

ORIGINAL RESEARCH

Genetically predicted cycling-related behaviors and erectile dysfunction: a two-sample Mendelian randomization study

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Abstract

Background: Observational studies have reported inconsistent associations between cycling and erectile dysfunction (ED). **Methods:** Genome-wide association study (GWAS) summary data for cycling-related exposures were obtained from the Integrative Epidemiology Unit (IEU) OpenGWAS database, specifically for bicycle commuting to work and cycling excluding work. GWAS summary data for ED were obtained from the European Bioinformatics Institute (EBI) database. Independent single-nucleotide polymorphisms (SNPs) associated with cycling-related exposures were selected as instrumental variables. The inverse-variance weighted method was used as the primary Mendelian randomization (MR) analysis, whereas MR-Egger, weighted median, weighted mode, and simple mode methods were used as complementary analyses. Heterogeneity, horizontal pleiotropy, outliers, and the robustness of the findings were assessed using Cochran's Q test, MR-Egger intercept test, MR-PRESSO (Mendelian Randomization Pleiotropy RESidual Sum and Outlier), and leave-one-out analysis, respectively. **Results:** For bicycle commuting to work, 30 SNPs were included as instrumental variables. The primary MR analysis showed no statistically significant evidence of a causal association between bicycle commuting to work and ED risk (odds ratio (OR) = 0.216, 95% confidence interval (CI): 0.034–1.389, $p = 0.107$). For cycling excluding work, 28 SNPs were included, and no statistically significant causal association with ED risk was observed (OR = 0.127, 95% CI: 0.012–1.385, $p = 0.090$). Sensitivity analyses indicated no substantial heterogeneity or directional horizontal pleiotropy, and leave-one-out analysis did not identify any single SNP that materially influenced the estimates. **Conclusions:** This two-sample MR study found no statistically significant evidence of a causal association between genetically predicted cycling-related behaviors and ED risk. However, given the wide confidence intervals, limited statistical power, potential sample overlap, and use of a relaxed SNP-selection threshold, these findings should be interpreted cautiously and warrant further validation.

Keywords

Erectile dysfunction; Male sexual dysfunction; Bicycle riding; Aerobic exercise; Mendelian randomization

1. Introduction

Erectile dysfunction (ED) is a common form of male sexual dysfunction [1]. ED is defined as the persistent inability to achieve or maintain a penile erection sufficient for satisfactory sexual intercourse, with symptoms persisting for more than 3 months. ED is an important global men's health problem [2–4]. According to Argiolas *et al.* [2], the prevalence of ED is increasing worldwide, and psychosocial stressors may further contribute to its burden. Earlier projections estimated that ED would affect nearly 322 million men by 2025 [1, 5]. Therefore, identifying modifiable risk factors for ED is important for developing appropriate prevention and management strategies.

Cycling is a common form of aerobic exercise. Although prolonged cycling can improve cardiopulmonary fitness and reduce all-cause mortality, it may also cause cycling-related injuries and have adverse health effects. In recent years, increasing attention has been directed to the potential effects of cycling on male sexual function [6, 7]. Previous studies have suggested that cycling may adversely affect erectile function through persistent compression of the perineum by the bicycle saddle, which can cause penile numbness and potentially impair neural function. Compression-related reductions in local blood flow may further contribute to penile pain and numbness [8, 9]. In contrast, a large cross-sectional study stratified cyclists by training duration and intensity and reported that

high-intensity cycling was not associated with worse erectile function and may be associated with better sexual function [10]. Another systematic review of physical-activity interventions suggested that aerobic exercise may improve erectile function [11]. However, other studies have reported no association between cycling and ED risk [12, 13]. Overall, the existing evidence remains inconclusive, partly because of the low certainty of evidence and substantial heterogeneity across studies. In addition, previous studies exploring the association between cycling and ED have predominantly used observational designs, especially cross-sectional studies, which are vulnerable to residual confounding, selection bias, and reverse causation. Therefore, the causal relationship between cycling and ED risk remains uncertain.

