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Causal Association Between Leukocyte Telomere Length and Psoriasis: A Two-Sample Bidirectional Mendelian Randomization Study

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Abstract

Background: Observational studies have demonstrated a relationship between leukocyte telomere length (LTL) and psoriasis. However, the causal association between them remains unknown.

Methods: Bidirectional Mendelian randomization (MR) analysis was performed using publicly available genome-wide association study (GWAS) summary statistics. The GWAS summary data involving 472,174 participants for ITL were obtained from the UKbiobank, while the summary data for psoriasis (8,075 cases) and its two main types, psoriasis vulgaris (PsV, 5,018 cases) and psoriatic arthritis (PsA, 2,919 cases) were obtained from the FinnGen consortium. The inverse variance weighted (IVW) method was used as the main analysis.

Results: The forward MR analyses indicated that genetically determined LTL was suggestively associated with psoriasis (IVW: OR: 0.858; 95% CI: 0.752-0.980; P= 0.024) and significantly associated with PsV (IVW: OR: 0.790; 95% CI: 0.671-0.931; P= 0.005), but not with PsA (IVW: OR: 0.845; 95% CI: 0.685-1.043; p= 0.117). The reverse MR analyses showed that no causal effects were observed in psoriasis and its two subtypes on LTL.

Conclusion: Our study suggested a potential causal effect of shortened LTL on the increased risk of psoriasis, especially PsV, providing LTL as a novel biomarker and therapeutic target for psoriasis.

Keywords: Mendelian randomization, leukocyte telomere length, psoriasis, inflammation, causal inference

1 | Introduction

Psoriasis is a chronic relapsing autoimmune skin disease affecting approximately 125 million

people worldwide[1]. The prevalence of psoriasis is highest in developed countries, ranging from 0.1% in east Asia to 1.5% in western Europe[2]. Psoriasis is characterized by abnormal keratinocyte proliferation and differentiation and inflammatory cell infiltration. Apart from skin manifestations, psoriasis can affect other body parts, such as joints, cardiovascular system, and central nervous system[3, 4]. According to clinical manifestation, psoriasis can be divided into several types. Psoriasis vulgaris (PsV), the most common type, is triggered by environmental factors including streptococcal infection, stress, smoking, obesity, and alcohol use as well as genetic predisposition [2]. Psoriatic arthritis (PsA), involving joint pain, stiffness, and swelling, affects approximately 10% to 30% of patients with psoriasis and may precede skin manifestations [5-7].

The pathological mechanisms of psoriasis remain unclear. DNA damage has been suggested to play important roles in the aberrant proliferation and differentiation of keratinocytes [8], which are the main features of psoriasis. Telomere is a DNA-protein complex that can protect DNA from damage and is crucial for maintaining genome stability. It consists of two core components, including repeated DNA sequences and specific DNA-binding proteins [9]. Telomere length gradually shortens with biological aging and each cell division, and eventually reaches a critical length, resulting in cellular senescence[10]. Accumulating evidence suggested that telomere dysfunction is closely associated with chronic inflammation and adaptive immunity[11-13]. Furthermore, recent studies indicated that accelerated shortened telomere length, a hallmark of aging, plays a causative role in several immune-related inflammatory diseases, such as multiple sclerosis and rheumatoid arthritis[14, 15]. Several previous studies have also reported that telomere length altered significantly in patients with psoriasis; however, the results were inconsistent. For instance, a previous study found shortened telomere length in CD4+ and CD8+ T cells of psoriasis patients[16]. However, contradictory findings were reported in two other studies which showed that psoriasis was associated with longer LTL[17, 18]. However, such observational studies are particularly vulnerable to reverse causality and residual confounding. Therefore, whether telomere attrition is casually associated with a higher risk of psoriasis or vice versa remains to be confirmed.

Mendelian randomization (MR) analysis utilized genetic variants (single nucleotide polymorphisms, SNPs) as proxies for risk factors to evaluate causal associations from genetically predictable exposures on outcomes[19]. Genetic variants are randomly distributed to simulate the randomization process in a randomized controlled trial, which is minimally affected by reverse causality and confounding effects. Herein, we conducted a bi-directional MR study to assess the causal effects and the direction of causality between LTL and psoriasis and its two major subtypes (PsV and PsA) using public data of genome-wide association studies (GWAS) [20].

