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Original article

Deciphering the bidirectional impact of leukocyte telomere length on multiple sclerosis progression: A Mendelian randomization study

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ABSTRACT

Observational studies have suggested a link between leukocyte telomere length (LTL) and multiple sclerosis (MS) progression, but the causal relationship remains uncertain. This study investigates the causal association between LTL and MS progression using a bidirectional two-sample Mendelian randomization (MR) approach.

We analyzed genome-wide association summary statistics data from 472,174 individuals for LTL and 12,584 MS patients for disease progression. The primary method was the inverse variance weighted (IVW) approach, supported by sensitivity analyses to ensure robustness.

The forward analysis revealed a significant positive causal relationship between LTL and MS progression ($\beta = 0.107$, 95 % CI = 0.006 to 0.209, $P = 0.037$). Conversely, the reverse analysis indicated a negative causal relationship ($\beta = -0.010$, 95 % CI = -0.020 to -0.001, $P = 0.037$). No heterogeneity or horizontal pleiotropy was found, and the sensitivity analyses confirmed consistent results.

These findings suggest that telomere dynamics play a complex role in MS progression and highlight their potential as therapeutic targets. Further research is essential to uncover the biological mechanisms underlying the influence of telomeres on MS progression.

1. Introduction

Multiple sclerosis (MS) is an autoimmune disease that causes chronic degeneration of the central nervous system (CNS), leading to neurodegeneration and long-term disability (Compston and Coles, 2002). Clinically, MS involves episodic neurological dysfunction, known as relapses, which are mostly reversible. These relapses occur alongside a persistent and progressive accumulation of chronic neurological impairment, referred to as disease progression (Thompson et al., 2018). While the exact cause of MS remains unknown, it is widely agreed that both genetic and environmental factors contribute significantly to its development and progression (Waubant et al., 2019). Research has also linked chronological and biological aging to MS development and progression (Graves et al., 2023). A well-known biological aging biomarker

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is telomere length (TL) (Blackburn et al., 2015).

Telomeres are nucleoprotein structures that protect the ends of chromosomes. They regulate cellular senescence and maintain genomic stability (Blackburn et al., 2015; Moyzis et al., 1988). Observational studies have reported that shorter leukocyte telomere length (LTL) is associated with the progressive form of MS (Guan et al., 2015), an increased risk of conversion to secondary progressive MS (Hecker et al., 2021), higher disability scores, and reduced brain volume in MS patients (Krysko et al., 2019). However, these studies face limitations in establishing causality and addressing confounding factors.

Mendelian randomization (MR) offers a powerful method to infer causality by using genetic variants as instrumental variables (IVs). MR is an approach that investigates causality in the absence of pleiotropic effects (Sanderson et al., 2022; Smith and Ebrahim, 2003). Since disease states do not affect germline DNA, MR studies are less susceptible to reverse causality (Smith and Ebrahim, 2003). Moreover, the MR approach can reduce confounding effects through the random assortment of genotypes (Smith and Ebrahim, 2003). MR methods are analogous to randomized controlled trials (RCTs) because the random distribution of genetic variations mimics the random assignment in treatment groups.

The causal relationship between LTL and MS progression remains unresolved, given that earlier studies primarily focused on MS susceptibility (Ma et al., 2024; Shu et al., 2022). Although over 200 genetic variants have been identified as influencing MS susceptibility in genome-wide association studies (GWAS) (International Multiple Sclerosis Genetics, 2019), these variants do not appear to impact MS progression significantly (George et al., 2016). This distinction highlights the need for MR studies to clarify the genetic factors underlying MS progression.

This study applies a bidirectional two-sample MR approach to explore the causal relationship between LTL and MS progression using GWAS data from the UK Biobank and the International Multiple Sclerosis Genetics Consortium. The findings provide fresh insights into telomere dynamics' role in MS's pathophysiology.

2. Methods

2.1. Mendelian randomization assumptions

This study employed bidirectional two-sample MR analyses using the latest GWAS summary statistics to investigate the relationship between LTL and MS progression. Additionally, we examined whether MS progression affects changes in LTL.

