Research Paper

# Genetically determined telomere length as a risk factor for hematological malignancies: evidence from Mendelian randomization analysis

**Tian Fang[1,*], Zhihao Zhang[2,*], Kexing Ren[1], Liqun Zou[1]**

[1]Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China
[2]Department of Breast Center, West China Hospital, Sichuan University, Chengdu, China
[*]Equal contribution and shared the first authorship

**Correspondence to:** Liqun Zou; **email:** zouliqun1971@163.com, https://orcid.org/0009-0003-1349-920X
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## ABSTRACT

**Background: Over the past years, the exact correlation between telomere length and hematological malignancies was still not fully understood.**

**Methods: We performed a two-sample Mendelian randomization study to investigate the causal relationship between telomere length and hematological malignancies. We selected genetic instruments associated with telomere length. The genetic associations for lymphoid and hematopoietic malignant neoplasms were obtained from the most recent publicly accessible FinnGen study R9 data. Inverse variant weighted (IVW) analysis was adopted as the primary method, and we also performed the weighted-median method and the MR-Egger, and MRPRESSO methods as sensitive analysis.**

**Results: Significant associations have been observed between telomere length and primary lymphoid (IVW: OR = 1.52, $P = 2.11 \times 10^{-6}$), Hodgkin lymphoma (IVW: OR = 1.64, $P = 0.014$), non-Hodgkin lymphoma (IVW: OR = 1.70, $P = 0.002$), B-cell lymphoma (IVW: OR = 1.57, $P = 0.015$), non-follicular lymphoma (IVW: OR = 1.58, $P = 1.7 \times 10^{-3}$), mantle cell lymphoma (IVW: OR = 3.13, $P = 0.003$), lymphoid leukemia (IVW: OR = 2.56, $P = 5.92E-09$), acute lymphocytic leukemia (IVW: OR = 2.65, $P = 0.021$) and chronic lymphocytic leukemia (IVW: OR = 2.80, $P = 8.21 \times 10^{-6}$), along with multiple myeloma (IVW: OR = 1.85, $P = 0.016$).**

**Conclusion: This MR study found a significant association between telomere length and a wide range of hematopoietic malignancies. But no substantial impact of lymphoma and hematopoietic malignancies on telomere length has been detected.**

## INTRODUCTION

Malignant tumors of the hematopoietic system occur in the blood-forming tissues. In 2020, more than 1.2 million people worldwide were diagnosed with malignant tumors of the hematopoietic system, and over 700,000 people died from these malignancies [1]. Hematological malignancies are broadly categorized into lymphoma, which originates from the lymphatic system; multiple myeloma (MM), which affects plasma cells in the bone marrow; and leukemia, which impacts cells in the bone marrow or blood [2]. Currently, many observational studies have investigated the etiology of hematological malignancies, including factors such as air pollution, chlamydia contamination, and dietary habits, among others [3, 4]. However, due to the multitude of confounding factors in retrospective studies, many causative factors still cannot be conclusively determined.

Telomeres are natural ends of chromosomes characterized by variable numbers of TTAGGG repeat sequences and associated proteins [5]. The role of telomeres in human health and disease is still not fully understood. But more and more studies have demonstrated that telomeres play a crucial role in the development and progression of cancer [6]. Several studies have found that longer telomeres may be associated with an increased risk of various cancers, including melanoma, acute myeloid leukemia, and chronic lymphocytic leukemia in cancer-prone families [7–9]. Bao et al. found that longer telomeres in leukocytes were identified as important risk factors for the development of myeloproliferative neoplasms [10]. However, several studies found that starting life with shorter telomeres may increases the risk of cancer [11]. The possible reason for generating these opposing views is the insufficient research methods.

Mendelian randomization (MR) uses genetic variation as an instrumental variable (IV), which has advantages compared with other research methods [12]. This approach utilizes genetic variants associated with the exposure of interest to estimate the causal effect on the outcome, thereby providing valuable insights into disease etiology [13–15]. In recent years, there has been growing interest in exploring the potential association between telomere length and other type of carcinomas using Mendelian randomization analysis [16]. However, the precise causal relationship between telomere length and the hematopoietic malignancies remains unclear.

This Mendelian randomization study aims to investigate the causal relationship between telomere length and hematopoietic malignancies. By utilizing large-scale genome-wide association studies (GWAS) data and applying rigorous statistical methods, we seek to provide robust evidence regarding the role of telomeres in hematopoietic malignancies and may have implications for risk prediction, prevention, and potentially targeted therapies.

## MATERIALS AND METHODS

### Study design

We performed a two-sample Mendelian randomization (MR) study to investigate the causal association between telomere length and hematological malignancies. As shown in Figure 1, in order for genetic variation to serve as a valid instrumental variable, it must adhere to three fundamental principles: (1) Genetic variants exhibit a robust correlation with the exposure of interest. (2) Genetic variants are not associated with potential confounders. (3) Genetic variants do not exert a direct influence on the outcome of interest. [17]. Figure 2 provides an overview of the study design. We reported this study according to the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) [18].

### Data sources of exposure

Data on the association between genetics and telomere length were extracted from a GWAS conducted on a European cohort comprising 472,174 individuals (study ID "ieu-b-4879" and can be downloaded from the IEU GWAS database (https://gwas.mrcieu.ac.uk/datasets/) [19]. All participants fell within the age range of 40-69 years, with approximately equal representation of males (45.8%) and females (54.2%). The quantification of telomere length was performed using a well-established quantitative PCR method, and multiple quality control measures were implemented to account for potential influences of ethnicity, gender, age, and technical variables, as delineated in a previous investigation.

We included SNPs reaching GWAS (GWAS $p < 5 \times 10-8$). Then, these SNPs were clumped based on the linkage disequilibrium (r 2 <0.001; kb = 10000) in the given genome region. Additionally, potential weak IVs (F-statistics <10) were excluded from the final analysis, as determined by calculating the F-statistics. Moreover, any palindromic SNPs with ambiguous minor allele frequencies (A/T or C/G) were discarded. Subsequently, we removed SNPs directly associated with hematological malignancies and confounding factors such as BMI [20] and tobacco smoking [21] through PhenoScanner datasets (http://www.phenoscanner.medschl.cam.ac.uk/).

