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ORIGINAL RESEARCH

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Causal associations between erectile dysfunction and high blood pressure, negative psychology: a Mendelian randomization study

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Abstract

Erectile dysfunction (ED) has been closely associated with both high blood pressure (HBP) and psychological traits, but the causal relationship between them remains unclear. Herein, we aimed to identify the causal risk factors for ED. We conducted univariable and multivariable Mendelian randomization (MR) analyses using genetic variants associated with metabolic syndrome and psychology traits at the genome-wide significance ($p < 5 \times 10^{-8}$) level obtained from corresponding genome-wide association studies. We used summary-level statistical data for ED from the European Bioinformatics Institute (EBI) database of complete Genome-Wide Association Studies (GWAS) summary data. We also conducted reverse causality and performed power calculations for MR. Our results showed that HBP was associated with increased odds of ED (odds ratio (OR) = 1.66 (95% confidence interval (CI), 1.13–2.45), a *p*-value for the inverse variance-weighted method (P_{IVW}) = 1.06×10^{-2}, Power = 100%), as were myocardial infarction (OR = 1.09 (95% CI, 1.02–1.17), $P_{IVW} = 1.18 \times 10^{-2}$, Power = 56%) and ischemic stroke (OR = 1.21 (95% CI, 1.02–1.43), $P_{IVW} = 2.87 \times 10^{-2}$, Power = 10%). In terms of psychological traits, irritable mood (OR = 1.86 (95% CI, 1.14–3.02), $P_{IVW} = 1.30 \times 10^{-2}$, Power = 96%) and neuroticism (OR = 1.36 (95% CI, 1.04–1.79), $P_{IVW} = 2.66 \times 10^{-2}$, Power = 80%) were associated with increased odds of ED. Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) showed no evidence of pleiotropic bias, and sensitivity analyses confirmed the robustness of our results. We have established a causal link between HBP and ED, and we have also found evidence suggesting a causal relationship between irritable mood and ED.

Keywords

Erectile dysfunction; High blood pressure; Negative psychology; Single-nucleotide polymorphisms; Mendelian randomization

1. Introduction

Erectile dysfunction (ED) refers to the inability to attain or maintain an erection sufficient for satisfactory sexual activity [1], ED (sexual dysfunction) affects approximately 8% to 22% of men worldwide, and its risk has been shown to increase significantly with age [2]. ED affects more than 50% of men over the age of 40, and more than 20% of men under the age of 40 [3]. However, less than 15% of these men seek a medical solution [4]. Erectile dysfunction (ED) is a multifactorial condition that involves both nonendocrine (neurogenic, vasculogenic, and iatrogenic) and endocrine pathways. It is dependent on a complex interaction of vascular and neural processes [5–10].

Middle-aged and older adults >40 years old with ED often suffer from metabolic syndrome [11], which is a collection of conditions (*i.e.*, high blood pressure (HBP), high blood sugar, excess body fat and abnormal cholesterol or triglyceride levels) that increase the risk of heart disease, stroke and diabetes. Studies have found that men with metabolic syndrome are at an increased risk of developing ED [12]. Although the precise mechanisms linking ED and metabolic syndrome are not yet fully understood, inflammation, oxidative stress and endothelial dysfunction have been proposed as key mediators. Notably, modifiable lifestyle factors such as poor dietary habits, sedentary lifestyles and smoking are recognized contributors to both conditions [13]. Type 2 diabetes mellitus, a well-established metabolic risk factor, has been found to be strongly associated with ED risk. In contrast, a Mendelian randomization (MR) study indicated that obesity and dyslipidemia were not significantly linked with ED [14]. Nonetheless, controversy remains regarding the true association between ED and blood pressure. Specifically, while Alberto *et al.* [15] reported that blood pressure control could improve erectile

function, Kratz *et al.* [16] found no significant effect of high systolic blood pressure (SBP) on ED. Thus, the causal relationship between blood pressure traits and ED remains controversial [17].

In contrast to older patients, younger patients under 40 years old are commonly diagnosed with psychogenic ED [18]. Psychogenic or adrenaline-mediated ED, is also known as non-organic ED is mediated by noradrenaline or sympathetic activation and is often associated with heightened anxiety related to the inability to achieve or maintain an erection before or during sexual activity [11]. In addition, stress, depression and anxiety are common psychological factors associated with psychogenic ED, which can result in dysfunctional beliefs about sexual function, negative thoughts and emotions, and discrimination based on age, gender and sexual orientation, *etc*. These psychological problems may often lead to reluctance to communicate and solve their underlying ED-related issues, ultimately exacerbating their conditions and leading to a vicious cycle of ED [8]. Specific vulnerable populations, such as those with homo/biphobia, are often more vulnerable to discrimination, dysfunctional beliefs about sexuality and lack of timely and effective care [9]. On the contrary, positive psychology (the positive emotion and positive character, *etc*.) increased happiness and decreased depressive symptoms, which may reduce the effect of negative psychological on ED [19]. These findings suggest that cognitive and emotional factors play a significant role in developing and maintaining male ED, especially in younger patients. Additionally, ED may serve as both a symptom and a sentinel marker of serious organic problems [11]. However, despite the various existing claims, most studies were observational. Therefore, more thorough investigations are needed to further assess the significance of individual psychological risk factors and their effects on ED.

A recent study proposes that an elevated neutrophil count (NC), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), as well as a decreased lymphocyte count (LC), may significantly augment the risk of ED. ED serves as an important biomarker in cardiovascular disease (CVD) risk assessment and prevention [20]. While the underlying causal relationship between individual CVD and ED remains poorly understood, randomized controlled trials (RCTs) appear to be the ideal study design to verify the causality between metabolic syndrome and ED. However, conducting RCTs in real-world clinical settings can present a daunting challenge.

Therefore, this study aims to apply univariable MR and Multivariable Mendelian randomization (MVMR) to evaluate the total and direct effects of HBP and psychological traits (IM) on ED risk.

2. Materials and methods

Mendelian randomization (MR) is a method that circumvents the drawbacks of traditional observational research by estimating the causal association between genetic variants associated with modifiable exposure or biological intermediates and a medically relevant result, bias caused by confounding factors or reducing reverse causality.

2.1 Study design and data sources

We categorized 62 risk factors into five groups: human blood cell (HBC) traits, psychological traits, individual cardiovascular and cerebrovascular disease traits, blood pressure traits and modifiable lifestyle factors traits. A meta-analysis of GWAS was performed to compile data on genetic variations related to these five groups (Table 1).

2.2 Human blood cell traits

The current investigation extracted instrumental variables (IVs) of HBC traits from the genome-wide univariable summary statistics accessed at http://www.bloodcellgenetics.org. The genetic variants used in this study have been previously associated with the properties of red cells, white cells, and platelets in a cohort of 173,480 European-ancestry individuals [21].

2.3 Psychological traits

IVs for psychological traits were extracted from four distinct genome-wide univariable summary statistics. These genetic variants were associated with 11 of the 12 mood traits analyzed in 380,506 individuals of European ancestry, as well as with depression and mood traits in 180,868 European-ancestry participants. In addition, we identified IVs for 5 personality traits in 17,357 European-ancestry participants, which are available from https://ctg.cncr.nl/ [22] and http://www.ncbi.nlm.nih.gov/dbgap [23]. We also included related to psychological traits, namely happiness and subjective well-being in our analysis of 152,348 and 298,420 European-ancestry participants [24], which are available from the MRC-IEU consortium and https://www.ebi.ac.uk/.

2.4 Cardiovascular and cerebrovascular diseases traits

IVs of cardiovascular and cerebrovascular diseases traits (*i.e.*, myocardial infarction and ischemic stroke) were extracted from a multi-ancestry genome-wide association study performed on 395,795 and 446,696 European-ancestry participants [25, 26].

2.5 Blood pressure traits

IVs of blood pressure traits (HBP, SBP and diastolic blood pressure (DBP)) were extracted from the Neale Lab consortium comprising 336,683 European-ancestry participants and from the ICBP (International Consortium of Blood Pressure) in comprising 757,601 European-ancestry participants [27].

2.6 Modifiable lifestyle factors traits

IVs of modifiable lifestyle factors traits, such as smoking, coffee intake and alcohol drinking, were extracted from the GSCAN consortium (the GWAS & Sequencing Consortium of Alcohol and Nicotine use), which was based on 607,291 European-ancestry participants [28], and the MRC-IEU consortium based on 428,860 European-ancestry participants, and from the Neale Lab consortium based on 336,965 European-ancestry participants.

TABLE 1. Genetic instrument sources and description.

Phenotype	Sample size	Ancestry	Consortium	GWAS ID	PMID	Unit
Blood pressures traits						
HBP	336,683	European	Neale Lab	ukb-a-437	NA	SD
SBP	757,601	European	ICBP	ieu-b-38	30224653	NA
DBP				ieu-b-39		
Human blood cell traits						
MPV	164,454			ebi-a-GCST004599		
EPWC	172,378			ebi-a-GCST004600		
RBCC	172,952			ebi-a-GCST004601		
MCV	172,433			ebi-a-GCST004602		
PC	166,066			ebi-a-GCST004603		
HCT	173,039			ebi-a-GCST004604		
MCHC	172,851			ebi-a-GCST004605		
EC	172,275			ebi-a-GCST004606		
PCT	164,339			ebi-a-GCST004607		
GPMWC	169,545			ebi-a-GCST004608		
MPWC	170,494			ebi-a-GCST004609		
WBCC	172,435			ebi-a-GCST004610		
HLSRC	170,761			ebi-a-GCST004611		
HLRPRC	170,763			ebi-a-GCST004612		
SNEC	170,384			ebi-a-GCST004613		
GC	169,822			ebi-a-GCST004614		
HC	172,925			ebi-a-GCST004615		
PDW	164,433	European	NA	ebi-a-GCST004616	27863252	NA
EPG	170,536			ebi-a-GCST004617		
BC	171,846			ebi-a-GCST004618		
RFCC	170,690			ebi-a-GCST004619		
SBNC	170,143			ebi-a-GCST004620		
RCT	170,641			ebi-a-GCST004622		
NPG	170,672			ebi-a-GCST004623		
SEBC	171,771			ebi-a-GCST004624		
MC	170,721			ebi-a-GCST004625		
MWCC	169,219			ebi-a-GCST004626		
LC	171,643			ebi-a-GCST004627		
IFR	170,548			ebi-a-GCST004628		
NC	170,702			ebi-a-GCST004629		
MCH	172,332			ebi-a-GCST004630		
BPWC	171,996			ebi-a-GCST004631		
LPWC	171,748			ebi-a-GCST004632		
NPWC	171,542			ebi-a-GCST004633		
BPG	170,223			ebi-a-GCST004634		
Cardiovascular and cerebrovascular diseases traits						
MI	395,795	European	NA	ebi-a-GCST011365	33532862	NA
IS	440,328			ebi-a-GCST005843	29531354	log OR

TABLE 1. Continued.