2 | Materials and methods

2.1 | Study design

Figure 1 shows an overview of the bidirectional MR design. To obtain valid causal estimates, genetic variants in MR analyses need to meet the three assumptions (Figure 1): (1) the independent genetic variants need to be significantly associated with exposure; (2) they should not be affected by confounders; (3) they should affect outcome only via exposure.

2.2 | Data sources

Summary-level GWAS statistics of LTL were obtained from a large meta-analysis that enrolled a total of 472,174 UK Biobank participants[21]. The GWAS summary statistics for psoriasis (PsO), PsV, and PsA are from the FinnGen consortium which included 8,075 psoriasis cases (including 5,018 PsV and 2,912 PsA subtypes) and 330,975 controls [22, 23]. The diagnosis of psoriasis and its two primary subtypes was in accordance with the ICD-10 (International Classification of diseases) criteria. Detailed descriptions of data sources are demonstrated in Table S1.

2.3 | Genetic instrument selection

Instrumental variables (IVs) were selected step-by-step according to the following criteria: 1) SNPs that are strongly associated with exposure ($P < 5 \times 10\text{-}8$); 2) Independent SNPs are obtained by excluding SNPs with linkage disequilibrium (LD) ($r2 \geq 0.001$ within LD distance $\leq$ 10,000 kb); 3) After harmonization, palindromic SNPs that cannot deduce their forward strand from corresponding effect allele frequency were omitted. Besides, if the IVs of exposure were not present in the outcome GWAS data, the SNPs were discarded. Next, we searched the "PhenoScanner V2" online database (http://www.phenoscanner.medschl.cam.ac.uk/) to exclude confounding SNPs to reduce possible pleiotropic biases[24]. Confounding factors of LTL and psoriasis that have been reported in previous studies were controlled, such as body mass index and tobacco smoking [2, 25] (Table S9). To promote the accuracy and robustness of the IVs, we performed heterogeneity tests to detect and control potential outliers The "ivw_radial" (alpha = 0.05, weights = 1, tol = 0.0001) function in the "RadialMR v1.0" R package (https://github.com/WSpiller/)[26] was employed in our MR study to calculate the modified Q statistic, and the outliers with P-value < 0.05 were discarded. Finally, each SNP with an F-statistic (representing the strength of IVs) value > 10 was used in our analyses[27].

2.4 | Statistical analysis

We primarily used the inverse-variance weighted (IVW) method to identify the causal associations in our study. The IVW method obtained and combined Wald estimates of each IV by dividing the SNP–outcome effect by the SNP–exposure effect[20]. This approach offers a consistent estimate of the causal effect of the exposure toward the outcome when the enrolled IVs are robustly valid. Four complementary methods, Weighted-median[28], Weighted mode[29], MR-Egger[30], and MR-RAPS[31] were used to further strengthen the reliability of the IVW

results. The weighted median method can provide unbiased estimates of effects when even up to half of IVs are invalid[28]. The weighted mode method is less influenced by biases and has lower type-I error rates than other methods[29]. MR-Egger can detect some violations of the three IV assumptions and offer an effect estimate not subject to the violations[30]. Accounting for idiosyncratic pleiotropy, MR-RAPS can draw a more robust inference with many weak IVs[31].

Then, we conducted several sensitivity analyses to verify the results of our MR analysis. First, the heterogeneity of the selected IVs was mainly measured with Cochrane's Q-statistic[32]. Second, we performed MR-Egger intercept test[30] and MR-PRESSO (Mendelian Randomization Pleiotropy RESidual Sum and Outlier) global test[33] to detect the presence of directional pleiotropy and horizontal pleiotropy. Leave-one-out analysis was used to find any influential SNPs by calculating the IVW estimate of remaining SNPs with each SNP removed. In addition, IVW radial plot was drawn to vividly reveal the detected outliers.