### Data sources of outcome

To investigate genetic associations with lymphoid and hematopoietic malignant neoplasms, we employed summary-level data obtained from the most recent publicly accessible R9 data release by Kurki et al. [22]. The FinnGen study is a comprehensive nationwide genetic investigation conducted in conjunction with electronic health records, aiming to collect genetic data. This study was adjusted for potential confounding factors including sex, age, genetic components, and genotyping batch.

Genetic associations with 13 lymphoid and hematopoietic malignant neoplasms GWAS databases were available from the FinnGen website (https://www.finngen.fi/en). Included outcomes were classified into five major categories according to the pathological pattern: (1) Primary lymphoid and hematopoietic malignant neoplasms (7519 cases and 299,952 controls); (2) HL (2602 cases and 299,952 controls); (3) NHL (1088 cases and 299,952 controls): FL (1081 cases and 299,952 controls),

Non-follicular lymphoma (NFL) (2602 cases and 299,952 controls), DLBCL (1010 cases and 287,137 controls), Mature T/NK-cell lymphomas (335 cases and 299,952 controls), Mantle cell lymphoma (MCL) (119 cases and 287,173 controls), Marginal zone B-cell lymphoma (MZBL) (192 cases and 287,137 controls); and (4) Lymphoid leukaemia (1493 cases and 299,952 controls) (Acute lymphocytic leukaemia (ALL) (184 cases and 287,136 controls), Chronic lymphocytic leukaemia (CLL) (624 cases and 287,133 controls)); (5) Multiple myeloma (MM) (674 cases and 376,603 controls).