The MR approach is based on three core assumptions (Fig. 1):

1. Single nucleotide polymorphisms (SNPs) are associated with the exposure.
2. SNPs are not influenced by confounding factors related to the relationship between the exposure and the outcome.
3. The outcome is affected by the SNPs only through exposure (Sekula et al., 2016) (Fig. 1).

2.2. Data sources

In the largest GWAS of LTL to date, genetic associations with LTL were identified in a cohort of 472,174 individuals of European ancestry from the UK Biobank (Codd et al., 2021). This study examined 20,134,421 SNPs in individuals aged 40–69 years. The dataset was adjusted for methodological factors, and associations with established LTL-related phenotypes, including sex, ethnicity, and age, were confirmed. Peripheral blood leukocytes were collected from the UK Biobank participants

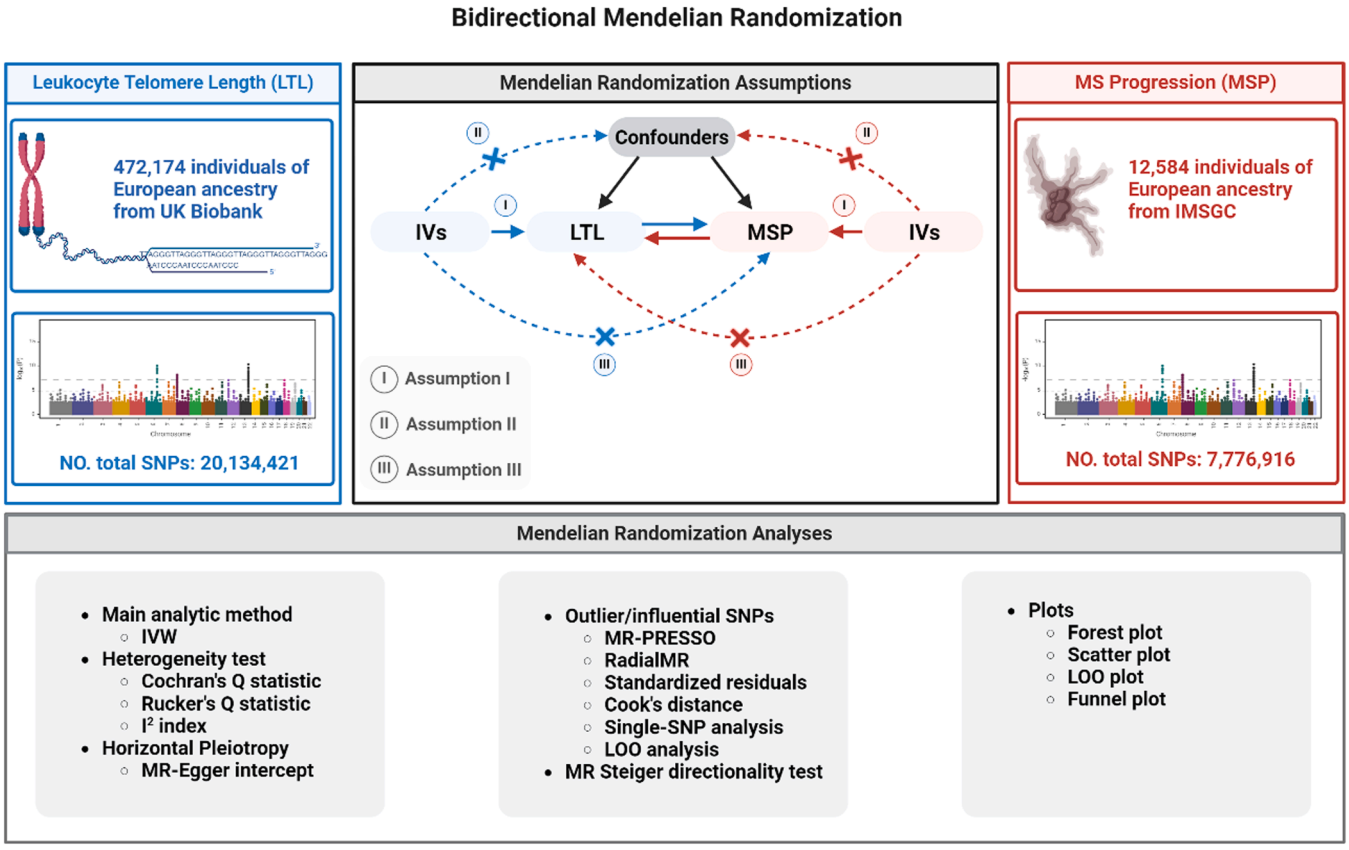

Fig. 1. The bidirectional Mendelian randomization design and assumptions for assessing the causality between exposure and outcome. IVs, instrumental variables; IVW, inverse variance weighted; LOO, leave-one-out; MS, multiple sclerosis; SNP, single nucleotide polymorphism.

to extract DNA.

For MS severity, summary statistics were obtained from the International Multiple Sclerosis Genetics Consortium (IMSGC), which conducted a GWAS on age-associated MS severity scores on 12,584 European ancestry cases (Harroud et al., 2023). This analysis included 7776,916 SNPs. Neurological disability was assessed using the Expanded Disability Status Scale (EDSS), which increases with neurodegenerative progress (Kurtzke, 1983). To control for aging effects, EDSS scores were transformed into the age-associated MS severity (ARMSS) score by ranking disability within age-specific groups (Manouchehrinia et al., 2017). Covariates included age at onset, sex, study center, date of birth, the top ten principal components, and genotyping platform.

2.3. Genetic instrument selection

