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Insights into Pathophysiological Pathways in ME/CFS Through Genetic Correlation and Mendelian Randomization

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Short Report

Keywords: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), genetic correlation, pleiotropy, Mendelian randomization, post-acute infection syndromes

Posted Date: April 21st, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9363637/v2

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Additional Declarations: The authors declare no competing interests.

Insights into Pathophysiological Pathways in ME/CFS Through Genetic Correlation and Mendelian Randomization

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Abstract

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and post-acute infection syndromes (PAIS) are multisystem disorders involving immune, vascular, neuroinflammatory, and metabolic abnormalities, yet the causal relevance of these processes remains unclear. Using genome-wide summary statistics from DecodeME (15,579 cases), we performed genetic correlation, pleiotropic heritability, and Mendelian randomization analyses.
Across 22 auxiliary traits spanning five mechanistic domains, cellular energetics, neurovascular regulation, and barrier–microbiome function showed the strongest genetic overlap with ME/CFS, with migraine and irritable bowel syndrome contributing most to shared pleiotropy. Immunothrombotic related and inflammatory traits showed smaller but measurable genetic correlations. Energetics-related traits, including type 2 diabetes and blood lactate, displayed consistent genetic correlation but relatively low shared pleiotropy, suggesting that metabolic dysfunction may act through broader physiological networks.
Mendelian randomization identified three biomarkers with evidence for causal effects on ME/CFS risk: higher mitochondrial DNA copy number was protective, whereas increased glycoprotein acetyls and mean platelet volume increased risk. Together, these findings indicate that ME/CFS susceptibility reflects interacting pathways involving barrier–microbiome dysfunction, neurovascular instability, inflammation, platelet activation, and impaired cellular energetics

Main Text

Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and post-acute infection syndromes (PAIS) represent heterogeneous, chronic, and debilitating conditions, with over 60% of long COVID patients meeting diagnostic criteria for ME/CFS(1), indicative of overlapping pathology. Multiple biological domains including immune dysregulation, neuroinflammation, vascular dysfunction, and impaired cellular energetics interact in complex ways, obscuring causal relationships(2). Identifying genetic contributors is therefore critical for establishing mechanistic clarity, informing biomarker development, and guiding therapeutic discovery(3, 4). Large-scale genome-wide summary statistics from DecodeME enable dissection of the genetic architecture of ME/CFS and PAIS (5). Here, we use genetic correlation and causal inference approaches to test a set of mechanistic hypotheses previously supported by biological and clinical evidence linking these processes to ME/CFS and PAIS. The mechanistic domains considered included inflammation, neuroimmune regulation, barrier–microbiome function, vascular regulation, cellular energetics, and platelet-mediated immunothrombosis (6-10). This approach enables a first robust genetic evaluation of candidate biological mechanisms underlying ME/CFS and PAIS, highlighting causal pathways that may inform biomarker discovery and therapeutic targeting.

Materials and Methods

We analyzed genome-wide association study (GWAS) summary statistics from DecodeME together with publicly available GWAS of auxiliary traits (Online Methods). Analyses were restricted to European-ancestry HapMap3 variants using standard LDSC preprocessing. We selected auxiliary traits to represent mechanistic domains repeatedly implicated in ME/CFS, including inflammation, neuroinflammation and immune dysregulation, barrier–microbiome function, vascular/perfusion control, platelet-mediated immunothrombosis, and cellular energetics. Detailed methods and full results are provided in the Online Methods and via a publicly available repository (14).

Results & Discussion

Inflammation. Focusing on innate immune activity, we used blood monocyte count and Glycoprotein acetyls (GlycA) as broad, well-powered proxies of low-grade systemic inflammation. Both traits showed significant positive genetic correlation with ME/CFS, supporting the involvement of chronic inflammatory processes.

