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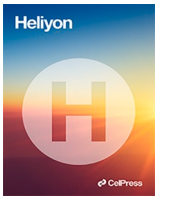

Research article

Peripheral blood leukocyte Telomere length and endometriosis: A Mendelian randomization study

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ABSTRACT

Background: The link between peripheral blood leukocyte telomere length (LTL) and endometriosis has remained uncertain. In order to investigate this association, a two-sample Mendelian randomization(MR) analysis was performed.

Methods: We extracted Single-nucleotide polymorphisms (SNPs) associated with LTL from a published genome-wide association study (GWAS) comprising 472,174 individuals. Data on endometriosis, including its seven subtypes, were sourced from the iue open gwas project. Four methods were employed for MR: Inverse-variance weighted analysis (IVW), Mendelian randomization-Egger regression (MR Egger), weighted-median analysis, and Weighted Mode.

Results: Genetically determined LTL was identified as a factor that can promote the occurrence of endometriosis. With every 1-SD increase in LTL, the risk of endometriosis increased by 26 % (OR = 1.260, 95 % CI = 1.073 to 1.479; $P = 0.005$). Genetically determined LTL also contributed to endometriosis subtypes: intestine (OR = 3.584, 95 % CI = 1.597 to 8.041; $P = 0.002$), ovary (OR = 1.308, 95 % CI = 1.033 to 1.655; $P = 0.026$), rectovaginal septum and vagina (OR = 1.360, 95 % CI = 1.000 to 1.851; $P = 0.049$). There was no observed causal relationship between LTL and the other four subtypes.

Conclusion: This study, utilizing genetic data, offers evidence that longer LTL may cause increased risks of endometriosis, specifically endometriosis of the intestine, ovary, rectovaginal septum and vagina. These findings not only suggest that LTL may serve as a predictive factor for assessing the prevalence of three endometriosis subtypes but also provide new insights into the study of endometriosis pathogenesis.

1. Introduction

Telomeres are segments of DNA at the terminal regions of chromosomes that gradually diminish with every cell division. When they become short enough, cells enter a stage of aging or undergo apoptosis. Therefore, the loss and shortening of telomeres are closely associated with human aging and diseases [1].White blood cell telomere length refers to the length of the DNA sequence repeat units at the terminal regions of white blood cell chromosomes. Researches have indicated that the change of white blood cell telomere length

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may result in impaired function of white blood cells, limiting their roles in inflammatory processes such as chronic obstructive pulmonary disease, rheumatoid arthritis, and diabetes [2–4].

Endometriosis is a gynecological condition that frequently results in intense pain and infertility, impacting approximately ten percent of women in their reproductive years [5]. This ailment is identified by the expansion of endometrial tissue beyond the uterine boundaries, reaching areas like the ovaries, pelvic cavity, and occasionally the intestines [6]. While the exact mechanism of endometriosis is unclear, markers of inflammation in patients are observed to be increased frequently [7]. Given the observed link of LTL with inflammation, the change of LTL may also involve in the pathogenesis of endometriosis.

Currently, studies on the relationship between LTL and endometriosis are contradictory. Roberta et al. found that LTL in endometriosis women was longer than that in the healthy women [8]. However, Naoko et al. reported that individuals with shorter LTL were more susceptible to endometriosis [9]. Limitations in sample size and variations in group composition may have contributed to the inconsistent results. In this study, we utilized MR to investigate the association between LTL and incidence of endometriosis, aiming to address these limitations.

2. Methods

2.1. Study design

By analyzing hazardous factors and disease outcomes with the publicly available large-scale genome-wide association study (GWAS) datasets, MR study recognizes whether a specific exposure has a causality on the occurrence of certain disease. MR is rooted in three hypotheses: genetic variation is closely correlated with the exposure; genetic variation is distinct from other confounding factors; genetic variation is solely connected to the outcome through the investigated exposure. Summary findings were obtained from published research, each of which had received approval from an institutional review board in their individual studies, and didn't necessitate further ethical clearance. A two-sample MR approach was used to study the relationship of causality between LTL and endometriosis.

2.2. Data sources

The genetic instruments for LTL (comprising 472,174 participants with clear features, data-freeze December 2020) were derived from the UK Biobank, which contains 805,426 single-nucleotide polymorphisms (SNPs) [10]. LTL measurements in participants were obtained using a rigorously validated qPCR assay, with numerous quality assessments conducted to manage and correct for technical variables [11].