The above MR analysis was extended to bidirectional causal inference between LTL and psoriasis. The statistical power of our MR study was calculated by applying Brion's method on an online web (https://shiny.cnsgenomics.com/mRnd/)(Table S11)[34]. All statistical analyses were carried out in the "TwoSampleMR v0.5.6" and "MR-PRESSO v1.0" R (version 4.2.2) packages. A Bonferroni correction was used in bidirectional multiple testing to lower false-positive rates. After correction, a two-sided P-value < 0.017 was considered as statistical significance, and associations with P-value ≥ 0.017 and < 0.05 were considered as suggestive significance.

3 | Results

Genetic instruments

After strict screening, 107 SNPs on psoriasis, 112 SNPs on PsV, and 117 SNPs on PSA were selected for forward MR analysis using ILT as exposure. Meanwhile, 18 psoriasis-related SNPs, 13 PsV-related SNPs, and 8 PsA-related SNPs were chosen for reverse MR analyses in which ILT was treated as the outcome. The F-statistics of these IVs were more than 20, which suggested no weak instrument bias in the estimated causal effects. However, statistical power did not reach adequately strong given minor case ratios (Table S11). The summary characteristics of these IVs were shown in Tables S2-S7. The information on the excluded confounding SNPs and the detected outliers by RadialMR were shown in Table S9 and Table S10.

Forward MR analyses of the effects of LTL on psoriasis and its main subtypes

The causal associations of forward MR analysis are illustrated in Figure 2A and Table S8. Genetically determined LTL was suggestively linked to psoriasis (IVW: OR: 0.858; 95% CI: 0.752-0.980; P= 0.024). Similar causal estimations were observed in the weighted median (OR: 0.785; 95% CI: 0.631-0.977; P= 0.030) and MR-RAPS approaches (OR: 0.812; 95% CI:

0.643-1.027; P= 0.049). Similarly, genetically determined LTL was significantly associated with PsV subtype (IVW: OR: 0.790; 95% CI: 0.671-0.931; P= 0.005), although relatively nonsignificant effects were obtained in weighted median (OR: 0.725; 95% CI: 0.539,0.976; P= 0.034), weighted model (OR: 0.723; 95% CI: 0.526- 0.993; P= 0.048) and MR-RAPS (OR: 0.805; 95% CI: 0.678-0.957; P = 0.014). These causal estimates are further illustrated in the scatter plots (Figure 3). The leave-one-out analyses of LTL on psoriasis and PsV did not find any SNPs significantly driving the combined estimates (Figures S3-S4). No heterogeneity and pleiotropy were found in further comprehensive sensitivity analyses (Table 1). Nevertheless, no causal effects of LTL on PsA subtype were observed (IVW: OR: 0.845; 95% CI: 0.685-1.043; p= 0.117) (Figure 2A, Figure S1, Figure S5). The forest plots of individual and combined SNP MR effect sizes were shown in Figures S7-S9. In addition, radial plots of the detected outliers were illustrated in Figure S11.

Reverse MR analyses of the effects of psoriasis and its main subtypes on LTL

The IVW estimates suggested no causal effects of psoriasis (OR: 0.992; 95% CI: 0.984-1.001; p= 0.070), PsV (OR: 0.995; 95% CI: 0.988-1.002; p= 0.137) or PsA (OR: 1.005; 95% CI: 0.999-1.011; p= 0.098) on LTL (Figure 2B and Table S8). However, the weighted median results of PsA effect on LTL were statistically significant, suggesting there are potential invalid SNPs among the eight IVs of PsA[28]. This situation violated the MR assumptions; therefore, the null result of PsA on LTL should be interpreted with caution, although no significant risk of weak instrument bias was observed in the F-statistic tests. Then, we found that the SNP rs28752958 notably influenced the causal effect in the leave-one-out analysis of PsA on LTL (Figure S6C). Hence, further MR analysis and sensitivity tests without rs28752958 were conducted to confirm the null causal effect of PsA on LTL (Figure 2B and Table 1). The scatter plots, leave-one-out analyses, forest plots, and radial plots of all reverse MR results were illustrated in Figure S2, Figure S6, Figure S10, and Figure S12.

4 | Discussion

To our knowledge, this is the first MR study investigating the bidirectional causal relationship between LTL and psoriasis and its main subtypes. We demonstrated that genetically determined LTL was causally linked to psoriasis and PsV but not PsA, based on the European population. Nevertheless, no causal effects were observed in psoriasis and its two subtypes on LTL. Our study provides LTL as a potential biomarker and therapeutic target of psoriasis.

