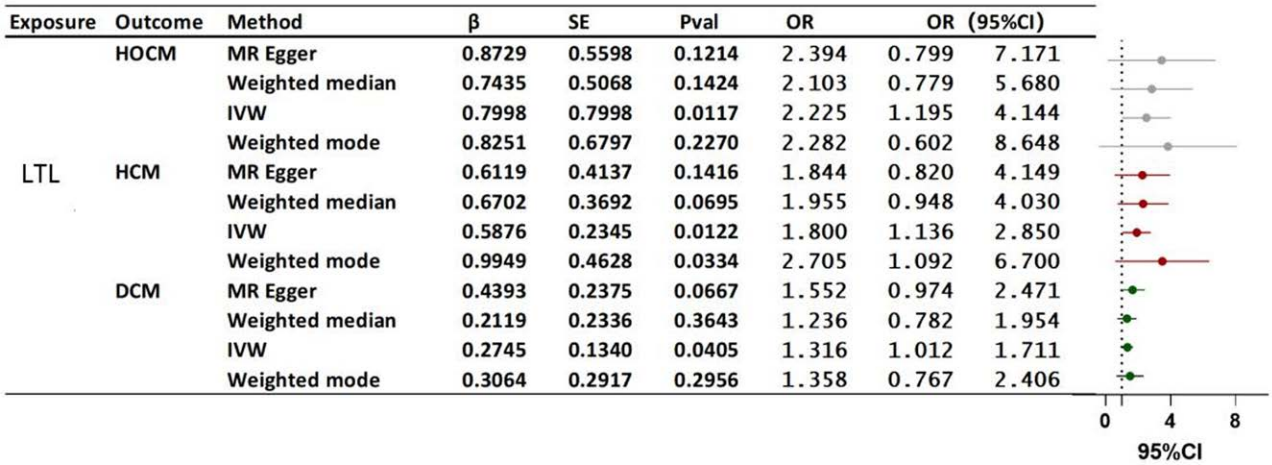

Figure 2. Causal relationship between LTL and cardiomyopathies assessed by MR analyses.

$$F = \frac{R^2}{1-R^2} \times \frac{N-K-1}{K} \quad R^2 = \beta^2 \times 2 \times MAF \times (1-MAF)$$

where N is the sample size of exposure; K is the number of SNPs included in the analysis; R^2 is the proportion of variance explained by the screened LTL-related SNPs, MAF is the minimum allele frequency. β is the effect value of LTL-associated SNPs; and MAF is the minimum allele frequency; F statistical value < 10 suggests that there may be a weak instrumental variable bias, and the larger the F value indicates that the instrumental variable is the less likely to be a weak instrumental variable, and IVs with F statistical value < 10 were excluded from the present analysis.

Additionally, we utilized the PhenoScanner database to eliminate confounding genes associated with HOCM, HCM and DCM such as diabetes, hypertension, and valvular diseases.[20]As a result, we identified 133 IVs related to LTL for HOCM, 133 for HCM, and 135 for DCM. Furthermore, after excluding genes associated with factors like smoking and alcohol consumption, which are known to influence LTL, we finally obtained 19 IVs for HOCM, 23 for HCM, and 22 for DCM that were pertinent to TL.

3. Statistical analysis

3.1. Causality analysis

In this study, we comprehensively utilized 4 different regression models: MR-Egger regression, Weighted Median Estimator (WME), Inverse-Variance-Weighted (IVW) method, and Weighted Mode (WM), to analyze the bidirectional causal relationship between LTL and HCM as well as DCM. MR-Egger regression is primarily used for detecting and correcting pleiotropy biases, while the WME provides an estimation for potential ineffective IVs. The IVW method offers estimates under the assumption that all IVs are effective, whereas the WM method evaluates the most common causal effects in the presence of pleiotropy. We used SNPs related to LTL and those associated with HCM and DCM as exposure and outcome variables for analysis, primarily relying on the results of the IVW method and MR-Egger regression. Through a multi-method comprehensive analysis strategy, we were able to thoroughly assess and understand the potential causal link between LTL and cardiomyopathies.[21]

