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Bidirectional Mendelian randomization reveals associations between telomere length and autoimmune diseases

Qin Jiang[1,2,3†], Chenxi Yu[1,2,3†], Shiben Zhu[4†], Yang Liu[1,2,3] and Min Ye[5*]

Abstract

Background Autoimmune diseases are a group of complex chronic illnesses that affect multiple organs or body systems. These diseases are characterized by tissue damage, impaired organ function, and increased risk of malignancies, and elevated mortality. Nevertheless, the casual correlation between autoimmune diseases and telomere length remains uncertain.

Objective Our bidirectional Mendelian randomization analysis was aimed to evaluate the causal association between autoimmune diseases and telomere length.

Methods To minimize bias, four demographic factors including body mass index (BMI), alcohol consumption, smoking, and income were assessed using two-sample Mendelian randomization analysis. Furthermore, this analysis was conducted to explore the causal relationships between telomere length and autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), type 1 diabetes (T1D), Graves' disease (GD), and psoriasis using two separate datasets from FinnGen and the UK Biobank.

Results When using inverse variance weighting (IVW) to assess the relationship between four available demographic factors and overall autoimmune diseases, no significant association was found ($p > 0.05$). However, a significant negative causal effect of telomere length on autoimmune diseases was observed (IVW: OR = 0.906, 95% CI = 0.832–0.986, $p = 0.022$). Reverse Mendelian randomization analysis revealed no significant correlation. Further analysis using two separate datasets for five common autoimmune diseases confirmed significant negative associations between telomere length and RA (UKB biobank: OR = 0.997, 95% CI 0.994–0.999, $p = 0.025$; FinnGen: OR = 0.860, 95% CI 0.741–0.998, $p = 0.047$), GD (UK Biobank: OR = 0.519, 95% CI 0.430–0.625, $p < 0.001$; FinnGen: OR = 0.623, 95% CI 0.496–0.785, $p < 0.001$), and psoriasis (UK Biobank: OR = 0.772, 95%CI = 0.642–0.928, $p = 0.006$; FinnGen: OR = 0.841, 95%CI = 0.727–0.973, $p = 0.020$). A significant positive association was found for SLE in the UK Biobank (OR = 1.718, 95% CI = 95% CI 1.155–2.558, $p = 0.007$). Reverse Mendelian randomization analysis identified a significant negative association between telomere length and SLE (UK Biobank: OR = 0.995, 95% CI 0.991–0.998, $p = 0.014$; FinnGen: OR = 0.988, 95% CI 0.977–0.998, $p = 0.029$) and psoriasis (FinnGen: OR = 0.992, 95% CI 0.988–0.997, $P = 0.005$), and a positive association with RA (UK Biobank: OR = 1.988 95% CI 1.056–3.743, $p = 0.031$).

Conclusions This Mendelian randomization analysis reveals a significant association between telomere length and autoimmune diseases such as RA, GD, and psoriasis, while a positive relationship was validated with SLE. These

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findings underscore the need for further investigation to better understand the underlying mechanisms and their potential clinical applications.

Keywords Telomere length, Autoimmune diseases, Casual effect, Mendelian randomization, GWAS, Graves' disease, Type 1 diabetes, Systemic lupus erythematosus, Rheumatoid arthritis, Psoriasis

Introduction

Autoimmune diseases comprise a group of at least 80 disorders, each characterized by immune-mediated tissue damage [1]. The increasing prevalence of these disorders with age presents significant healthcare challenges, particularly due to the lack of effective treatments. A recent cohort study in the UK found that, contrary to previous estimates of 3 to 9%, 19 of the most common autoimmune diseases now affect approximately 10% of the population, with 13% of women and 7% of men impacted [2]. Although extensive research has been conducted, the exact causes of autoimmune diseases remain unclear, particularly concerning the roles of genetic factors. These diseases can affect multiple organs and body systems, leading to serious complications and contributing to considerable patient distress, disability, and mortality [3]. For example, the mortality rate for systemic lupus erythematosus (SLE) ranges from 5 to 10% [4], while all-cause mortality for diabetes may reach 19.7% [5]. Given the absence of effective treatments, developing novel diagnostic and therapeutic strategies is crucial for improving patient outcomes.

Telomeres are specialized DNA–protein complexes, consisting of repetitive nucleotide sequences (TTAGGG), that are located at the ends of chromosomes and play a crucial role in maintaining genomic stability. During cellular division, telomeres progressively shorten due to constraints in end-replication, eventually reaching a critical length that triggers cellular senescence and apoptosis. This process has established telomere length as a potential biomarker for biological aging. Recent investigations have associated short telomere length with a higher diseases risk, such as SLE [6], rheumatoid arthritis (RA) [7], systemic sclerosis [8], and type 1 diabetes (T1D) [9]. However, the bidirectional relationship between telomere length and autoimmune diseases, along with its potential as a predictive biomarker, requires further systematic exploration and validation through robust genetic evidence.

Mendelian randomization is an epidemiological approach that uses genetic variation related to exposure as an instrumental variable (IV) to investigate causal relationships between that exposure and disease. Similar to a randomized controlled trial, Mendelian randomization can be particularly useful when conducting an randomized controlled trial is impractical or unethical [10]. Since genotypes are established prior to disease onset and are generally unaffected by disease progression, reverse causality is unlikely. Therefore, reassessing the causal relationship between telomere length and autoimmune diseases using Mendelian randomization, which is rarely confounded by external factors, is important. Mendelian randomization provides a robust method for causal inference, minimizing the risks of reverse causality and confounding [11]. However, no Mendelian randomization study has systematically explored the associations between telomere length and autoimmune diseases.

To minimize potential confounding, we used two-sample bidirectional Mendelian randomization to investigate the relationships between autoimmune diseases and four demographic factors including body mass index (BMI), alcohol consumption, smoking, and income. Then, our study builds on previous work by employing a bidirectional Mendelian randomization framework to examine the link between telomere length and autoimmune diseases (Fig. 1). We also leverage two separate datasets from FinnGen and the UK Biobank to validate the relationship between telomere length and five common autoimmune diseases including Graves' disease (GD), T1D, SLE, RA, and psoriasis. By identifying traits that influence telomere length, our study explores its impact on the human phenome, thereby enhancing our understanding of telomere biology and its relevance to health.