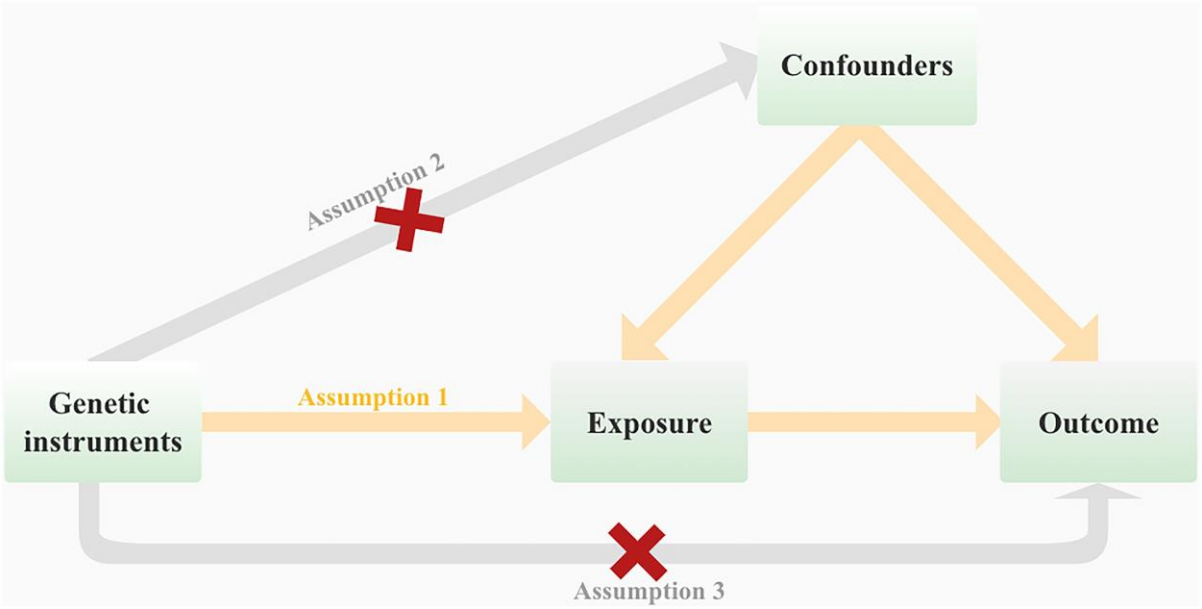


**Figure 1. Mendelian randomization (MR) analysis is based on three fundamental assumptions at its core.**

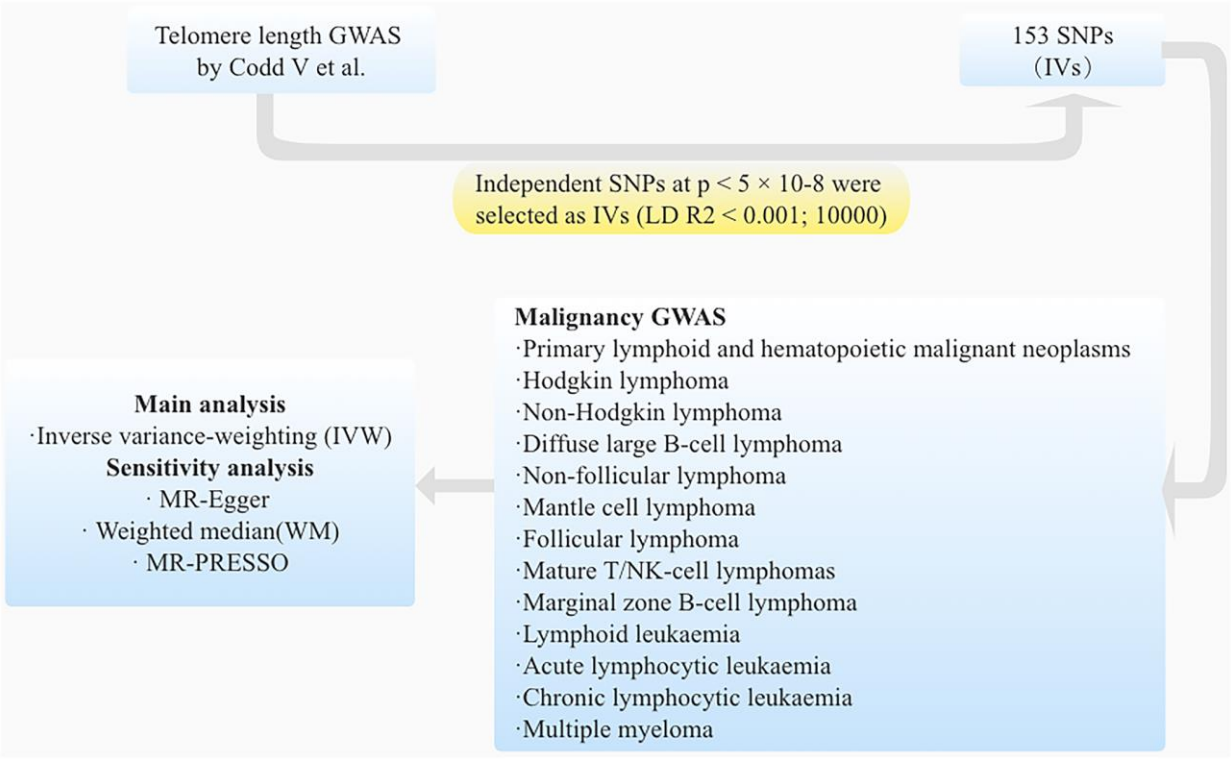


**Figure 2. The flow diagram illustrates the sequential process of the MR study.**

### Primary MR analysis

The Wald ratio was used to assess the effect of telomere length on lymphoid and hematopoietic malignant neoplasms for each SNP. All SNP effects were meta-analyzed by the inverse-variance weighted (IVW) method [14]. This study used the multiplicative random-effects IVW method as the main MR analysis. In order to examine the potential causal relationship between telomere length and lymphoid and hematopoietic malignant neoplasms, we conducted MR analyses employing four distinct methods: IVW, MR-Egger, MR-PRESSO, and weighted median. The IVW method assumes the absence of pleiotropy, wherein instrumental variables (IVs) solely affect telomere length and not through alternative pathways. The MR-Egger approach provides a valid estimate of causal effect [23]. For the weighted median approach to be applicable, it necessitates that at least half of the IVs are valid [24]. The MR-PRESSO method effectively identifies potential IV abnormalities and automatically eliminates them to ensure an unbiased causal effect estimation. To assess heterogeneity, Cochran's *Q* test was performed. In cases where no heterogeneity was observed in the IVW analysis, the fixed-effect model was utilized; otherwise, the random-effect model was employed.

### Sensitivity analysis

In sensitivity analyses, MR-Egger [23] and weighted median (WM) methods [24] were applied to account for horizontal pleiotropic effects. The MR-Egger method was based on the Instrument Strength Independent of Direct Effect (InSIDE) assumption, which often provides imprecise and low statistical power MR results, especially when meeting small sizes of SNPs (e.g., <10) [23]. In our MR study, MR-Egger was mainly used to detect pleiotropy; the value of the intercept term is far from zero, indicating horizontal pleiotropy ($P < 0.05$) [25]. The WM method was more reliable if more than 50% of SNPs were invalid instruments (e.g., due to pleiotropy) [26]. In addition, MR-PRESSO analysis was used to detect outliers, which can reduce heterogeneity by removing those outliers that may lead to heterogeneity (Figure 3) [27]. We performed leave-one-out method analysis to determine potentially influential SNPs by removing each SNP. We adjusted the multiple testing by false discovery rate (FDR).

### MR procedures

To ensure unbiased results by addressing potential heterogeneity, we followed a three-step approach in our study (Figure 3). In Step 1, we initially conducted MR analysis using the selected SNPs mentioned above, subsequently employing the MRPRESSO outlier test. If any outliers were detected ($P < 0.05$), we proceeded to Step 2. In Step 2, we reevaluated the MR analysis after excluding all outliers ($P < 0.05$). If heterogeneity persisted, we entered Step 3, wherein SNPs with a *P*-value less than 1 in the MR-PRESSO test were excluded, and the MR analysis was reevaluated. Furthermore, we exercised caution in interpreting the results if any potentially influential SNPs were identified through the leave-one-out test.

For our MR study, we utilized several R packages including "TwoSampleMR" [28], "MendelianRandomization" [24], and "MRPRESSO" [27] packages. The forestploter R packages were employed for data visualization. All statistical analyses were conducted using R software version 4.3.1 (R Foundation, Vienna, Austria, https://www.R-project.org/).

## RESULTS

We identified 34857 SNPs that showed a significant association with telomere length in the discovery cohort consisting of 472,174 European participants, as reported by Codd V et al. [19]. These SNPs reached the genome-wide significance level (*p*-value < 5 × 10−8). To ensure the independence of instrumental variables for telomere length (TL), SNPs in linkage disequilibrium (with r2 >0.001 and clump distance <10,000 kb) were excluded. Notably, rs7705526 was excluded due to its significant association with some hematological malignancies directly by screening PhenoScanner datasets ($P < 5 \times 10-8$). Ultimately, 153 independent SNPs remained as instrumental variables. Supplementary Table 1 provides detailed information on the selected SNPs. The F statistics of these SNPs ranged from 29 to 1628, suggesting no weak instrumental variables exited [29]. The instrumental variables accounted for 3.36% of the variance in explaining the exposure.

### MR main analysis

Genetically predicted longer telomere length could increase the risk of all types of primary lymphoid, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL), non-follicular lymphoma (NFL), mantle cell lymphoma (MCL), acute lymphoid leukemia (ALL), chronic lymphoid leukemia (CLL) after FDR control (FDR <0.05; Figure 4 and Table 1). Specifically, a 1-SD increase of telomere length could increase the risk of all types of primary lymphoid (OR = 1.52, $P = 2.11\times10^{-6}$) by 52%, HL (OR = 1.64, $P = 0.014$) by 64%, NHL (OR = 1.70, $P = 0.002$) by 70%, DLBCL (OR = 1.57, $P = 0.015$) by 57%, NFL (OR = 1.58, $P = 1.73 \times 10^{-4}$) by

58%, MCL (OR = 3.13, $P$ = 0.003) by 213%, ALL (OR = 2.65, $P$ = 0.021) by 165%, CLL (OR = 2.80, $P$ = $8.21 \times 10^{-6}$) by 180%, and Multiple myeloma 1.85 (OR = 1.85, $P$ = 0.016) by 85%. However, telomere length was not associated with increase in odds of follicular lymphomas (FL), mature T/NK cell lymphoma, and marginal zone B-cell lymphoma (MZBL).