SNPs significantly associated with the exposure were chosen as IVs. For LTL, SNPs with genome-wide significance $P < 5 \times 10^{-8}$ were selected. For MS progression, the threshold was relaxed to $P < 5 \times 10^{-5}$ to include a sufficient number of IVs. A criterion of $r^2 < 0.001$ within a 10,000 kb clumping window was established to eliminate linkage disequilibrium (LD). IVs were extracted from the outcome of interest, followed by clumping.Selected SNPs were harmonized to ensure consistent reference alleles across the exposure and outcome datasets. Palindromic SNPs were excluded if present. The strength of the SNP-exposure association was measured using the average F-statistics ($F = \beta^2/se^2$). IVs with an F-statistic < 10 were classified as weak and excluded from the analysis.

2.4. Mendelian randomization analysis

The inverse variance weighted (IVW) method was the primary approach to estimate the causal association between exposure and outcome. To ensure the reliability and robustness of the findings, additional methods were applied, including MR-Egger approaches, median-based estimation, mode-based estimation, and advanced techniques such as Robust Adjusted Profile Score (RAPS), MR-Lasso, MR-Constrained Maximum Likelihood (MR-cML), and Model-Based Estimation (MBE) (Slob and Burgess, 2020).

Heterogeneity in the analysis was addressed using methods, including Rucker's Q statistic for MR-Egger, Cochran's Q statistic, and the I^2 index (Bowden et al., 2019; Burgess et al., 2019). Horizontal pleiotropy was assessed via MR-Egger intercept tests (Burgess and Thompson, 2017). Outliers, which may indicate horizontal pleiotropy, were identified and corrected using the Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test (Verbanck et al., 2018; Zhu, 2021).RadialMR was also applied to detect outliers with potential pleiotropy (Hemani et al., 2018). Additionally, cook's distance and standardized residuals were used to identify influential or outlier SNPs (Verbanck et al., 2018). A leave-one-out (LOO) analysis was performed to assess the influence of individual genetic variants, with LOO plots used to visualize these effects (Burgess et al., 2019). Forest, funnel, and scatter plots were generated to visualize genetic associations, detect directional pleiotropy, investigate causal estimates, and identify outliers (Bowden et al., 2015). The MR Steiger test confirmed the directionality of causal relationships (Hemani et al., 2017).