Phenotype	Sample size	Ancestry	Consortium	GWAS ID	PMID	Unit
Psychology traits						
IM	366,726	European	NA	ebi-a-GCST006941	29500382	NA
FL	376,352			ebi-a-GCST006942		
FM	376,097			ebi-a-GCST006943		
EMS	373,733			ebi-a-GCST006944		
FG	373,380			ebi-a-GCST006945		
WLEE	367,725			ebi-a-GCST006946		
FFU	374,971			ebi-a-GCST006947		
FN	373,121			ebi-a-GCST006948		
FW	372,869			ebi-a-GCST006950		
FH	372,047			ebi-a-GCST006951		
FT	371,318			ebi-a-GCST006952		
DEP	180,866			ebi-a-GCST003769		
SWB	298,420			ebi-a-GCST003766		
HAP	152,348			ukb-b-4062		
NEUR	380,506			ebi-a-GCST006940	29500382	NA
OPEN	17,375			ebi-a-GCST000922	21173776	arbitrary score
EXTR				ebi-a-GCST006328		
CONS				ebi-a-GCST006326		
NAGR				ieu-a-113		
Modifiable lifestyle factors traits						
SMI	607,291	European	GSCAN	ieu-b-4877	30643251	NA
CI	428,860		MRC-IEU	ukb-b-5237	NA	SD
DRIN	336,965		Neale Lab	ukb-a-25	NA	SD

GWAS: Genome-Wide Association Studies; SD: Standard deviations (mg/dL); Neale Lab: Neale Laboratory; ICBP: International Consortium of Blood Pressure; GSCAN: GWAS & Sequencing Consortium of Alcohol and Nicotine use; OR: odds ratio; ukb: UK Biobank; MRC-IEU: MRC Integrative Epidemiology Unit; MPV: Mean platelet volume; EPWC: Eosinophil percentage of white cells; RBCC: Red blood cell count; MCV: Mean corpuscular volume; PC: Platelet count; HCT: Hematocrit; MCHC: Mean corpuscular hemoglobin concentration; EC: Eosinophil counts; PCT: Plateletcrit; GPMWC: Granulocyte percentage of myeloid white cells; MPWC: Monocyte percentage of white cells; WBCC: White blood cell count; HLSRC: High light scatter reticulocyte count; HLRPRC: High light scatter reticulocyte percentage of red cells; SNEC: Sum neutrophil eosinophil counts; GC: Granulocyte count; HC: Hemoglobin concentration; PDW: Platelet distribution width; EPG: Eosinophil percentage of granulocytes; BC: Basophil count; RFCC: Reticulocyte fraction of red cells; SBNC: Sum basophil neutrophil counts; RCT: Reticulocyte count; NPG: Neutrophil percentage of granulocytes; SEBC: Sum eosinophil basophil counts; MC: Monocyte count; MWCC: Myeloid white cell count; LC: Lymphocyte counts; IFR: Immature fraction of reticulocytes; NC: Neutrophil count; MCH: Mean corpuscular hemoglobin; BPWC: Basophil percentage of white cells; LPWC: Lymphocyte percentage of white cells; NPWC: Neutrophil percentage of white cells; BPG: Basophil percentage of granulocytes; MI: Myocardial infarction; IS: Ischemic stroke; HBP: High blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure; IM: Irritable mood; FL: Feeling lonely; FM: Feeling miserable; EMS: Experiencing mood swings; FG: Feeling guilty; WLEE: Worry too long after an embarrassing experience; FFU: Feeling fed-up; FN: Feeling nervous; FW: Feeling worry; FH: Feeling hurt; FT: Feeling tense; DEP: Depression; SWB: Subjective well-being; HAP: Happiness; NEUR: neuroticism; OPEN: Openness; EXTR: Extraversion; CONS: Conscientiousness; NAGR: Neo-agreeableness; SI: Smoking initiation; CI: coffee intake; DRIN: drinking. NA: not available; SMI: Smoking initiation.

2.7 Erectile dysfunction

Complete GWAS summary data of ED from the EBI database comprised 223,805 European-ancestry participants, including 6175 cases and 217,630 controls [29].

2.8 MR design and statistical analysis

During the MR analysis, the extracted MR-IVs complied with the following three requirements: (1) IVs were closely related to the exposure; (2) there were no confounding variables that could affect the IVs; and (3) IVs did not affect the risk of ED through any other pathways besides exposure (**Supplementary Figs. 1, 2**).

We utilized single nucleotide polymorphism (SNPs) that were significant at the genome-wide level ($p < 5 \times 10^{-8}$). The chosen SNPs were not in linkage disequilibrium, meaning they were independent ($r^2 = 0.001$, kb = 10,000). The genetic variants (R^2) value and F-statistic were used to determine the instrument strength of each SNP, and the amount of variance in those SNP was calculated using the following formula: the F statistic was related to the proportion of variance in the exposure explained by R^2, sample size (N) and number of instruments (K) by the formula $F = \frac{R^2}{1-R^2} \times \frac{(N-K-1)}{K}$. For a single variant, the F statistic is equal to the square of the genetic association with the exposure divided by the square of its standard deviation [30]:

$$F_1\ statistic = \frac{R^2}{1-R^2} \times (N-2)$$

or

$$F_2\ statistic = \left(\frac{\beta}{se}\right)^2$$

(SNPs, F statistic less than 10 indicates the presence of weak instruments, which would be removed) ($F < 10$).

Where R^2 can be written again as:

$$R^2 = 2 \times MAF \times (1-MAF) \times \left(\frac{\beta}{sd}\right)^2$$

Alternatively, for a biallelic SNP, R^2 can be approximated as $2 \times \beta^2 \times MAF\ (1-MAF)$ where β is the genetic association with the exposure measured in standard deviation units of the exposure, and β is the minor allele frequency. β in the exposed GWAS represents its variance (sd = se $\times \sqrt{}$n); N is the number of samples of exposed GWAS species; K is the number of exposed species screened from the number of SNPs. Detailed information can be found in **Supplementary Table 2**.

I^2 statistic is the observed between-study variation (due to true heterogeneity rather than chance) as a percentage [31, 32]. It is calculated as I^2 = 100% × (Q−df)/Q, where Q is Cochran's Q heterogeneity statistic; df is the degree of freedom in Cochran's Q heterogeneity statistic, and df is the degree of freedom. Since I^2 takes 0 for all negative values, the value of I^2 is between 0% and 100% (**Supplementary Table 3**).

We used simplified data to run two-sample MR analyses to estimate the effect of exposure on the outcome for each IV. Then we tested the durability of the results using many complementary MR techniques, such as inverse variance weighting (IVW), weighted median (WM), Mendelian Randomization-Egger (MR-Egger), simple median (SM) and Robust adjusted profile score (RAPS), and set the threshold at $p < 0.05$ [33, 34]. IVW was used as our primary reference framework, while the other methods were used as supplements. Moreover, we conducted the reverse MR to exclude reverse causality (**Supplementary Table 1**). Moreover, multivariable MR (MVMR) is used to evaluate each risk factor's direct effect, and thus can avoid the impacts of other potentially related risk factors, the threshold was set at $p < 0.05$ (**Supplementary Table 1**). Furthermore, to ensure the robustness of our findings, we conducted various sensitivity analyses using the MR-Egger intercept and MR-PRESSO methods. These analyses aimed to investigate if any heterogeneity or pleiotropy issues exist within the genetic instruments and to exclude the possibility of any violation of the MR assumptions. By implementing these rigorous analytical approaches, we can confidently validate the accuracy and reliability of our MR results [34–36] (**Supplementary Table 3**).

Cochrane's Q test was used to assess the heterogeneity of individual genetic variations [36]. A leave-one-out analysis (which entailed sequential exclusion of one SNP at a time) was carried out to investigate the impact of outlier values.

In order to evaluate the total and direct effects of HBP and psychological traits on ED risk, the MVMR analysis was conducted using R packages, "TwoSampleMR". To calculate the statistical power of the Mendelian randomization analysis, we employed the mRnd tool, which is available at https://cnsgenomics.shinyapps.io/mRnd/ [37–39]. In general, we applied 100%, 96% and 80% statistical powers to find the differences in the risk of HBP, IM and NEUR (Type-I error rate 0.05) (**Supplementary Table 3**).

Phenoscanner was used to remove SNPs that violated the principles of MR (http://www.phenoscanner.medschl.cam.ac.uk) (**Supplementary Table 2**).

R version 4.2.1 software (R Foundation for Statistical Computing, Vienna, Austria). Packages: TwoSampleMR version 0.5.6 (Gibran Hemani, Bristol, UK) and MR-PRESSO version 1.0 (Marie Verbanck, NY, USA) were used for all studies. In statistics, $p < 0.05$ was considered significant.