Several studies have examined the relationship of LTL with psoriasis; however, the findings remain inconsistent. For instance, a previous study involving 16 patients with psoriasis and 30 normal controls revealed that mean terminal restriction fragments in CD4+ and CD8+ T cells were significantly shorter in psoriasis[16]. However, a case-control study of 56 PsA patients and 130 healthy controls found that mean LTL was longer in the patient group[17]. A recent research involving 41 psoriatic patients and 30 healthy controls reported similar findings that psoriasis was associated with longer LTL [18]. The contradictory findings from the epidemiological studies

mentioned above may be attributed to differences in study design, methods used for measuring telomere length, and limited study sample size. Moreover, these findings are inevitably influenced by confounders and reverse causation. In comparison to the above observation studies, our bidirectional MR analysis provided more convincing evidence supporting the causality of shortened telomere length on the risk of psoriasis, especially its main subtype PsV, rather than the reverse causality.

Our findings suggest that telomeres might serve as a target for alternative measures to lower the risk of psoriasis, especially PsV. It is noteworthy that efforts have been made in some studies to identify methods of prolonging telomeres[35, 36], although effective measures are not yet available for clinical application. Nevertheless, the protective effects of longer LTL on reduced risk of psoriatic diseases should be interpreted with caution, because longer LTL has been confirmed to be a causal factor for various cancers[37]. In the current study, we did not observe a significant causal effect of PsA on LTL, probably due to the small case ratio of PsA in our study. Taken together, this MR study provides alternative etiological evidence for causality between LTL and psoriasis. Further studies are warranted to confirm our findings and to evaluate the clinical value of manipulating telomere length in psoriasis management.

The pathophysiological roles of telomeric alterations in psoriasis remain unknown. Immune dysregulation caused by shortened telomere length may play an important role in this process. The natural aging process with accelerated telomere attrition is concerned with a series of issues, such as the worsening immunity, the senescent immune cells, and the increased risk of developing immune-related inflammation[38]. Studies have indicated that telomere shortening may be of great significance in the senescence of T-cell immunity[39], which plays an essential role in the pathogenesis of psoriasis[2]. Immune cells in senescence have increased metabolic activity and release elevated concentrations of proinflammatory cytokines such as IL-6, TNF-a, and interferons [11, 40], which can activate proinflammatory pathways that may involve in the progression of psoriasis [2]. It is noteworthy that telomere attrition is regarded as a strong senescence-induced factor. Even one disorder of telomere can lead to continuous cell cycle arrest [11]. Furthermore, the loss of telomere sequence can trigger the release of multiple pro-inflammatory cytokines by various cells in senescence, a phenomenon called "senescence-associated secretory phenotype" [11, 41-43]. Nevertheless, although these explanations seem to be biologically plausible, future work is needed to unveal the causal mechanisms behind shortened telomere length in the development of psoriasis.

Our MR study has several significant advantages. First, it is the first investigation to examine the bidirectional causal relationships of telomere length and psoriasis, including both PsV and PsA subtypes, with a two-sample MR approach. Second, the current MR analysis utilized SNPs from the latest and largest GWAS statistics of both exposures and outcomes. Third, five different MR methods were adopted to ensure the consistency and stability of our causal estimation. Fourth, no significant heterogeneity and horizontal pleiotropy were detected in our study, suggesting the validity and robustness of our results.

However, several limitations should be noted in this research. First, psoriasis has two age peaks of onset [44]; however, we were not able to explore the causal effects in different age subgroups due to the lack of individual-level statistics. In addition, weak statistical power for a relatively

small case ratio is also a defect of this study. Further investigations with a large sample size are warranted to confirm our findings. Moreover, as the data sources in this study included participants of European ancestry, whether our results could be generalized to other ethnicities remains to be determined. Therefore, further studies of other ethnicities are required to confirm our findings.