All statistical analyses were performed using R software (version 4.3.2) with packages including "MendelianRandomization," "TwoSampleMR," "MRPracticals," "MR-PRESSO," and "mr.raps." The results are reported as β coefficients with corresponding 95 % confidence intervals (CIs), and associations with $P < 0.05$ were considered indicative of a relationship.

3. Results

3.1. Causal association between leukocyte telomere length and multiple sclerosis progression

Details about data preparation, MR analyses, and findings are provided in the Supplementary File and can also be accessed through the HTML link: https://hani-sabaie.github.io/LTL-MSP-MR/MR-Report.html

Using 121 SNPs, we identified a causal relationship between LTL and MS progression through the IVW method (β = 0.107, 95 % CI = 0.006 to 0.209, $P = 0.037$). This finding was consistent across multiple MR approaches, including Penalized IVW (β = 0.107, 95 % CI = 0.006 to 0.209, $P = 0.037$), Robust IVW (β = 0.097, 95 % CI = 0.009 to 0.185, $P = 0.030$), Penalized Robust IVW (β = 0.097, 95 % CI = 0.009 to 0.185, $P = 0.030$), RAPS (β = 0.108, 95 % CI = 0.006 to 0.210, $P = 0.038$), MR-Lasso (β = 0.107, 95 % CI = 0.006 to 0.209, $P = 0.037$), MR-cML (β = 0.109, 95 % CI = 0.007 to 0.211, $P = 0.036$), and dIVW (β = 0.108, 95 % CI = 0.006 to 0.211, $P = 0.037$) (see Fig. 2).

No evidence of heterogeneity was found in the relationship between LTL and MS progression, as indicated by Cochran's Q value ($Q = 102.784$, $P = 0.870$), Rucker's Q value ($Q = 102.737$, $P = 0.856$), and $I^2 = 0.0$ % statistic. The MR-Egger intercept test showed no signs of horizontal pleiotropy (MR-Egger intercept = −0.0005, $P = 0.829$).

Scatter plots (Figure S2, Supplementary File) and LOO plots (Figure S3, Supplementary File) were visually inspected to evaluate the impact of outliers further. Funnel and forest plots illustrating the causal association between LTL and MS progression are provided in the Supplementary File (Figures S4 and S5).

The MR Steiger test confirmed a correct causal direction ($P < 0.05$). A scatter plot was also created to visually compare results across various MR methods (Fig. 3).

3.2. Causal association between multiple sclerosis progression and leukocyte telomere length

Using 63 SNPs, our MR analysis identified a causal relationship between MS progression and LTL through IVW (β = −0.010, 95 % CI = −0.020 to −0.001, $P = 0.037$). This finding remained consistent across multiple MR methods, including Penalized IVW (β = −0.010, 95 % CI = −0.020 to −0.001, $P = 0.037$), Robust IVW (β = −0.010, 95 % CI = −0.019 to −0.001, $P = 0.031$), Penalized robust IVW (β = −0.010, 95 % CI = −0.019 to −0.001, $P = 0.031$), RAPS (β = −0.011, 95 % CI = −0.0208 to −0.0002, $P = 0.045$), MR-Lasso (β = −0.010, 95 % CI = −0.020 to −0.001, $P = 0.037$), MR-cML (β = −0.010, 95 % CI = −0.020 to −0.001, $P = 0.036$), and dIVW (β = −0.011, 95 % CI = −0.021 to −0.001, $P = 0.037$) (Fig. 4).

The Cochran's Q statistic ($Q = 34.486$, $P = 0.998$), Rucker's Q statistic ($Q = 34.486$, $P = 0.998$), and the I^2 statistic (0.0 %) showed no significant heterogeneity in the association between multiple sclerosis progression and LTL. The MR-Egger intercept test (intercept = 1.271×10^{-5}, $P = 0.989$) confirmed the absence of horizontal pleiotropy.

Scatter plots (Figures S7, Supplementary File) and LOO plots (Figures S8, Supplementary File) were examined to assess potential outliers. Funnel and forest plots provided in the Supplementary File (Figures S9 and S10) visually represented the causal estimates.