3. Results

The number of SNPs ranged from 0 to 446 and showed a significant association with the investigated five groups of factors after the elimination of SNPs associated with potential confounders from the online GWAS database and the removal of pairwise linkage disequilibrium and coding alleles. The F statistics of each SNP and the overall F statistics exceeded the empirical threshold of 10 (F statistics >10), indicating that all SNPs were sufficiently valid (**Supplementary Table 2**). Findings of the genetic correlations between the five groups and the risk of ED are shown in **Supplementary Table 1** and **Supplementary Fig. 1**. We also found that MR-PRESSO

showed no pleiotropic bias, and the sensitivity analysis results were robust (**Supplementary Table 3**, **Supplementary Fig. 1**).

3.1 MR effect size for blood pressure traits (HBP, SBP and DBP) on ED

Our study utilized a MR approach to investigate the potential causal relationship between blood pressure traits and ED. Using MR, we genetically predicted that HBP and DBP could increase the risk of ED. Our MR results revealed that HBP was associated with an odds ratio (OR) of 1.660 (95% CI, 0.88–0.99), with a *p*-value for the inverse variance-weighted method (P_{IVW}) of 1.06×10^{-2} and a power of 100%. Meanwhile, DBP was associated with an OR of 1.012 (95% CI, 1.000–1.024), with a P_{IVW} of 4.67×10^{-2} and a power of 5%. On the other hand, systolic blood pressure (SBP) was not significantly associated with ED (OR = 1.005 (95% CI, 0.998–1.013), $P_{IVW} = 1.07 \times 10^{-1}$, Power = 5%), and the multivariable MR (MVMR) analysis suggested that HBP might be the independent risk factor of ED (adjusted OR = 3.633, $p = 0.29 \times 10^{-1}$). These results are presented in **Supplementary Table 1**, Figs. 1–4. We also performed a reverse MR analysis, which indicated no significant associations (**Supplementary Table 1**). Furthermore, following a Bonferroni-corrected significance threshold ($p < 1.67 \times 10^{-2}$), HBP remained significantly associated with ED.

3.2 MR effect size for cardiovascular and cerebrovascular diseases traits on ED

In addition, our MR results suggested a significant causal relationship between ischemic stroke (IS) (OR = 1.21 (95% CI, 1.02–1.43), $P_{IVW} = 2.87 \times 10^{-2}$, Power = 10%), myocardial infarction (MI) (OR = 1.09 (95% CI, 1.02–1.17), $P_{IVW} = 1.18 \times 10^{-2}$, Power = 56%) and ED. The reverse MR showed no relationship and followed the Bonferroni-corrected significance threshold ($p < 2.50 \times 10^{-2}$) (**Supplementary Table 1**; Figs. 5, 6). MVMR analysis indicated both of them could increase the risk of ED, including ischemic stroke (adjusted OR = 1.186, $p = 0.036$) and MI (OR = 1.084, $p = 0.038$) (**Supplementary Table 1**; Fig. 4), meaning both MI and IS could increase the risk of ED.

3.3 MR effect size for psychological traits on ED

We found that psychological traits (irritable mood and neuroticism) could increase the risk of ED, including irritable mood (IM) (OR = 1.86 (95% CI, 1.14–3.02), $P_{IVW} = 1.30 \times 10^{-2}$, Power = 96%) and neuroticism (NEUR) (OR = 1.36 (95% CI, 1.04–1.79), $P_{IVW} = 2.66 \times 10^{-2}$, Power = 80%). The reverse MR indicated no significance (**Supplementary Table 1**; Figs. 7–9). The multivariable MR analysis suggested that IM might be the independent risk factor of ED (adjusted OR = 3.219, $p = 2.36 \times 10^{-3}$) (**Supplementary Table 1**; Fig. 4). Moreover, our MR results revealed that happiness and subjective well-being was associated with an odds ratio of 0.99 (95% CI, 0.07–13.74) and 0.96 (95% CI, 0.11–8.30), and these IVs were not statistically significant with the outcome ($p > 0.05$). The MR result suggested that positive psychological traits (happiness and subjective well-being) did not benefit ED, while negative psychological traits (IM) could increase the risk of ED, although following the Bonferroni-corrected significance threshold ($p < 2.63 \times 10^{-3}$). Likewise, we obtained 0–92 genome-wide SNPs for the 14 mood traits and 5 personality traits. The median *F*-statistic (another parameter for measuring the strength of IVs) was 39.4 (range, 29.8–138.4), meaning that all IVs were strong (*F*-statistic >10) for the MR analyses (**Supplementary Table 2**).

3.4 MR effect size for human blood cell traits on ED

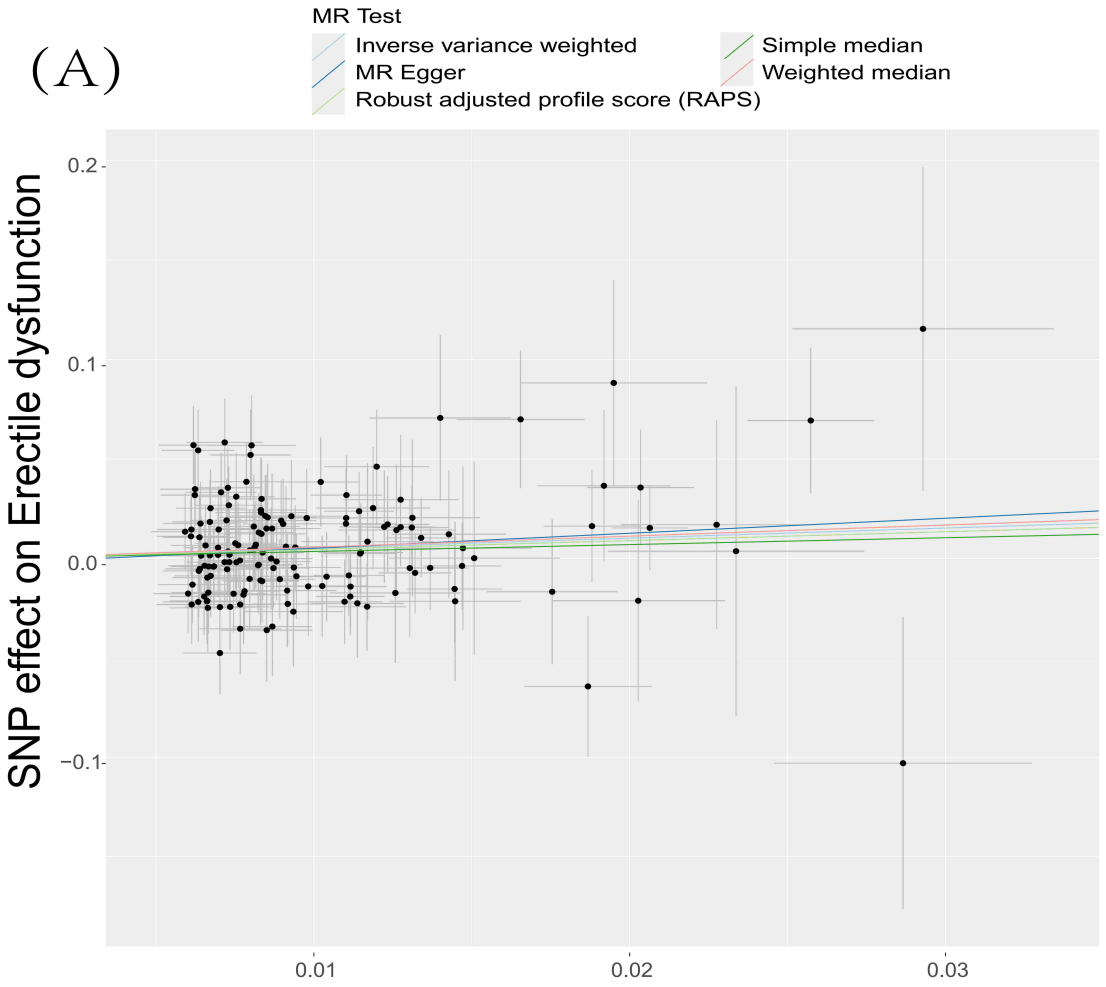
The results of MR analysis of HBC traits showed that a bigger mean platelet volume (MPV) was associated with a reduced risk of ED, while a higher platelet count (PC) could lead to an increased ED risk. The MR method of IVW identified two HBC traits that showed significant associations with ED, and both were associated with platelet, including MPV (OR = 0.93 (95% CI, 0.88–0.99), $P_{IVW} = 1.40 \times 10^{-2}$, Power = 5%), and PC (OR = 1.1 (95% CI, 1.02–1.20), $P_{IVW} = 1.43 \times 10^{-2}$, Power = 6%), with the reverse MR showing significant statistical difference (**Supplementary Table 1**; Figs. 10–12). However, the result of MVMR analysis indicated that MPV (adjusted OR = 0.929, $p = 6.3 \times 10^{-2}$), PC (adjusted OR = 1.031, $p = 5.4 \times 10^{-1}$) and ED might not be significant (**Supplementary Table 1**; Fig. 4), and following the Bonferroni-corrected significance threshold ($p < 1.43 \times 10^{-3}$), meaning that both might not be related. We obtained 57–219 genome-wide SNPs for the 35 HBC traits. The median *F*-statistic was 132.2 (range, 29.8–4248.1), similarly suggesting that all IVs were strong (*F*-statistic is >10) for the MR analyses (**Supplementary Table 2**).

3.5 MR effect size for modifiable lifestyle factors traits on ED

According to the MR analysis, we genetically discovered that modifiable lifestyle factors had no significant relationship with ED, including smoking (OR = 1.093 (95% CI, 0.89–1.35), $P_{IVW} = 4.05 \times 10^{-1}$, Power = 9%), coffee intake (OR = 1.054 (95% CI, 0.675–1.646), $P_{IVW} = 8.16 \times 10^{-1}$, Power = 6%) and drinking (OR = 0.915 (95% CI, 0.738–1.136), $P_{IVW} = 4.22 \times 10^{-1}$, Power = 22%), with the reverse MR showing significant statistical difference (**Supplementary Table 1**; Figs. 13–16). Moreover, the result of MVMR analysis indicated that the evidence of causality between smoking (adjusted OR = 1.003, $p = 3.46 \times 10^{-1}$), coffee intake (adjusted OR = 0.952, $p = 8.41 \times 10^{-1}$), drinking (adjusted OR = 0.915, $p = 4.35 \times 10^{-1}$) and ED were not significantly different (**Supplementary Table 1**; Fig. 4).