**Sensitivity analysis**

All WM and MR-Egger sensitivity analyses were directionally consistent in the IVW results except for FL and mature T/NK-cell lymphomas. The MR-PRESSO results suggested that the causal relationship still holds after removing outliers. No heterogeneity was detected

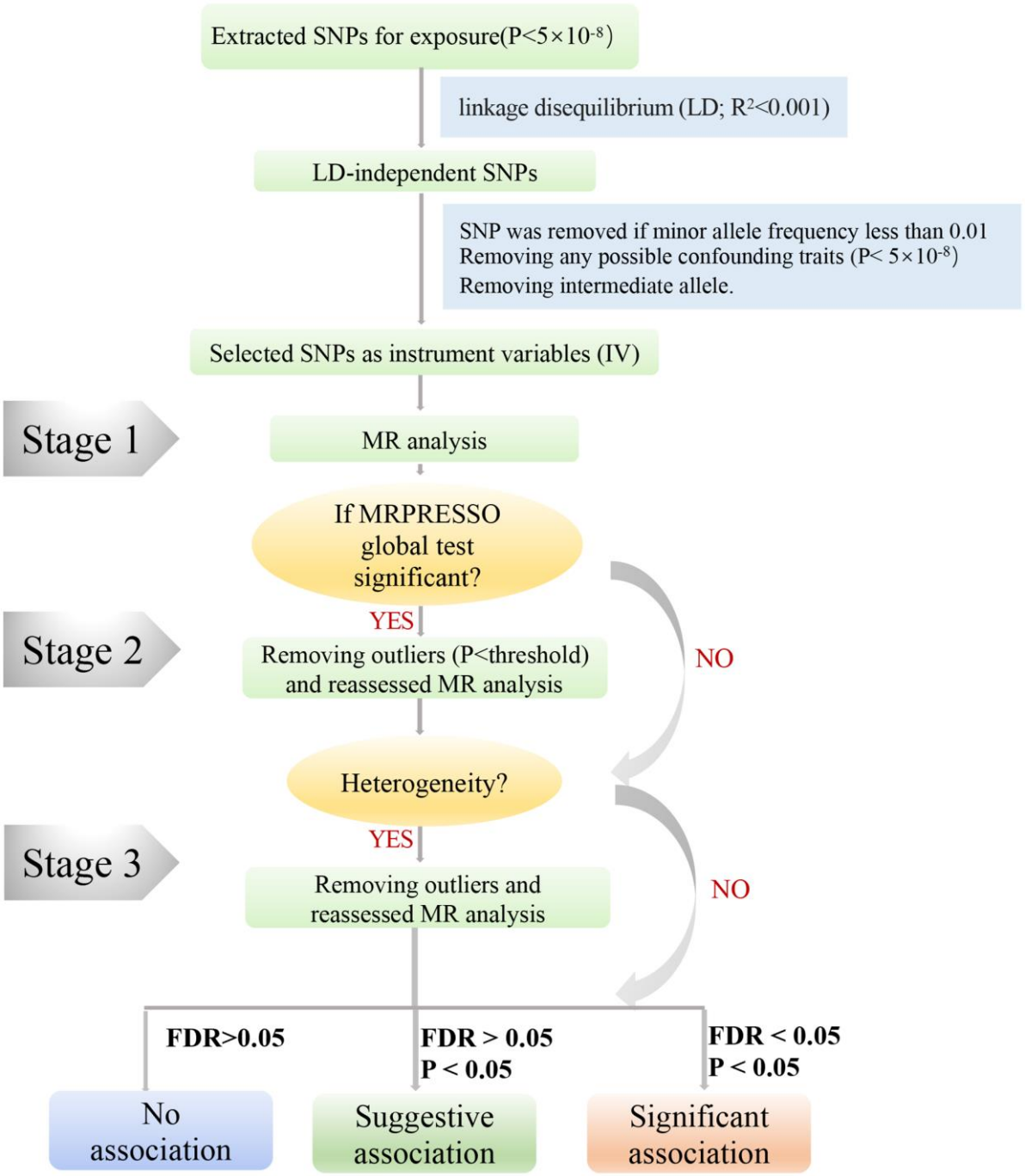


**Figure 3. A step-by-step flow chart demonstrates the analytical methods employed and outlines the sequential execution of MR analysis.** Step 1 involved conducting the MR analysis using the selected SNPs, followed by performing the MRPRESSO outlier test. If significance was detected ($P$ < 0.05), we proceeded to step 2. In step 2, the MR analysis was reevaluated after removing all identified outliers ($P$ < 0.05). Should heterogeneity persist, step 3 entailed excluding SNPs with a MR-PRESSO test $P$-value below 1 and reevaluating the MR analysis.

except for primary lymphoid and FL. Furthermore, no horizontal pleiotropy was observed in this MR analysis across all subsets (Supplementary Table 2). Moreover, Leave-one-out analysis revealed that no SNP drove the results (Supplementary Figure 1).

To further investigate the causal relationship, we examined the effect of these malignancies as a risk factor for telomere length, thus ruling out the possibility of a bidirectional causal effect between telomere length and all types of lymphoma and lymphoid leukemia.