Materials and methods

Study design

This study applied bidirectional two-sample Mendelian randomization analysis. To minimize potential confounding, we first investigated the relationships between autoimmune diseases and four demographic factors including BMI, alcohol consumption, smoking, and income using two-sample bidirectional Mendelian randomization. Next, we examined the potential causal effect of telomere length on autoimmune diseases, followed by reverse Mendelian randomization to assess the effect of disease status on telomere length. Additionally, bidirectional causal inference was conducted separately for telomere length and five common autoimmune diseases using datasets from FinnGen and the UK Biobank. Since the original studies have undergone ethical review and the data are anonymized, no further ethical approval

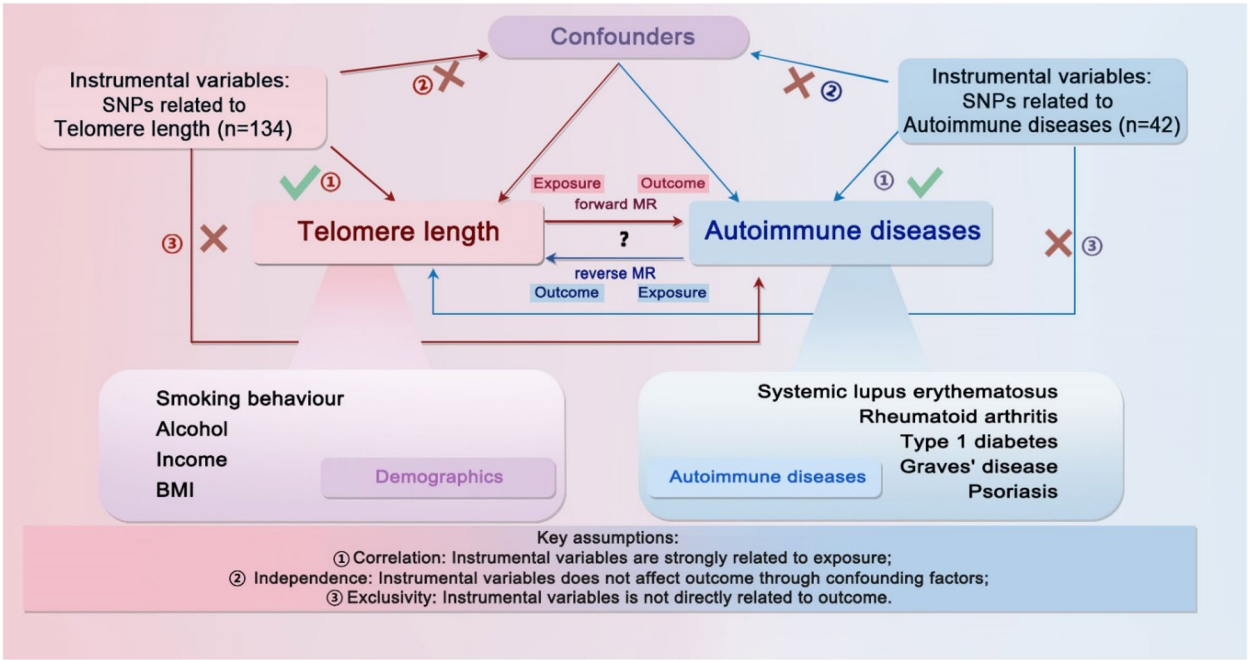

Fig. 1 Overview of research design. MR: Mendelian randomization. SNP: single-nucleotide polymorphism

or individual informed consent was required. Figure 1 provides a comprehensive overview of the technical workflow.

Selection of IVs

Candidate single-nucleotide polymorphisms (SNPs) were selected using a stringent significance threshold ($p < 5\times 10^{-8}$) to ensure statistical reliability. To confirm the independence of these instruments, SNPs were grouped within 10-Mb genetic windows, applying a strict linkage disequilibrium threshold ($r^2 < 0.001$). The effect directions between exposure and outcome variants were harmonized using the PhenoScanner database (http://www.phenoscanner.medschl.cam.ac.uk), excluding SNPs with inconsistent allelic directions or palindromic structures. The validity of the instruments was further assessed using *F*-statistics (β^2/SE^2), where β represents the SNP effect estimates on exposures and SE is the standard error. SNPs with $F > 10$ were retained to meet the first Mendelian randomization assumption and minimize weak instrument bias. To ensure robustness, only SNPs with valid detection across all traits were included as IVs, and no proxy SNPs were used to fill missing data in outcome datasets.

Data source

The data were sourced from the genome-wide association study (GWAS) catalog (https://www.ebi.ac.uk/gwas/). Telomere length was studied using UK Biobank data by Codd et al. (2021), which included 472,174 participants and over 20 million genetic markers. Autoimmune diseases were analyzed using the FinnGen 2021 release, encompassing 218,792 individuals, including 176,590 controls, and 16 million genetic variants. For SLE, two studies were included: one from the UK Biobank (Bentham J, 2015; 14,267 cases and 9066 controls) and another from FinnGen (2021; 218,377 participants). RA data combined UK Biobank research by Ben Elsworth (2018; 462,933 participants) with FinnGen 2021 results (218,792 individuals). T1D data included a UK Biobank study (Inshaw JRJ, 2021; 17,685 participants) and FinnGen 2021 data (189,113 individuals). GD was studied using UK Biobank data by Sakaue S (2021; 458,620 participants) and FinnGen 2021 results (500,348 individuals). Psoriasis studies incorporated UK Biobank data (Stuart PE, 2021; 44,161 participants) and FinnGen 2021 analyses (216,752 individuals). All diseases included both sexes, focused on individuals of European ancestry, and used GWAS identifiers such as ieu-b- 4879 or finn-b-AUTOIMMUNE for cross-referencing. The genetic markers examined ranged from 7 million to over 24 million SNPs per study. A detailed description of the data is provided in Table 1. Furthermore, the 45 autoimmune diseases included in the overall autoimmune disease category are detailed in Supplementary Table S1.