Neuroinflammation and immune dysregulation/autoimmunity. To capture sleep–autonomic and neuroimmune regulation, we included insomnia and morning cortisol as proxies of HPA-axis involvement. Both traits showed positive genetic correlation with ME/CFS, with insomnia reaching strong significance ($r_g = 0.243$, $p = 8.4\times10^{-13}$, Figure 1A). Their PHBC patterns were similar: each showed measurable single-trait pleiotropy with ME/CFS, yet removing either trait from the multi-trait model produced only a modest reduction in shared pleiotropic heritability, as PHBC estimates the proportion of heritability shared across traits(11). This indicates that the neuroimmune and autonomic processes indexed by these proxies are largely captured through covariance with other auxiliary traits rather than representing pleiotropic pathways uniquely tied to insomnia or cortisol (Figure 1B). Across adaptive and autoimmune traits, systemic lupus erythematosus (SLE) demonstrated the strongest association with ME/CFS ($r_g = 0.200$, $p = 1.15\times10^{-10}$), with multiple sclerosis (MS) showing a smaller but consistent pattern. For both traits, the leave-one-out results indicated that the shared genetic architecture is broadly distributed across related immune traits rather than being isolated to any single autoimmune pathway. As a control for general neurodegeneration, Alzheimer's disease showed no genetic correlation with ME/CFS and minimal single-trait pleiotropy. However, removing it from the full PHBC model reduced the overall estimate of shared pleiotropy, suggesting that Alzheimer's contributes indirectly through its covariance with other auxiliary traits, rather than reflecting mechanisms specific to ME/CFS.

Barrier–microbiome. Given well-established links between epithelial stress, microbial translocation, and gut–brain signaling (5), we used IBS as a clinical proxy for barrier and

