



# Genetically predicted telomere length and its relationship with neurodegenerative diseases and life expectancy



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## ABSTRACT

Telomere length (TL) is a biomarker of biological aging. Shorter telomeres have been associated with mortality and increased rates of age-related diseases. However, observational studies are unable to conclude whether TL is causally associated with those outcomes. Mendelian randomization (MR) was developed for assessing causality using genetic variants in epidemiological research. The objective of this study was to test the potential causal role of TL in neurodegenerative disorders and life expectancy through MR analysis. Summary level data were extracted from the most recent genome-wide association studies for TL, Alzheimer's disease (AD), Parkinson's disease, Frontotemporal dementia, Amyotrophic Lateral Sclerosis, Progressive Supranuclear Palsy and life expectancy. MR estimates revealed that longer telomeres inferred a protective effect on risk of AD (OR = 0.964; adjusted p-value = 0.039). Moreover, longer telomeres were significantly associated with increased life expectancy ( $\beta_{IVW} = 0.011$ ; adjusted p-value = 0.039). Sensitivity analyses suggested evidence for directional pleiotropy in AD analyses. Our results showed that genetically predicted longer TL may increase life expectancy and play a protective causal effect on AD. We did not observe significant causal relationships between longer TL and other neurodegenerative diseases. This suggests that the involvement of TL on specific biological mechanisms might differ between AD and life expectancy, with respect to that in other neurodegenerative diseases. Moreover, the presence of pleiotropy may reflect the complex interplay between TL homeostasis and AD pathophysiology. Further observational studies are needed to confirm these results.

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**Abbreviations:** AD, Alzheimer's disease; ALS, Amyotrophic lateral sclerosis; CI, Confidence Interval; FTD, Frontotemporal dementia; GWAS, Genome-wide association study; IV, Instrumental Variable; IVW, Inverse-Variance Weighted; LRR34, Leucine Rich Repeat Containing 34; MR, Mendelian Randomization; MR-PRESSO, MR-Pleiotropy RESidual Sum and Outlier; OR, Odds ratio; PD, Parkinson's disease; PSP, Progressive Supranuclear Palsy; SE, Standard Error; SNP, Single Nucleotide Polymorphism; TL, Telomere length.

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## 1. Introduction

Aging is a major risk factor for most neurodegenerative diseases [1]. As life expectancy rises worldwide [2], the prevalence of neurodegenerative diseases also increases [3,4]. Numerous studies speculated that neurodegenerative diseases are expressions of accelerated biological aging [1]. Traditionally, chronological age has been used as a proxy to estimate the gradual physiological deterioration that all living beings experience with time [5,6]. However, chronological age is an imperfect measure of biological aging, which is the true cause of morbidity and disability [7].

Telomere length (TL) is a well-known hallmark of biological aging [8], being telomere shortening associated with age-related diseases [9,10]. For instance, shorter telomeres have been found in Alzheimer's disease (AD) patients [11,12], and it has been proposed as a valuable predictor of the AD incidence [13]. Nevertheless, its association with other neurodegenerative diseases and age-related processes remains unclear. At these crossroads, observational studies fail to discern whether aging-related changes in the brain are harbingers or mere consequences of neurodegeneration [14]. Mendelian Randomization (MR) approaches were developed to assess causality in observational studies. MR approaches use genetic instrumental variables (IVs) (i.e., Single Nucleotide Polymorphisms, SNPs) whose estimation of the exposure of interest (i.e., TL) is not influenced by confounding or reverse causation [15,16]. Previous MR studies have described potential causal effects of genetically predicted TL on the risk of AD [17–20]. However, other MR studies failed to provide evidence of causal associations between TL and the risk of Parkinson's disease (PD) [21] or Amyotrophic lateral sclerosis (ALS) [22].

The aim of this study was to assess the existence of common biological aging mechanisms (through telomere biology) to several neurodegenerative diseases and life expectancy. We perform multiple independent two-sample MR analyses to evaluate whether TL may play a causal role in the risk of neurodegenerative diseases and life expectancy by using instrumental variables from recent genome-wide association studies (GWAS).

## 2. Methods

### 2.1. Genetic instrumental variables of telomere length

Summary statistics from a genome-wide meta-analysis of leukocyte TL across large-scale European-descent studies including up to 78,592 individuals were obtained from [23]. We selected summary data (i.e., allele frequency, beta value, standard error, and p-values) for 21 SNPs genome-wide associated with leukocyte TL ( $p$ -value  $< 5 \times 10^{-8}$ ) (Supplementary Table S1). Further details of the GWAS can be found in Supplementary Table S2.