Mendelian randomization (MR) is an analytical approach for investigating potential causal relationships between an exposure and an outcome using genome-wide association study (GWAS) data, with genetic variants such as single-nucleotide polymorphisms (SNPs) serving as instrumental variables (IVs). Because alleles are randomly allocated at conception and generally precede outcome onset, MR can theoretically reduce bias from reverse causation and certain confounding factors when the instrumental-variable assumptions are satisfied [14]. In this study, two-sample MR was used to investigate the potential causal association between genetically predicted cycling-related behaviors and ED risk.

2. Materials and methods

2.1 Data sources for the exposures and outcome

Data for the cycling-related exposures were obtained from the IEU OpenGWAS database (<https://GWAS.mrcieu.ac.uk>). Both exposure datasets were derived from the UK Biobank (UKB) consortium. A total of 245,364 participants were included in the Medical Research Council (MRC)-IEU dataset, including 19,179 bicycle-commuting cases and 226,185 controls. The Neale Lab dataset included 335,650 participants, including 23,918 cases of cycling (excluding work) and 311,732 controls. GWAS summary data for ED were obtained from the EBI database, which included 223,805 participants, including 6175 ED cases and 217,630 controls. ED was defined using International Classification of Diseases, 10th Revision codes

N48.4 and F52.2, a history of ED-related medical intervention (oral medication or surgery), or self-reported ED. Because the exposure GWAS datasets were derived from UK Biobank-related resources and the ED GWAS dataset may also have included UK Biobank participants, potential sample overlap between the exposure and outcome datasets could not be completely excluded. Because only summary-level data were available, the extent of sample overlap could not be accurately quantified. Details of the datasets are provided in Table 1.

2.2 Selection of genetic instrumental variables

To conduct a valid MR analysis, the SNPs selected as instrumental variables (IVs) must satisfy the following three core assumptions [15, 16]: (a) the relevance assumption, requiring the selected genetic variants to be associated with the exposure; (b) the independence assumption, requiring genetic variants to be independent of exposure–outcome confounders; and (c) the exclusion-restriction assumption, requiring genetic variants to affect the outcome only through the exposure and not through alternative pathways (Fig. 1). The GWAS datasets used in this MR study were previously published, and informed consent was obtained from participants in the original studies; therefore, no additional ethical approval was required.

To address the relevance assumption while retaining a sufficient number of instruments for analysis, SNPs associated with cycling-related exposures were selected using a relaxed significance threshold of $p < 5 \times 10^{-6}$. The conventional genome-wide significance threshold of $p < 5 \times 10^{-8}$ was not used as the primary threshold because only a limited number of SNPs were available for the cycling-related phenotypes under this stricter criterion, which would have reduced the feasibility and statistical power of the MR analyses and sensitivity analyses. To avoid the potential influence of linkage disequilibrium, linkage disequilibrium clumping was performed at $r^2 < 0.001$ within a 10,000-kb window to ensure the independence of the selected SNPs. During data harmonization, palindromic SNPs with intermediate allele frequencies were excluded to avoid ambiguity in allele alignment. To evaluate potential weak-instrument bias, the strength of each instrumental variable was assessed using the F -statistic, calculated as follows: $F = \text{beta}^2/\text{SE}^2$ (beta is the SNP-exposure effect estimate; SE is the standard error) [17]. SNPs with an F -statistic greater than 10 were considered sufficiently strong instruments and were

TABLE 1. GWAS datasets used for the two-sample Mendelian randomization analysis.

	GWAS ID	Phenotype	Number of cases	Number of controls	Number of SNPs	Population
Exposure	UKB-b-15787	Transport type for commuting to workplace: Cycle	19,179	226,185	9,851,867	European
	UKB-a-481	Types of transport used (excluding work): Cycle	23,918	311,732	10,894,596	European
Outcome	EBI-a-GCST006956	Erectile dysfunction	6175	217,630	9,310,196	European

GWAS, Genome-wide association study; SNPs, single-nucleotide polymorphisms; UKB, UK Biobank; EBI, European Bioinformatics Institute.