The integrated GWAS data for endometriosis were sourced from the iue open gwas project, a European-led global research effort. The definition of endometriosis and its seven subtypes was based on International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)-WHO Version for; 2016. All the specific details are presented in Table 1.

We identified 154 SNPs associated with LTL through a primary meta-analysis, meeting the genome-wide significance threshold of $P < 5x10^{-8}$. Since the *P*-value of the instrumental variable with the outcome must not be less than $5x10^{-5}$ [12,13], we carefully selected and obtained 139 SNPs for the MR analysis. Values of $r^2 = 0.01$ and kb = 10000 were applied as parameters to alleviate the effects of linkage disequilibrium among the variables. We determined the F-statistic for each SNP individually as well as the total F-statistic for the entire array of SNPs. The individual F-statistic for the SNP set was determined using the formula [14]: $F=beta^2/se^2$. In the equation, the term "beta" indicates the impact magnitude of the IV on the exposure, while "se" represents the standard error of "beta.". Additionally, the total F-statistic for the SNP set was determined with the formula [14]: $F = (N-K-1)/k \times R^2 /(1-R^2) \times R^2 = 2 \times eaf \times (1 - eaf) \times beta^2$, where "N" denotes the number of samples for the exposure, "K" represents the quantity of SNPs, "R^2" stands for the percentage of exposed variance determined by SNPs, "eaf" refers to the frequency of the effect allele in the SNPs, and "beta" represents the impact of SNPs on the exposure. The F statistic was employed to assess sample overlap effects and weak instrumental bias, where an F value exceeding 10 indicates a robust defense against bias from weak instrumental variables [15]. After harmonization, SNPs rs2276182, rs2306646, rs56178008, and rs670180 were removed, resulting in a final count of 135 SNPs associated with LTL and endometriosis for the MR analysis. Additionally, SNP rs9940099 was excluded following harmonization within seven endometriosis subtypes. Thus, the

Table 1
Aggregated GWAS Data for Endometriosis in Europe - iue open gwas project.

Outcomes	Dataset	ICD10	ncase	ncontrol	Number of SNPs
Endometriosis	finn-b-N14_ENDOMETRIOSIS	N80	8288	68,969	16,377,306
Endometriosis of intestine	finn-b-N14_ENDOMETRIOSIS_INTESTINE	N80.5	177	68,969	16,376,157
Endometriosis of ovary	finn-b-N14_ENDOMETRIOSIS_OVARY	N80.1	3231	68,969	16,376,686
Endometriosis of rectovaginal septum and vagina	finn-b-N14_ENDOMETRIOSIS_ RECTPVAGSEPT_VAGINA	N80.4	1360	68,969	16,376,472
Endometriosis of pelvic peritoneum	finn-b-N14_ENDOMETRIOSIS_ PELVICPERITONEUM	N80.3	2953	68,969	16,376,599
Endometriosis of fallopian tube	finn-b-N14_ENDOMETRIOSIS_ FALLOPIAN_TUBE	N80.2	116	68,969	16,376,156
Endometriosis of uterus	finn-b-N14_ENDOMETRIOSIS_UTERUS	N80.0	2372	68,969	16,376,529
Unspecified/other endometriosis	finn-b-N14_ENDOMETRIOSIS_NOS	N80.8	1435	68,969	16,376,331

SNPs, single-nucleotide polymorphisms; ICD, International Classification of Diseases, ncase, number of case; ncontrol, number of control.