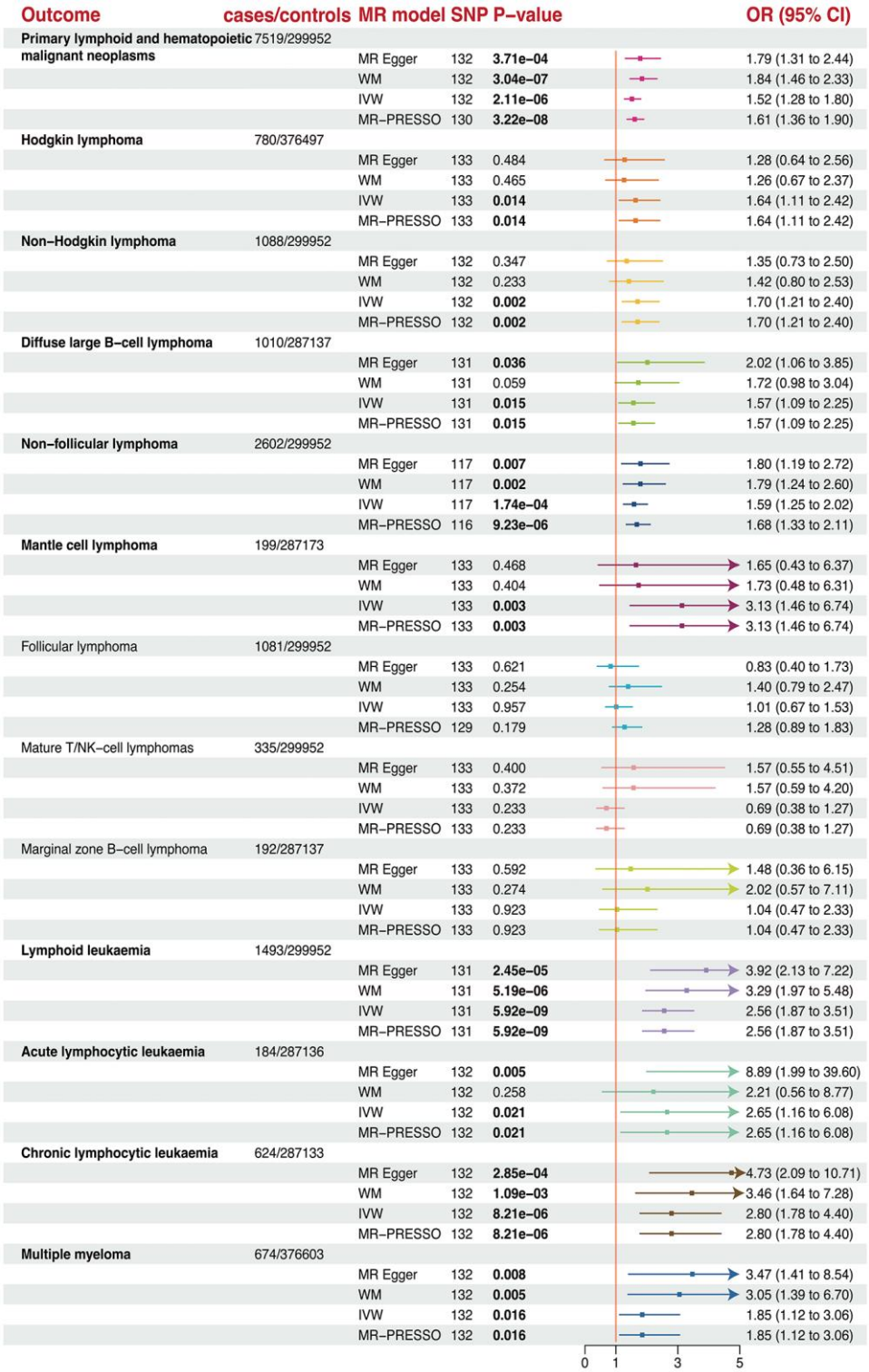


**Figure 4. The forest plots revealed the causal association of telomere length with different lymphoma and hematopoietic malignancies.**

**Table 1. False discovery rate adjusted *p*-values for the tested associations of telomere length and outcomes.**

| Outcome | SNPs | Original *P*-value | Benjamini-Hochberg adjusted *P*-value | Significant using an FDR of 0.05? |
|---|---|---|---|---|
| Primary lymphoid and hematopoietic malignant neoplasms | 132 | 2.11E-06 | 1.37E-05 | Yes |
| Hodgkin lymphoma | 117 | 0.014 | 0.026 | Yes |
| Non-Hodgkin lymphoma | 132 | 0.002 | 0.006 | Yes |
| Diffuse large B-cell lymphoma | 133 | 0.015 | 0.019 | Yes |
| Non-follicular lymphoma | 131 | 0.000 | 0.001 | Yes |
| Mantle cell lymphoma | 133 | 0.003 | 0.007 | Yes |
| Follicular lymphoma | 133 | 0.957 | 0.957 | No |
| Mature T/NK-cell lymphomas | 133 | 0.233 | 0.276 | No |
| Marginal zone B-cell lymphoma | 133 | 0.923 | 1.000 | No |
| Lymphoid leukaemia | 131 | 5.92E-09 | 7.69E-08 | Yes |
| Acute lymphocytic leukaemia | 132 | 2.09E-02 | 3.02E-02 | Yes |
| Chronic lymphocytic leukaemia | 132 | 0.000 | 0.000 | Yes |
| Multiple myeloma | 132 | 0.016 | 0.026 | Yes |

Different SNPs associated with various lymphomas were considered, but no significant effect was found under any of the MR models. These results demonstrate the credibility of our conclusions.

## DISCUSSION

The objective of this study is to investigate the association between telomere length and various hematopoietic malignancies by MR analysis. Through our research, we found that telomere length may increase the risk of primary lymphoid, Hodgkin lymphoma, non-Hodgkin lymphoma, DLBCL, NFL, MCL, ALL, CLL and multiple myeloma. These findings were supported by rigorous statistical analysis, with a corrected FDR of less than 0.05. Furthermore, this study demonstrated no homogeneity and horizontal pleiotropy across all investigations.