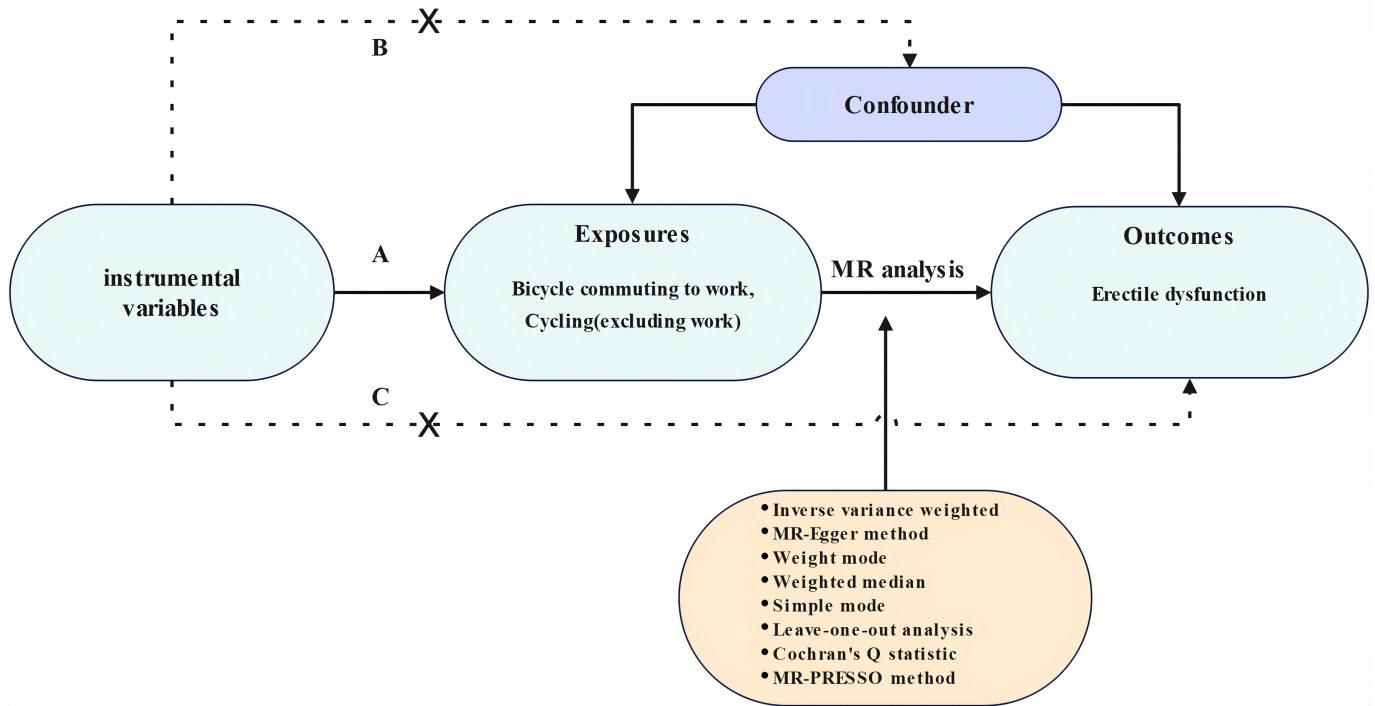


FIGURE 1. Flowchart of the two-sample Mendelian randomization study. MR, Mendelian randomization; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier.

included in the subsequent MR analyses. In addition, the MR-Egger intercept test was used to assess directional horizontal pleiotropy at the overall analysis level.

2.3 MR analysis

The inverse-variance weighted (IVW) method, MR-Egger, weighted median, simple mode, and weighted mode methods were used to evaluate the causal effects of cycling-related exposures on ED. The IVW method was used as the primary MR analysis. This method assumes that all included genetic variants are valid instrumental variables and estimates the causal effect by combining SNP-specific Wald ratio estimates using inverse-variance weighting [18]. MR-Egger, weighted median, simple mode, and weighted mode were used as complementary methods to assess the robustness of the results under different assumptions regarding instrument validity and horizontal pleiotropy [18–20]. Concordance in the direction and magnitude of association across these methods was considered supportive of greater robustness of the causal inference [19].

To assess robustness and potential violations of the core MR assumptions, multiple sensitivity analyses were performed, including heterogeneity tests, horizontal pleiotropy tests, MR-PRESSO, and leave-one-out analysis. Heterogeneity was assessed using Cochran's Q test. A *p*-value greater than 0.05 indicated no statistically significant evidence of heterogeneity among the SNPs. MR-PRESSO was used to assess global horizontal pleiotropy and identify potential outlier SNPs. If outliers were detected, and the MR analysis was repeated after their exclusion, and the original and outlier-corrected estimates were compared. The MR-Egger intercept test was used to assess directional horizontal pleiotropy. A statistically

significant MR-Egger intercept was interpreted as evidence of directional horizontal pleiotropy [18]. Leave-one-out analysis was performed to evaluate whether the MR estimates were driven by any single SNP.