3.2. Reliability analysis

In this study, we employed multiple statistical methods to ensure the rigor and robustness of our analysis. Firstly, we utilized funnel plots and the MR-Egger intercept test to detect pleiotropy among genes and to assess the robustness of our study results. Funnel plots are graphical tools used to identify systematic biases or inconsistencies, and MR-Egger intercept test is specifically designed to detect the presence of pleiotropy. Secondly, we applied the MR-PRESSO test to assess differences in the results of MR analyses before and after correction.[22] If significant differences were observed, the relevant genes would be excluded from the analysis to ensure the accuracy of the results. In addition, to assess the heterogeneity among SNPs involved in the experiment, we used the Cochran Q test.[23] When the P-value of the test is <0.05, it indicates significant heterogeneity. In this case, considering the heterogeneity among different SNPs, we used the IVW random effects model for analysis. Conversely, in the absence of observed heterogeneity among SNPs, we used the IVW fixed effect model for analysis. Lastly,[24] we also adopted a "leave-one-out" analysis method.[25] By successively excluding each SNP and recalculating the combined effect of the remaining SNPs, we could observe the impact of each individual SNP on the overall results. If the results of the "leave-one-out" analysis are inconsistent with the overall causal effect analysis, it indicates the presence of nonspecific SNPs that may distort the estimation of causal effects. We conducted these statistical analyses using the Two Sample MR package in R software, setting the significance level (α) at 0.05.

4. Result

4.1. Causal relationship between leukocyte telomere length and cardiomyopathies

After screening, $133_{LTL\text{-}HOCM}$, $133_{LTL\text{-}HCM}$, and $135_{LTL\text{-}DCM}$ SNPs closely associated with LTL ($P < 5 \times 10^{-8}$) were identified, with each SNP being mutually independent from the others ($R^2 < 0.001$), the details of the SNPs are shown in Tables S1, S2, and S3, Supplemental Digital Content, http://links.lww.com/MD/N839. Using the IVW method as the primary MR analysis technique, we found a significant correlation between the length of LTL and the incidence of HOCM, HCM, and DCM. Moreover,