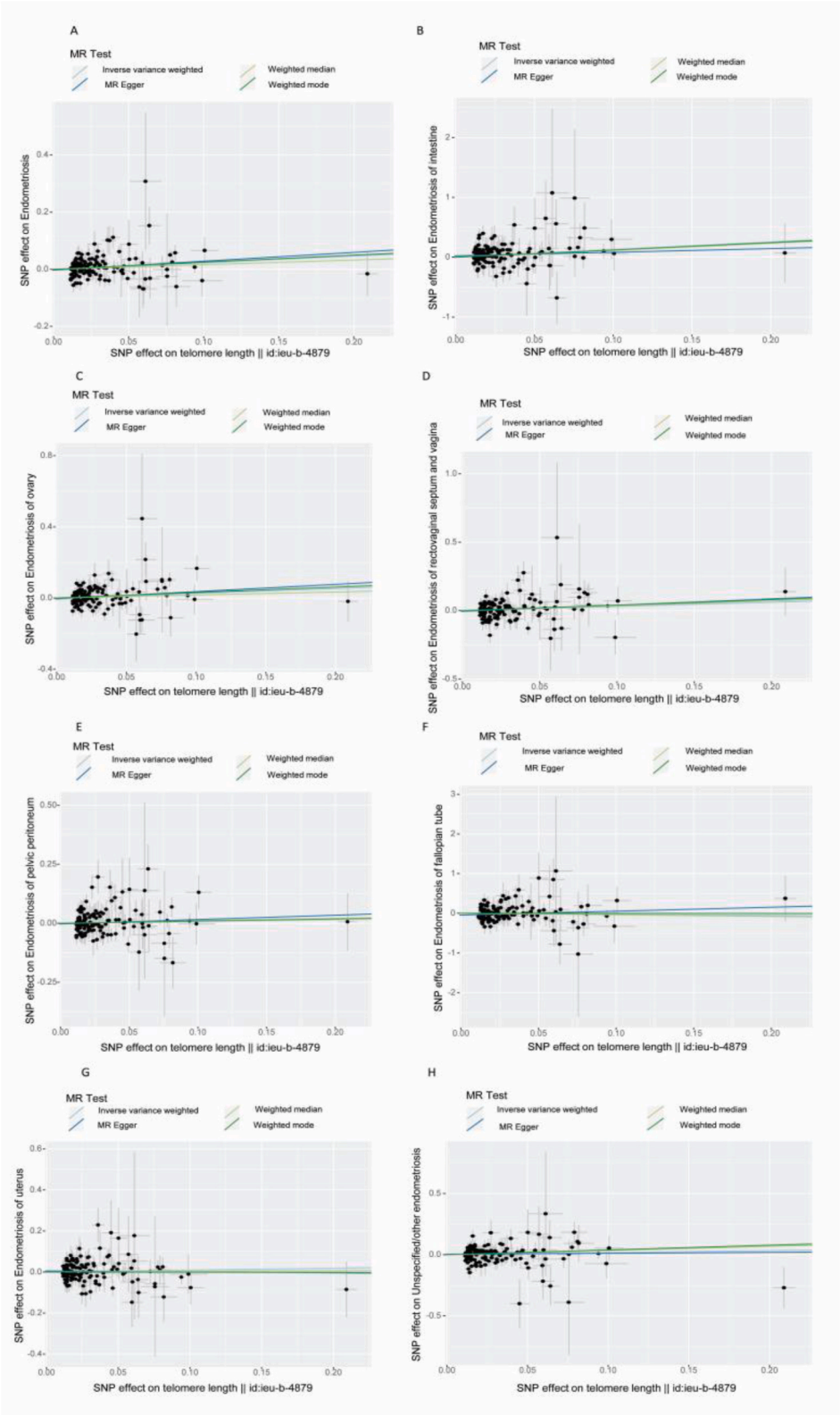

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Fig. 1. Scatter plots visualizing the effect of leukocyte telomere length (LTL) on the risk of endometriosis and its seven subtypes. The scatterplot presents a linear regression analysis of the data from the SNPs using four different methods. This plot is used to test the validity of the instrumental variable (IV). The horizontal axis represents the effect of the IV on the exposure, while the vertical axis represents the effect of the IV on the outcome. The equation of the line is $y = bx + a$, where the slope is denoted by beta. Straight lines with positive slopes indicate a positive correlation between exposure and outcome, whereas lines with negative slopes indicate a negative correlation between exposure and outcome. MR, Mendelian Randomization; IVW, Inverse-Variance Weighted; SNP, Single-nucleotide polymorphism. (A): SNP effect on endometriosis; (B): SNP effect on endometriosis of intestine; (C): SNP effect on endometriosis of ovary; (D): SNP effect on endometriosis of rectovaginal septum and vagina; (E): SNP effect on endometriosis of pelvic peritoneum; (F): SNP effect on endometriosis of fallopian tube; (G): SNP effect on endometriosis of uterus; (H): SNP effect on Unspecified/other endometriosis.

combined count of SNPs correlated with LTL and six endometriosis subtypes (including endometriosis of the intestine, rectovaginal septum and vagina, pelvic peritoneum, fallopian tube, uterus, and unspecified/other endometriosis) for the MR analysis was 134. Lastly, the combined count of SNPs correlated with LTL and endometriosis of the ovary for the MR analysis was 133, with SNP rs10774624 being removed due to being an outlier.