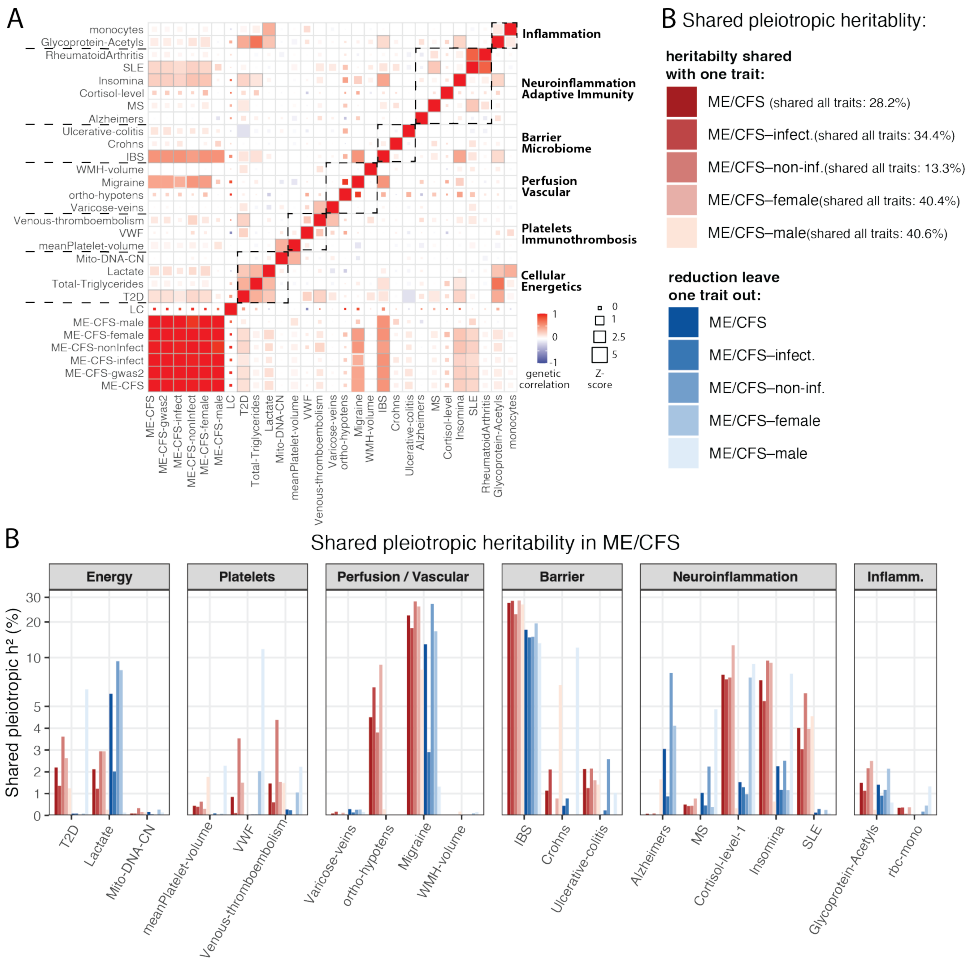


Figure 1. Genetic correlation and shared pleiotropic heritability of ME/CFS, long COVID (LC), and related traits. (A) Matrix of LDSC genetic correlations (rg) estimated from European-ancestry GWAS summary statistics; Traits span inflammatory, immune/neuroinflammatory, barrier–microbiome, vascular/perfusion, platelet, and energetic domains. (B) Shared pleiotropic heritability between ME/CFS and each auxiliary trait estimated using the PHBC framework. Red bars indicate pairwise shared heritability from single-trait models; blue bars show the reduction in shared heritropy in leave-one-out analyses of the multi-trait model. Complete results, data sources, and analysis outputs are available in a publicly available repository (14).

microbiome dysfunction. IBS showed the strongest evidence for shared genetic architecture with ME/CFS, consistent across both LDSC (rg = 0.527, p = 2.23×10^{-27}) and PHB-C analyses. The drop in shared pleiotropy when IBS was removed indicates that barrier–microbiome processes form a distinct pleiotropic axis not captured by autoimmune or vascular traits (Figure 1B). Ulcerative colitis showed a weaker but coherent signal, whereas Crohn's disease displayed a weaker, non-significant overlap.

Perfusion & vascular regulation. To evaluate vascular contributions relevant to postural orthostatic tachycardia syndrome (POTS)-like physiology, we examined proxies of cerebral blood flow and systemic perfusion instability. Migraine, a common comorbidity of POTS reflecting impaired neurovascular reactivity (10), showed a clear positive genetic correlation with ME/CFS (rg=0.45, $p<10^{-6}$). PHBC analyses mirrored this result: migraine exhibited substantial single-trait

shared pleiotropy with ME/CFS, and its removal from the multi-trait model produced a marked reduction in shared pleiotropy, indicating that neurovascular dysregulation represents a key pleiotropic axis underlying ME/CFS risk. White matter hyperintensity (WMH) volume was uncorrelated, suggesting structural damage is likely secondary rather than causal. Orthostatic hypotension, capturing systemic hemodynamic control relevant to POTS, showed a similar but non-significant positive trend. Although orthostatic hypotension showed high single-trait pleiotropy, removing it did not reduce shared pleiotropy, indicating its signal is captured by traits such as migraine and metabolic proxies. Along with the null result for varicose veins, which represent the structural venous end of this physiology, these findings support a model in which impaired perfusion control stems primarily from functional rather than structural vascular mechanisms in ME/CFS.

Platelets and immunothrombosis. To explore the hypothesis that platelet hyperactivation contributes to endothelial activation and microvascular dysfunction, we used mean platelet volume (MPV) as a proxy for platelet reactivity. ME/CFS showed a small but significant positive genetic correlation with MPV, consistent with a prothrombotic or platelet-primed phenotype suggested for PAIS. As a proxy for downstream endothelial activation and immunothrombosis, venous thromboembolism (VTE) showed a higher and significant correlation with ME/CFS, whereas von Willebrand factor (vWF), despite its correlation with VTE, showed no direct genetic overlap. PHBC analyses showed low single-trait pleiotropy for VTE, MPV and vWF, with little reduction when either trait was removed.

Cellular energetics. To assess genetic contributions to impaired energy metabolism, we examined type 2 diabetes (T2D) and total triglycerides as proxies of systemic metabolic inflexibility. Both traits showed strong positive genetic correlation with ME/CFS (T2D rg=0.15, $p=3\times10^{-10}$), indicating a shared predisposition to reduced oxidative capacity. In line with this, blood lactate levels, a product of anaerobic glycolysis, also correlated positively (rg=0.15, $p=4.8\times10^{-4}$), reflecting a biochemical shift toward glycolytic energy production when oxidative metabolism is constrained. The PHBC results only partially mirrored these correlations. T2D and lactate each showed relatively low single-trait pleiotropy with ME/CFS, and removing T2D from the multi-trait model produced virtually no reduction in shared pleiotropy, suggesting that its genetic overlap with ME/CFS is largely captured by other traits in the analysis. In contrast, removing lactate notably reduced shared pleiotropy, consistent with a pleiotropic axis related to altered energy metabolism. Although mitochondrial DNA copy number (mtDNA-CN) showed no genome-wide correlation with ME/CFS, it represents a proxy for mitochondrial biogenesis and integrity and is a core determinant of cellular energy supply. The strong genetic correlations of energetics-related traits with ME/CFS suggest that energetic constraints represent a key pathophysiological feature shared across ME/CFS and PAIS, underscoring post-exertional symptom exacerbation (PEM) as the clinical hallmark of these disorders.