4. Discussion

Our MR study provides evidence for a causal association between blood pressure traits (HBP and DBP), Cardiovascular and cerebrovascular diseases traits (IS and MI), psychological traits (IM and NEUR), HBC traits (MPV and PC) and risk of erectile dysfunction. However, after the SNPs related to other



(B)

Exposure	Outcome	Method	No. of IVs	OR (95% CI)	*p* value
HBP	ED	Inverse variance weighted	149	1.66(1.13−2.45)	0.0106
HBP	ED	Robust adjusted profile score (RAPS)	149	1.75(0.95−3.22)	0.0729
HBP	ED	Weighted median	149	1.41(0.80−2.50)	0.2347
HBP	ED	Simple median	149	1.56(1.04−2.35)	0.0316
HBP	ED	MR Egger	149	2.13(0.65−6.94)	0.2130
HBP	ED	MR PRESSO	149	1.66(1.28−2.05)	0.0098

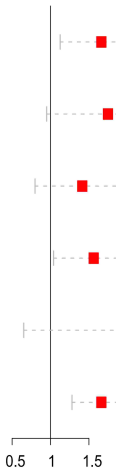


FIGURE 1. Univariable MR results for the effects of blood pressure traits on ED. (A) Each point represents the SNP effects on HBP and ED. (B) The adjusted forest plot of MR estimates the effects of HBP on ED. Error bars represent 95% CI. MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; IVs, the number of instrumental variables; ED, erectile dysfunction; HBP, high blood pressure; CI, confidence interval; OR, odds ratio. SNP, single nucleotide polymorphism.

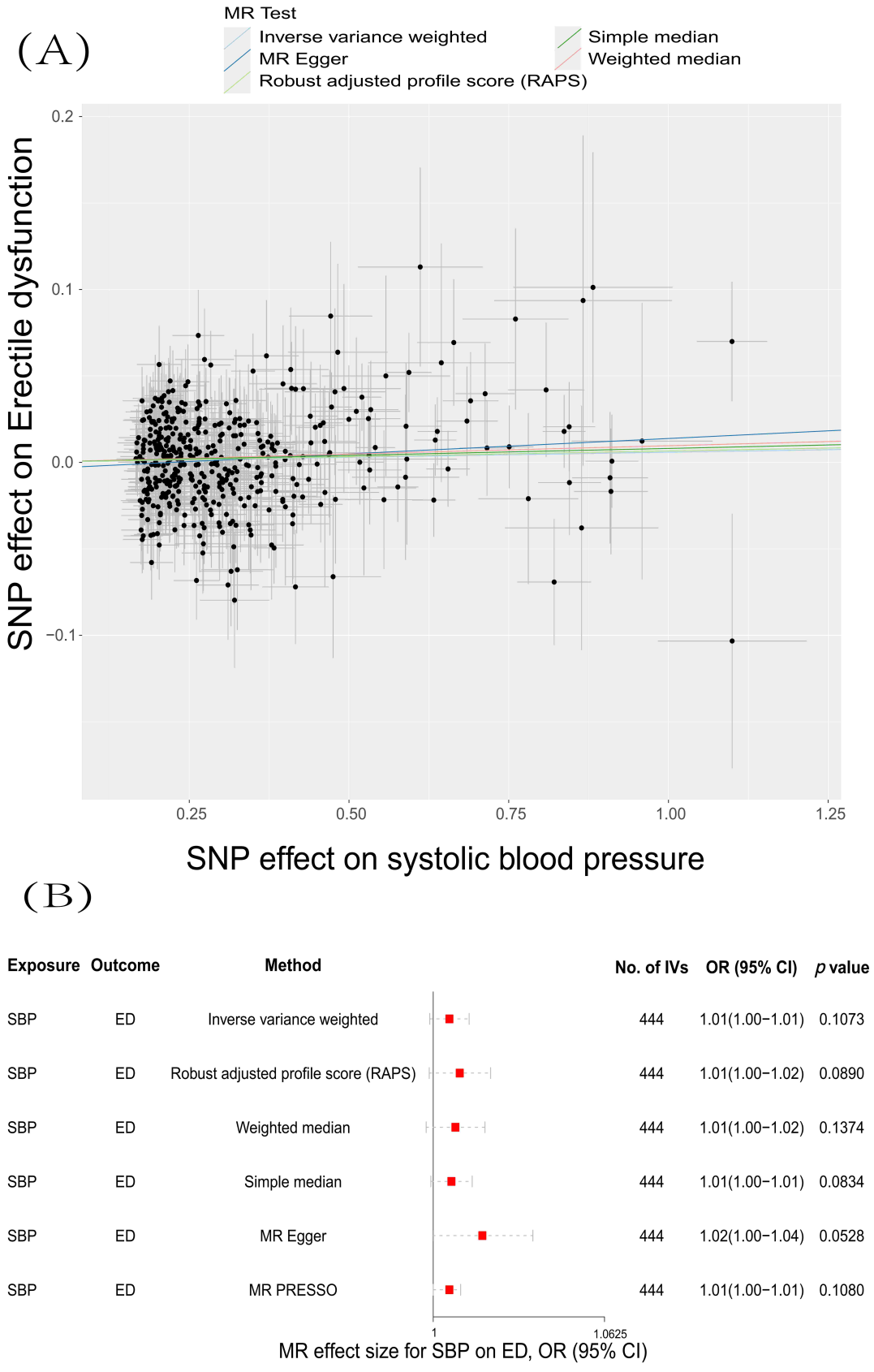


FIGURE 2. Univariable MR results for the effects of blood pressure traits on ED. (A) Each point represents the SNP effects on SBP and ED. (B) The forest plot of MR estimates for SBP on ED. Error bars represent 95% CI. MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; IVs, the number of instrumental variables; ED, erectile dysfunction; SBP, systolic blood pressure; CI, confidence interval; OR, odds ratio. SNP, single nucleotide polymorphism.

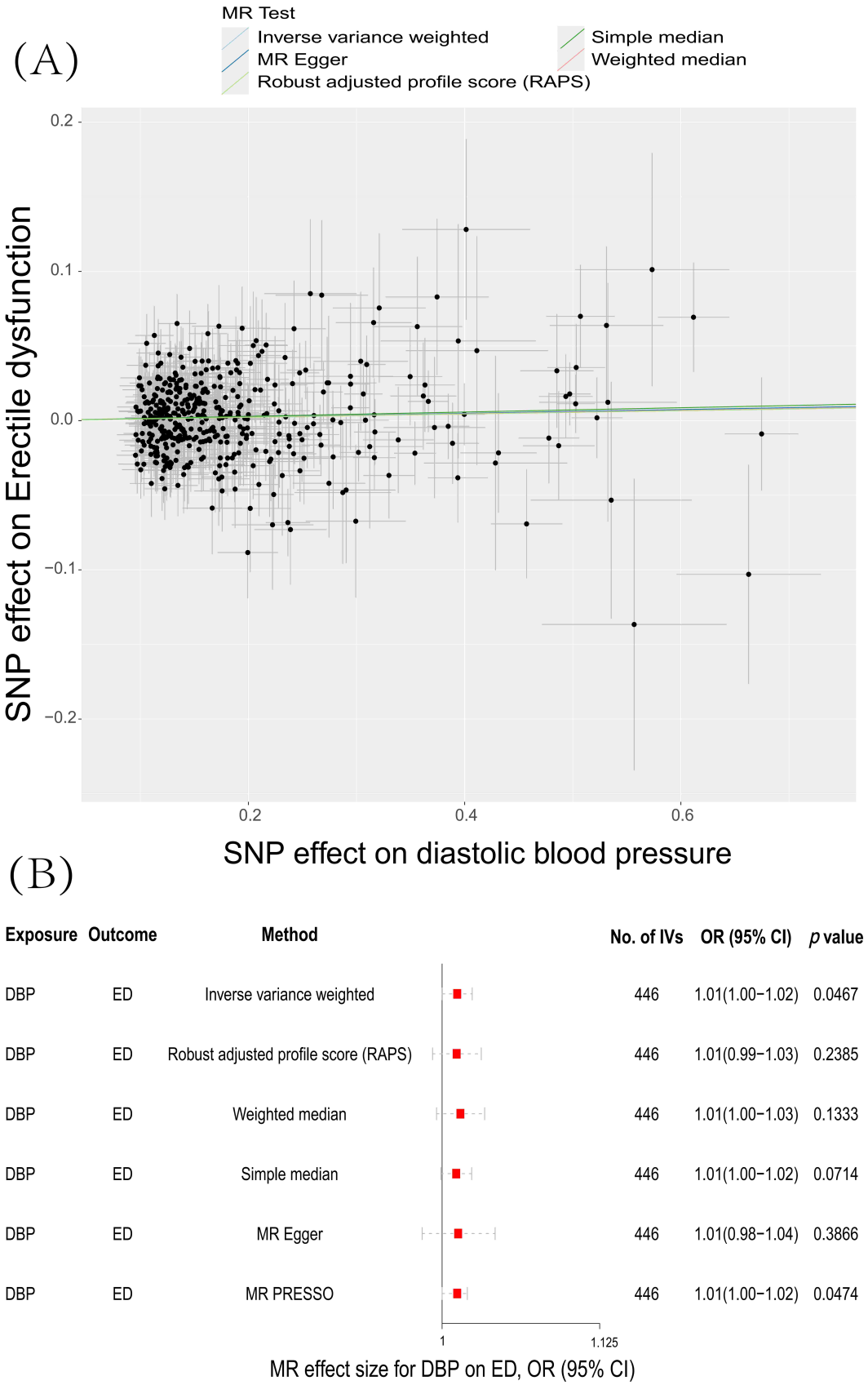


FIGURE 3. Univariable MR results for the effects of blood pressure traits on ED. (A) Each point represents the SNP effects on DBP and ED. (B) The forest plot of MR estimates for the effects of DBP on ED. Error bars represent 95% CI. MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; IVs, the number of instrumental variables; ED, erectile dysfunction; DBP, diastolic blood pressure; CI, confidence interval; OR, odds ratio. SNP, single nucleotide polymorphism.