2.3. Statistical analysis

We employed a two-sample MR analysis to assess the influence of LTL on the probability of endometriosis occurrence. MR analysis was performed using the IVW model, MR Egger, weighted-median analysis, and Weighted Mode. IVW served as the main approach to examine the potential causal connection between LTL and endometriosis [16]. To gauge the extent of pleiotropy, we analyzed the symmetry of the funnel plot and checked for significant deviation from zero in the intercept of the MR-Egger regression [16]. Additional sensitivity analyses were conducted utilizing the MR Pleiotropy RESidual Sum and Outlier test (MR-PRESSO) [17] to tackle weak instrument bias and potential pleiotropy. The sensitivity of individual SNPs in our MR research was examined using Cochran's Q test (heterogeneity) to investigate discrepancies among various IVs [18]. Results from the MR analysis with a P-value <0.05 were interpreted as statistically significant. Odds ratios (OR) and 95 % confidence intervals (CIs) were used to estimate the relative risks. Analysis of all data was conducted using the R (version 4.3.0) software, developed by the R Foundation for Statistical Computing in Vienna, Austria. Our study protocol and details were not pre-registered.

3. Results

3.1. Findings from the MR investigation assessing association relationships

The consistency in genetic variant-exposure associations between the exposure and outcome samples arises from their shared origin in European populations. Nevertheless, there was no crossover of participants between the exposure and outcome studies. The exposure group for LTL includes 472,174 participants with well-defined characteristics. The outcome of endometriosis comprises 8288 cases and 68,969 controls. When endometriosis is divided into seven subtypes, the number of cases varies among the subtypes, but the number of controls remains constant. Table 1 provides detailed information on the ICD disease codes, the number of cases and controls, as well as the SNP counts for endometriosis and its seven subtypes. Different MR strategies, namely IVW, MR Egger, weighted median regression, and Weighted Mode, were employed to study the risk linkage between LTL and endometriosis, as well as its seven subtypes. Fig. 1 displays scatter plots illustrating the SNP-outcome associations in relation to SNP-LTL associations, allowing for the visualization of the potential risk relationships estimate for each individual SNP on endometriosis. Fig. 2 presents funnel plots depicting each SNP's Wald ratio in relation to their precision. In Figs. 1 and 2, A-H represent various outcomes, with A representing endometriosis and B–H representing the seven subtypes. Fig. 3 provides forest plots demonstrating the estimated values for each outcome based on IVW MR methodologies. The IVW analysis suggest a positive risk correlation between LTL and endometriosis (OR = 1.260, 95 % CI = 1.073 to 1.479, $P = 0.005$), endometriosis of intestine (OR = 3.584, 95 % CI = 1.597 to 8.041, $P = 0.002$), endometriosis of ovary (OR = 1.308, 95 % CI = 1.033 to 1.655, $P = 0.026$), endometriosis of rectovaginal septum and vagina (OR = 1.360, 95 % CI = 1.000 to 1.851, $P = 0.049$). Nevertheless, Table 2 reveals that three other MR analyses did not yield any statistically relationships for these three subtypes of endometriosis. However, there is some encouraging news as the MR-Egger method suggests a positive relationship between LTL and endometriosis (OR = 1.363, 95 % CI = 1.025 to 1.812, $P = 0.035$).

3.2. Analysis of sensitivity including heterogeneity and pleiotropy

The results for LTL in relation to endometriosis of the intestine, ovary, and rectovaginal septum and vagina remained consistent in sensitivity analyses (Table 3). Heterogeneity was detected in three groups, including endometriosis (MR IVW, Q = 196.697, $P = 3.26 \times 10^{-4}$), endometriosis of the ovary (MR IVW, Q = 184.305, $P = 0.002$), and endometriosis of the pelvic peritoneum (MR IVW, Q = 174.862, $P = 0.009$). However, there was no evidence of heterogeneity in endometriosis of the intestine, rectovaginal septum and vagina, fallopian tube, uterus, and Unspecified/other endometriosis ($P > 0.05$). Furthermore, the MR-Egger regression analysis found no signs of pleiotropy in all groups (Table 3).