5 | Conclusion

Our study confirmed that shortened LTL was causally associated with an increased risk of PsV and suggestively associated with psoriasis, providing LTL as a potential biomarker and therapeutic target of psoriasis. Further study is warranted to unveil the potential mechanisms underlying the causal relationships between shortened LTL and the risk of psoriasis.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgement

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Appendix

Figure legends

Figure 1: Study design framework. In the forward MR analysis (in red), leukocyte telomere length (LTL) is the exposure; psoriasis (PsO), psoriasis vulgaris (PsV), and psoriasis arthritis (PsA) are the outcomes. In the reverse MR analysis (in blue), psoriasis, PsV, and PsA are the exposure; LTL is the outcome. MR, mendelian randomization; SNP, single nucleotide polymorphism; GWAS, genome-wide association study; LD, linkage disequilibrium.

Figure 2: Forest plot of the associations between genetically predicted leukocyte telomere length (LTL) and psoriasis (PsO), psoriasis vulgaris (PsV) and psoriasis arthritis (PsA). SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval. (A: Forward MR analyses results; B: Reverse MR analyses results, * Removing rs28752958 detected by leave-one-out analysis)

Figure 3: Scatter plots of main MR results. The slope of each line corresponds to the estimated MR effect in different models. A) causal effects of leukocyte telomere length (LTL) on psoriasis (PsO); B): causal effects of psoriasis vulgaris (PsV). SNP, single nucleotide polymorphism.