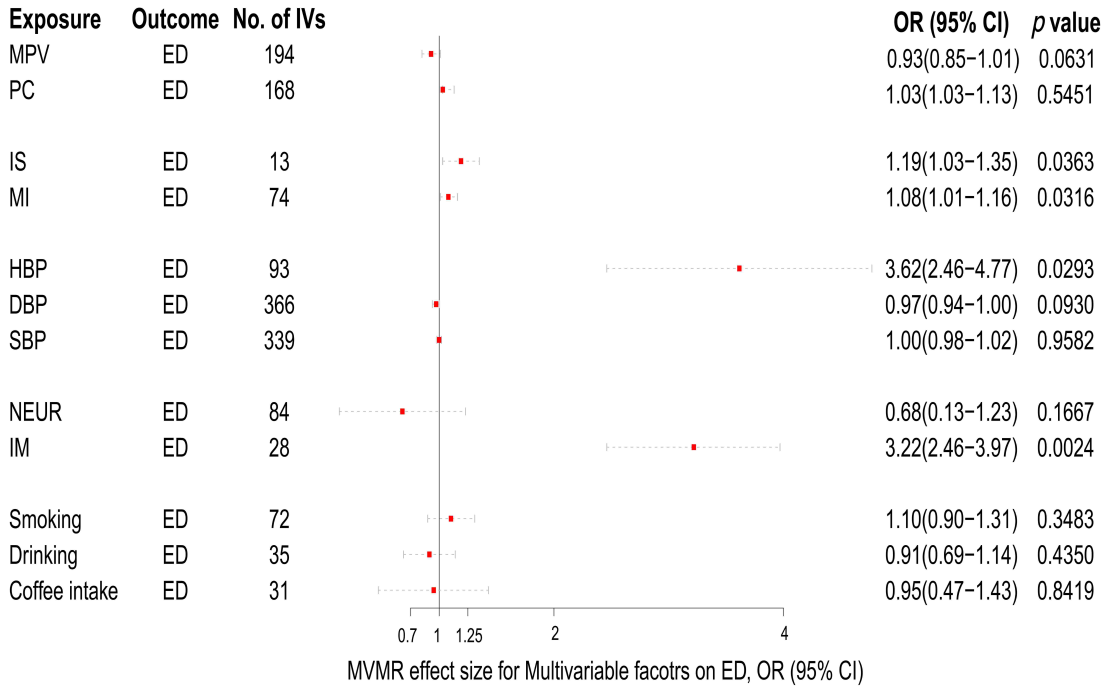


FIGURE 4. Multivariable MR results for the effects of blood pressure traits, cardiovascular and cerebrovascular diseases, psychology traits, human blood cell traits, and modifiable lifestyle factors on ED. IVs, the number of instrumental variables; ED, erectile dysfunction; CI, confidence interval; OR, odds ratio. MVMR: multivariable MR. MPV: Mean platelet volume. PC: platelet count. IS: Ischemic stroke; HBP: High blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure; IM: Irritable mood. MI: Myocardial infarction; NEUR: neuroticism.

risk factors were excluded, the multivariable MR indicated that HBP, MI, IS and IM remained statistically significant while the other were not. In addition, there was no evidence that SBP, other HBC traits (except MPV and PC) and psychological traits (except IM and NEUR), or modifiable lifestyle factors traits (smoking, coffee intake and alcohol drinking) were causally associated with ED.

Our findings of HBP were consistent with previous studies. In a cross-sectional investigation, it was found that among 692 men, 337 experienced new onset ED after being followed for over 7762 person-years [40]. The relative risk (RR) was 1.21 with a 95% CI of 1.04–1.41. These findings suggest that hypertension is a contributing factor in the development of ED. Sarma *et al.* [40] demonstrated that higher SBP was associated with increased ED risk. Hsiao *et al.* [41] described higher average SBP was associated with a higher risk of ED in a dose-dependent manner, a cohort study involving a large sample size of 39,320 newly diagnosed hypertensive men subjects, with an overall incidence of 13.9% of erectile dysfunction (ED), demonstrated that wide variation in blood pressure control was associated with an increased incidence of ED (OR 95% CI: 1.359 (1.258–1.469)) [41]. Thus, our MR analysis indicated that the association between DBP, SBP and ED was slightly attenuated in the multivariable MR analysis with adjustment for genetically predicted BP liability, which may not be the effect of a single blood pressure trait, but more likely the combined effect of SBP and DBP, or the potential involvement of more factors. The mechanisms and pathophysiology for the effect of HBP on ED, such as vascular endothelial dysfunction and immune-inflammatory responses, could be engaged in the occurrence of ED. Hypertension, or HBP, is a multifaceted condition that can have a detrimental impact on the body's vascular and erectile structures. One of the key mechanisms behind this impact is the sustained and widespread release of pro-contractile factors, such as angiotensin II, endothelin 1, and aldosterone. These factors disrupt the delicate balance between vasoconstrictors and vasodilators, leading to a reduction in blood flow and erectile function. This highlights the need for targeted interventions that aim to restore this balance and improve vascular and erectile health [42–46]. Moreover, the body's natural immune system, specifically Toll-like receptor 4, may contribute to hypertension and erectile dysfunction by causing inflammation and oxidative stress. Understanding this process can help us develop better treatments for these conditions [46–50]. We confirmed that HBP directly causes erectile dysfunction with a larger study. This helps us understand ED better and find better treatments.

ED is a widespread problem whose relation to cardiovascular and cerebrovascular diseases (CCD) has been scientifically proven. IS, MI and ED have many risk factors in common [13]. Shamlou *et al.* [6] described ED could be a strong predictor for coronary artery disease. Koehn *et al.* [51] found that ED can get worse after a stroke due to problems with the network that controls penile erection. This network operates at the cellular level. The multivariable MR analysis indicated that IS and MI were both risk factors for ED, but the statistical power for MR was not significant. IS, MI and ED may arise from distinct clinical presentations but are rooted in shared pathophysiological mechanisms. These mechanisms include atherosclerosis, endothelial dysfunction, and inflammation,