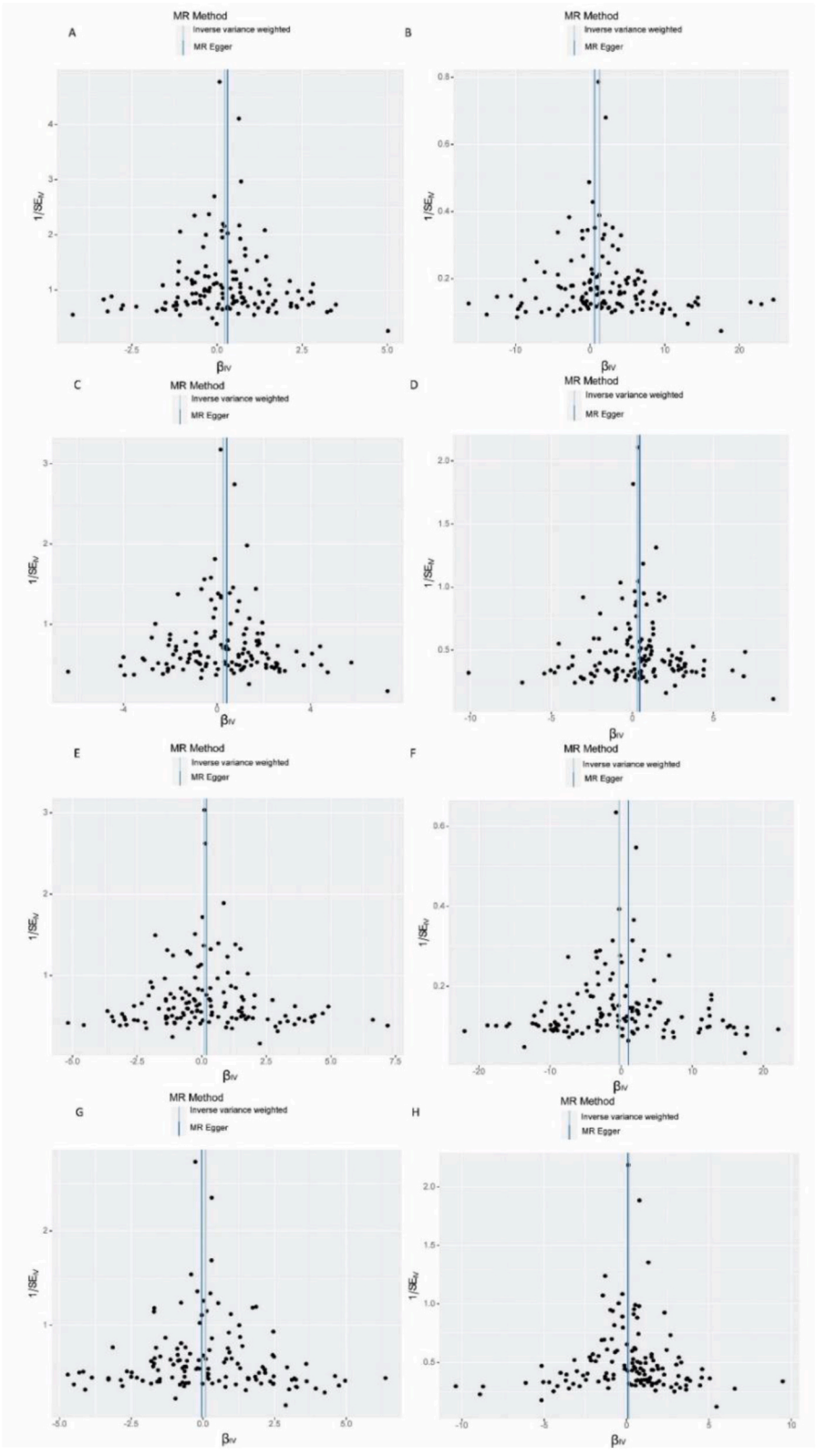

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Fig. 2. Funnel plots illustrating the overall heterogeneity of Mendelian Randomization(MR) estimates for the effect of leukocyte telomere length (LTL) on the risk of endometriosis and its seven subtypes. The funnel plot is commonly used to assess bias. In this plot, the horizontal axis primarily represents the degree of variation, while the vertical axis represents the sample size or total effect size. A line is drawn to indicate the main effect size, typically using the inverse variance weighted method. Symmetrical distribution of points on both sides of the line suggests the absence of bias. Conversely, asymmetrical distribution indicates the presence of bias. SNP, Single-nucleotide polymorphism. (A): Endometriosis; (B): Endometriosis of intestine; (C): Endometriosis of ovary; (D): Endometriosis of rectovaginal septum and vagina; (E): Endometriosis of pelvic peritoneum; (F): Endometriosis of fallopian tube; (G): Endometriosis of uterus; (H): Unspecified/other endometriosis.