Telomere length plays a critical role in maintaining genomic stability and preventing cellular senescence or apoptosis [30, 31]. Shortened telomeres are commonly observed in various cancer types and are generally associated with genomic instability and tumor progression [32–34]. Our findings add to the existing body of evidence by highlighting the importance of telomere length in hematopoietic malignancies. Previous studies have concluded that blood malignancies (NHL, MCL, ALL, CLL) have shorter telomere lengths than the control group [35–39]. Roos et al. found that shortened telomere length in chronic lymphocytic leukemia (CLL) patients is consistent with other classic biological factors of CLL, including unmutated immunoglobulin heavy chain variable region genes (UM-IGVH), positive CD38 and ZAP-70 (>30%), and short lymphocyte doubling time (<6 months) [40]. In a study conducted by Sellmann et al., a correlation was observed between the frequency of IGHV gene mutations and the length of telomeres [41]. The study conducted on CLL patients indicated that those with reduced telomere length demonstrated poorer clinical outcomes, including decreased progression-free survival (PFS) and overall survival (OS) [42]. However, their findings do not elucidate a causal relationship between telomere length and hematologic malignancies. Furthermore, it is worth noting that Furtado et al. [43] suggest that telomere shortening is an early event in the development of leukemia, as short telomeres are already present in small abnormal B-cell clones in monoclonal B-cell lymphocytosis. This disease precedes chronic lymphocytic leukemia, consistent with the causal relationship we deduced through Mendelian randomization. Several underlying mechanisms could explain the observed association between telomere length and hematopoietic cancers. One possibility is that telomere dysfunction is directly involved in the initiation and progression of these malignancies. Shortened telomeres may lead to chromosomal abnormalities, DNA damage, and genomic instability, ultimately contributing to the development of cancer cells. Additionally, alterations in telomerase activity or mutations in genes involved in telomere regulation could contribute to telomere length abnormalities. Telomerase, the enzyme responsible for adding telomeric repeats, is often upregulated in cancer cells, allowing them to maintain or even lengthen their telomeres [44]. Dysregulation of telomerase activity

could lead to differences in telomere length among individuals affecting their susceptibility to hematopoietic malignancies [30, 31].

Currently, research on telomere therapy is still in the early stages, and there is no definitive treatment plan. However, some studies have begun to explore potential treatment methods. One possible treatment approach is to extend telomere length through stem cell transplantation. Researchers have found that during the process of differentiation, stem cells can restore telomere length, which may be helpful in treating certain telomere shortening-related diseases [45]. In addition, certain drugs and compounds are being studied for their potential in intervening with telomere length. For example, some anti-aging compounds are speculated to have potential telomere protection effects, such as telomerase activators, antioxidants, and certain vitamins [46–48]. However, it should be noted that the relationship between telomere length and various diseases is complex. Treating telomere length involves considering the cellular environment, genetic factors, and other relevant factors [16]. Telomere therapy is still in the research stage and requires further clinical trials and studies to validate its safety, efficacy, and applicability.

Importantly, our findings have clinical implications for the diagnosis, prognosis, and treatment of hematopoietic malignancies. Telomere length could serve as a potential biomarker for disease risk assessment, allowing for early detection and intervention. Moreover, telomere length could be used to predict treatment response and patient outcomes, enabling personalized therapeutic strategies [49].

While this study provides valuable insights, there are certain limitations that should be acknowledged. Genetic and environmental factors that influence telomere length were not extensively investigated in this study. Further research is needed to elucidate these factors and their interactions.

However, there are some concomitant limitations in our study. First, due to the unavailability of individual-level data, we can only perform causal association MR analysis and cannot further examine the sensitivity and specificity of the outcomes. Additionally, the FinnGen database does not disclose detailed disease diagnostic information, which may introduce errors in our phenotypic analysis. However, the FinnGen database links genotypes with specific data using unique national identification numbers, and the disease classification is primarily based on ICD. Therefore, the possibility of misclassification influencing the outcomes is likely to be small. Second, further investigation into the direct impact of telomerase activity on hematological tumor development is necessary as telomere length is primarily influenced by telomerase. This research may provide new insights into the mechanisms through which telomeres contribute to cancer development. However, due to the lack of comprehensive telomerase-related GWAS (genome-wide association studies) at present, we are currently unable to analyze the relationship between telomerase and hematological tumors. In the future, relevant studies will be necessary. Third, a significant portion of the participants included in this investigation were of European origin; hence, it is not possible to extrapolate our results to encompass all racial groups.

## CONCLUSION

In conclusion, our study found that telomere length is a risk factor for a wide ride of hematopoietic malignancies. Understanding the role of telomere length in the pathogenesis of these cancers could pave the way for innovative diagnostic and therapeutic approaches. Further investigation into the underlying mechanisms and the identification of specific bio-markers associated with telomere length may contribute to improved clinical management and patient outcomes in hematopoietic malignancies.

### Abbreviations

HL: Hodgkin lymphoma; NHL: Non-Hodgkin lymphoma; DLBCL: Diffuse large B-cell lymphoma; NFL: Non-follicular lymphoma; MCL: Mantle cell lymphoma; FL: Follicular lymphoma; MZBL: Marginal zone B-cell lymphoma; ALL: Acute lymphocytic leukaemia; CLL: Chronic lymphocytic leukaemia; MM: Multiple myeloma; GWAS: Genome-wide association studies; IVW: Inverse-variance weighted; SNPs: Single nucleotide polymorphisms; IVs: Instrumental variables; WM: Weighted median; FDR: False discovery rate; OR: Odds ratio; CI: Confidence interval.

## AUTHOR CONTRIBUTIONS

TF designed the study. TF, ZZ, and KR conducted data analysis. TF conceived the project and wrote the manuscript. LZ revised and approved the paper. All authors contributed to the article and approved the submitted version.

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## CONFLICTS OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## ETHICAL STATEMENT

No ethical statement is required because the study was based on GWAS publicly available data.