The MR Steiger test supported the correct causal direction ($P < 0.05$). Similarly, in the reverse MR analysis, a scatter plot was generated to compare results across different MR methods (Fig. 5).

4. Discussion

Observational studies often face challenges such as biases that complicate determining causal relationships. In this study, we applied a bidirectional two-sample MR approach to assess the causal relationship between LTL and MS progression and the reverse association.

Method	nSNPs	P-value	Beta (95% CI)
Inverse Variance Weighted (IVW)	121	0.037	0.107 (0.006 to 0.209)
Penalized IVW	121	0.037	0.107 (0.006 to 0.209)
Robust IVW	121	0.030	0.097 (0.009 to 0.185)
Penalized Robust IVW	121	0.030	0.097 (0.009 to 0.185)
MR-Egger	121	0.196	0.125 (-0.065 to 0.315)
Penalized MR-Egger	121	0.196	0.125 (-0.065 to 0.315)
Robust MR-Egger	121	0.075	0.129 (-0.013 to 0.272)
Penalized Robust MR-Egger	121	0.075	0.129 (-0.013 to 0.272)
Simple Median	121	0.742	0.027 (-0.133 to 0.186)
Weighted Median	121	0.064	0.150 (-0.009 to 0.309)
Penalized Weighted Median	121	0.065	0.150 (-0.009 to 0.309)
Simple Mode	121	0.801	0.040 (-0.277 to 0.357)
Weighted Mode	121	0.229	0.111 (-0.073 to 0.295)
Robust Adjusted Profile Score (RAPS)	121	0.038	0.108 (0.006 to 0.210)
MR-Lasso	121	0.037	0.107 (0.006 to 0.209)
MR-Constrained Maximum Likelihood (MR-cML)	121	0.036	0.109 (0.007 to 0.211)
Debiased IVW (dIVW)	121	0.037	0.108 (0.006 to 0.211)
Mode-Based Estimation (MBE)	121	0.238	0.111 (-0.073 to 0.295)

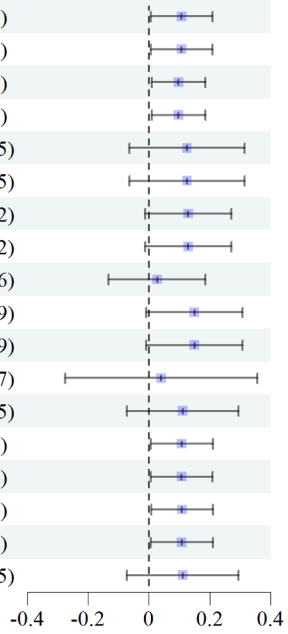

Fig. 2. A forest plot illustrating the various methods employed in forward Mendelian randomization analysis. The results are presented based on β coefficients with a 95 % confidence interval (CI).