### 2.2. Genome-wide association study data for neurodegenerative conditions

We used summary-level data from the most recent large-scale GWAS on five neurodegenerative diseases: AD ( $N = 455,258$ ) [24], Parkinson's disease (PD) ( $N = 1,437,688$ ) [25], Frontotemporal dementia (FTD) ( $N = 6,462$ ) [26], Amyotrophic lateral sclerosis (ALS) ( $N = 36,052$ ) [27] and Progressive Supranuclear Palsy (PSP) ( $N = 12,308$ ) [28]. Further details of the GWASs can be found in Supplementary Table S2. To reduce potential bias from population stratification, we only drew on summary-level data from European-descent individuals. Proxies for the genetic instrumental missing variables were included when possible through LDlink [29] (Supplementary Table S3).

### 2.3. Genome-wide association study data for life expectancy

For life expectancy, we used summary-level data from a GWAS using age at death of parents of middle-aged UK Biobank participants of European descent ( $N = 45,627$  with age at death data for both parents, excluding early deaths) [30]. Further details can be found in Supplementary Table S2.

### 2.4. Statistical analysis

Alleles were harmonized to take as reference the effect allele associated with longer TL. In this study, we used Inverse-Variance Weighted (IVW) [31], MR-Egger regression [32], weighted median [33] and maximum likelihood [34] methods with summarized data to estimate the causal effect of genetically predicted longer TL on the outcomes of the study. MR-Egger regression intercept-test [32], leave-one-SNP-out and Cochran Q statistic [35] were used as *ad hoc* sensitivity analysis for evaluating the robustness of significant results. MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) was also used to identify horizontal pleiotropic outliers [36]. Effect sizes were reported in Odds Ratio (OR) for all the pathologies and the SD change in life expectancy ( $\beta_{IVW}$ ) per copy of the allele associated with longer telomere length. False Discovery Rate corrections for multiple comparisons were performed at significant level 0.05. MR-Egger regression intercept-test was used as *ad hoc* sensitivity analysis for evaluating directional pleiotropy [37]. P-values for intercept terms below 0.05 were indicators of pleiotropy. All analyses were conducted under R software, version 4.1.0 [38]. MR analyses were performed using the MendelianRandomization package in R [39]. Further details about the statistical procedure can be found in Supplementary Methods.

## 3. Results

IVW estimates revealed that longer TL inferred a protective effect on risk of AD ( $OR_{IVW} = 0.964$ ;  $q$ -value = 0.039) (Table 1; Fig. 1). Maximum likelihood, MR-Egger regression, weighted median and weighted mode methods suggested similar protective effects. MR-Egger intercept test provided evidence for directional pleiotropy in AD analyses ( $p$ -value = 0.021). Nevertheless, there was no sign of increased heterogeneity according to both Cochran Q and MR-PRESSO (Table 1). IVW leave-one-out analysis showed MR estimates did not fluctuate after sequentially removing each of the 21 SNPs used as IVs (Supplementary Figure S1). No statistically significant associations were identified between genetically predicted longer TL and other neurodegenerative diseases (Supplementary Table S4; Supplementary Figures S2–S5). Leave-one-out analysis showed similar null effects when sequentially leaving out genetic variants from the analyses (Supplementary Figures S6–S9).

Moreover, longer TL was significantly associated with increased life expectancy ( $\beta_{IVW} = 0.011$ ;  $q$ -value = 0.039) (Fig. 2). Maximum likelihood, MR-Egger regression weighted median and weighted mode methods suggested analogous patterns of effect on life expectancy. In this case, MR-Egger intercept test did not suggest the presence of unbalanced directional pleiotropy ( $p$ -value = 0.462). Cochran Q and MR-PRESSO further supported the absence of heterogeneity in MR estimates (Table 1). Leave-one-out analysis showed IVW estimates lost significance when excluding rs10936600 from life expectancy analysis (Fig. 3).