Long COVID. Overall, the Long COVID GWAS summary statistics (13) showed genetic correlations with the same direction and comparable magnitude as those observed for ME/CFS across most traits. In some domains, such as migraine, insomnia, and rheumatoid arthritis the correlation coefficients were even higher than for ME/CFS, yet none reached statistical significance, reflected by low z-scores and smaller squares in Figure 1. This lack of significance likely reflects increased variance due to smaller case numbers, phenotypic heterogeneity, or ancestry differences. Consequently, several traits showed reversed correlation directions, most plausibly reflecting dataset variance rather than biological divergence.

Mendelian randomization (MR). Whereas LDSC and PHB-C quantify shared genetic architecture, Mendelian randomization (MR) enables causal inference by using genetic variants as natural experiments. Conceptually, MR resembles a randomized controlled trial: individuals who carry genetic variants that increase an exposure (e.g., platelet activity or mitochondrial DNA copy number) are analogous to participants randomized to the “intervention” arm, whereas non-carriers act as the “control” group. Because genotypes are assigned at conception and not influenced by disease processes, MR can provide evidence for directional, potentially causal effects under appropriate assumptions (13). We restricted MR analyses to biomarker traits. Of the nine biomarkers tested, three showed evidence of a causal relationship with ME/CFS in the

primary inverse-variance weighted (IVW) analysis. Higher mitochondrial DNA copy number was associated with a lower risk of ME/CFS (OR ≈ 0.83 per SD increase), consistent across multiple sensitivity analyses (Figure 2). In contrast, higher glycoprotein acetyls, a marker of chronic inflammation, increased ME/CFS risk (OR ~ 1.12). Mean platelet volume also showed a positive causal effect (OR ≈ 1.09), supporting a role for platelet activation in ME/CFS pathophysiology. No significant causal effects were observed for lactate, triglycerides, vWF, or monocyte count. Full sensitivity analyses, heterogeneity estimates, and reverse-direction MR results are provided in a publicly available repository (14).

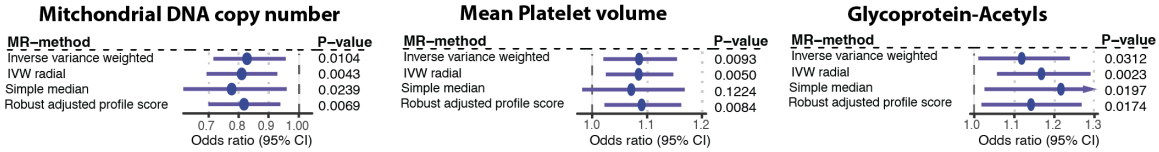


Figure 2. Mendelian randomization estimates for biomarker effects on ME/CFS risk. Points show IVW odds ratios (95% CI) for mitochondrial DNA copy number, mean platelet volume, and glycoprotein acetyls. Additional sensitivity analyses are shown for each exposure to assess robustness to pleiotropy and instrument validity. Complete MR results, instrument characteristics, and additional sensitivity analyses are available in a publicly available repository (14).

Limitations of study: Several limitations should be considered when interpreting these findings. First, although LDSC and PHBC provide robust estimates of genetic correlation and shared heritability, both methods rely on additive polygenicity and therefore cannot capture nonlinear or interactive biological processes that are likely relevant to ME/CFS pathophysiology. Second, many auxiliary traits represent imperfect biological proxies, for example, IBS for epithelial–microbiome dysfunction or migraine for impaired neurovascular reactivity, which constrains domain specificity. Third, the Long COVID summary statistics, while invaluable, are limited by smaller sample sizes and phenotypic heterogeneity, which may increase statistical variance and reduce power to detect significant genetic correlations. Fourth, Mendelian randomization analyses depend on strong instrument validity and are susceptible to horizontal pleiotropy, particularly for highly interconnected immune and metabolic biomarkers. Taken together, these limitations suggest that our results should be interpreted as identifying broad mechanistic domains rather than isolated causal pathways, providing a foundation for more targeted analyses as additional domain relevant GWAS become available

Acknowledgments

We thank the DecodeME research team, its participants and its funders for their contributions to generating and making available the DecodeME data. This work was supported by the Vienna Science and Technology Fund (WWTF) and the WE&ME Foundation through their joint ME/CFS Call 2024 (Grant agreement No. ME-CFS24-002).