2.4 Statistical analysis

Statistical analyses were performed using the TwoSampleMR package (version 0.5.11) and the MR-PRESSO package (version 1.0) in R (version 4.3.3). Causal estimates were expressed as odds ratios (ORs). The statistical significance level was $\alpha = 0.05$ unless otherwise specified.

Statistical power was evaluated using mRnd, a web-based tool for power calculations in Mendelian randomization studies, available at <https://shiny.cnsgenomics.com/mRnd/>. For the power calculations, the proportion of variance in the exposure explained by the genetic instruments was estimated using the effect allele frequency and SNP-exposure association estimates. The variance explained by each SNP was calculated using the following formula: $R^2 = 2 \times \text{EAF} \times (1 - \text{EAF}) \times \beta^2$.

Here, EAF denotes the effect allele frequency, and β denotes the SNP-exposure association estimate. The total R^2 for each cycling-related exposure was obtained by summing the R^2 values across all included SNPs. Statistical power was then evaluated in mRnd using the total R^2 , the outcome sample size, the proportion of cases in the outcome GWAS, a type I error rate of 0.05, and a range of clinically meaningful odds ratios. In the ED GWAS dataset, the proportion of cases was calculated as 6175/223,805.

3. Results

3.1 Causal effect of bicycle commuting to work on ED risk

Based on the instrumental-variable selection criteria, 36 SNPs associated with bicycle commuting to work were initially identified. After excluding six palindromic SNPs with effect allele frequencies between 0.3 and 0.7 (rs10124019, rs112074443, rs115433139, rs1423824, rs191997416, and rs9939394), 30 SNPs remained for the MR analysis (**Supplementary Table 1**). The selected SNPs all had F values ≥ 10 , suggesting adequate instrument strength according to the conventional threshold. The IVW analysis showed that no statistically significant evidence of an association between genetically predicted bicycle commuting to work and ED risk (OR = 0.216, 95% confidence interval (CI): 0.034–1.389, $p = 0.107$) (Table 2 and Fig. 2A). The complementary MR methods, including MR-Egger, weighted median, simple mode, and weighted mode, yielded generally consistent results, with no statistically significant causal association observed (Table 2 and Fig. 2B). Sensitivity analyses showed no significant heterogeneity based on Cochran's Q test, no evidence of directional horizontal pleiotropy based on the MR-Egger intercept, and no significant outlier SNPs based on MR-PRESSO. Leave-one-out analysis did not identify any single SNP that materially influenced the estimate (Table 3 and Fig. 2C).

3.2 Causal effect of cycling excluding work on ED risk

A total of 35 SNPs associated with cycling excluding work were initially identified. After excluding seven palindromic SNPs (rs10066711, rs12054984, rs13099750, rs1638525, rs367042, rs61874825, and rs7915066), 28 SNPs remained for the MR analysis. The IVW analysis showed no statistically significant evidence of an association between genetically predicted cycling excluding work and ED risk (OR = 0.127, 95% CI: 0.012–1.385, $p = 0.090$) (Table 2; **Supplementary Table 2**; Fig. 3A,B). Cochran's Q test indicated no significant heterogeneity among the included SNPs. MR-PRESSO detected no significant outlier SNPs, and the MR-Egger intercept test showed no evidence of directional horizontal

pleiotropy. Leave-one-out analysis suggested that the MR estimate was not driven by any single SNP (Table 3 and Fig. 3C).

4. Discussion

Using publicly available GWAS data from large study populations, this study applied two-sample MR to investigate the potential causal association between genetically predicted cycling-related behaviors and ED risk. The analyses found no statistically significant evidence supporting a causal association between genetically predicted cycling-related behaviors and ED risk.