Table 1 An overview of the GWAS summary statistics

Traits	Data source	Author and year	Sample size	Control	SNPs	Sex	Ancestry	GWAS ID
Telomere length	UK Biobank	Codd et al. (2021)	472,174	472,174	20,134,421	M/F	European	ieu-b- 4879
Autoimmune diseases	FinnGen	NA (2021)	218,792	176,590	16,380,466	M/F	European	finn-b-AUTOIMMUNE
SLE	UK Biobank	Bentham J (2015)	14,267	9,066	7,071,163	M/F	European	ebi-a-GCST003156
	FinnGen	NA (2021)	218,377	218,254	16,380,466	M/F	European	finn-b-SLE_OTH
RA	UK Biobank	Ben Elsworth (2018)	462,933	457,732	9,851,867	M/F	European	ukb-b- 9125
	FinnGen	NA (2021)	218,792	212,463	16,380,466	M/F	European	finn-b-M13_RHEUMA_INCLAVO
T1D	UK Biobank	Inshaw JRJ (2021)	17,685	10,218	7,740,245	M/F	European	ebi-a-GCST90000529
	FinnGen	NA (2021)	189,113	183,185	16,380,008	M/F	European	finn-b-E4_DM1
GD	UK Biobank	Sakaue S (2021)	458,620	456,942	24,189,816	M/F	European	ebi-a-GCST90018847
	FinnGen	NA (2021)	500,348	496,386	21,327,062	M/F	European	finngen_R12_E4_GRAVES_STRICT
Psoriasis	UK Biobank	Stuart PE (2021)	44,161	28,194	8,470,172	M/F	European	ebi-a-GCST90019017
	FinnGen	NA (2021)	216,752	212,242	16,380,464	M/F	European	finn-b-L12_PSORIASIS

Statistical analysis

Statistical analysis was conducted using R software (version 4.3.2). To minimize bias in examining the relationship between telomere length and autoimmune diseases, four demographic factors were incorporated. The primary analysis employed inverse variance weighting (IVW) [12] to assess the causal relationship between telomere length and autoimmune diseases. To ensure result robustness, five complementary statistical methods were applied: weighted median [13], MR-Egger [14], robust adjusted profile score [15], maximum likelihood [16], and simple mode [17], providing a comprehensive validation of the causal effects. For the analysis of telomere length and five common autoimmune diseases (SLE, RA, GD, T1D, and psoriasis), three Mendelian randomization methods were used: IVW, MR-Egger, and weight median. Visualization of the results was shown through leave-one-out analysis, scatter plots, and funnel plots. Cochran's *Q* test assessed potential heterogeneity, while MR-Egger regression evaluated pleiotropy. The MR-PRESSO method was employed to identify and exclude potential outliers. Finally, Bonferroni correction was applied for multiple comparison adjustments, with a p-value threshold of 0.005 for statistical significance. All other significant thresholds were set at 0.05.

Results

Demographic variables

We investigated the relationship between four demographic factors (BMI, alcohol, smoking, and income) and autoimmune diseases. Data for these factors were extracted from the UKB biobank database (Supplementary Table S2). Using the IVW assessment, we found no significant correlation ($p > 0.05$) between these demographic factors and autoimmune diseases (Supplementary Fig. S1).

Bidirectional Mendelian randomization results between telomere length and autoimmune diseases

During IVs selection, after applying stringent criteria to exclude SNPs, we identified 134 statistically SNPs as genetic tools for investigating the association between telomere length and autoimmune diseases. In this study, each SNP exhibited *F*-statistics exceeding 10, with a combined *F*-statistic of 120. During the reverse Mendelian randomization analysis, a total of 42 SNPs were ultimately included after undergoing a series of quality control measures. Furthermore, all IVs demonstrated *F*-statistics significantly exceeding 10.

The results of our forward Mendelian randomization analysis are shown in Fig. 2, indicating a significant negative association between telomere length and autoimmune diseases. When telomere length was considered as the exposure, the IVW analysis revealed a statistically significant negative causal relationship with autoimmune diseases (OR = 0.906, 95% CI = 0.832–0.986, $p = 0.022$). These findings were consistent with results from the weighted median, robust adjusted profile score, and maximum likelihood methods. In contrast, our reverse Mendelian randomization analysis found no association between autoimmune diseases and telomere length (IVW: OR = 0.992, 95% CI = 0.980–1.003, $p = 0.161$). This reverse finding was consistent across all the other five analytical methods (Fig. 2).

Figure 3 presents the scatter plot, leave-one-out plot, and funnel plot visualizations. In the forward Mendelian randomization analysis, the scatter plot reveals a significant negative correlation between telomere length and autoimmune diseases. The funnel plot for this analysis

Exposure	Outcome	nsnp	Method	OR (95% CI)	p
TL	Autoimmune diseases	134	Inverse variance weighted	0.906(0.832, 0.986)	0.022
		134	MR Egger	0.895(0.769, 1.040)	0.149
		134	Weighted median	0.852(0.757, 0.958)	0.007
		134	Simple median	0.907(0.804, 1.024)	0.116
		134	Robust adjusted profile score	0.887(0.816, 0.965)	0.005
		134	Maximum likelihood	0.905(0.846, 0.969)	0.003
Autoimmune diseases	TL	42	Inverse variance weighted	0.992(0.980, 1.003)	0.161
		42	MR Egger	1.004(0.978, 1.030)	0.762
		42	Weighted median	1.002(0.987, 1.017)	0.790
		42	Simple median	0.994(0.980, 1.009)	0.448
		42	Robust adjusted profile score	0.994(0.982, 1.005)	0.289
		42	Maximum likelihood	0.991(0.983, 1.000)	0.057

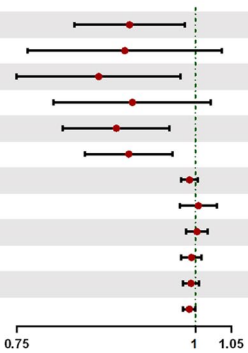

Fig. 2 Forest plot of the two-sample Mendelian randomization for telomere length and autoimmune diseases