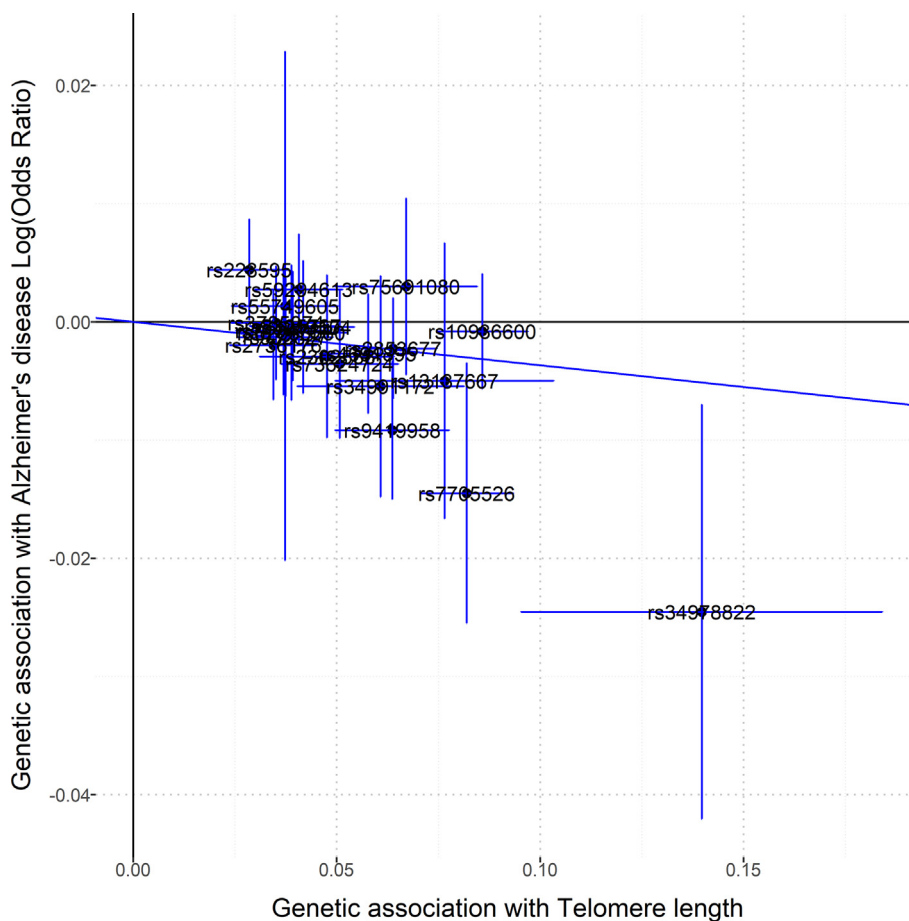
## 4. Discussion

In this study, we explored the potential causal role of genetically predicted longer TL on the risk of neurodegenerative diseases

**Table 1**  
Mendelian randomization results for the relationship between genetically predicted longer telomere length, life expectancy and Alzheimer's disease.

Causal inference methods	Life expectancy				Alzheimer's disease			
	$\beta$	SE	p-value	q-value	OR	95 % CI	p-value	q-value
Inverse-variance weighted	0.011	0.004	<b>0.010</b>	<b>0.039</b>	0.964	(0.936, 0.992)	<b>0.013</b>	<b>0.039</b>
Maximum likelihood	0.011	0.004	<b>0.010</b>	<b>0.043</b>	0.964	(0.936, 0.993)	<b>0.014</b>	<b>0.043</b>
MR-Egger regression	0.020	0.013	0.113	0.339	0.884	(0.818, 0.956)	<b>0.002</b>	<b>0.012</b>
Weighted median	0.013	0.006	<b>0.038</b>	0.165	0.966	(0.932, 1.001)	0.055	0.165
Weighted mode	0.021	0.009	<b>0.021</b>	0.126	0.976	(0.934, 1.020)	0.282	0.432
<b>Sensitivity methods</b>	<b>p-value</b>				<b>p-value</b>			
Cochran Q, heterogeneity test	0.978				0.101			
MR-PRESSO, global test	0.982				0.106			
MR-Egger, intercept test	0.462				<b>0.021</b>			

Legend: CI, Confidence Intervals; MR, Mendelian Randomization; OR, Odds Ratio; SE, Standard Error; PRESSO, Pleiotropy RESidual Sum and Outlier.