Epidemiological studies indicate that ED is common in men and becomes more prevalent with age. ED can substantially impair quality of life and psychological well-being and is an important men's health concern [21]. Multiple studies suggest that physical activity can improve penile vascular endothelial function and promote nitric oxide (NO) production, thereby potentially reducing the risk of ED [11, 22–25]. Cycling is widely used for transportation, sport, and recreation. However, although the cardiovascular benefits of aerobic exercise may support erectile function in some populations, the extent to which these benefits are offset by cycling-related perineal compression and trauma remains unclear. A recent systematic review reported that prolonged or high-intensity cycling may be associated with genital numbness and an increased risk of ED, with saddle design, riding posture, and cycling intensity potentially affecting perineal pressure. However, the evidence was mainly derived from observational studies, highlighting the need for robust causal evidence [26].

Previous studies have produced conflicting findings regarding whether cycling protects against or contributes to ED. For example, Sanford *et al.* [27] reported that repeated perineal loading and vibration during cycling may contribute to microtrauma and potentially increase the risk of pudendal neuropathy. A forward riding position can increase pressure beneath the pubic arch and compress the pudendal nerve as it passes through the pudendal or Alcock canal [28]. Moreover, bicycle-saddle pressure can temporarily reduce penile blood

TABLE 2. Mendelian randomization estimates for cycling-related exposures and erectile dysfunction.

Exposure	Outcome	MR method	SNPs	beta	SE	OR	95% CI	p-Value
Bicycle commuting to work	ED	MR-Egger	30	−7.342	3.895	0.001	0.000–1.339	0.070
		Weighted median	30	−0.829	1.308	0.436	0.034–5.662	0.526
		IVW	30	−1.533	0.950	0.216	0.034–1.389	0.107
		Simple mode	30	−0.119	2.607	0.888	0.005–146.924	0.964
		Weighted mode	30	−0.295	2.540	0.745	0.005–108.223	0.908
Cycling (excluding work)	ED	MR-Egger	28	−4.671	3.896	0.009	0.000–19.375	0.241
		Weighted median	28	−1.410	1.701	0.244	0.009–6.844	0.407
		IVW	28	−2.063	1.219	0.127	0.012–1.385	0.090
		Simple mode	28	−2.198	3.307	0.111	0.000–72.474	0.512
		Weighted mode	28	−1.579	3.283	0.206	0.000–128.423	0.634

IVW, inverse-variance weighted; ED, erectile dysfunction; SNPs, single-nucleotide polymorphisms; SE, standard error; OR, odds ratio; CI, confidence interval; MR, Mendelian randomization.

TABLE 3. Sensitivity analyses for cycling-related exposures and erectile dysfunction.

Exposure	Outcome	Pleiotropy		Heterogeneity				Global test by MR-PRESSO	
		Horizontal pleiotropy (Egger intercept)	Horizontal pleiotropy (<i>p</i> -value)	MR-Egger	Inverse-variance weighted		Residual Sum of Squares observed	<i>p</i> -value	
				Heterogeneity (Q)	Heterogeneity (<i>p</i> -value)	Heterogeneity (Q)	Heterogeneity (<i>p</i> -value)		
Bicycle commuting to work	ED	0.027	0.135	18.734	0.906	21.099	0.856	26.877	0.903
Cycling (excluding work)	ED	0.011	0.487	22.174	0.679	22.671	0.703	35.167	0.525

ED, erectile dysfunction; MR, Mendelian randomization; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier.

flow and oxygenation. With prolonged exposure, repeated neurovascular compression may contribute to erectile symptoms [29]. However, the mechanisms linking perineal compression, altered blood flow, and penile numbness to persistent ED remain incompletely understood. Huang *et al.* [30] proposed that repeated cycling-related perineal compression may contribute to endothelial injury and arterial insufficiency, potentially leading to chronic hypoxemia and local tissue fibrosis. However, the pressure and exposure duration required to cause clinically meaningful vascular or neurogenic injury remain uncertain [30]. In contrast, a large multinational study reported no adverse association between recreational or high-intensity cycling and erectile function and suggested that some cycling patterns may be associated with better sexual function [10]. Marceau's study similarly showed that moderate-intensity cyclists had lower rates of ED than non-cyclists [31]. In Taylor's study of 688 male cyclists, increased cycling time was not significantly associated with ED after adjustment for age, hypertension, diabetes, and other ED risk factors [13]. Similarly, Molina *et al.* [32] reported no association between cycling and ED in a study of 58 men. However, inconsistencies among observational studies may partly reflect self-reported exposure assessment, exposure misclassification, heterogeneous cycling patterns, and residual confounding. A meta-analysis by Gan *et al.* [12] found no significant overall difference in ED prevalence between cyclists and non-cyclists (OR = 0.99, 95% CI: 0.87–1.14). However, subgroup analyses based on age, hypertension, diabetes, and other factors suggested that ED risk may vary among different cyclist subgroups; saddle type and contact-area characteristics may also influence the association.