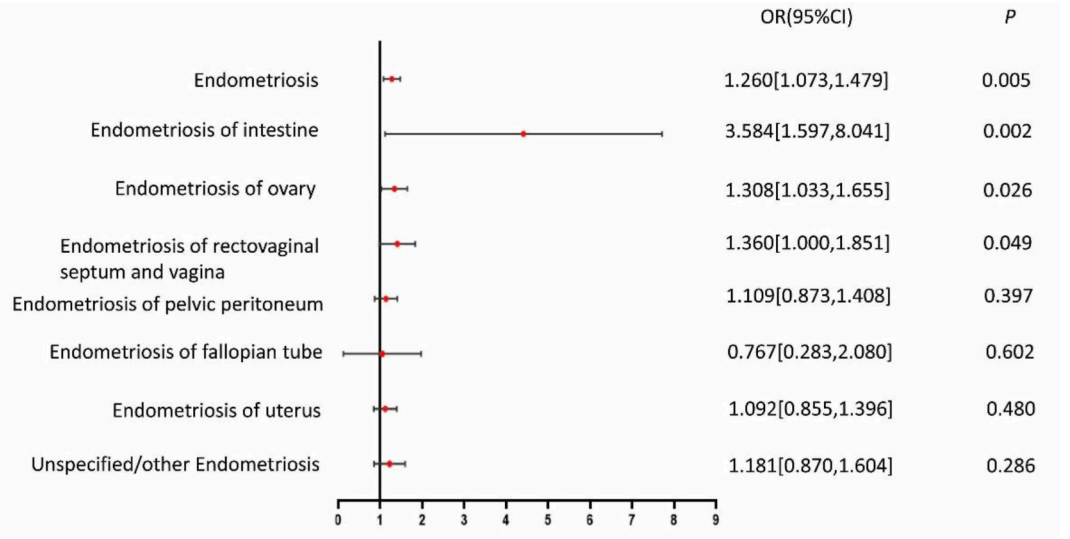

Fig. 3. Forest plot presenting effect estimates as odds ratios for endometriosis and its seven subtypes per 1-unit-higher log-odds of leukocyte telomere length (LTL). The results are displayed for Inverse-Variance Weighted (IVW). OR, odds ratios; CI, confidence interval.

Table 2
MR analyses of causal associations between LTL and endometriosis, including its seven subtypes.

Outcomes	Number of SNPs	MR Inverse-Variance Weighted (MR IVW)		MR Egger regression (MR Egger)		MR Weighted Median		MR Weighted Mode	
		OR(95%CI)	*P*	OR(95%CI)	*P*	OR(95%CI)	*P*	OR(95%CI)	*P*
Endometriosis	135	1.260 (1.073–1.479)	0.005	1.363 (1.025–1.812)	0.035	1.176 (0.923–1.500)	0.190	1.280 (0.962–1.702)	0.093
Endometriosis of intestine	134	3.584 (1.597–8.041)	0.002	1.827 (0.436–7.654)	0.411	3.220 (0.868–11.953)	0.081	3.400 (0.853–13.560)	0.085
Endometriosis of ovary	133	1.308 (1.033–1.655)	0.026	1.507 (0.993–2.288)	0.056	1.183 (0.832–1.682)	0.347	1.361 (0.911–2.035)	0.135
Endometriosis of rectovaginal septum and vagina	134	1.360 (1.000–1.851)	0.049	1.571 (0.910–2.712)	0.107	1.432 (0.859–2.386)	0.168	1.500 (0.832–2.705)	0.180
Endometriosis of pelvic peritoneum	134	1.109 (0.873–1.408)	0.397	1.204 (0.788–1.840)	0.392	1.105 (0.772–1.581)	0.587	1.092 (0.722–1.654)	0.676
Endometriosis of fallopian tube	134	0.767 (0.283–2.080)	0.602	2.697 (0.462–15.729)	0.272	0.675 (0.130–3.501)	0.640	0.983 (0.163–5.921)	0.985
Endometriosis of uterus	134	1.092 (0.855–1.396)	0.480	0.958 (0.620–1.479)	0.845	1.029 (0.709–1.492)	0.882	0.989 (0.643–1.521)	0.959
Unspecified/other endometriosis	134	1.181 (0.870–1.604)	0.286	1.078 (0.627–1.854)	0.787	1.403 (0.837–2.350)	0.199	1.475 (0.830–2.623)	0.188

MR, Mendelian Randomization; LTL, leukocyte telomere length, SNPs, single-nucleotide polymorphisms, OR, odds ratios; CI, confidence interval.