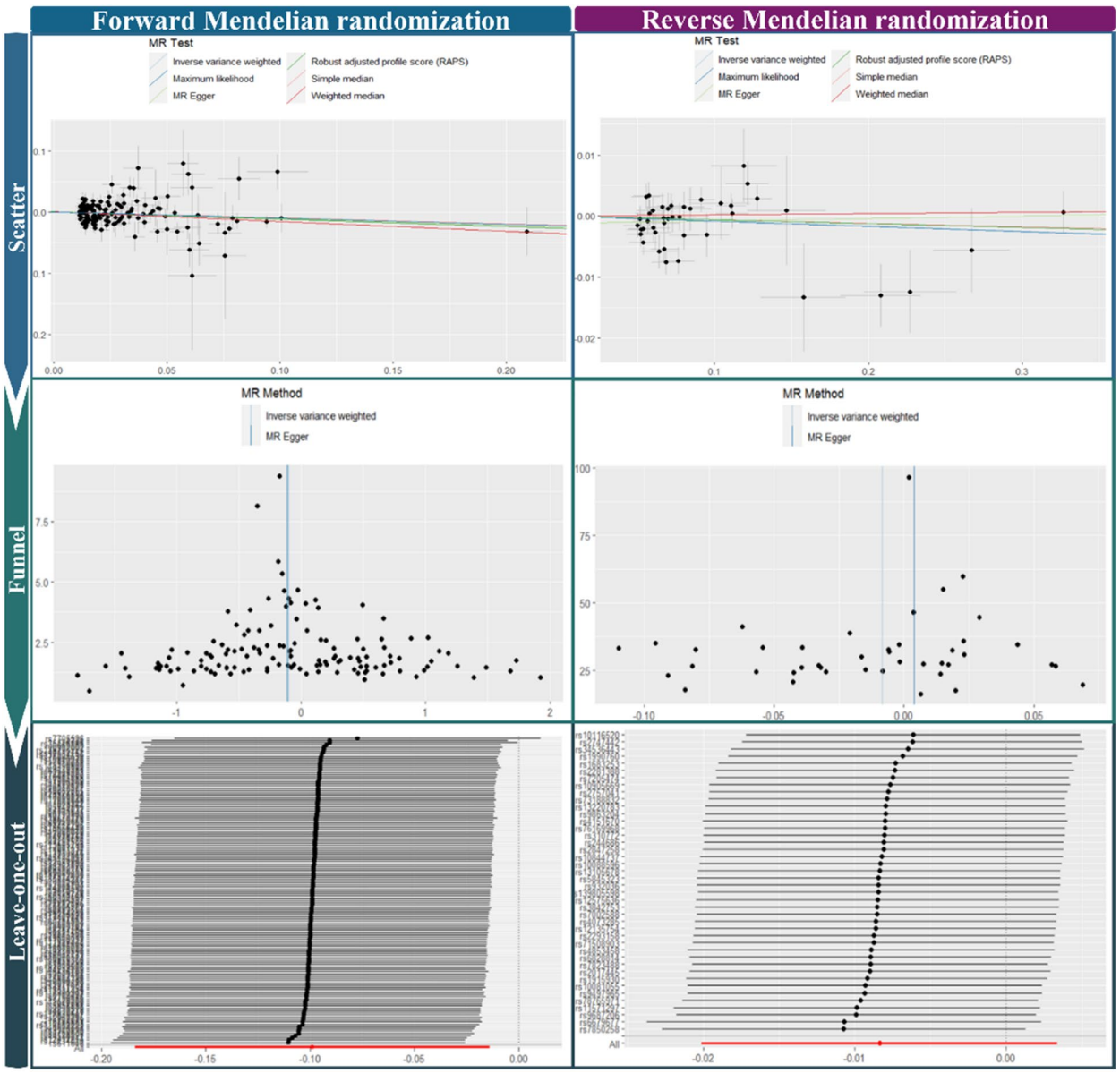

Fig. 3 Visualization of Mendelian randomization analysis between telomere length and autoimmune diseases

shows a symmetrical inverted funnel shape, with effect sizes tightly clustered around the average. In contrast, the funnel plot for the reverse Mendelian randomization analysis exhibits a gap on one side, suggesting a potential absence of smaller studies indicating a particular outcome. The leave-one-out analysis demonstrated that the remaining SNPs remained stable after the stepwise removal of each individual SNP.

Sensitivity analysis of Mendelian randomization between telomere length and autoimmune diseases

Table 2 reveals significant heterogeneity in both directions of causality between telomere length and autoimmune diseases, with no evidence of pleiotropy in either case. In the forward Mendelian randomization, where telomere length is the exposure and autoimmune diseases are the outcome, 134 SNPs were used, with an R^2 value of 0.037 and an *F*-statistic of 120, indicating moderate strength of the instrumental variables. Significant heterogeneity was observed in both MR-Egger ($Q = 212.554$, $p < 0.001$) and IVW ($Q = 212.618$, $p < 0.001$) methods, but no significant pleiotropy was detected (MR-Egger intercept = < 0.001, $p = 0.842$). In the reverse analysis, where autoimmune diseases are the exposure and telomere length is the outcome, 42 SNPs were analyzed, with an R^2 of 0.067 and an *F*-statistic of 104.672. Heterogeneity was again significant in both MR-Egger ($Q = 72.859$, $p = 0.001$) and IVW ($Q = 74.877$, $p = 0.001$) methods, but no significant pleiotropy was found (MR-Egger intercept = − 0.001, $p = 0.298$).

Subgroup Mendelian randomization results between telomere length and autoimmune diseases

Subgroup bidirectional Mendelian randomization analysis between telomere length and five common autoimmune diseases was performed and validated using data from the UK Biobank and FinnGen databases. SNPs were selected as genetic instruments, and all IVs exhibited *F*-statistics greater than 10.