However, previous studies investigating the association between bicycling and ED were predominantly observational, limiting the ability to exclude residual confounding, selection bias, and reverse causation. Accordingly, we used a two-sample MR approach to investigate the potential causal asso-

ciation between cycling-related exposures and ED. Five MR methods were applied to estimate the effects of cycling-related exposures on ED. Unlike some previous observational studies, the present MR analysis found no statistically significant evidence supporting a causal association between genetically predicted cycling-related exposures and ED risk. The MR-Egger intercept test showed no evidence of directional horizontal pleiotropy, and the other sensitivity analyses did not identify substantial heterogeneity, influential single variants, or MR-PRESSO outliers. Thus, some associations reported in observational studies may partly reflect residual confounding or other sources of bias, including differences in age, smoking, hypertension, diabetes, and other lifestyle or clinical factors.

Nevertheless, several limitations should be acknowledged. First, both the exposure and outcome GWAS datasets predominantly comprised individuals of European ancestry. Therefore, the generalizability of our findings to other populations may be limited. Differences in allele frequencies, linkage disequilibrium structures, lifestyle patterns, and gene–environment interactions across ancestries may contribute to heterogeneous causal estimates. Future studies using multi-ancestry GWAS datasets are needed to assess the generalizability of these findings.

Second, because only a limited number of SNPs were available for cycling-related phenotypes under the conventional genome-wide significance threshold of $p < 5 \times 10^{-8}$, a relaxed significance threshold of $p < 5 \times 10^{-6}$ was used to select instrumental variables. Although instrument strength was evaluated using *F*-statistics to reduce concern about weak-instrument bias, the selected variants did not reach the conventional genome-wide significance threshold. Therefore, the possibility of weak-instrument bias cannot be fully excluded.

Third, the present study may have had limited statistical power. The genetic instruments explained a very small proportion of the variance in cycling-related exposures. The total R^2 values were 0.0002178415 for bicycle commuting to work