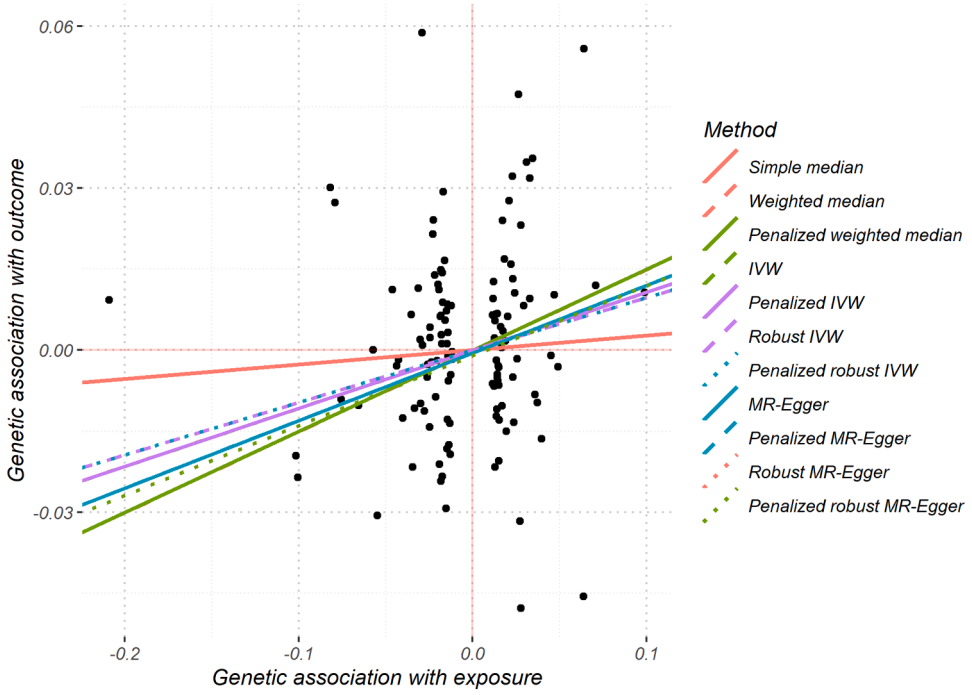

Fig. 3. Comparison of the various Mendelian randomization methods. All methods show a positive relationship between leukocyte telomere length and multiple sclerosis progression.

In the forward MR analysis, we identified a significant positive causal relationship between LTL and MS progression. Shortened telomeres are the result of cellular replication, senescence pathways, and DNA damage responses, leading to an early senescence state that exacerbates MS disability (Miner and Graves, 2021). Senescent cells release inflammatory cytokines, fueling chronic inflammation and accelerating MS progression (Miner and Graves, 2021). Previous studies have also highlighted this link. For example, Guan et al. (Guan et al., 2015) identified reduced TL and increased lipid peroxidation as markers of severe MS stages. Hecker et al. (Hecker et al., 2021) reported that shorter TL correlates with MS progression over 10 years. Moreover, Krysko et al. (Krysko et al., 2019) demonstrated that TL is associated with disability progression in MS. However, Habib et al. (Habib et al., 2020) reported that patients with primary progressive MS (PPMS) and secondary progressive MS (SPMS) had shorter TLs than those with relapsing-remitting MS (RRMS); however, this reduction was not linked to the progression of clinical disability. Our findings contrast with earlier observational studies suggesting shorter telomeres are associated

Methods	nSNPs	P-value	Beta (95% CI)
Inverse Variance Weighted (IVW)	63	0.037	-0.010 (-0.020 to -0.001)
Penalized IVW	63	0.037	-0.010 (-0.020 to -0.001)
Robust IVW	63	0.031	-0.010 (-0.019 to -0.001)
Penalized Robust IVW	63	0.031	-0.010 (-0.019 to -0.001)
MR-Egger	63	0.334	-0.010 (-0.031 to 0.011)
Penalized MR-Egger	63	0.334	-0.010 (-0.031 to 0.011)
Robust MR-Egger	63	0.385	-0.008 (-0.027 to 0.010)
Penalized Robust MR-Egger	63	0.385	-0.008 (-0.027 to 0.010)
Simple Median	63	0.103	-0.011 (-0.024 to 0.002)
Weighted Median	63	0.133	-0.010 (-0.023 to 0.003)
Penalized Weighted Median	63	0.133	-0.010 (-0.023 to 0.003)
Simple Mode	63	0.227	-0.019 (-0.051 to 0.014)
Weighted Mode	63	0.323	-0.016 (-0.048 to 0.016)
Robust Adjusted Profile Score (RAPS)	63	0.045	-0.011 (-0.021 to 0.000)
MR-Lasso	63	0.037	-0.010 (-0.020 to -0.001)
MR-Constrained Maximum Likelihood (MR-cML)	63	0.036	-0.010 (-0.020 to -0.001)
Debiased IVW (dIVW)	63	0.037	-0.011 (-0.021 to -0.001)
Mode-Based Estimation (MBE)	63	0.287	-0.016 (-0.046 to 0.014)

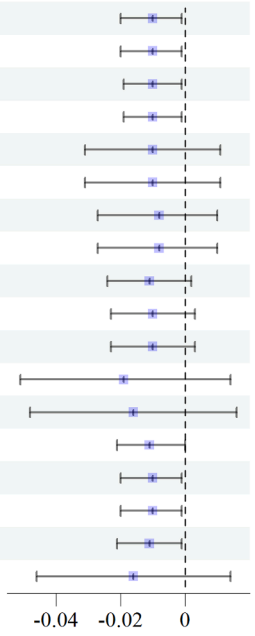

Fig. 4. A forest plot illustrating the various methods employed in reverse Mendelian randomization analysis. Results are presented based on β coefficients and a 95 % confidence interval (CI).