Figure 4 shows forward Mendelian randomization analysis results investigating the relationship between telomere length and five autoimmune diseases using data from the UK Biobank and FinnGen. For SLE, the UK Biobank showed a significant positive association with telomere length in all three methods (IVW OR = 1.718, 95% CI 1.155–2.558, $p = 0.007$), while no significant association was found in FinnGen (*p*-values > 0.05). For RA, a significant negative association was observed in the UK Biobank with IVW (OR = 0.997, 95% CI 0.994–0.999, $p = 0.025$), and in FinnGen with IVW (OR = 0.860, 95% CI 0.741–0.998, $p = 0.047$), while other methods yielded non-significant results. For T1D, no significant associations were found in either dataset (*p*-values > 0.05). In GD, both datasets showed consistent significant negative associations with IVW (UK Biobank OR = 0.519, 95% CI 0.430–0.625, $p < 0.001$; FinnGen OR = 0.623 95% CI 0.496–0.785, $p < 0.001$), MR Egger, and weighted median. For psoriasis, both UK Biobank (OR = 0.772, 95%CI = 0.642–0.928, $p = 0.006$) and FinnGen (OR = 0.841, 95%CI = 0.727–0.973, $p = 0.020$) showed a significant negative association with IVW.

Figure 5 indicates reverse Mendelian randomization results investigating the causal relationship between five autoimmune diseases and telomere length. For SLE, the UK Biobank data reveal significant negative associations, with the MR Egger method estimating an OR of 0.991 (95% CI = 0.985–0.998, $p = 0.005$). Similarly, the FinnGen data show a negative association between SLE and telomere length, with the weighted median method reporting an OR of 0.988 (95% CI = 0.997–0.998, $p < 0.001$). In RA, the UK Biobank data show a significant positive association. However, the FinnGen data reveal no significant association (OR = 1.001, $p = 0.645$). Psoriasis is significant negative association (UK Biobank: OR = 0.992, 95%CI = 0.986–0.998, $p = 0.012$, FinnGen: OR = 0.992, 95%CI = 0.988–0.997, $p = 0.005$) with telomere length in both datasets. For T1D and GD, no associations are found in either UK Biobank or FinnGen datasets.

Figure 6 presents the scatterplot results from the bidirectional Mendelian randomization analysis, illustrating the relationship between telomere length and five common autoimmune diseases. In the forward Mendelian randomization analysis, a positive association is observed between telomere length and SLE in the UK Biobank, but not in FinnGen. RA shows a negative trend in both datasets, suggesting that longer telomeres may be associated

Table 2 Heterogeneity and pleiotropy between telomere length and autoimmune diseases

Exposure	Outcome	SNPs	R^2	*F*	Heterogeneity				Pleiotropy	
					MR Egger		IVW		MR-Egger regression	
					Q	*p*	*Q*	*p*	Intercept	*p*
Telomere length	Autoimmune diseases	134	0.037	120	212.554	< 0.001	212.618	< 0.001	< 0.001	0.842
Autoimmune diseases	Telomere length	42	0.067	104.672	72.859	0.001	74.877	0.001	− 0.001	0.298

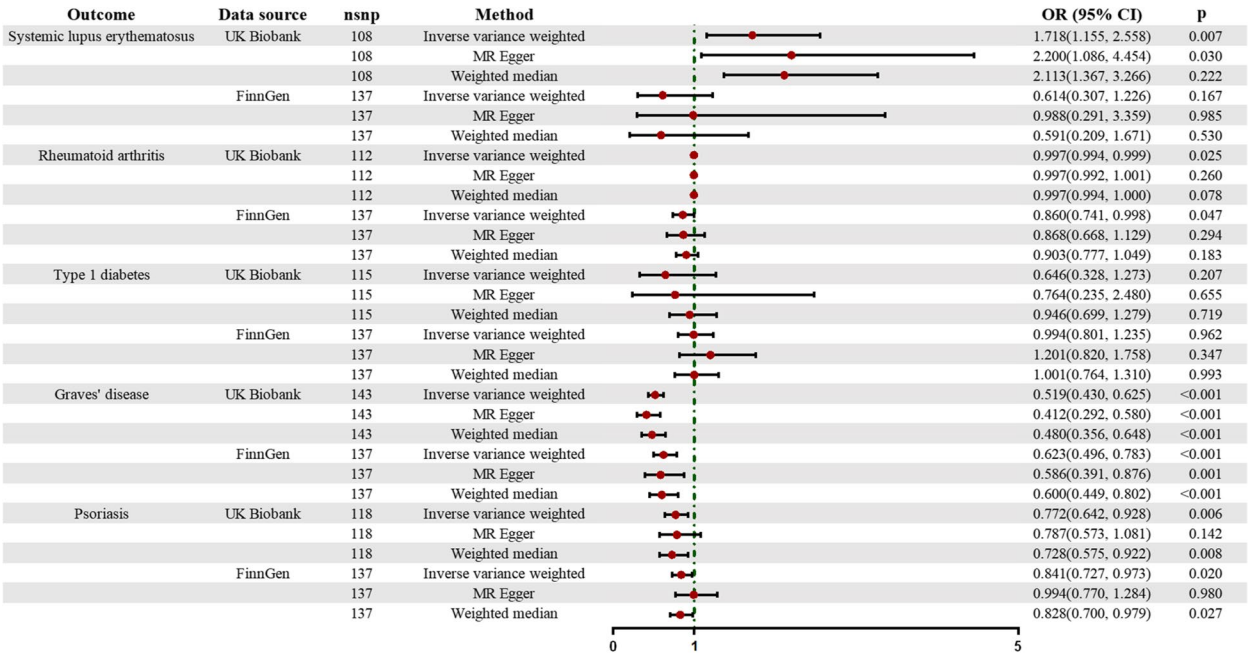

Fig. 4 Forest plot of the forward Mendelian randomization analysis between telomere length and five common autoimmune diseases