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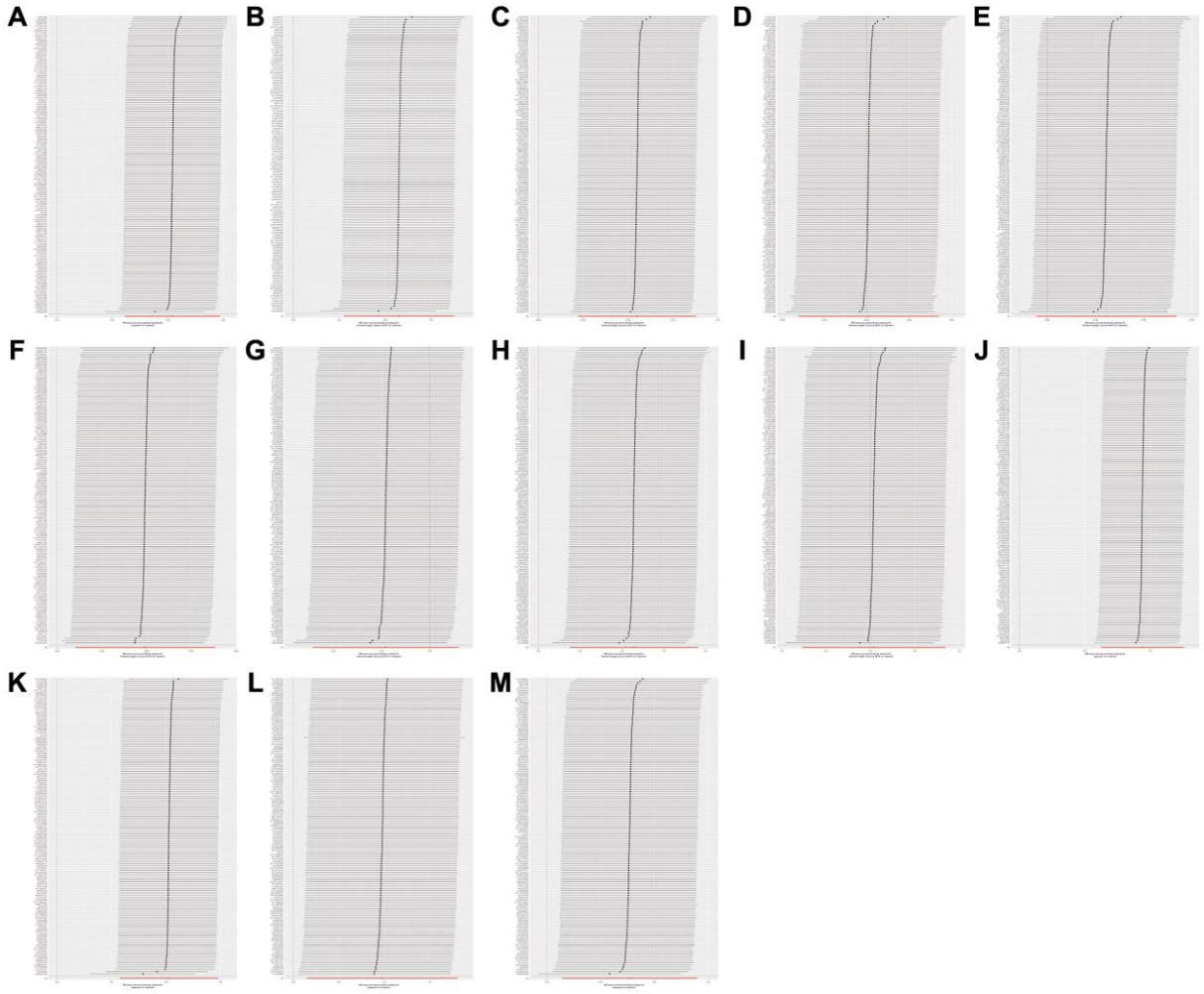
## SUPPLEMENTARY MATERIALS

### Supplementary Figure




**Supplementary Figure 1. Sensitivity analysis of the leave-one-out test for the MR analysis to assess the impact of telomere length on various cancer risks.** (**A**) TL on primary lymphoid and hematopoietic malignant neoplasms. (**B**) TL on non-follicular lymphoma. (**C**) TL on non-Hodgkin lymphoma. (**D**) TL on follicular lymphoma. (**E**) TL on diffuse large B-cell lymphoma. (**F**) TL on Hodgkin lymphoma. (**G**) TL on mature T/NK-cell lymphomas. (**H**) TL on mantle cell lymphoma. (**I**) TL on marginal zone B-cell lymphoma. (**J**) TL on lymphoid leukaemia. (**K**) TL on chronic lymphocytic leukaemia. (**L**) TL on acute lymphocytic leukaemia. (**M**) TL on multiple myeloma.

## Supplementary Tables

Please browse Full Text version to see the data of Supplementary Table 1.