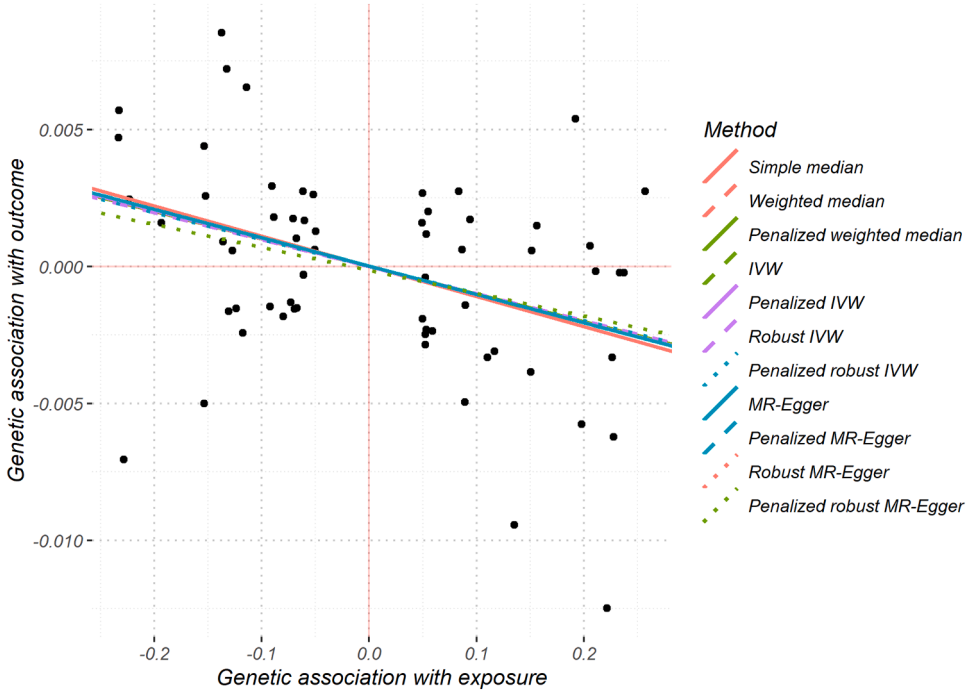

Fig. 5. Comparison of the causal estimates from various Mendelian randomization approaches. All methods indicate a negative association between multiple sclerosis progression and leukocyte telomere length.

with MS progression or phenotype. However, they align with two prior MR studies (Shu et al., 2022; Ma et al., 2024) that reported a positive causal relationship between LTL and MS risk in European populations. Both studies used GWAS summary statistics from IMSGC for MS susceptibility. Specifically, Shu et al. (Shu et al., 2022) used data from the UK Biobank GWAS (with 472,174 samples), and Ma et al. (Ma et al., 2024) employed data from a recent GWAS meta-analysis (with 78,592 samples of European ancestry). These discrepancies highlight the complexity of telomere biology in MS development and progress.