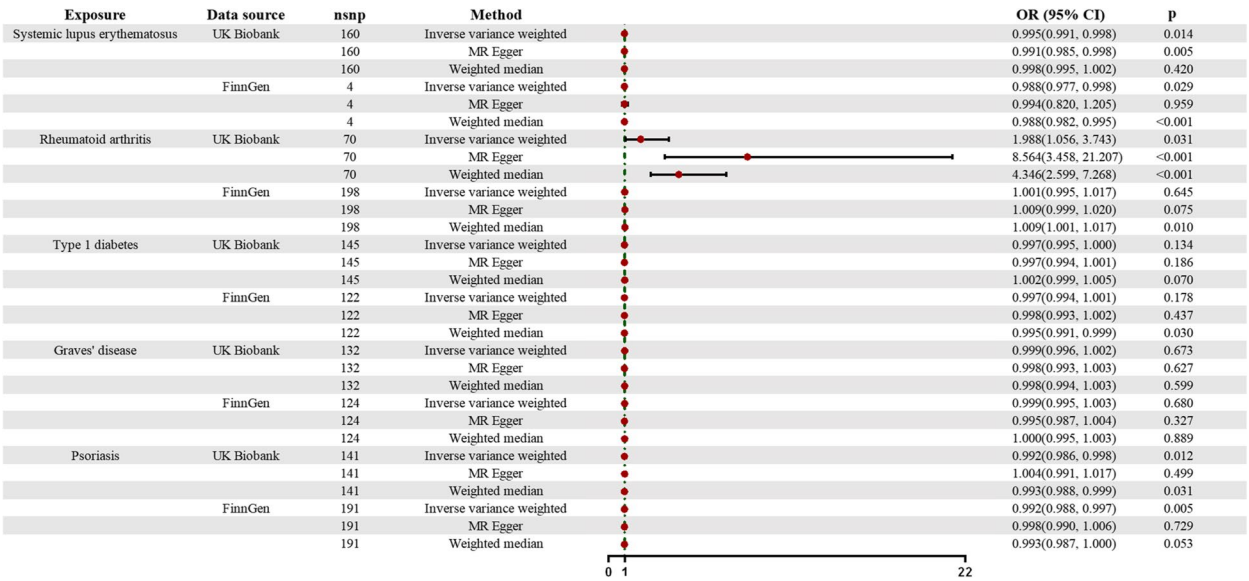

Fig. 5 Forest plot of the reverse Mendelian randomization analysis between telomere length and five common autoimmune diseases

with a reduced risk. No significant trend is found for T1D in either dataset. Both datasets, however, show a consistent negative association with GD, indicating that longer telomeres may lower the likelihood of developing this condition. A similar negative trend is observed for psoriasis in both the UK Biobank and FinnGen datasets. In the reverse Mendelian randomization analysis, a negative trend is seen between telomere length and SLE in both the UK Biobank and FinnGen datasets. For RA, a positive trend is noted in the UK Biobank, while no trend is observed in FinnGen. No significant trends are detected for T1D, GD, or psoriasis in either dataset. Supplementary Fig. S2 and Supplementary Fig. S3 present the leave-one-out and funnel plots, respectively. The funnel plots

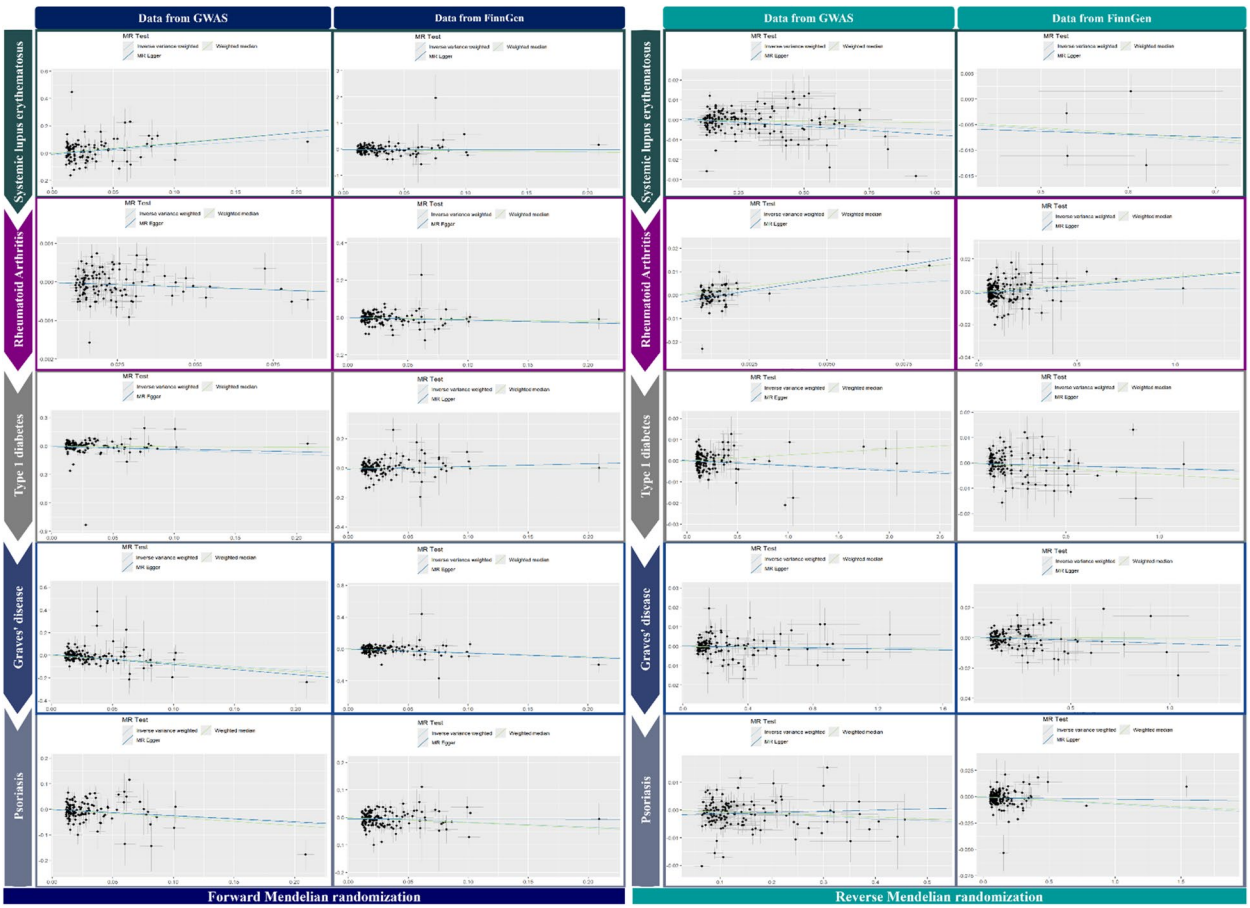

Fig. 6 Scatterplots for the Mendelian randomization between telomere length and five common autoimmune diseases

in the forward Mendelian randomization analysis show a symmetrical inverted funnel with effect sizes near the average, while the reverse Mendelian randomization analysis reveals a gap, suggesting a lack of smaller studies. The leave-one-out plots show that SNP stability is maintained after sequential removal of each SNP. Both plots validate and confirm the above associations.