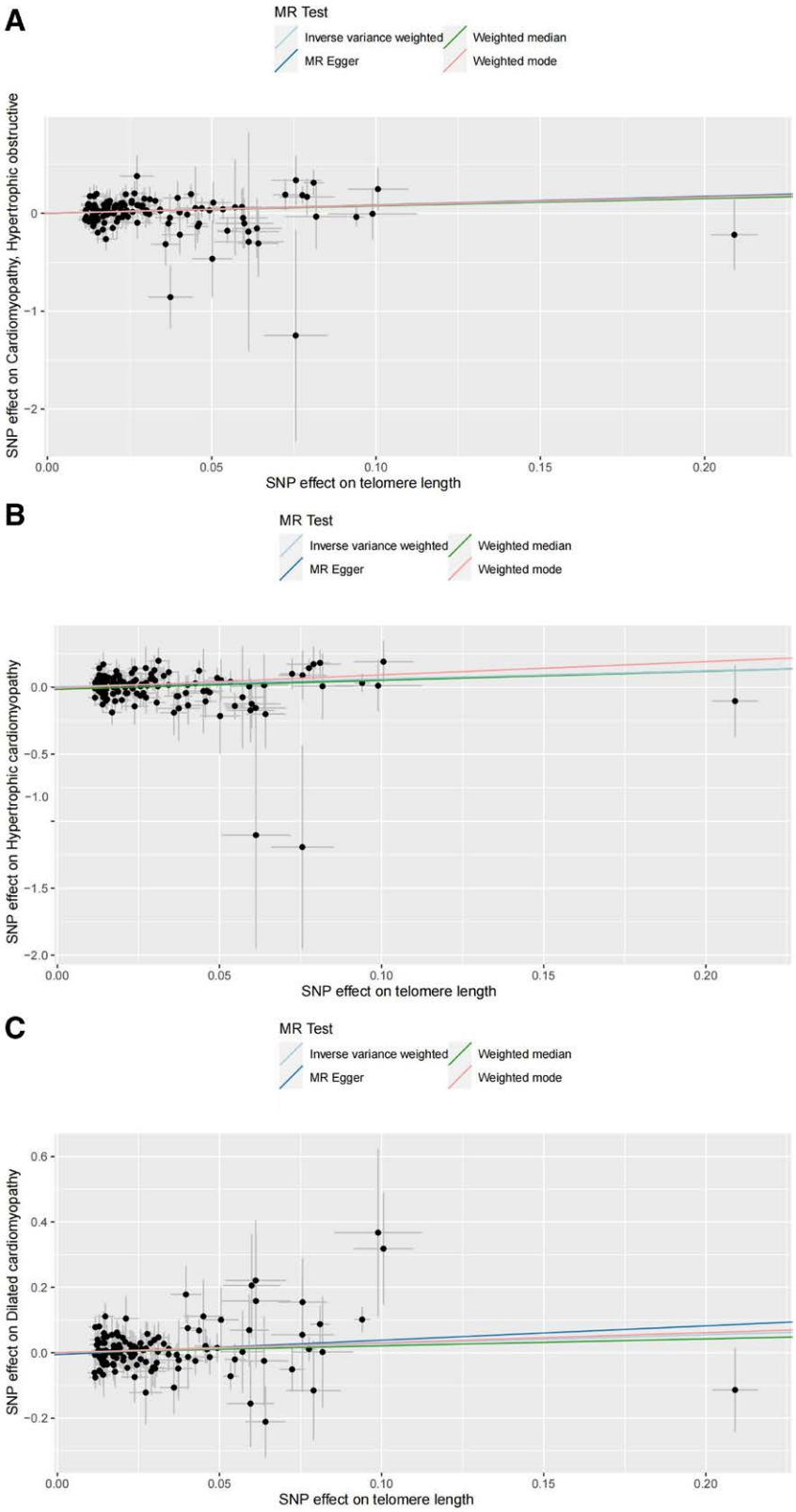

Figure 3. Scatter plots for MR analyses of the correlation between LTL and cardiomyopathies. (A) LTL-HOCM. (B) LTL-HCM. (C) LTL-DCM.

Table 2

Horizontal multiplicity of causality between LTL and cardiomyopathies.

Information		MR-Egger intercept test			MR-PRESSO test	
Exposure	Outcome	SE	Intercept	*P*	Global RSSobs	Global *P*
LTL	HOCM	0.0161	−0.0025	.874	124.6287	.728
	HCM	0.0119	−0.0008	.943	110.9569	.940
	DCM	0.0066	−0.0056	.401	147.5308	.266

DCM = dilated cardiomyopathy, HCM = hypertrophic cardiomyopathy, HOCM = hypertrophic obstructive cardiomyopathy, LTL = leukocyte telomere length.