Figure 1

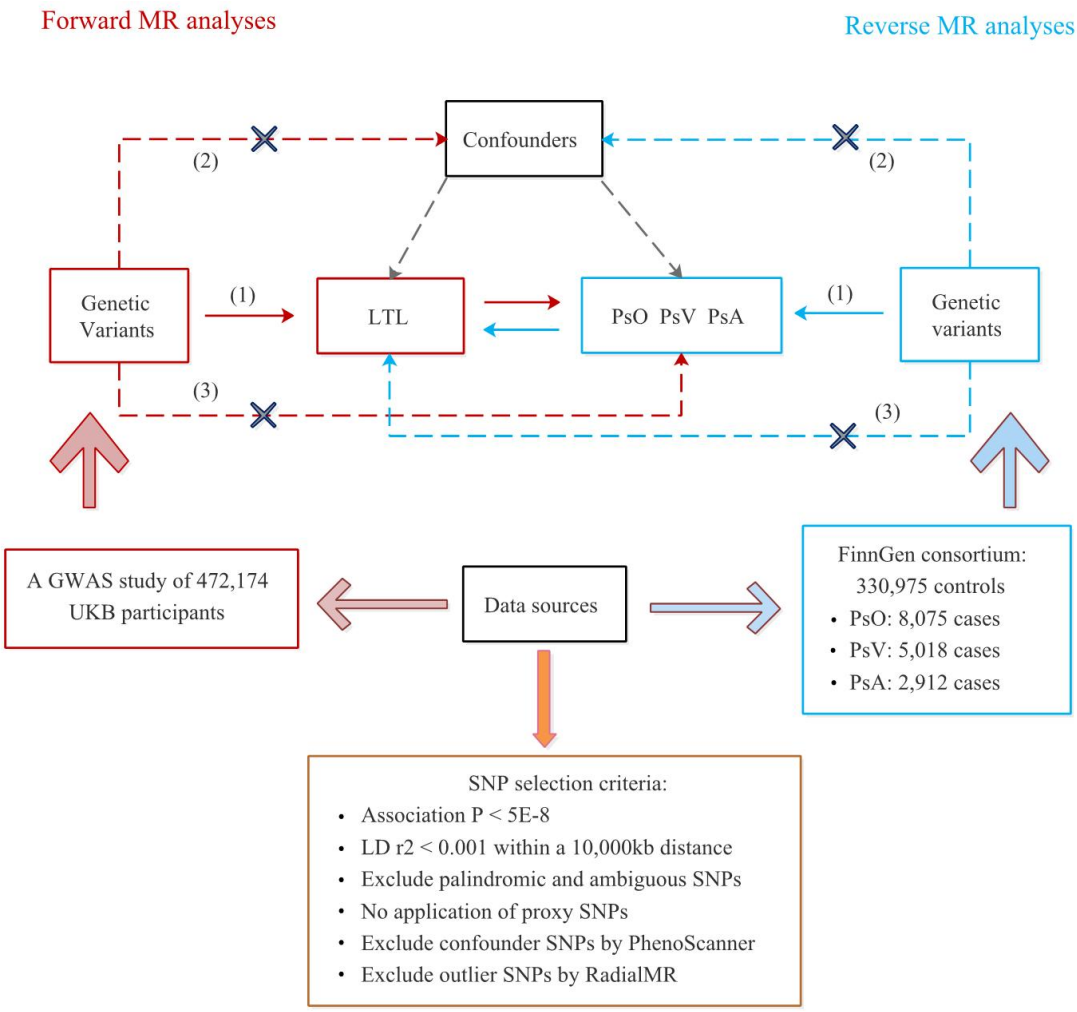
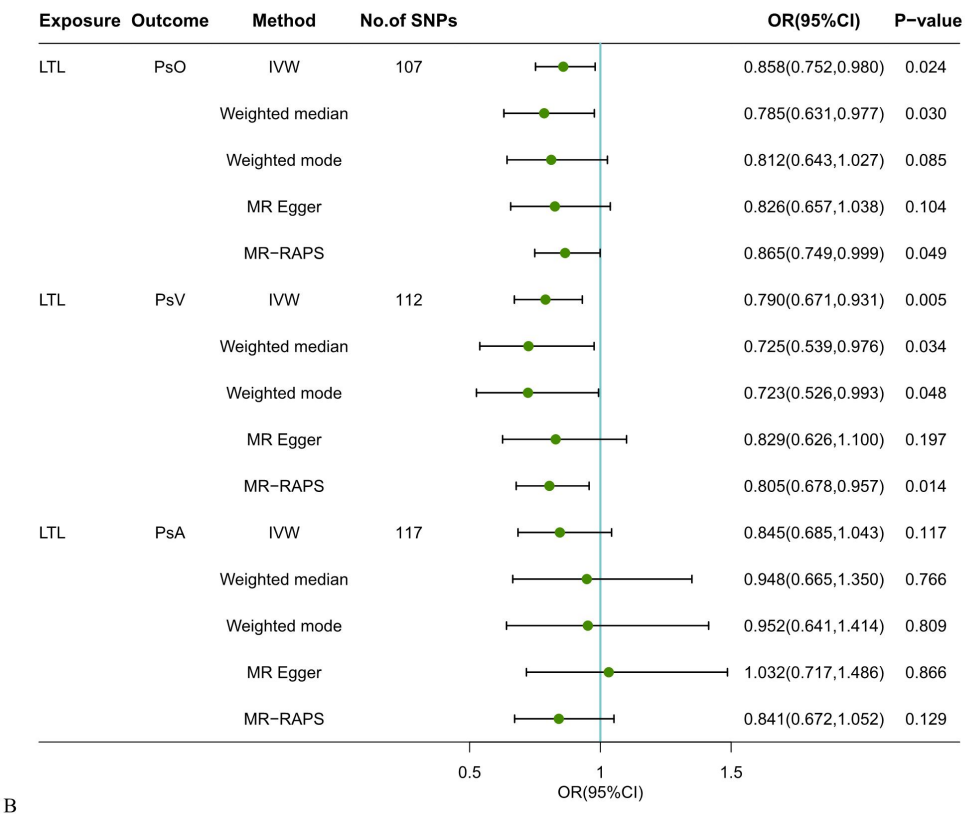

Forward MR analyses
Reverse MR analyses
Confounders
(2)
(2)
Genetic Variants
(1)
LTL
PsO PsV PsA
(1)
Genetic variants
(3)
(3)
A GWAS study of 472,174 UKB participants
Data sources
FinnGen consortium:
330,975 controls
• PsO: 8,075 cases
• PsV: 5,018 cases
• PsA: 2,912 cases
SNP selection criteria:
• Association P < 5E-8
• LD r2 < 0.001 within a 10,000kb distance
• Exclude palindromic and ambiguous SNPs
• No application of proxy SNPs
• Exclude confounder SNPs by PhenoScanner
• Exclude outlier SNPs by RadialMR