Subgroup sensitivity analysis between telomere length and autoimmune diseases

In the forward Mendelian randomization analysis, the association between telomere length and SLE from the UK Biobank is evaluated using 108 SNPs, with an R^2 value of 0.037. The IVW method yields an *F*-statistics of 280.890 and a *p*-value of <0.001, providing strong evidence for a causal relationship between telomere length and SLE. Similar results are observed for other diseases, such as RA from the UK Biobank, where the *F*-statistic is 192.977 with a *p*-value of <0.001. Additionally, MR Egger regression results report an intercept of -0.008 with a *p*-value of 0.407 for SLE from the UK Biobank, suggesting no significant pleiotropy in these analyses (Table 3).

In the reverse Mendelian randomization analysis, 160 SNPs are used to assess the impact of SLE from the UK Biobank on telomere length, with an R^2 value of 0.287. The IVW *F*-statistic is 585.575, and the *p*-value is <0.001, indicating strong evidence for the causal effect of SLE on telomere length. Similarly, RA from the UK Biobank shows an *F*-statistic of 207.196 with a *p*-value of <0.001. In contrast, psoriasis from the UK Biobank yields an MR Egger intercept of -0.001 with a *p*-value of 0.039, suggesting the presence of possible pleiotropy. Heterogeneity and pleiotropy tests further reveal these effects across the analysis (Table 3).

Discussion

This study is the first to systematically evaluate the causal relationship between telomere length and autoimmune diseases in a European population using Mendelian randomization analysis. The forward analysis revealed that longer telomeres were associated with a reduced overall risk of autoimmune diseases (OR $=0.906$, $p=0.022$). Specifically, significant negative associations were observed for RA (UK Biobank: OR $=0.997$; FinnGen: OR $=0.860$),

Table 3 Heterogeneity and pleiotropy between telomere length and five common autoimmune diseases

Exposure	Outcome	SNPs	R^2	*F*	Heterogeneity				Pleiotropy	
					MR Egger		IVW		MR-Egger regression	
					Q	*p*	*Q*	*p*	Intercept	*p*
Telomere length	SLE from UK Biobank	108	0.037	120	280.890	< 0.001	282.720	< 0.001	− 0.008	0.407
SLE from UK Biobank	Telomere length	160	0.287	133.141	585.575	< 0.001	590.946	< 0.001	< 0.001	0.23
Telomere length	SLE from FinnGen	137	0.037	120	169.738	0.022	170.817	0.023	− 0.016	0.355
SLE from FinnGen	Telomere length	4	0.004	19.061	17.796	< 0.001	17.832	< 0.001	− 0.003	0.955
Telomere length	RA from UK Biobank	112	0.037	120	192.977	< 0.001	192.979	< 0.001	− 1.696	0.977
RA from UK Biobank	Telomere length	70	0.007	41.301	207.196	< 0.001	257.564	< 0.001	− 0.003	< 0.001
Telomere length	RA from FinnGen	137	0.037	120	399.467	< 0.001	399.487	< 0.001	< 0.001	0.933
RA from FinnGen	Telomere length	198	0.042	41.045	536.175	< 0.001	546.097	< 0.001	< 0.001	0.058
Telomere length	T1D from UK Biobank	115	0.037	120	1537.288	< 0.001	1538.873	< 0.001	− 0.005	0.733
T1D from UK Biobank	Telomere length	145	0.581	131.16	321.548	< 0.001	321.79	< 0.001	< 0.001	0.743
Telomere length	T1D from FinnGen	137	0.037	120	246.374	< 0.001	248.899	< 0.001	− 0.006	0.245
T1D from FinnGen	Telomere length	122	0.048	66.628	310.268	< 0.001	310.332	< 0.001	− 9.296	0.874
Telomere length	GD from UK Biobank	143	0.037	120	152.008	0.248	154.648	0.221	0.007	0.119
GD from UK Biobank	Telomere length	132	0.009	27.757	177.624	0.003	177.75	0.004	< 0.001	0.761
Telomere length	GD from FinnGen	137	0.037	120	249.019	< 0.001	249.267	< 0.001	0.002	0.714
GD from FinnGen	Telomere length	124	0.009	31.114	214.536	< 0.001	215.943	< 0.001	< 0.001	0.372
Telomere length	Psoriasis from UK Biobank	118	0.037	120	206.742	< 0.001	206.779	< 0.001	< 0.001	0.886
Psoriasis from UK Biobank	Telomere length	141	0.242	75.479	492.349	< 0.001	507.610	< 0.001	− 0.001	0.039
Telomere length	Psoriasis from FinnGen	137	0.037	120	315.413	< 0.001	321.049	< 0.001	− 0.005	0.122
Psoriasis from FinnGen	Telomere length	191	0.037	38.339	369.881	< 0.001	375.438	< 0.001	< 0.001	0.093

autoimmune diseases

GD (UK Biobank: OR = 0.519; FinnGen: OR = 0.623), and psoriasis (UK Biobank: OR = 0.772; FinnGen: OR = 0.841). However, a significant positive association was found for SLE in the UK Biobank (OR = 1.718, p = 0.007). The reverse analysis revealed no significant associations, except for a negative relationship with SLE (UK Biobank: OR = 0.995; FinnGen: OR = 0.988) and psoriasis (OR = 0.992 in both datasets), and a positive association with RA (UK Biobank: OR = 8.564). No associations were found for T1D or GD in either direction. These findings suggest that longer telomeres may reduce the risk of certain autoimmune diseases, such as RA, GD, and psoriasis, while potentially increasing the risk of SLE, highlighting the potential of telomere length as a biomarker for disease susceptibility and a target for future clinical interventions.