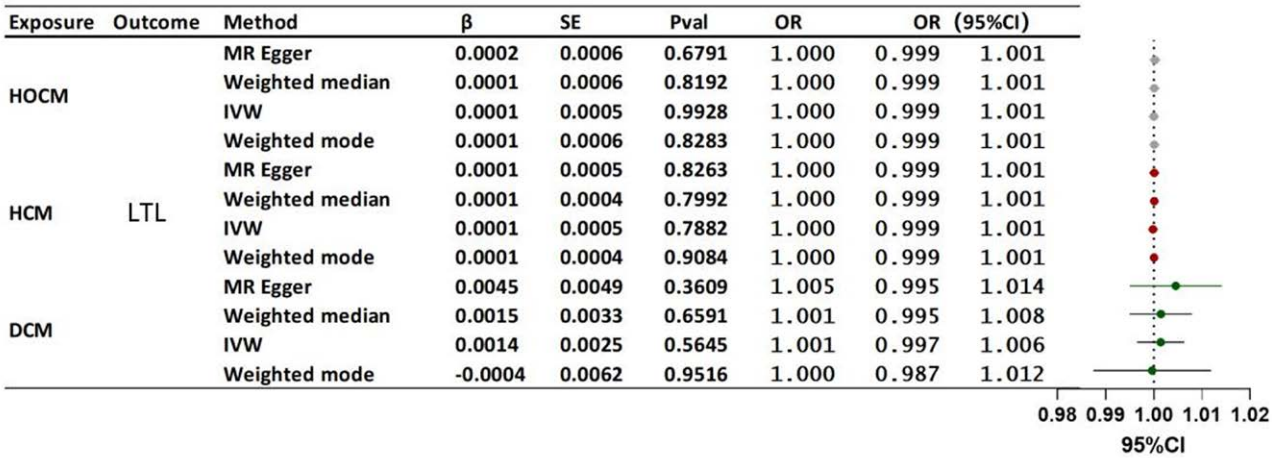

Figure 4. Causal relationship between cardiomyopathies and LTL assessed by MR analyses.

Table 3

Heterogeneity of the causal relationship between LTL and cardiomyopathies.

Cochran *Q* test				
Exposure	Outcome	Method	Cochran *Q*	*Q_P*-value
LTL	HOCM	IVW	117.1676	.7443478
		MR-Egger	117.1425	.7638124
	HCM	IVW	103.1046	.9547254
		MR-Egger	103.0995	.9482449
	DCM	IVW	130.1904	.4788041
		MR-Egger	129.4807	.4715413

DCM = dilated cardiomyopathy, HCM = hypertrophic cardiomyopathy, HOCM = hypertrophic obstructive cardiomyopathy, LTL = leukocyte telomere length.

a longer LTL was associated with a higher probability of disease onset. Specifically, the odds ratios were as follow: HOCM (IVW: OR = 2.23, 95% CI 1.19–4.14), HCM (IVW: OR = 1.80, 95% CI 1.14–2.85), and DCM (IVW: OR = 1.32, 95% CI 1.01–1.71). The details are provided in Figure 2, scatter plots are shown in Figure 3, and trend charts can be found in Figure S1, Supplemental Digital Content, http://links.lww.com/MD/N840.

4.2. Reliability analysis of leukocyte telomere length on causality in cardiomyopathies

The results of the MR-Egger intercept test are presented in Table 2. When LTL is treated as the exposure, the intercepts for MR-Egger regression are −0.0025, −0.0008, and −0.0056, respectively. All 3 values are close to zero, and their *P*-values respectively are > 0.05, suggesting that the influence of pleiotropy on this study is limited. Utilizing the MR-PRESSO test, the *P*-values for studies with leukocyte TL as the exposure are 0.728, 0.940, and 0.266. All 3 *P*-values > 0.05, indicating that there is no horizontal pleiotropy in the genes involved in this study, as shown in Table 2. Applying the Cochran *Q* method to assess the heterogeneity of the genes included in this study, we found that none of the 3 studies exhibited heterogeneity ($P > .05$), as seen in Table 3. Upon inspecting the funnel plots, we observed that the genes are evenly distributed on both sides of the β-value, resembling the image formed by the scatter plots. This suggests that there are no pronouncedly biased genes and no significant differences among the genes, as evident in Figure S2, Supplemental Digital Content, http://links.lww.com/MD/N841.

The "leave-one-out" analysis method was applied to the IVW results, as seen in Figure S3, Supplemental Digital Content, http://links.lww.com/MD/N842. After sequentially removing each SNP, the obtained results did not show significant changes. All results were situated to the right of the null value of 0, with $P < .05$. These findings are consistent with the IVW results in the causal effect analysis, indicating that there are no nonspecific SNPs that would impact the causal estimation results.

4.3. Causal effect of cardiomyopathies on leukocyte telomere length

After screening, we identified $19_{HOCM\text{-}LTL}$, $23_{HCM\text{-}LTL}$, and $22_{DCM\text{-}LTL}$ SNPs associated with cardiomyopathies ($P < 1 \times 10^{-5}$), with each SNP being mutually independent from the others ($R^2 < 0.001$), the details of the SNPs are shown in Tables S4, S5, and S6, Supplemental Digital Content, http://links.lww.com/MD/N839. Using the IVW method as the primary MR analyses technique, our study, with HOCM, HCM, and DCM as exposures, revealed that there is no significant causal relationship between the onset of these diseases and the length of leukocyte telomeres ($P > .05$). The details are provided in Figure 4, scatter plots are shown in Figure 5, and trend charts can be found in Figure S4, Supplemental Digital Content, http://links.lww.com/MD/N843.