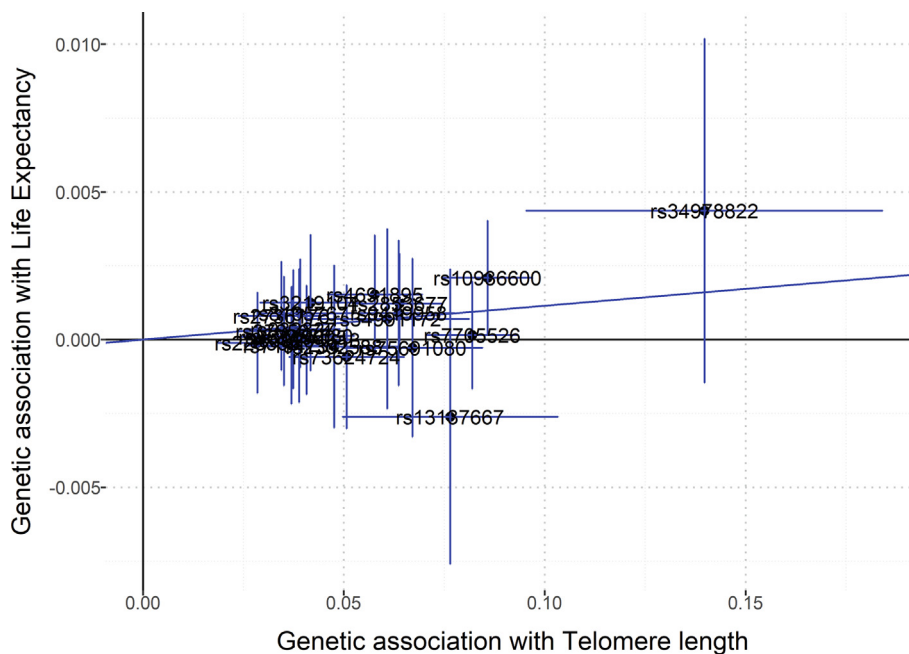
**Fig. 1.** Scatter plot representing the significant causal effects of genetically predicted longer telomere length on Alzheimer's disease risk. The slope of the line represents the Inverse-Variance Weighted causal estimate.

and life expectancy through a multiple independent two-sample MR approach. We observed that genetically predicted longer TL was associated with increased life expectancy and lower risk of developing AD. No associations were observed in relation to other neurodegenerative diseases.

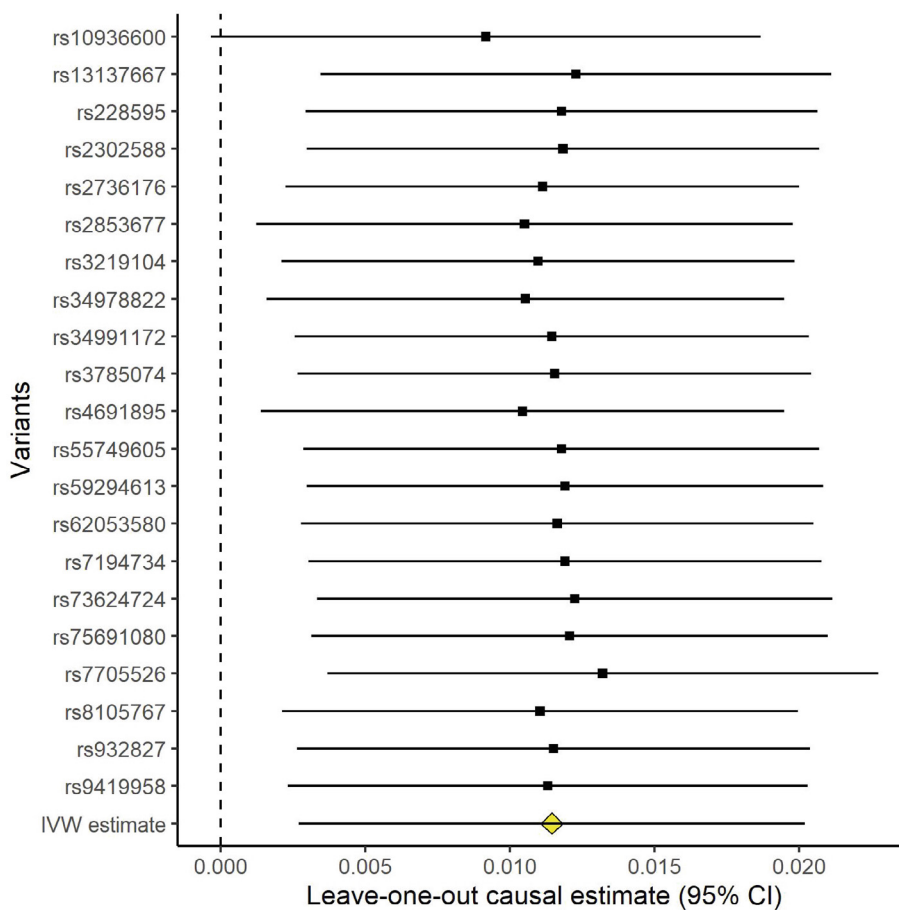
Our study confirms and extends previous MR studies regarding TL association with AD risk [17–20]. Nevertheless, we observed evidence of directional pleiotropy and AD estimates were relatively inconsistent when using several MR methods. Interestingly, [40] reported a similar pattern of MR estimates when using summary-level data from [24], where AD cases were both clinically diagnosed or AD-by-proxy (i.e., based on parental diagnoses). Despite the heritability of sporadic AD (~80%) [41], and the proven

value of proxy case-control association studies [42], this could partially explain the decreased statistical power to detect consistent causal associations through robust MR methods.