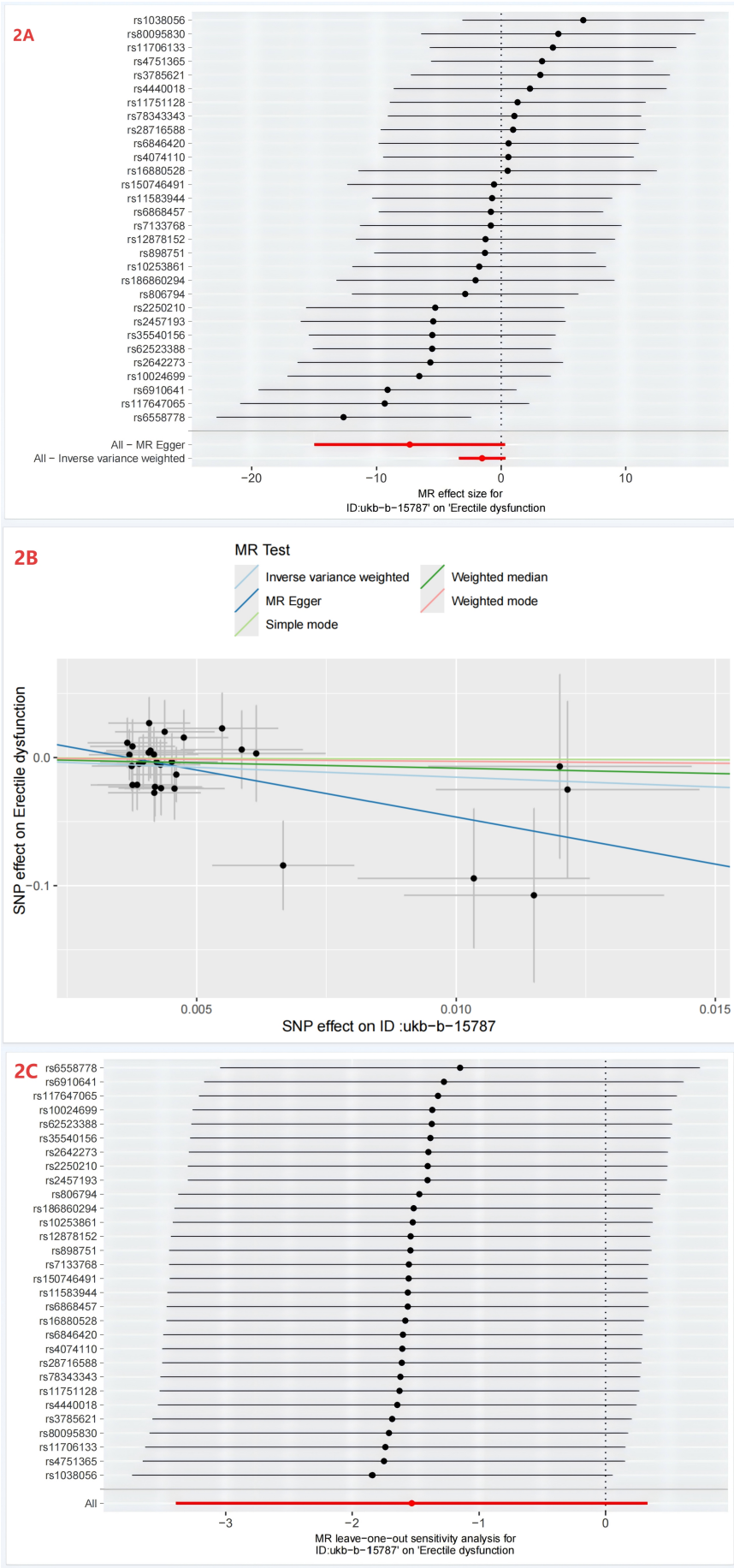


FIGURE 2. Causal estimates for genetically predicted bicycle commuting to work and erectile dysfunction. (A) Forest plot. (B) Scatter plot. (C) Leave-one-out plot. MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms.