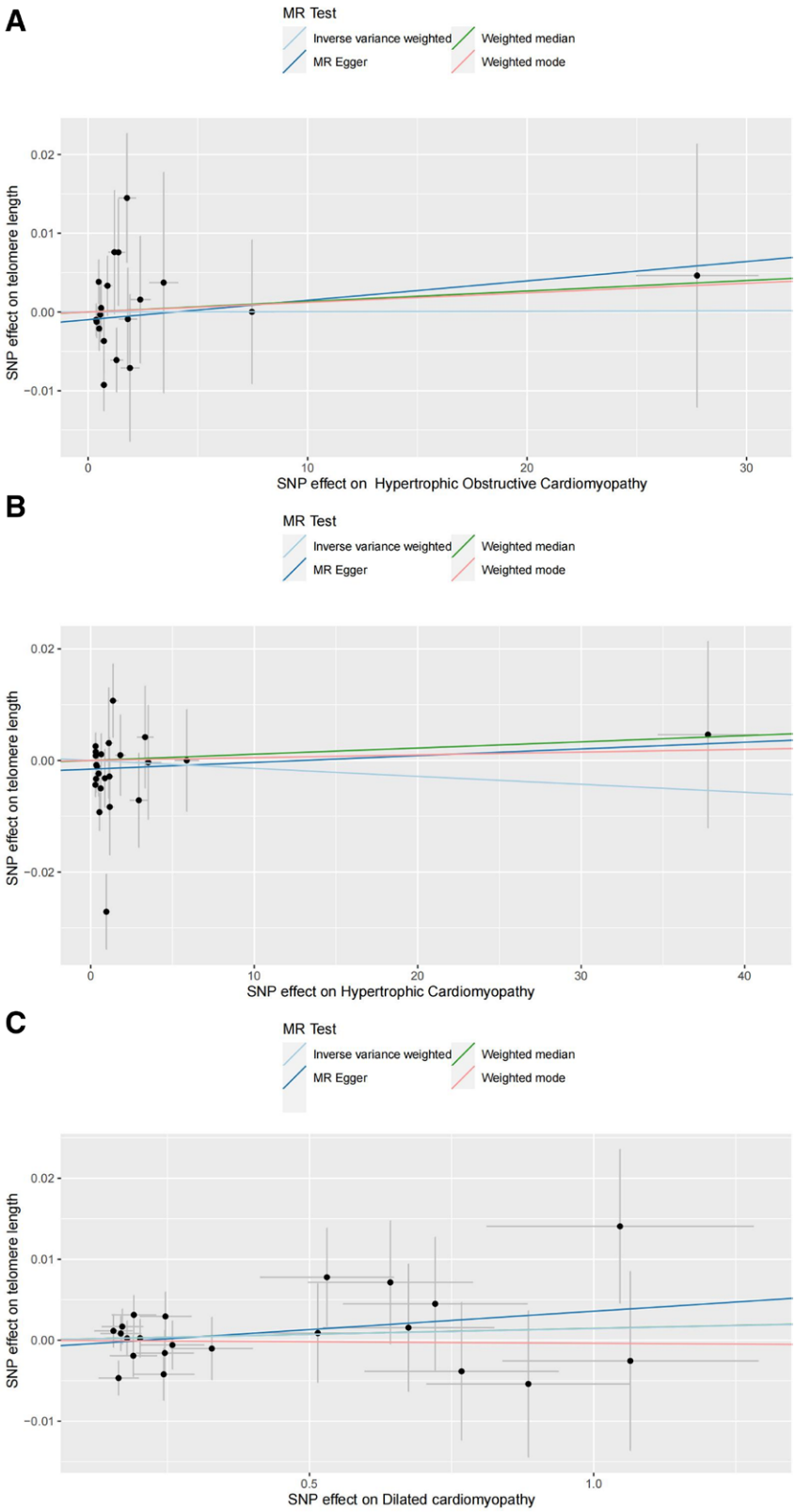

Figure 5. Scatter plots for MR analyses of the correlation between cardiomyopathies and LTL. (A) HOCM-LTL. (B) HCM-LTL. (C) DCM-LTL.