Data Availability

All data used in this study are publicly available. Genome-wide association study summary statistics were obtained from published sources. All analysis outputs, and reproducible code are archived on Zenodo at https://doi.org/10.5281/zenodo.18198370 The analysis pipeline and source code are also available at https://github.com/Mwielscher/pleioh2g_MECFS

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Online methods:

Data

All genome-wide association study (GWAS) summary statistics, including download links, publication year, originating study, and number of participants, are listed in Table 1. All primary analyses were performed using the GRCh38 genome build. Summary statistics provided in GRCh37 were lifted over to GRCh38 using Picard tools. Data were harmonized using custom scripts and restricted to HapMap3 variants for LDSC, PHBC, and related analyses to ensure consistent linkage disequilibrium reference and robust heritability estimation.

trait	paper	year	Functional group	included in MR
T2D	PMID:30297969	2018	Energy / Cellular energetics	0
nmr-Total-Triglycerides	PMID:40436851	2025	Energy / Cellular energetics	1
nmr-Lactate	PMID:40436851	2025	Energy / Cellular energetics	1
Mito-DNA-CN	PMID:34859289	2022	Energy / Cellular energetics	1
rbc-meanPlatelet-volume	PMID:32888493	2020	Immunothrombosis / Platelets	1
VWF	PMID:37794186	2023	Immunothrombosis / Platelets	1
Venous-thromboembolism	PMID:36777996	2022	Immunothrombosis / Platelets	0
Varicose-veins	PMID:36653477	2023	Perfusion / Vascular	0
ortho-hypotens	PMID:30104761	2019	Perfusion / Vascular	1
Migrane	PMID:39024449	2024	Perfusion / Vascular	0
WMH-volume	PMID:33293549	2020	Perfusion / Vascular	0
IBS	PMID:34741163	2021	Barrier / Microbiome–epithelium	0
Crohns	PMID:37156999	2023	Barrier / Microbiome–epithelium	0
Ulcerative-colitis	PMID:37156999	2023	Barrier / Microbiome–epithelium	0
Alzheimers	PMID:34493870	2021	Neuroinflammation & Adaptive skew	0
MS	PMID:31604244	2019	Neuroinflammation & Adaptive skew	0
Cortisol-level-1	PMID:33469137	2021	Neuroinflammation & Adaptive skew	1
Insomina	PMID:30804565	2019	Neuroinflammation & Adaptive skew	0
SLE	PMID:36750564	2023	Neuroinflammation & Adaptive skew	0
RheumatoidArthritis	PMID: 36333501	2022	Neuroinflammation & Adaptive skew	0
nmr-Glycoprotein-Acetyls	PMID:40436851	2025	inflammatory	1
rbc-mono	PMID:32888493	2020	inflammatory	1

Online Methods Table 1. Overview of GWAS summary statistics included in the analyses. The source publication for each trait is identified by PubMed ID and publication year. Traits are

assigned to functional groups corresponding to the mechanistic domains shown in Figure 1 and referenced throughout the manuscript. The column Included in MR indicates whether a trait was analyzed using Mendelian randomization (1 = included, 0 = not included). Sample sizes and direct download links to all summary statistics are available at Zenodo: https://doi.org/10.5281/zenodo.18198370

Linkage Disequilibrium Score Regression (LDSC)

Linkage Disequilibrium Score Regression was performed as previously described to estimate SNP-based heritability and pairwise genetic correlations. Analyses were conducted using European-ancestry LD scores and standard preprocessing steps. A detailed description of the LDSC pipeline and parameter settings is provided in our prior work (https://doi.org/10.21203/rs.3.rs-7528705/v1).

