Genetically predicted leucocyte telomere length correlates with age at onset in multiple sclerosis

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BACKGROUND

- **Telomeres** are DNA–protein structures at chromosome ends that maintain genomic stability and shorten with age, contributing to neurodegeneration and immune dysfunction. In multiple sclerosis (MS), shorter **leukocyte telomere length** is linked to faster disability progression, brain atrophy, and earlier transition to progressive disease, though causality remains unclear.
- **Polygenic scores for genetically predicted telomere length (gLTL)** allow assessment of inherited telomere length independent of disease or environment. Whether gLTL influences **age at onset (AAO)** of MS remains unknown.

OBJECTIVES

- To explore whether **genetically predicted telomere length** is associated with age at onset in MS.
- To investigate the **polygenic architecture** of gLTL by testing the effect of **multiple polygenic risk scores (gLTL-PRS),** constructed at different significance thresholds, with AAO.

METHODS

- **Cohort**: 2,955 relapsing–remitting MS patients recruited at San Raffaele Hospital, Milan, Italy. After quality control (QC), **2,824 patients** were retained. AAO was defined as age at first neurological symptom.
- **Genotyping & Quality Control:** Genome-wide genotypes were obtained using Illumina platforms and imputed against the Haplotype Reference Consortium panel. Standard QC excluded samples with low call rate, extreme heterozygosity, or relatedness. Population structure and platforms effect were controlled via principal component analysis (PC1–PC4 included as covariates).
- **PRS Construction:** Summary statistics from the **UK Biobank GWAS** on leukocyte telomere length (**Codd et al**[1]. n ≈ 465,000) were used. Eight gLTL-PRS were generated using a clumping and thresholding approach, including one **genome-wide significant** score (137 SNPs) and seven secondary scores at increasingly lenient **p-value thresholds** (5×10^{-8}, 5×10^{-5}, 5×10^{-4}, 0.001, 0.05, 0.1 and 0.2).
- **Statistical Analysis:** Associations between standardized PRS and AAO were tested fitting linear regression models, adjusted for PCs. PRS were standardized as Z-scores. Additional analyses included logistic regression for early- vs late-onset MS, extreme-group comparisons, and evaluation of incremental variance explained (coefficient of determination R^2). All analyses were conducted in R.

RESULTS

Association of gLTL-PRS with AAO

Higher gLTL-PRS, scaled to reflect genetically longer telomeres, **was associated with later age at onset** across all thresholds. Associations were directionally consistent, supporting a **polygenic contribution** of telomere length to AAO.

Name	P Threshold	SNPs number	beta	pvalue
PRS1	genome-wide	137	0.41	0.023*
PRS2	$P < 5 \times 10^{-6}$	1762	0.29	0.110
PRS3	$P < 5 \times 10^{-5}$	2816	0.36	0.043*
PRS4	$P < 5 \times 10^{-4}$	6288	0.37	0.042*
PRS5	$P < 5 \times 10^{-3}$	22942	0.34	0.060
PRS6	P < 0.05	116068	0.41	0.032*
PRS7	P < 0.1	197236	0.45	0.025*
PRS8	P < 0.2	316984	0.57	0.008*

Table 1. Linear regression results for gLTL-PRS at different p-value thresholds, showing effect estimates and p-values for association with AAO.

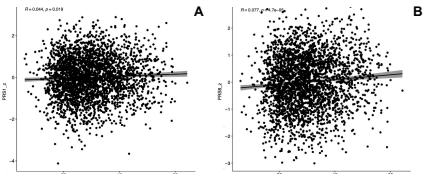

Figure 1. Scatter plots showing the association between AAO and genetically predicted telomere length using **PRS1** (A) and **PRS8** (B).

Extreme AAO groups – PRS8

Comparing **early-onset** (≤18 years – 234 subjects) and **late-onset** (≥50 years – 97 subjects) patients, PRS8 showed a positive trend toward later onset (**beta = 0.19**), though not statistically significant (p = 0.22).

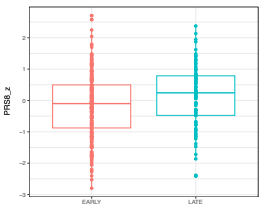

Figure 2. Distribution of PRS8 (p < 0.2) in early- vs late-onset MS patients

PRS8 decile comparison

Stratifying patients by **deciles** of PRS8, we observed that those in the highest decile had a mean AAO of **31.35 years**, compared with **28.09 years** in the lowest decile, a difference of **+3.26 years.**

Welch's t = −4.09,
p = 4.97 × 10^{-5},
95% CI −4.81 to −1.69

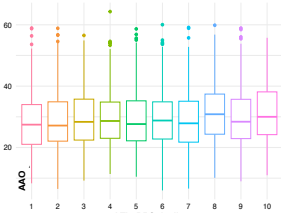

Figure 3: Boxplots of AAO across deciles of PRS8

Variance explained by PRS

The baseline model (**model 0**) including only population structure (PC1–PC4) explained 1.47% of AAO variance. Adding gLTL-PRS increased the explained variance modestly but significantly: **+0.19%** for the genome-wide score – PRS1 (**p = 0.022**) and **+0.23%** for PRS8 (**p = 0.011**).

MODELS TESTED:

- **Model 0:** AAO ~ PC1 + PC2 + PC3 + PC4
- **Model PRS1:** AAO ~ PC1 + PC2 + PC3 + PC4 + PRS1 (GW significant SNPs)
- **Model PRS8:** AAO ~ PC1 + PC2 + PC3 + PC4 + PRS8 (SNPs with p < 0.2)

Modello	R^2 Totale	Incremental R^2	p-value (ANOVA)
Model 0 (PC1-PC4)	0.0147 (1.47%)	–	–
Model PRS1	0.0166 (1.66%)	0.0019 (0.19%)	0.022*
Model PRS8	0.0170 (1.70%)	0.0023 (0.23%)	0.011*

Table 1. Variance in AAO explained by gLTL-PRS models compared with model 0

CONCLUSIONS

- **Genetically longer LTL** is associated with **later AAO in MS**. The strength of associations at more inclusive PRS thresholds highlights the **polygenic nature** of telomere biology. We can speculate that constitutional telomere length may influence the timing of MS onset, **linking ageing biology to disease heterogeneity.**
- These findings support the potential of **telomere-based genetic markers** to refine patient stratification and guide studies on **age-related disease mechanisms**.

1) Codd, V., Wang, Q., Allara, E. *et al.* Polygenic basis and biomedical consequences of telomere length variation. *Nat Genet* **53**, 1425–1433 (2021)

DISCLOSURES: GV, MS, FC, EM, MT, NB, SA: nothing to disclose. AG received consulting fees and travel grants from Sinounis. MA received consultancy and/or speaker honoraria from Sanofi, GSK, Biogen, Roche and Immunic therapeutics. MF received financial research support from Biogen Idec, Merck-Serono, Novartis, Roche, the Italian Ministry of Health, the Italian Ministry of University and Research, and Fondazione Italiana Sclerosi Multipla; consulting fees from Alexion, Almirall, Biogen, Merck, Novartis, Roche, Sanofi; honoraria from Bayer, Biogen, Celgene, Chiesi Italia SpA, Eli Lilly, Genzyme, Janssen, Merck-Serono, Neopharmed Gentili, Novartis, Novo Nordisk, Roche, Sanofi, Takeda, and TEVA, Biogen, Merck, Roche, Celgene, Bristol-Myers Squibb, Lilly, Novartis, Sanofi-Genzyme. FE received consulting fees from Merck Serono and Genzyme