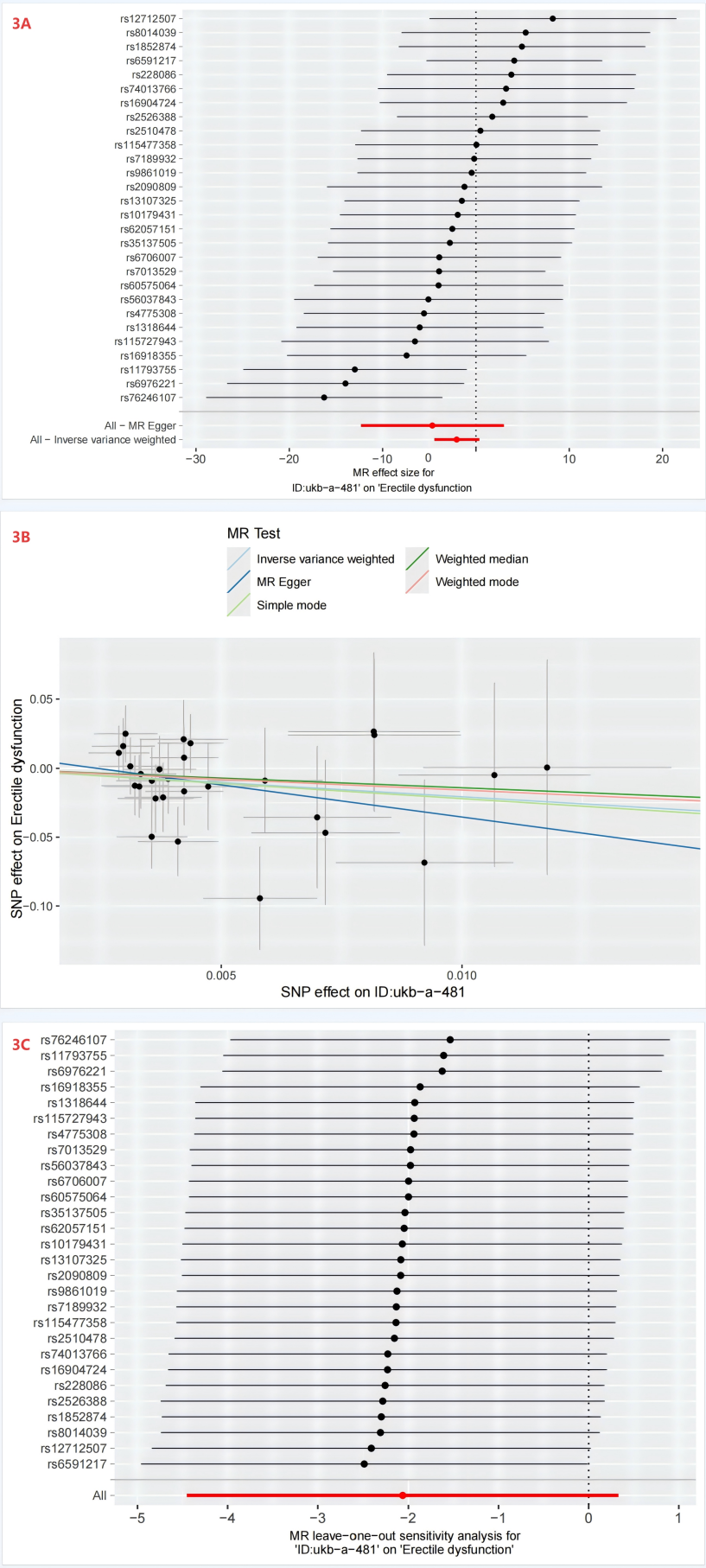


FIGURE 3. Causal estimates for genetically predicted cycling (excluding work) and erectile dysfunction. (A) The forest plot. (B) The scatter plot. (C) Leave-one-out plot. MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms.

and 0.0001323246 for cycling excluding work. These low values indicate limited power to detect small or modest causal effects. Therefore, the non-significant MR findings should not be interpreted as definitive evidence of the absence of a causal association. Rather, no statistically significant association was detected with the available instruments and sample size. A small or modest causal effect cannot be completely excluded.

Fourth, Mendelian randomization estimates the effect of lifelong genetic liability to cycling-related behaviors rather than the effect of actual cycling behavior at specific ages or under specific training conditions. Therefore, the present non-significant findings should not be interpreted as definitive evidence that prolonged, intensive, or occupation-specific cycling cannot contribute to ED in certain clinical circumstances. Moreover, the genetic instruments used in this study may not adequately capture clinically relevant dimensions of cycling exposure, including cycling intensity, duration, bicycle fit, saddle characteristics, or cumulative perineal mechanical trauma, which may be more directly related to ED risk. Future studies using larger GWAS datasets, stronger instrumental variables, and more precisely defined cycling-related phenotypes are needed to clarify these findings.

5. Conclusions

In conclusion, this two-sample Mendelian randomization study found no statistically significant evidence supporting a causal association between genetically predicted cycling-related behaviors and the risk of erectile dysfunction. However, the findings should be interpreted cautiously because of the wide confidence intervals, limited statistical power, potential sample overlap, the use of a relaxed SNP-selection threshold, and the inability of the genetic instruments to capture specific cycling characteristics such as intensity, duration, saddle-related factors, and cumulative perineal mechanical trauma. Further studies using larger, multi-ancestry GWAS datasets and more detailed cycling-related phenotypes are warranted.

AVAILABILITY OF DATA AND MATERIALS

The GWAS summary statistics analyzed in this study are publicly available from the IEU Open GWAS database (<https://gwas.mrcieu.ac.uk/>).

AUTHOR CONTRIBUTIONS

FL—designed the experiments and completed the initial draft of the manuscript. SLG and JHW—performed the experiments and gave critical feedback during the study and during the submission of the manuscript. All authors made a significant contribution to the work reported and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical review and approval were not required for this study in human subjects in accordance with the local laws and institutional requirements.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at <https://oss.jomh.org/files/article/2105171139741270016/attachment/Supplementary%20material.docx>.

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