We did not find further significant associations between genetically predicted TL and other neurodegenerative disease, which also confirms results from previous studies. For instance, two previous MR studies did not find significant causal associations between TL and the risk of PD [21], ALS and FTD [22]. Additionally, most observational studies showed contradictory results [43–45]. On the other hand, as far as we know, no previous MR studies have evaluated the causal role of TL on PSP. Although neurodegenerative diseases share common pathological pathways [46], our results might suggest that different hallmarks of aging could distinctly



**Fig. 2.** Scatter plot representing the significant causal effects of genetically predicted longer telomere length on life expectancy. The slope of the line represents the Inverse-Variance Weighted causal estimate.



**Fig. 3.** Leave-one-out permutation analysis plot for life expectancy obtained by leaving out the SNP indicated and repeating the Inverse-Variance Weighted method with the rest of the instrumental variables.

interact with the complex etiology of these diseases [3,47]. Indeed, a composite biomarker panel of aging could increase the predictive power of these studies by pointing to different aspects of the aging process [48].

Additionally, we observed a statistically significant association between genetically predicted longer TL and increased life expectancy. Telomere shortening rate is known to predict species lifespan [49]. Nonetheless, little evidence of association between genetically predicted TL and parental lifespan has been previously described [50]. Importantly, we found that rs10936600, located at the leucine rich repeat (*LRRC34*) gene, was primarily driving the results of the MR analysis. Although the role of *LRRC34* in telomere biology is not fully understood yet, gene-enrichment analysis has identified *LRRC34* as the most significant gene associated with telomere length [51].

Therefore, our results support a potential causal relationship between shorter telomeres, AD risk, and increased life expectancy. Indeed, [30] described that offspring of longer-lived parents had more protective alleles for AD. Interestingly, AD contributes to a shortened life expectancy, although non-Alzheimer's dementia usually show shorter life expectancy than AD [52]. Together with our results, this suggests that telomere biology might play a shared role in life expectancy and the pathophysiology of AD but no other neurodegenerative processes. Nonetheless, the higher prevalence of AD compared to other neurodegenerative diseases could also explain our results [4].

The causal effect of TL cannot be empirically tested in humans; therefore, MR approach provides a unique opportunity to disentangle the effect of TL in human health. Nevertheless, our study is not free of limitations. On the one hand, we found evidence of directional pleiotropy on AD analysis. Although supplementary sensitivity analyses did not support the presence of increased heterogeneity, IVW estimates could be biased in the presence of pleiotropy [33]. In this sense, although robust MR methods produced similar patterns of effects, the lack of significant associations encountered by applying the generally conservative MR methods (i.e. weighted median and weighted mode) could indicate a lack of statistical power or the presence of non-valid instrumental variants in AD analyses [37]. Indeed, we cannot fully ensure other MR assumptions have not been violated. In addition, proxies for some SNPs were used as IVs in MR analyses on PD, FTD and PSP. On the other hand, MR statistical power is dependent on the sample size of each GWAS. In this sense, the GWAS of FTD included a relatively small sample size (N cases = 2,154) and different FTD subtypes [25], which could explain the wide confidence intervals obtained in MR analyses (Supplementary Table S4). Moreover, the GWAS included in the MR analyses were exclusively performed in individuals of European ancestry, thus these results should not be extrapolated to other populations. Finally, telomere length in the GWAS [23] was measured in leukocytes. Although leukocyte TL is a valid proxy of TL in other tissue types including the brain [53], measuring TL among distinct brain cell types could help addressing the molecular mechanisms that connect telomere biology to AD risk.

As future research, MR analysis focused on addressing the role of TL on the pathological mechanisms of neurodegeneration could further help to identify which molecular pathways are involved in this potential causal association. Furthermore, the use of meta-GWAS including both larger samples and higher number of cases will increase the statistical power of future MR analysis. Finally, further observational studies could help to elucidate such associations.

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## CRedit authorship contribution statement

**Blanca Rodríguez-Fernández:** Conceptualization, Data curation, Methodology, Formal analysis, Visualization, Writing – original draft. **Juan Domingo Gispert:** Writing – review & editing. **Roderic Guigo:** Writing – review & editing. **Arcadi Navarro:** Writing – review & editing. **Natalia Vilor-Tejedor:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Marta Crous-Bou:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.csbj.2022.08.006>.

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## Further Reading

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