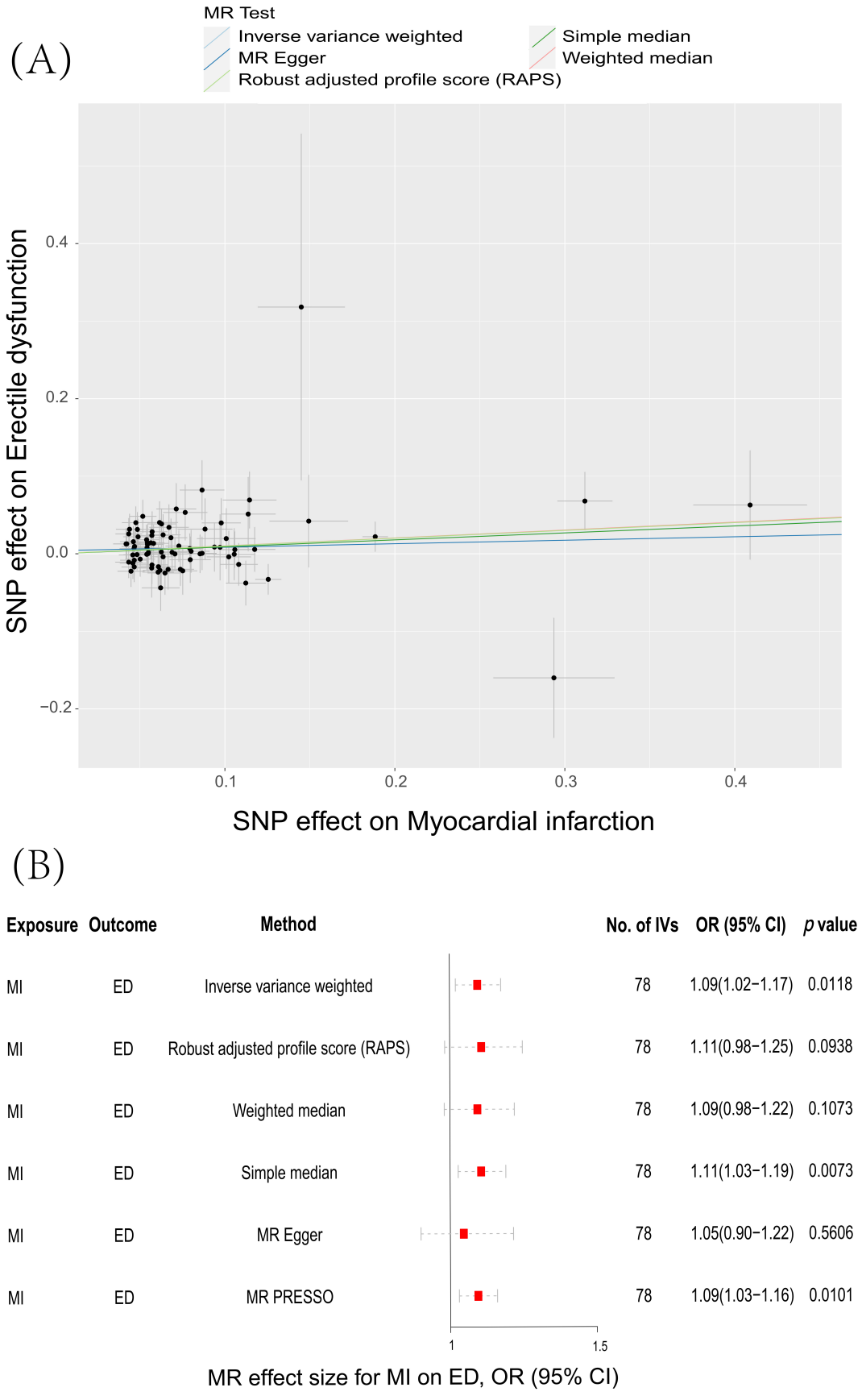
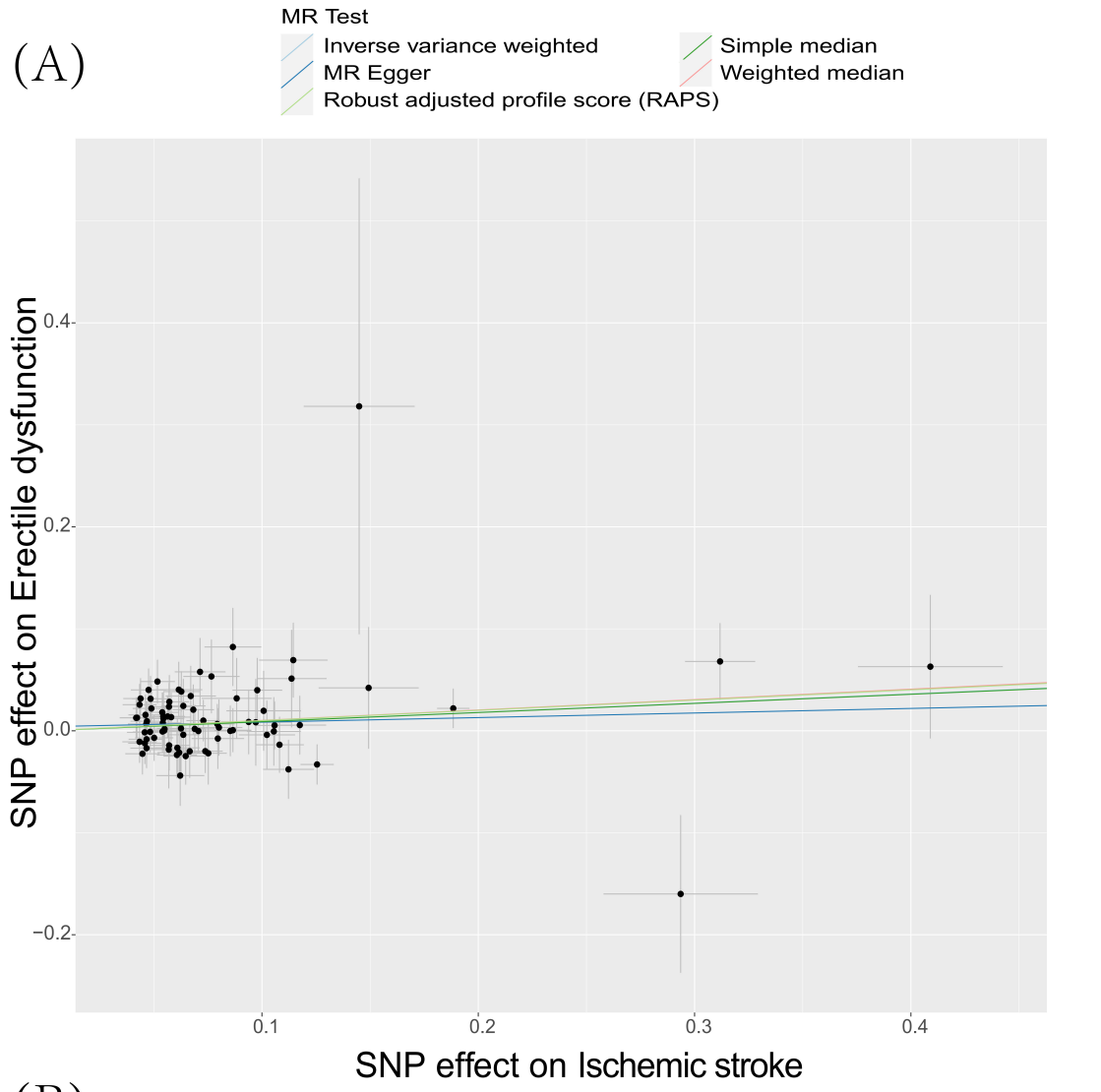


FIGURE 5. Univariable MR results for the effects of cardiovascular and cerebrovascular diseases on ED. (A) Each point represents the SNP effects on MI and ED. (B) The forest plot of MR estimates for MI and ED. Error bars represent 95% CI. MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; IVs, the number of instrumental variables; ED, erectile dysfunction; MI, myocardial infarction; CI, confidence interval; OR, odds ratio. SNP, single nucleotide polymorphism.



(B)

Exposure	Outcome	Method	No. of IVs	OR (95% CI)	*p* value
IS	ED	Inverse variance weighted	18	1.21(1.02−1.43)	0.0287
IS	ED	Robust adjusted profile score (RAPS)	18	1.21(0.95−1.53)	0.1237
IS	ED	Weighted median	18	1.21(1.00−1.53)	0.1159
IS	ED	Simple median	18	1.20(1.00−1.43)	0.0472
IS	ED	MR Egger	18	2.28(0.93−5.63)	0.0917
IS	ED	MR PRESSO	18	1.21(1.15−1.26)	0.0429

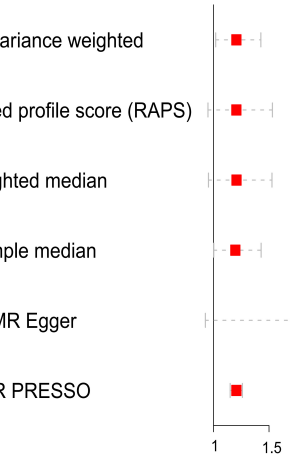
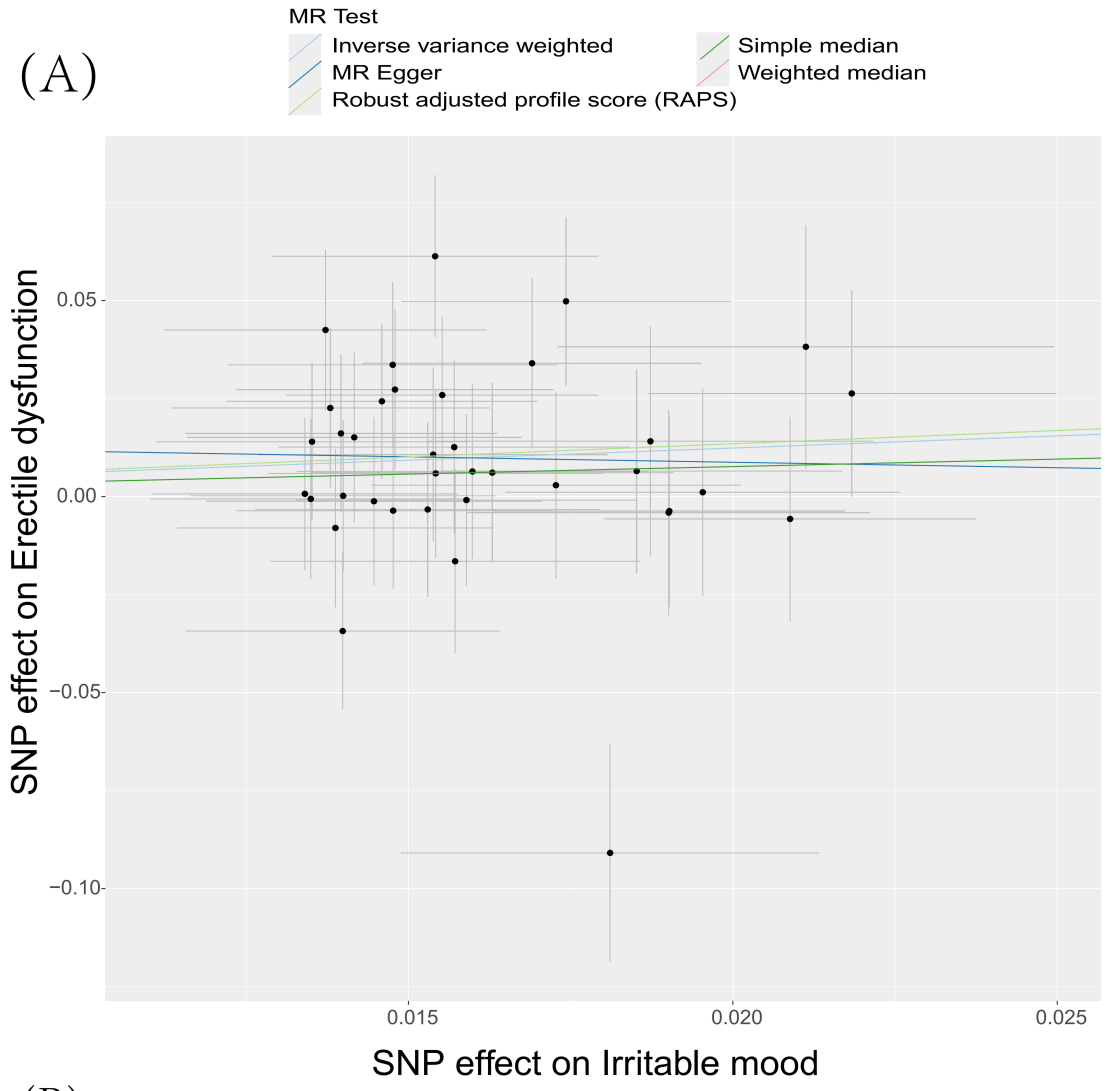


FIGURE 6. Univariable MR results for the effects of cardiovascular and cerebrovascular diseases on ED. (A) Each point represents the SNP effects on IS and ED. (B) The adjusted forest plot of MR estimates for IS on ED. Error bars represent 95% CI. MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; IVs, the number of instrumental variables; ED, erectile dysfunction; IS, ischemic stroke; CI, confidence interval; OR, odds ratio. SNP, single nucleotide polymorphism.