4.4. Reliability analysis of the causal effect of cardiomyopathies on leukocyte telomere length

For MR-Egger regression with cardiomyopathies as the exposure, the intercepts are −0.0009, −0.0015, and −0.0009, respectively, all of which are close to zero with *P*-values >0.05. MR-PRESSO tests with cardiomyopathies as the exposure yield *P*-values of 0.423, 0.055, and 0.758, all above 0.05. Both testing methods indicate that there is no existence of horizontal pleiotropy at the genetic level in the reverse MR analysis, as shown in Table 4.

Table 4

Horizontal multiplicity of causality between cardiomyopathies and LTL.

Information		MR-Egger intercept test			MR-PRESSO test	
Exposure	Outcome	SE	Intercept	*P*	Global RSSobs	Global *P*
HOCM	LTL	0.0010	−0.0009	.363	21.78243	.423
HCM		0.0010	−0.0015	.141	45.99097	.055
DCM		0.0012	−0.0009	.465	18.10957	.758

DCM = dilated cardiomyopathy, HCM = hypertrophic cardiomyopathy, HOCM = hypertrophic obstructive cardiomyopathy, LTL = leukocyte telomere length.

Table 5

Heterogeneity of the causal relationship between cardiomyopathies and LTL.

Cochran *Q* test				
Exposure	Outcome	Method	Cochran *Q*	*Q_P*-value
HOCM	LTL	IVW	19.75755	.2868178
		MR-Egger	20.77173	.2910857
HCM		IVW	35.18073	.0269720
		MR-Egger	39.08895	.0137844
DCM		IVW	15.98608	.7174872
		MR-Egger	16.54091	.7385314

DCM = dilated cardiomyopathy, HCM = hypertrophic cardiomyopathy, HOCM = hypertrophic obstructive cardiomyopathy, LTL = leukocyte telomere length.

Applying the Cochran *Q* test reveals that there is no heterogeneity in studies with HOCM and DCM as exposures, while there is heterogeneity present in studies with HCM as the exposure ($P < .05$), as displayed in Table 5. Hence, random IVW model analysis was conducted on the data, and the results are shown in the above table.

Upon utilizing the "leave-one-out" analysis method on the IVW results, and sequentially removing each SNP, the obtained results did not show significant changes. The results for HCM, DCM, and HOCM all touch the line of null effect, consistent with the IVW results in the causal effect analysis, which indicates that there is no relationship between cardiomyopathies exposure and TL. The funnel plots can be found in Figures S5, Supplemental Digital Content, http://links.lww.com/MD/N844 and the "leave-one-out" plots are in Figure S6, Supplemental Digital Content, http://links.lww.com/MD/N845.

5. Discussion

At present, research on TL is gaining momentum. Evidence suggests that detecting LTL can provide insights into potential diseases and mortality risks. Shorter LTL are associated with an increased risk of cardiovascular disease and a heightened incidence of sudden death.[26–28] Conversely, longer LTL may indicate tissue cell proliferation, which is linked with tissue hyperplasia, hypertrophy, and even a higher tumor risk.[29–31] However, multiple factors can influence TL, including emotions, habits, and illnesses. This myriad of influencing factors has led to a growing number of conflicting clinical observational studies, which have muddled the relationship between heart disease and TL.

To unravel the relationship between TL and cardiomyopathies, we conducted this MR study. In alignment with certain earlier studies,[32] our findings indicate a positive correlation between LTL and cardiomyopathies occurrence. Specifically, for each standard deviation increase in TL, the prevalence risk rises by 2.23-fold for HOCM, 1.8-fold for HCM, and 1.32-fold for DCM. Interestingly, our reverse MR analysis revealed that the development of cardiomyopathies does not directly influence LTL. This suggests that it's the prolonged cellular telomeres that instigate the onset of cardiomyopathies, rather than cardiomyopathies influencing cellular TL alterations.