Pleiotropic Heritability Block Correction (PHBC):

Shared pleiotropic heritability was estimated using the PHBC framework, based on the methodology and core code described in the pleioh2g preprint (https://doi.org/10.1101/2025.06.10.25329261) and repository (https://github.com/cran/pleioh2g). PHBC extends standard Linkage Disequilibrium Score Regression (LDSC) by decomposing trait heritability into components that are shared across traits versus trait-specific, thereby quantifying pleiotropic genetic contributions beyond pairwise genetic correlation. Liability-scale heritability estimates were computed for binary traits using established transformations incorporating sample and population prevalence; all prevalence assumptions and resulting estimates are provided via Zenodo (https://doi.org/10.5281/zenodo.18198370). To characterize the structure of pleiotropic overlap, PHBC analyses were conducted in three complementary configurations. First, single-trait PHBC models were used to estimate pairwise shared heritability between ME/CFS and each auxiliary trait individually. Second, a full multi-trait PHBC model including all auxiliary traits simultaneously was fitted to estimate the total proportion of ME/CFS heritability attributable to shared pleiotropy across domains. Third, leave-one-out models were constructed by excluding each auxiliary trait in turn from the multi-trait model; reductions in shared pleiotropic heritability relative to the full model were interpreted as evidence that the excluded trait captures a distinct pleiotropic component not explained by the remaining traits. These analyses form the basis of the barplot shown in Figure 1B.

Rather than using the original wrapper functions, we implemented a two-step pipeline that (i) computes cross-trait LDSC estimates with and without jackknifing and (ii) applies the PHBC model to partition shared pleiotropic heritability across multiple auxiliary traits. This implementation enables flexible execution in distributed computing environments and ensures reproducible software deployment via containerization. All scripts, a Docker container (https://hub.docker.com/r/mwielsch/pleioh2g), and the corresponding Dockerfile are provided in a GitHub repository (https://github.com/Mwielscher/pleioh2g_MECFS).

Mendelian Randomization (MR)

Mendelian randomization analyses were conducted to assess potential causal relationships between selected biomarker traits and ME/CFS using established two-sample MR frameworks. Genetic instruments were selected based on genome-wide significance and linkage disequilibrium pruning. Primary causal estimates were obtained using the inverse-variance weighted (IVW) method, with additional sensitivity analyses performed to assess robustness to horizontal pleiotropy and instrument heterogeneity. To account for multiple testing across nine biomarker exposures, a Bonferroni-corrected significance threshold of $p < 5.6 \times 10^{-3}$ was applied. Primary IVW results that did not meet this threshold were interpreted as suggestive evidence and evaluated in conjunction with consistency across sensitivity analyses. Full methodological details, including instrument selection and sensitivity analyses, are described in our prior work (https://doi.org/10.21203/rs.3.rs-7528705/v1) and accompanying code repository (https://github.com/Mwielscher/Shiftwork_PRS).

exposure	SNPs	In Analysis	F_mean	Steiger: causal direction	het_Q	het_Q_df	het_Q_pval
Cortisol-level-1	1	1	42.4	TRUE			
Mito-DNA-CN	84	84	85.5	TRUE	87.7	82	3.14E-01
Glycoprotein-Acetyls	82	80	110.9	TRUE	109.2	78	1.13E-02
Lactate	21	21	51.8	TRUE	23.8	19	2.03E-01
Total-Triglycerides	123	123	72.6	TRUE	186.0	121	1.35E-04
meanPlatelet-volume	608	608	93.5	TRUE	779.2	606	2.27E-06
monocytes	628	628	85.2	TRUE	844.3	626	1.14E-08
VWF	7	7	75.8	TRUE	4.8	5	4.46E-01

Online Methods Table 2. Mendelian randomization (MR) instrument characteristics and quality-control summary for biomarker exposures. Shown are the number of genome-wide significant SNP instruments retained for analysis, mean F-statistic of retained instruments, Steiger directionality test results, and Cochran's Q heterogeneity statistics. Full harmonisation/QC output—including SNP-level instrument lists, identified radial MR outliers, heterogeneity estimates after outlier exclusion, and the corresponding outlier-excluded sensitivity MR results—is available via Zenodo: https://doi.org/10.5281/zenodo.18198370