(B)

Exposure	Outcome	Method	No. of IVs	OR (95% CI)	*p* value
IM	ED	Inverse variance weighted	37	1.86(1.14−3.02)	0.0126
IM	ED	Robust adjusted profile score (RAPS)	37	1.46(0.78−2.76)	0.2368
IM	ED	Weighted median	37	1.47(0.75−2.86)	0.2610
IM	ED	Simple median	37	1.96(1.22−3.15)	0.0054
IM	ED	MR Egger	37	0.76(0.02−31.61)	0.8850
IM	ED	MR PRESSO	37	1.87(1.36−2.38)	0.0174

FIGURE 7. Univariable MR results for the effects of psychology traits on ED. (A) Each point represents the SNP effects on IM and ED. (B) The adjusted forest plot of MR estimates for IM on ED. Error bars represent 95% CI. MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; IVs, the number of instrumental variables; ED, erectile dysfunction; IM, irritable mood; CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism.

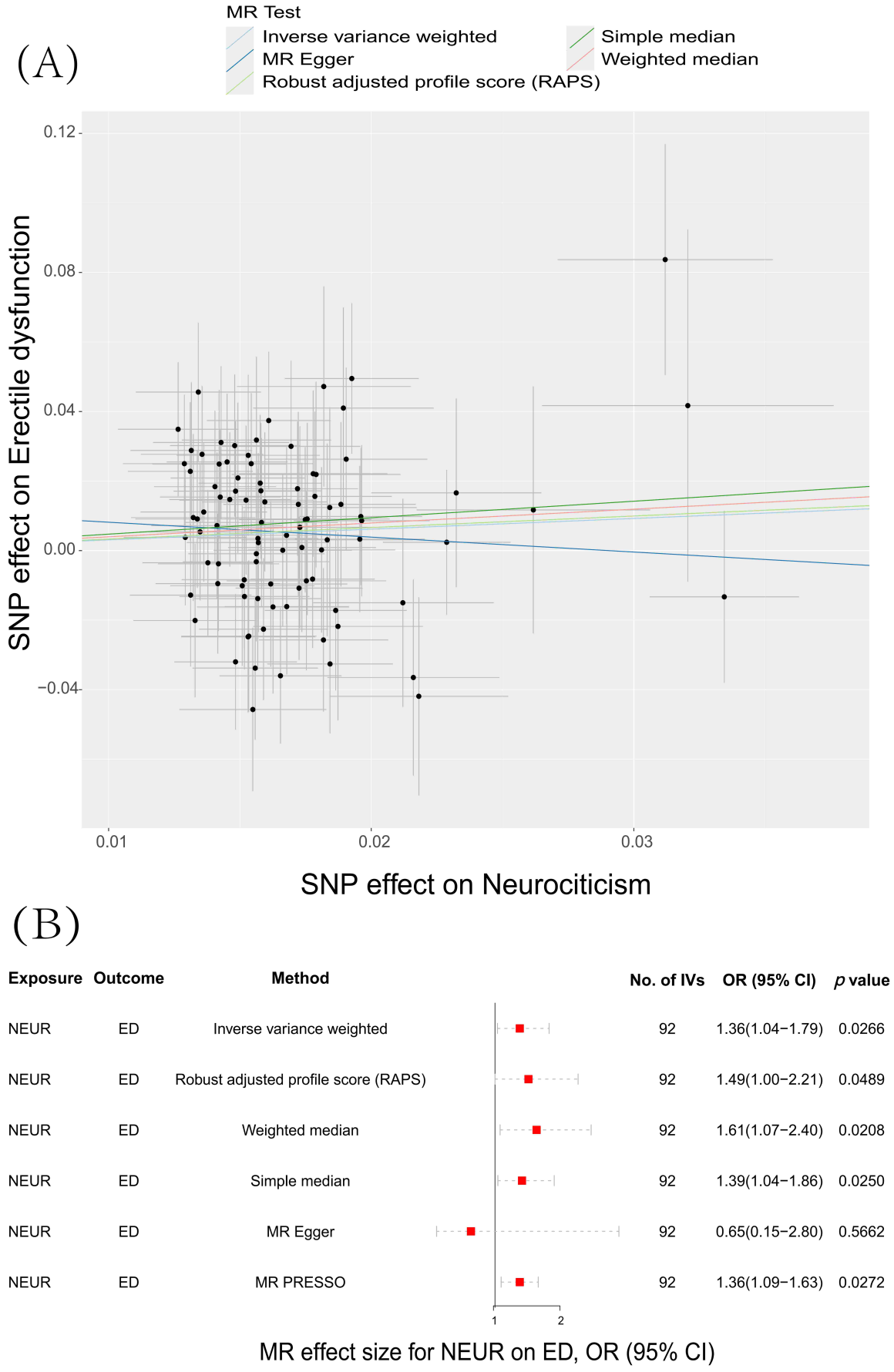


FIGURE 8. Univariable MR results for the effects of psychology traits on ED. (A) Each point represents the SNP effects on NEUR and ED. (B) The forest plot of MR estimates for NEUR on ED. Error bars represent 95% CI. MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; IVs, the number of instrumental variables; ED, erectile dysfunction; NEUR, neuroticism; CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism.

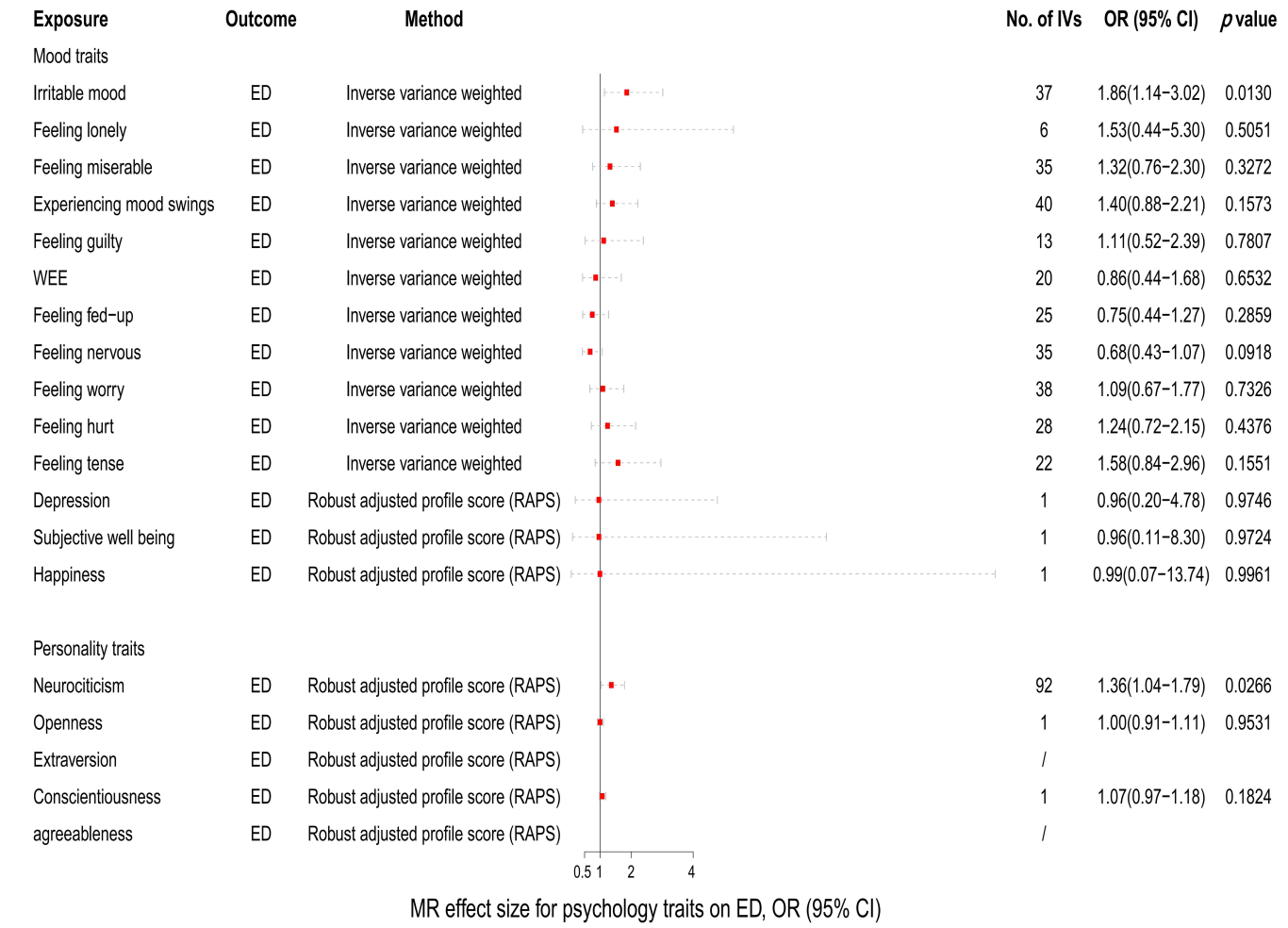


FIGURE 9. The forest plot of Mendelian randomization estimates for psychological traits (14 mood traits and 5 personality traits) on ED. ED, erectile dysfunction; WEE, Worry too long after an embarrassing experience; CI, confidence interval; OR, odds ratio; IVs, the number of instrumental variables. Error bars represent 95% CI.

which can manifest in various forms across the three conditions [52–54]. A possible mechanism could be Angpt2-mediated stress and inflammatory response persistence after the onset of CAD [55], considering its intimate association with chronic low-grade inflammation, which may also occur in the ED [52, 56]. Moreover, the decline in erectile function after stroke may be linked to disruptions in the central autonomic network that regulate penile erection. Specifically, recent studies have shed light on the complex relationship between the location of ischemic lesions and erectile dysfunction. Specifically, the deterioration of erectile function appears to be most prominent in certain regions of the brain. Right hemisphere occipital lobe and adjacent parietal cortex and thalamus, and left hemisphere insula and adjacent temporal and parietal joint cortex, appear to be particularly affected. Understanding these associations is essential to develop effective treatment strategies for those affected by erectile dysfunction, particularly in cases where ischemic lesions are present. By continuing to investigate these relationships, we can gain a better understanding of the underlying mechanisms of ED and develop targeted interventions to improve the quality of life for affected individuals [57].