4. Discussion

Elucidating the pathogenesis of endometriosis continues to be a great obstacle. In the context of the MR framework, our study has demonstrated a remarkable contribution of LTL to the susceptibility to endometriosis, specifically endometriosis of the intestine, ovary, rectovaginal septum and vagina. With every 1-SD increase of LTL, the probability of developing endometriosis and these three subtypes were respectively increased by 26 %, 258 %, 31 %, and 36 %. An analysis of sensitivity has reaffirmed the validity of these

Table 3
Sensitivity analysis of endometriosis and its seven subtypes.

Endometriosis	Test of heterogeneity				Test of pleiotropy	
	MR Inverse-Variance Weighted (MR INW)		MR Egger regression (MR Egger)		MR Egger regression (MR Egger)	
	Cochrane Q	*P*	Cochrane Q	*P*	Egger intercept	*P*
Endometriosis	196.973	$3.26x10^{-4}$	196.340	$2.95x10^{-4}$	−0.003	0.514
Endometriosis of intestine	116.012	0.853	114.765	0.858	0.023	0.266
Endometriosis of ovary	184.305	0.002	183.388	0.002	−0.005	0.420
Endometriosis of rectovaginal septum and vagina	139.293	0.337	138.881	0.323	−0.005	0.533
Endometriosis of pelvic peritoneum	174.862	0.009	174.580	0.008	−0.003	0.645
Endometriosis of fallopian tube	118.142	0.818	115.271	0.850	−0.044	0.093
Endometriosis of uterus	148.497	0.170	147.917	0.163	0.005	0.473
Unspecified/other endometriosis	147.719	0.181	147.540	0.168	0.003	0.689

MR, Mendelian Randomization.

findings, indicating a causal connection between LTL and these three endometriosis subtypes that is independent of confounding factors. These results point to a significant causal link between LTL and these particular endometriosis subtypes.

As discussed in the introduction, prior investigations have indicated the connection between LTL and endometriosis, yielding inconsistent results [8,9,19]. These inconsistencies might arise from limitations in the number of samples and variations in the study groups' composition. In our research, we addressed these limitations by using MR to probe the causal association between LTL and the incidence of endometriosis. Our study suggests that LTL is a danger element for endometriosis, aligning with previous reports by Bai et al. [20]. However, our subtype analysis revealed that longer LTL specifically increases the risk for only three endometriosis subtypes. It is noteworthy that previous studies did not precisely categorize endometriosis subtypes, which may account for the incomplete or contradictory results reported.

Endometriosis, a frequent chronic disorder in women's reproductive health, has a pathogenesis that is still not entirely defined. Previous studies have shown an association between physical traits (including pigmentation traits and eye color) and the localization of endometriosis, suggesting a possible genetic predisposition for specific localizations of the disease [21,22]. Given that inflammation is a proposed mechanism for the disease's pathogenesis, it is plausible that genetically determined markers are significant in causing inflammation and contributing to the disease's development [7,23]. Wu et al. have highlighted the essential role of leukocytes in the inflammatory response by homing to damaged tissue and releasing inflammatory mediators to facilitate repair and combat irritants [24]. Several studies have established links between LTL and inflammation [25–27]. Longer LTL is associated with various inflammatory diseases, such as systemic lupus erythematosus [28]. Longer telomeres may enhance cellular replication and function, enabling leukocytes to participate more effectively in the inflammatory response [26]. In light of these findings, it is hypothesized that genetically determined longer LTL may contribute to exacerbated inflammation and heightened leukocyte replication in women with endometriosis localized to the intestine, ovary, rectovaginal septum, and vagina. This provides a biological basis for our findings.

However, our MR investigation didn't reveal any causal link between genetically determined LTL and four other subtypes of endometriosis, including endometriosis of the pelvic peritoneum, fallopian tube, uterus, and unspecified/other endometriosis. This suggests that the inflammatory process is not the primary factor contributing to these subtypes of endometriosis. Several studies have proposed the hypothesis that the regurgitation of endometrial tissue, cellular debris, and fluid with rich protein into the pelvic cavity via the fallopian tubes during menstrual cycles is the most plausible cause [29–31]. This process results in recurrent cycles of cellular proliferation, damage, and healing within lesions, encouraging the transformation of fibroblasts into myofibroblasts and the development of fibrosis. Additionally, micrometastasis of endometriosis to distant organs has been confirmed in a murine model [32]. Consequently, our findings align with the theory of degenerative endometrial tissue migration and reflux, affirming that the pathogenesis of these four subtypes of endometriosis may be attributed to the migration and reflux of endometrial tissue.