Unexpectedly, our reverse MR analysis revealed a significant negative causal relationship between MS progression and LTL. LTL exhibits significant variation among individuals, a phenomenon observed even in newborns. It tends to be longer in females than males and varies by ancestry, being longer in individuals of African ancestry compared to those of European ancestry (Aviv and Shay, 2018). LTL also varies based on parental age and environmental factors (Aviv and Shay, 2018). While shorter TL is widely regarded as a marker of advanced biological age (López-Otín et al., 2013), recent evidence suggests that both short and

long telomeres are linked to increased risks of various age-related diseases (Aviv and Shay, 2018; Codd et al., 2021; Haycock et al., 2017). Recent evidence indicates that the dynamic interaction between selective evolutionary forces and TL may result in trade-offs that impact specific health outcomes (Aviv and Shay, 2018). A common hypothesis posits that TL actively influences human diseases: short telomeres increase the risk of conditions associated with limited cell proliferation, such as cardiovascular disease (Fajemiroye et al., 2018), while long telomeres elevate the risk of diseases characterized by enhanced proliferative growth, including significant cancers (Tsatsakis et al., 2023). Consequently, both short and long TL may indicate telomere dysfunction. Studies have suggested correlations between long and short telomeres and the risk of developing various cancers, such as lung, thyroid, esophageal, and pancreatic (Tsatsakis et al., 2023). Moreover, a reverse U-shaped association between TL and cancer risk has been identified, suggesting a correlation between both extremes of TL and cancer development (Tsatsakis et al., 2023). It remains uncertain if and how these mechanisms account for the dual role of telomeres in MS progression.

The bidirectional causal relationship between LTL and MS progression carries important clinical implications. Understanding this association can inform therapeutic strategies targeting telomere dynamics to modify disease outcomes potentially. TL also holds promise as a prognostic biomarker, correlating with more severe MS manifestations and enabling stratification of patients based on their risk of progression (Guan et al., 2015; Hecker et al., 2021). Telomere-targeting therapies, such as telomerase gene therapy, have shown promise in other models (Bär et al., 2016) and could offer novel approaches for MS treatment.

Our study has several strengths. First, we employed a two-sample MR approach using SNPs as IVs to mitigate the effect of confounders and examine the causal relationship between exposure and outcome. Second, IVs were drawn from highly reliable GWAS datasets, enabling a robust causality evaluation. Third, we carefully addressed potential bias from outliers and considered the diverse effects of IVs. Finally, we conducted pleiotropy and heterogeneity tests, along with sensitivity analyses, to ensure the reliability of our findings.

However, this study has limitations. First, the GWAS datasets were based on European populations, limiting findings' generalizability to other ancestries. Future research should prioritize diverse populations through multi-ethnic GWAS or pooled international cohorts. Second, population stratification and relatedness biases in GWAS data may confound causal estimates. Using advanced statistical methods and individual-level data could address these issues more effectively. Third, the requirement for a single comprehensive dataset limited our ability to examine non-linear associations. Future studies could integrate detailed data across larger populations and employ stratified non-linear MR analyses or machine learning approaches. Finally, the relatively small GWAS sample size for MS progression reduces the power to detect weaker genetic signals. Larger GWAS focusing on MS progression are essential to enhance statistical power and refine causal estimates.

5. Conclusion

This study provides evidence of a causal link between long and short TL and MS progression, identified through MR analysis. These findings highlight the significant role of telomere dynamics as a potential driver of MS progression, extending beyond simple observational correlations. Further research is needed to uncover the biological mechanisms by which telomeres influence MS progression. Insights from telomere biology could help clinicians improve treatment outcomes for MS patients by developing innovative therapies that address the symptoms and the root causes of disease progression.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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CRediT authorship contribution statement

Hani Sabaie: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Ali Taghavi Rad:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Motahareh Shabestari:** Writing – review & editing, Writing – original draft, Investigation. **Sahar Seddiq:** Writing – review & editing, Writing – original draft, Investigation. **Toktam Saadattalab:** Writing – review & editing, Writing – original draft, Investigation. **Danial Habibi:** Writing – review & editing, Writing – original draft, Formal analysis. **Amir Hesam Saeidian:** Writing – review & editing, Writing – original draft, Investigation. **Mohadeseh Abbasi:** Writing – review & editing, Writing – original draft, Investigation. **Hanifeh Mirtavoos-Mahyari:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgments

Not applicable.

Data availability statement

The original data used are publicly available and the details of the MR analyses and their findings are available through the provided HTML link: https://hani-sabaie.github.io/LTL-MSP-MR/MR-Report.html

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2025.106277.

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