**Supplementary Table 1. The baseline characteristics of the selected SNPs in the IEU GWAS.**

**Supplementary Table 2. Mendelian randomization results of different results.**

| Outcome | Cases | Controls | MR model | SNP | OR | ll-96% | ul-95% | *P*-value | P(heterogeneity) | P_pleiotropy |
|---|---|---|---|---|---|---|---|---|---|---|
| Primary lymphoid and hematopoietic malignant neoplasms | 7519 | 299952 | | | | | | | | |
| | | | MR Egger | 132 | 1.787 | 1.309 | 2.439 | 3.713E-04 | 1.744E-06 | |
| | | | WM | 132 | 1.842 | 1.458 | 2.327 | 3.042E-07 | | |
| | | | IVW | 132 | 1.517 | 1.277 | 1.803 | | 1.326E-06 | 0.219 |
| | | | MR-PRESSO | 130 | 1.607 | 1.358 | 1.901 | 3.223E-08 | 5.669E-05 | 0.211 |
| Non-follicular lymphoma | 2602 | 299952 | | | | | | | | |
| | | | MR Egger | 117 | 1.796 | 1.187 | 2.717 | 6.512E-03 | 1.645E-01 | |
| | | | WM | 117 | 1.793 | 1.238 | 2.597 | 2.019E-03 | | |
| | | | IVW | 117 | 1.585 | 1.246 | 2.017 | 1.736E-04 | 1.717E-01 | 0.470 |
| | | | MR-PRESSO | 116 | 1.677 | 1.334 | 2.107 | 9.234E-06 | 5.396E-01 | 0.555 |
| Non-Hodgkin lymphoma | 1088 | 299952 | | | | | | | | |
| | | | MR Egger | 132 | 1.348 | 0.725 | 2.504 | 3.468E-01 | 5.594E-01 | |
| | | | WM | 132 | 1.420 | 0.798 | 2.526 | 2.325E-01 | | |
| | | | IVW | 132 | 1.701 | 1.208 | 2.396 | 2.368E-03 | 5.646E-01 | 0.378 |
| | | | MR-PRESSO | 132 | 1.701 | 1.208 | 2.396 | 2.368E-03 | 5.646E-01 | 0.378 |
| Follicular lymphoma | 1081 | 299952 | | | | | | | | |
| | | | MR Egger | 133 | 0.831 | 0.399 | 1.730 | 6.213E-01 | 1.660E-05 | |
| | | | WM | 133 | 1.395 | 0.788 | 2.471 | 2.535E-01 | | |
| | | | IVW | 133 | 1.012 | 0.669 | 1.531 | 9.566E-01 | 1.871E-05 | 0.525 |
| | | | MR-PRESSO | 129 | 1.280 | 0.893 | 1.835 | 1.792E-01 | 1.322E-01 | 0.605 |
| Diffuse large B-cell lymphoma | 1010 | 287137 | | | | | | | | |
| | | | MR Egger | 133 | 1.643 | 0.865 | 3.121 | 1.320E-01 | 1.318E-01 | |
| | | | WM | 133 | 1.077 | 0.631 | 1.839 | 7.851E-01 | | |
| | | | IVW | 133 | 1.357 | 0.944 | 1.952 | 9.898E-02 | 1.380E-01 | 0.481 |
| | | | MR-PRESSO | 132 | 1.464 | 1.035 | 2.071 | 3.109E-02 | 4.109E-01 | 0.557 |
| Hodgkin lymphoma | 780 | 376497 | | | | | | | | |
| | | | MR Egger | 133 | 1.281 | 0.642 | 2.560 | 4.836E-01 | 3.973E-01 | |
| | | | WM | 133 | 1.264 | 0.674 | 2.370 | 4.646E-01 | | |
| | | | IVW | 133 | 1.636 | 1.106 | 2.420 | 1.377E-02 | 4.041E-01 | 0.403 |
| | | | MR-PRESSO | 133 | 1.636 | 1.106 | 2.420 | 1.377E-02 | 4.041E-01 | 0.403 |
| Mature T/NK-cell lymphomas | 335 | 299952 | | | | | | | | |
| | | | MR Egger | 133 | 1.574 | 0.549 | 4.510 | 3.998E-01 | 4.145E-01 | |
| | | | WM | 133 | 1.568 | 0.586 | 4.201 | 3.705E-01 | | |
| | | | IVW | 133 | 0.694 | 0.380 | 1.266 | 2.332E-01 | 3.571E-01 | 0.066 |
| | | | MR-PRESSO | 133 | 0.694 | 0.380 | 1.266 | 2.332E-01 | 3.571E-01 | 0.066 |
| Mantle cell lymphoma | 199 | 287173 | | | | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | MR Egger | 133 | 1.651 | 0.428 | 6.370 | 4.684E-01 | 6.627E-01 | |
| | | | WM | 133 | 1.734 | 0.476 | 6.315 | 4.035E-01 | | |
| | | | IVW | 133 | 3.134 | 1.457 | 6.739 | 3.452E-03 | 6.557E-01 | 0.261 |
| | | | MR-PRESSO | 133 | 3.134 | 1.457 | 6.739 | 3.452E-03 | 6.557E-01 | 0.261 |
| Marginal zone B-cell lymphoma | 192 | 287137 | | | | | | | | |
| | | | MR Egger | 133 | 1.478 | 0.355 | 6.146 | 5.920E-01 | 2.707E-01 | |
| | | | WM | 133 | 2.019 | 0.573 | 7.111 | 2.743E-01 | | |
| | | | IVW | 133 | 1.041 | 0.465 | 2.328 | 9.227E-01 | 2.840E-01 | 0.559 |
| | | | MR-PRESSO | 133 | 1.041 | 0.465 | 2.328 | 9.227E-01 | 2.840E-01 | 0.559 |
| Lymphoid leukaemia | 1493 | 299952 | | | | | | | | |
| | | | MR Egger | 131 | 3.917 | 2.126 | 7.218 | 2.453E-05 | 4.347E-01 | |
| | | | WM | 131 | 3.287 | 1.970 | 5.484 | 5.190E-06 | | |
| | | | IVW | 131 | 2.560 | 1.865 | 3.514 | 5.915E-09 | 3.976E-01 | 0.114 |
| | | | MR-PRESSO | 131 | 2.560 | 1.865 | 3.514 | 5.915E-09 | 3.976E-01 | 0.114 |
| Chronic lymphocytic leukaemia | 624 | 287133 | | | | | | | | |
| | | | MR Egger | 132 | 4.734 | 2.091 | 10.714 | 2.846E-04 | 8.525E-01 | |
| | | | WM | 132 | 3.456 | 1.642 | 7.275 | 1.089E-03 | | |
| | | | IVW | 132 | 2.797 | 1.780 | 4.395 | 8.208E-06 | 8.303E-01 | 0.132 |
| | | | MR-PRESSO | 132 | 2.797 | 1.780 | 4.395 | 8.208E-06 | 8.303E-01 | 0.132 |
| Acute lymphocytic leukaemia | 184 | 287136 | | | | | | | | |
| | | | MR Egger | 132 | 8.887 | 1.994 | 39.598 | 4.856E-03 | 7.909E-01 | |
| | | | WM | 132 | 2.214 | 0.559 | 8.771 | 2.578E-01 | | |
| | | | IVW | 132 | 2.655 | 1.159 | 6.080 | 2.092E-02 | 7.367E-01 | 0.059 |
| | | | MR-PRESSO | 132 | 2.655 | 1.159 | 6.080 | 2.092E-02 | 7.367E-01 | 0.059 |
| Multiple myeloma | 674 | 376603 | | | | | | | | |
| | | | MR Egger | 132 | 3.470 | 1.410 | 8.540 | 7.694E-03 | 1.273E-01 | |
| | | | WM | 132 | 3.053 | 1.391 | 6.701 | 5.406E-03 | | |
| | | | IVW | 132 | 1.852 | 1.121 | 3.059 | 1.616E-02 | 1.052E-01 | 0.103 |
| | | | MR-PRESSO | 132 | 1.852 | 1.121 | 3.059 | 1.616E-02 | 1.052E-01 | 0.103 |

p heterogeneity, *p*-value of Cochrane's *Q*-value in heterogeneity test, P_pleiotropy, *p*-value of MR-Egger intercept.