Figure 2

A


Exposure Outcome Method No.of SNPs OR(95%CI) P−value
LTL PsO IVW 107 0.858(0.752,0.980) 0.024
Weighted median 0.785(0.631,0.977) 0.030
Weighted mode 0.812(0.643,1.027) 0.085
MR Egger 0.826(0.657,1.038) 0.104
MR−RAPS 0.865(0.749,0.999) 0.049
LTL PsV IVW 112 0.790(0.671,0.931) 0.005
Weighted median 0.725(0.539,0.976) 0.034
Weighted mode 0.723(0.526,0.993) 0.048
MR Egger 0.829(0.626,1.100) 0.197
MR−RAPS 0.805(0.678,0.957) 0.014
LTL PsA IVW 117 0.845(0.685,1.043) 0.117
Weighted median 0.948(0.665,1.350) 0.766
Weighted mode 0.952(0.641,1.414) 0.809
MR Egger 1.032(0.717,1.486) 0.866
MR−RAPS 0.841(0.672,1.052) 0.129
0.5
1
1.5
OR(95%CI)

B

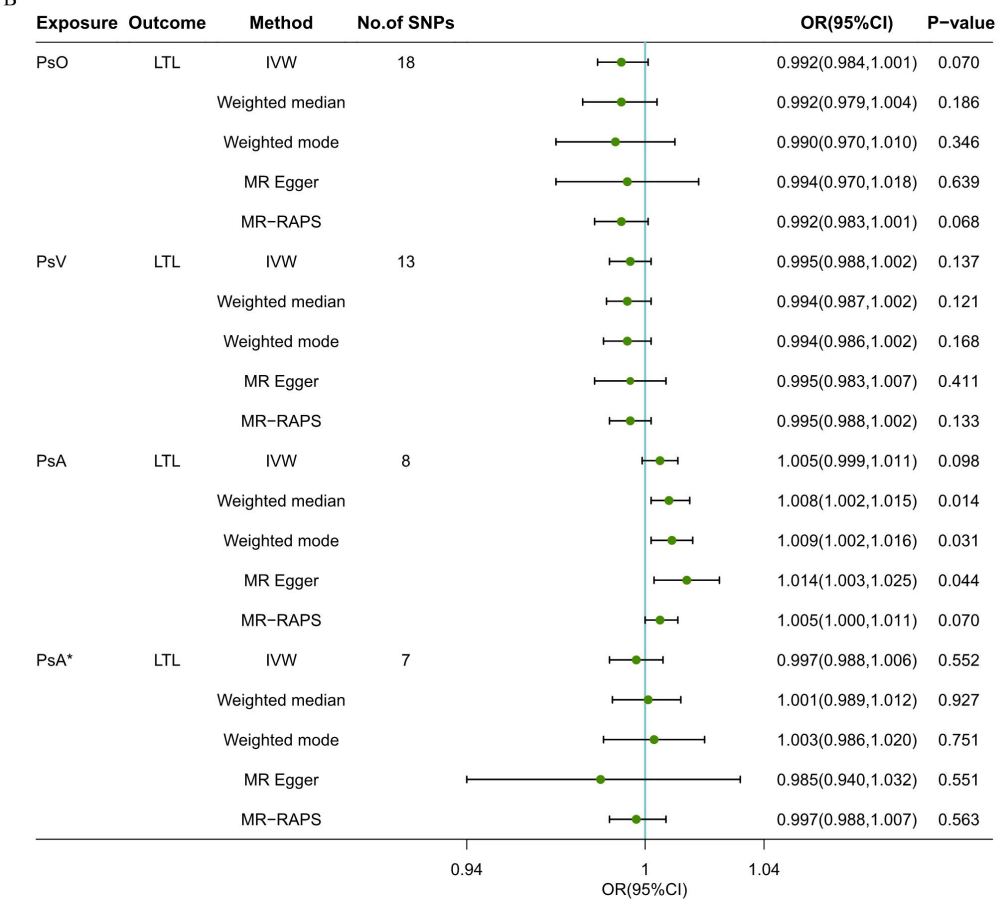

Exposure Outcome Method No.of SNPs OR(95%CI) P−value
PsO LTL IVW 18 0.992(0.984,1.001) 0.070
Weighted median 0.992(0.979,1.004) 0.186
Weighted mode 0.990(0.970,1.010) 0.346
MR Egger 0.994(0.970,1.018) 0.639
MR−RAPS 0.992(0.983,1.001) 0.068
PsV LTL IVW 13 0.995(0.988,1.002) 0.137
Weighted median 0.994(0.987,1.002) 0.121
Weighted mode 0.994(0.986,1.002) 0.168
MR Egger 0.995(0.983,1.007) 0.411
MR−RAPS 0.995(0.988,1.002) 0.133
PsA LTL IVW 8 1.005(0.999,1.011) 0.098