Our MR research first thoroughly looked into the causal link of LTL with endometriosis, encompassing a broad database and seven distinct typologies. To establish this causal relationship, we employed a combination of SNPs identified from two GWAS datasets and four different methods, including IVW, MR Egger, weighted median, and Weighted Mode. In our data analysis, we observed that the IVW model produced statistically significant findings in certain groups, including endometriosis of the intestine, ovary, rectovaginal septum and vagina, while the MR-Egger method did not. The primary explanation for this discrepancy lies in the known statistical limitations of the MR-Egger method, which includes factors such as reduced statistical power, susceptibility to outlier SNPs, higher standard deviation compared to other methods, and the potential presence of undetected pleiotropy [16,33].

There are several notable strengths in our research. Firstly, our MR investigation stands as the first extensive assessment of the causal connection between LTL and endometriosis, encompassing seven distinct subtypes. This comprehensive approach provides a compelling explanation for the longstanding debates surrounding the association between LTL and endometriosis. Secondly, based on our findings, LTL may have the potential to serve as a predictive factor for assessing the prevalence of endometriosis subtypes involving the intestine, ovary, rectovaginal septum and vagina. Moreover, considering the role of LTL in inflammation, our study offers a genetic rationale for the inflammatory hypothesis in the pathogenesis of endometriosis. Consequently, controlling and monitoring inflammation may be a preferred treatment strategy for these three subtypes of endometriosis.

However, our study does have certain limitations. First, it's worth noting that our study's participants were exclusively from the

European ancestry GWAS database. Consequently, further validation of these causal links in other demographic groups is necessary. Second, while our results suggest the presence of heterogeneity, it's important to mention that we did not identify any outliers in the data. This lingering heterogeneity could be attributed to several factors: 1) Nonlinear Relationships: The presence of outliers suggests the potential of nonlinear associations. Under such circumstances, even after outlier exclusion, variations in effect sizes or directions may persist, leading to heterogeneity in the results.2) Insufficient Sample Size: In scenarios with limited sample sizes, the elimination of outliers might not completely resolve heterogeneity due to inadequate statistical power.3) Measurement Error: Outliers might be caused by measurement errors, which could also affect other variables. Even after outlier removal, errors in the measurement of other variables might still cause heterogeneity in the findings. 4) Multiple Pathogenic Mechanisms: Outliers could represent different pathogenic mechanisms. The removal of certain outliers doesn't preclude the existence of others, which might reflect separate biological mechanisms, thereby adding to the heterogeneity in the results [18]. Furthermore, as genetics is just one factor in the complex mosaic of endometriosis, which also includes hormonal, environmental, and immune influences. In the future, if more detailed GWAS data is available, we can conduct stratified analysis based on the various confounding factors mentioned above to obtain more accurate results.

5. Conclusions

The findings from our two-sample MR study offer genetic support for the hypothesis that longer LTL causally contributes to the development of endometriosis, specifically involving the intestine, ovary, rectovaginal septum and vagina. This suggests that LTL may be a potential marker for predicting the incidence of these three subtypes of endometriosis. This causal relationship is likely mediated by increased inflammation, resulting from enhanced leukocyte replication associated with longer LTL, thus providing a genetic basis for the theory of inflammation in the development of endometriosis. Nevertheless, no genetically determined causal relationship was found between LTL and the other four endometriosis subtypes (pelvic peritoneum, fallopian tube, uterus, and unspecified/other endometriosis), suggesting that the primary pathogenic basis for these subtypes may be related to the theory of degenerative endometrial tissue migration and reflux. Although the results are promising, it's premature to consider LTL as a clinical tool without further studies confirming its practical utility. Prospective studies will be essential in the future to confirm the causality and practical utility.

Data availability statement

The exposure datasets are accessible in the MR-base repository [https://gwas.mrcieu.ac.uk/datasets/ieu-b-4879/]. The outcome datasets were listed in Table 1. Further inquiries can be obtained by contacting the corresponding authors.

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CRediT authorship contribution statement

Ying Wang: Writing – review & editing, Writing – original draft, Funding acquisition. **Fenyong Sun:** Writing – original draft, Investigation. **Chaoyan Yue:** Writing – review & editing, Software, Formal analysis, Data curation, Conceptualization. **Qiuhong Man:** Writing – review & editing, Validation, Resources.

Declaration of competing interest

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

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