Marques FZ studied the TL of cardiomyocytes at critical ages during the individual onset of myocardial hypertrophy and failure in polygenic left ventricular hypertrophic rats (HHR) and compared them with a control strain of normal-heart rats,[32] which showed that cardiomyocytes of such neonatal rats had longer initial telomeres and were more telomerase-activated than those of the normal rats, and it is noteworthy that this study also demonstrated that The TL of cardiomyocytes from HHR rats correlate with LTL, demonstrating that long TL may be predictive of cardiomyopathies at birth, and this study demonstrates the plausibility of our MR analyses.

Although some clinical studies have shown that in patients with end-stage HCM and DCM, their LTL are shorter than those of the healthy population, it is not clear to pursue the underlying cause: whether the causality is due to the shortening of cell telomeres because of the progression of the deterioration of cardiomyopathies, or whether it is due to the shortening of cell telomeres that promotes the onset of cardiomyopathies.[14] the study by Chang ACY showed that in patients who have deceased patients with HOCM/HCM/DCM, the telomeres of their cardiomyocytes were shortened, whereas the TL of cells not required to express contractile proteins or of other cells were unaltered, suggesting that LTL may not necessarily be proportional to those of the histiocytes in some specific diseases.[33] In addition, this study extracted pluripotent stem cells from cardiomyopathies patients for induced differentiation into HCM and DCM cells, and ultimately found telomere reduction in cardiomyocytes, but unfortunately, the study did not mention the LTL in blood. However, it has also been reported that African populations have longer cell telomeres than European and Asian populations,[34] and epidemiology has indicated that African populations are more susceptible to hereditary cardiomyopathies,[35] so does this predict that the longer the telomeres at birth, the more susceptible they are to cardiomyopathies? Although there is also a clinical study that showed no significant association between the LTL and the development of idiopathic dilated cardiomyopathy in Africans, this study also indicated that the results of the study need to be scrutinized as there are so many factors that can influence TL.[36]

The IVs in MR analyses, namely genetic variants, are established at birth and remain consistent throughout one's life.[37] As such, the associations derived from MR aren't vulnerable to reverse causation and are unaffected by confounders.[38] Based on our MR analyses findings, we can hypothesize that the LTL and cardiomyocytes of patients might be longer than average during the early phase of the life. However, as the disease progresses, factors such as inflammatory stress, diminished quality of life, reduced work tolerance, emotional aspects, and eventual heart failure might contribute to the shortening of cellular telomeres.[39,40] This is in line with clinical observations that often find shortened telomeres in later disease stages. Importantly, it's the shortest TL within a specific cell group that dictates the function of the cellular structure. Thus, the average relative TL only provides a glimpse of telomeres influence on cellular function, and cannot directly determine the functioning of a particular organization. The results of the present study therefore do not overlook the important contribution of cardiomyocyte

telomere wear to the pathogenesis of cardiovascular disease and admit the fact that telomere shortening occurs in the later stages of cardiomyopathies.

Finally, limitations of the present study remain. First, all GWAS data were from individuals of European ancestry, and it remains to be determined whether the results observed in this study are applicable to other populations. Therefore, future studies using MR analyses to study the relationship between LTL and cardiomyopathies should consider including samples from different ethnic groups to increase the generalizability of the results. Second, the MR analyses used in the current study to analyze LTL as a regression model in the relationship between exposure and cardiomyopathies as an outcome showed positivity only for IVW. Although the results of the MR analyses can be considered positive as long as the *P*-value of IVW is <0.05 and the trend of the β values of the rest of the regression models is consistent, the authors believe that the results of the present study still need to be scrutinized.

6. Conclusion

Our MR analyses study shows that there is a positive relationship between LTL and HOCM, HCM and DCM. And these 2 kinds of cardiomyopathies do not directly affect LTL. These results may suggest that TL of cells may be longer than average in patients with cardiomyopathy in the early stages of life (embryonic period, neonatal period) and therefore warrant our attention.

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Writing – original draft: Lanshuo Hu, Xuanchun Huan.
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Design research: Jun Li.
Supervision: Jun Li.
Editing, review, revision: Jun Li.
Funding: Jun Li.

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