Our study offers four key advantages that enhance the validity and reliability of the findings. To minimize potential bias, we controlled four confounding demographic factors including BMI, alcohol consumption, smoking, and income. No association with these factors strengthens the confirmed relationship between telomere length and autoimmune diseases. We expanded our analysis to include five common autoimmune diseases including SLE, RA, T1D, GD, and psoriasis, providing a broader understanding of the relationship between telomere length and autoimmune conditions. By employing bidirectional Mendelian randomization, we gained a comprehensive understanding of these associations. Additionally, we validated our findings using two independent datasets, UK Biobank and FinnGen, ensuring the robustness of the results. Finally, we performed a systematic sensitivity analysis for all Mendelian randomization models, further confirming the reliability of these associations.

Our findings, particularly the negative association between telomere length and autoimmune diseases, align with previous research. Xu-Fan Wang et al. [18] validated this negative relationship between telomere length and SLE using two racially distinct databases, supporting our results. However, their study did not account for potential confounding factors. Giorgia et al. [19] in a small sample study (N = 60), reported a significant association between shorter telomeres and increased psoriasis risk, potentially due to a senescent and cytotoxic or proinflammatory profile of CD8 + T cells. A bidirectional Mendelian randomization study [20] found no significant causal effect between telomere length and RA, contrasting with

our findings. Our study, which included a larger sample size and applied five Mendelian randomization methods, yielded more robust results. Andrzej et al. [21] conducted a cross-sectional study examining the limited association between telomere length and T1D but did not establish causality.

These findings have prompted a comprehensive exploration of potential biological mechanisms, particularly regarding the impact of telomere length on the immune system. Telomere shortening may disrupt immune homeostasis by limiting the proliferative capacity of lymphocytes. For instance, a negative association (OR < 1) between telomere length and disease risk has been observed in conditions such as GD and PSO. This mechanism may be linked to premature telomere loss in T cells: carriers with telomerase deficiency and short telomere length may experience cellular senescence, while T cells exhibiting short telomere length could trigger DNA damage response (DDR) pathways and upregulate endogenous apoptotic processes [22]. A positive association (OR > 1) between telomere length and SLE risk suggests that excessively long telomeres may sustain T cell proliferation and increase disease susceptibility. Long telomeres could also disrupt DNA methylation and histone modifications [23], contributing to genomic instability and higher antinuclear antibody production. Telomere shortening is a key marker of aging and is linked to age-related diseases [24, 25]. In RA, SLE, and PSO, persistent activation of T and B cells promotes chronic inflammation, accelerating telomere attrition [26, 27]. These findings support the observation of reduced telomere length in patients with RA, SLE, and PSO, but further research is needed to clarify the mechanisms behind telomere length and autoimmune disease risk.

Emerging evidence highlights the clinical significance of telomere length in immune dysregulation, offering novel avenues for diagnostic and therapeutic innovation. As telomere attrition contributes to autoimmune diseases pathogenesis, measuring telomere length could predict disease susceptibility and progression trajectories. In high-risk populations such as GD and psoriasis patients, telomere length monitoring enables precision risk stratification, prompting targeted surveillance protocols including thyroid function assessments and specialized dermatological evaluations. Therapeutically, approaches like telomerase activation (e.g., TA- 65 protectants) have garnered commercial attention for their potential to restore immune equilibrium. However, caution is warranted regarding potential oncogenic risks, particularly in elderly populations with autoimmune diseases [28]. Recent advances in transient TERT mRNA delivery [29] show promise for achieving safer genomic modulation, though current limitations in delivery systems require resolution before clinical translation [30]. Mechanistically, lifestyle factors including smoking [31], obesity [32], and alcohol abuse [33] accelerate telomeric erosion through synergistic pathways involving ROS-mediated oxidative damage and chronic inflammation [34] (evidenced by elevated IL- 6/TNF-α), thereby amplifying risks for immunosenescence-related pathologies such as cardiovascular disease and diabetes [35]. These insights position telomere preservation strategies as pivotal interventions for mitigating both autoimmune disease progression and age-associated comorbidities.

Our study has several limitations. First, the exclusive focus on participants of European ancestry limits the generalizability of our findings to other racial groups. Second, due to the unavailability of public data for all autoimmune diseases studies, the representativeness of our autoimmune disease results may be restricted. All autoimmune diseases cannot be described in detail. Third, while we examined telomere length in peripheral leukocytes, the telomere length in other tissues was not considered. The representativeness of telomere length in peripheral blood leukocytes remains questionable. We did not directly analyze telomere length in tissues specifically affected by each autoimmune disease. However, telomere length in individuals is generally highly correlated with tissue-specific effects [36, 37]. Fourth, although we selected BMI, smoking, alcohol consumption, and income as potential covariates based on existing research, other demographic and mediating factors may still be unaccounted for, considering the complex clinical context and pathogenesis of autoimmune diseases.

Conclusion

Our study reveals an association between telomere length and autoimmune diseases such as GD, PSO, SLE, and RA. These findings bear significance for the interpretation and formulation of supplementary experiments concerning telomere length, as well as for potential strategies aimed at disease prevention.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-08831-9.

Additional file 1.

Additional file 2.

Additional file 3.

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Authors' contributions
All authors have reviewed and approved the final version of the manuscript. QJ (Qin Jiang) contributed to conceptualization, methodology, coding, data curation, formal analysis, original draft preparation, and review and editing of the manuscript. CY (Chenxi Yu) was involved in methodology, data curation, original drafting, and manuscript review and editing. SZ (Shiben Zhu) contributed to methodology, and the review and editing of the manuscript. YL (Yang Liu) also participated in the review and editing of the manuscript. MY (Min Ye) contributed to conceptualization, methodology, project administration, and supervision.

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Data availability
This study leveraged publicly available datasets, particularly drawing from GWAS data provided by the IEU Open GWAS Project. These datasets are accessible to the public at https://gwas.mrcieu.ac.uk/. All R codes are included in the Supplementary Material.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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