Weighted median 1.008(1.002,1.015) 0.014
Weighted mode 1.009(1.002,1.016) 0.031
MR Egger 1.014(1.003,1.025) 0.044
MR−RAPS 1.005(1.000,1.011) 0.070
PsA* LTL IVW 7 0.997(0.988,1.006) 0.552
Weighted median 1.001(0.989,1.012) 0.927
Weighted mode 1.003(0.986,1.020) 0.751
MR Egger 0.985(0.940,1.032) 0.551
MR−RAPS 0.997(0.988,1.007) 0.563
0.94
1
1.04
OR(95%CI)

Figure 3

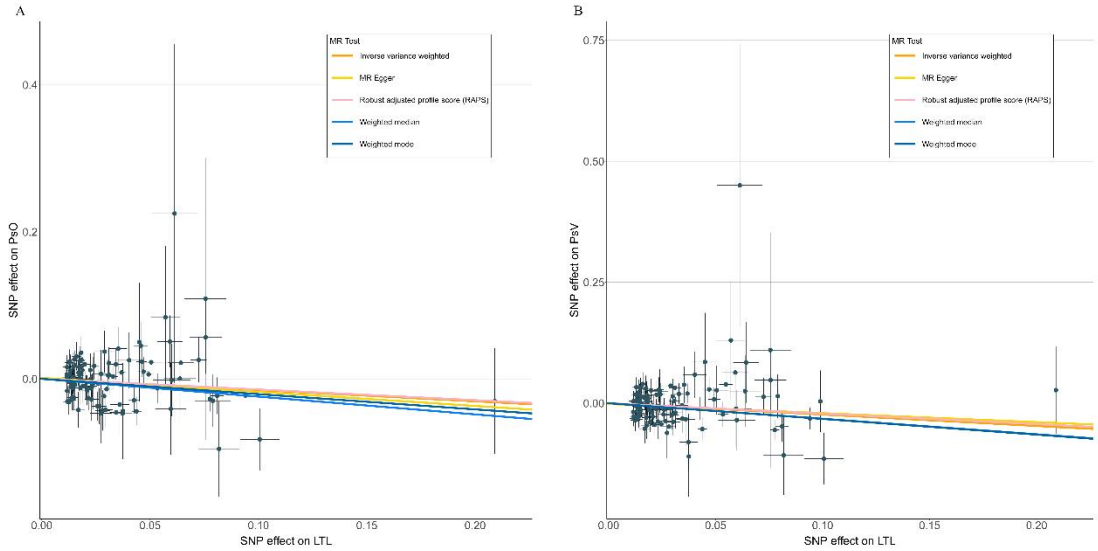


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Table 1: Sensitivity analyses of MR

	Exposure	Outcome	Cochran Q test		MR-Egger		MR-PRESSO
			Q value	P	Intercept	P	global test P
Forward MR	LTL	PsO	106.06	4.80E-01	1.41E-03	6.85E-01	4.90E-01
	LTL	PsV	107.29	5.82E-01	-1.75E-03	6.81E-01	5.55E-01
	LTL	PsA	99.97	8.56E-01	-7.18E-03	1.92E-01	8.56E-01
Reverse MR	PsO	LTL	16.63	4.80E-01	-3.08E-04	8.62E-01	4.89E-01
	PsV	LTL	16.76	1.59E-01	4.90E-05	9.77E-01	2.28E-01
	PsA	LTL	8.17	3.17E-01	-2.90E-03	1.10E-01	2.95E-01
	PsA*	LTL	6	7.64E-01	2.38E-03	6.16E-01	7.23E-01

* Removing rs28752958 detected by leave-one-out analysis.

PsO: psoriasis; PsV: psoriasis vulgaris; PsA: psoriasis arthritis; LTL: leukocyte telomere length; MR: mendelian randomization.