Young people are frequently affected by psychogenic and psychosocial EDs, which often begin prior to the onset of ED symptoms [58, 59]. A Cognitive-Emotional Model questionnaire of 352 men supported the role of cognitive and emotional factors on the predisposition to and maintenance of male ED [8]. Our study confirmed that psychological traits (IM and NEUR) might increase the risk of ED. After the SNPs related to other risk factors were excluded, the multivariable MR suggested that IM was still associated with ED while NEUR was not. It was the first time that IM was found to increase the risk of ED (OR = 1.86, 95% CI: 1.14–3.02). A causal relationship between depression and ED has been demonstrated: depression might increase the risk of ED [60, 61]. However, there are few studies that have examined the relationship between IM, which is the opposite of depression in bipolar disorder, and ED. Irritable individuals, who have an increased proneness to anger relative to their peers at the same developmental level [62], are often linked to depression due to shared genetic variance [63, 64]. Thus, they may share similar mechanisms that lead to the onset of ED: (1) dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis [65], different psychological stressors can interfere with sexual thoughts and cause ED. This is because stress increases muscle tension that can counteract the necessary blood flow for an erection. It is important to understand this connection

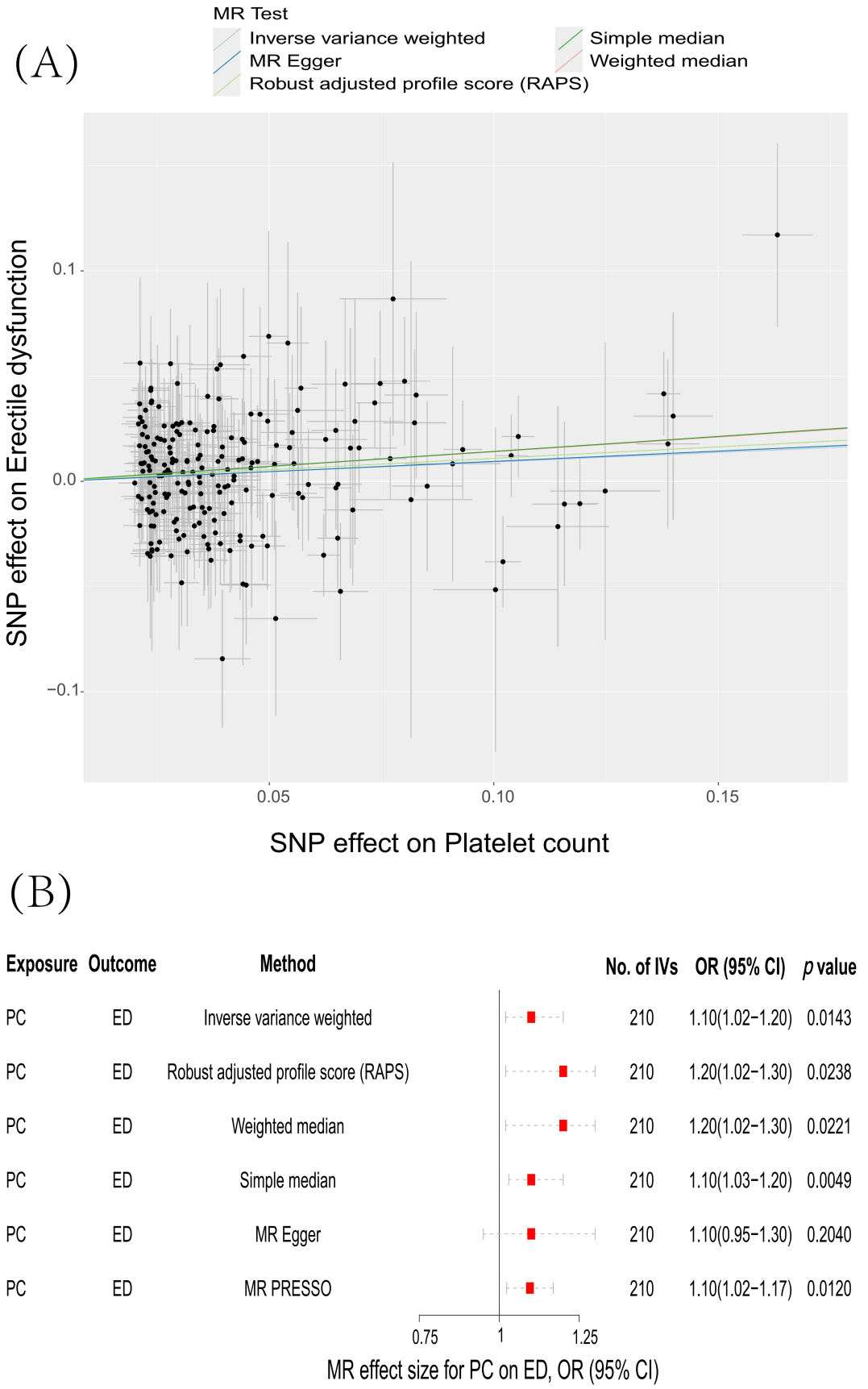


FIGURE 10. Univariable MR results for the effects of HBC traits on ED. (A) Each point represents the SNP effects on PC and ED. (B) Each point represents the SNP effects on MPV and ED. Error bars represent 95% CI. MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; IVs, the number of instrumental variables; ED, erectile dysfunction; HBC, human blood cell; MPV, mean platelet volume; CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism; CI, confidence intervals.

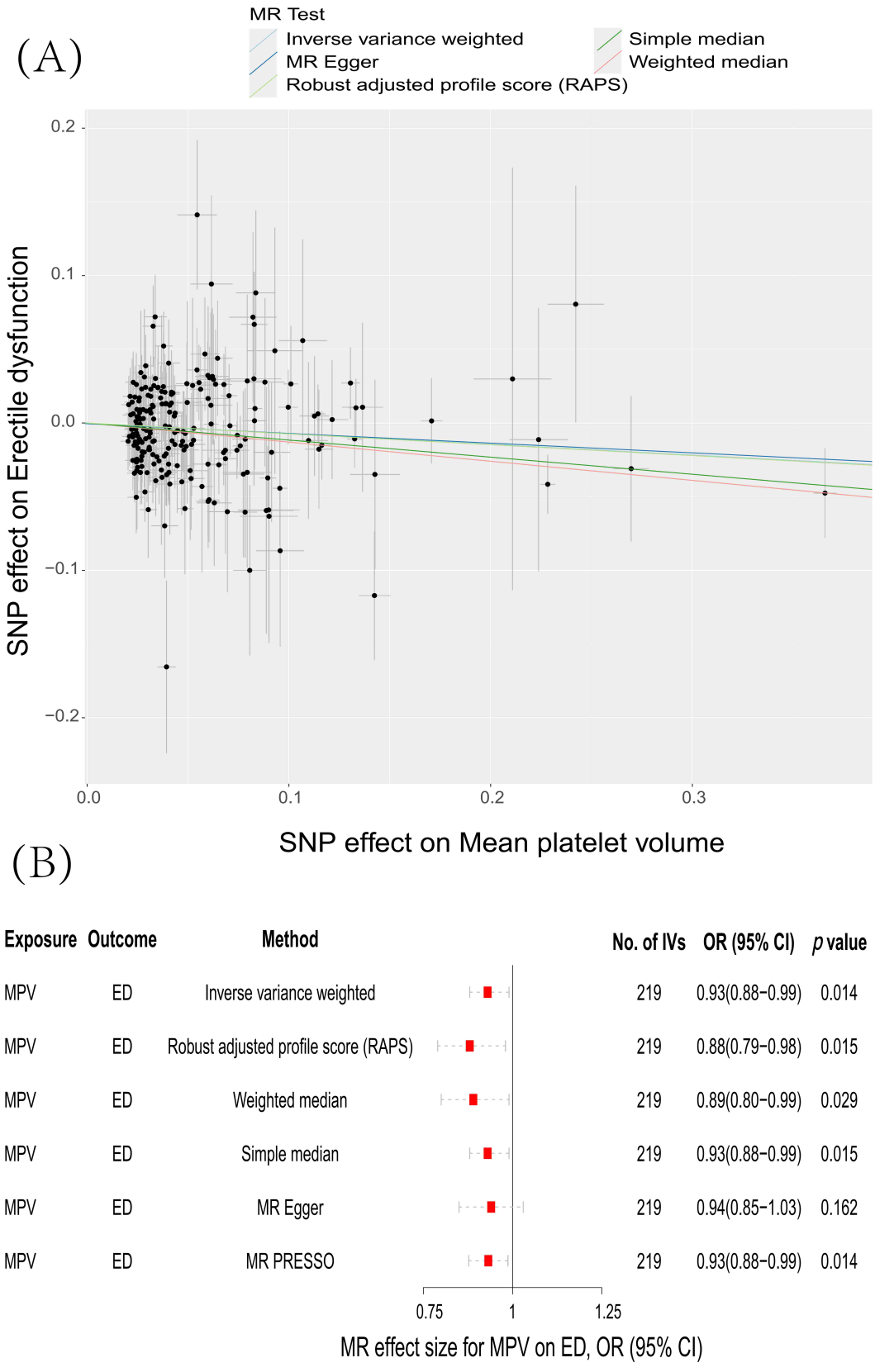


FIGURE 11. Univariable MR results for the effects of HBC traits on ED. (A) The forest plot of MR estimates for PC on ED. (B) The forest plot of MR estimates for MPV on ED. Error bars represent 95% CI. MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; IVs, the number of instrumental variables; ED, erectile dysfunction; HBC, human blood cell; MPV, mean platelet volume; CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism; CI, confidence intervals.

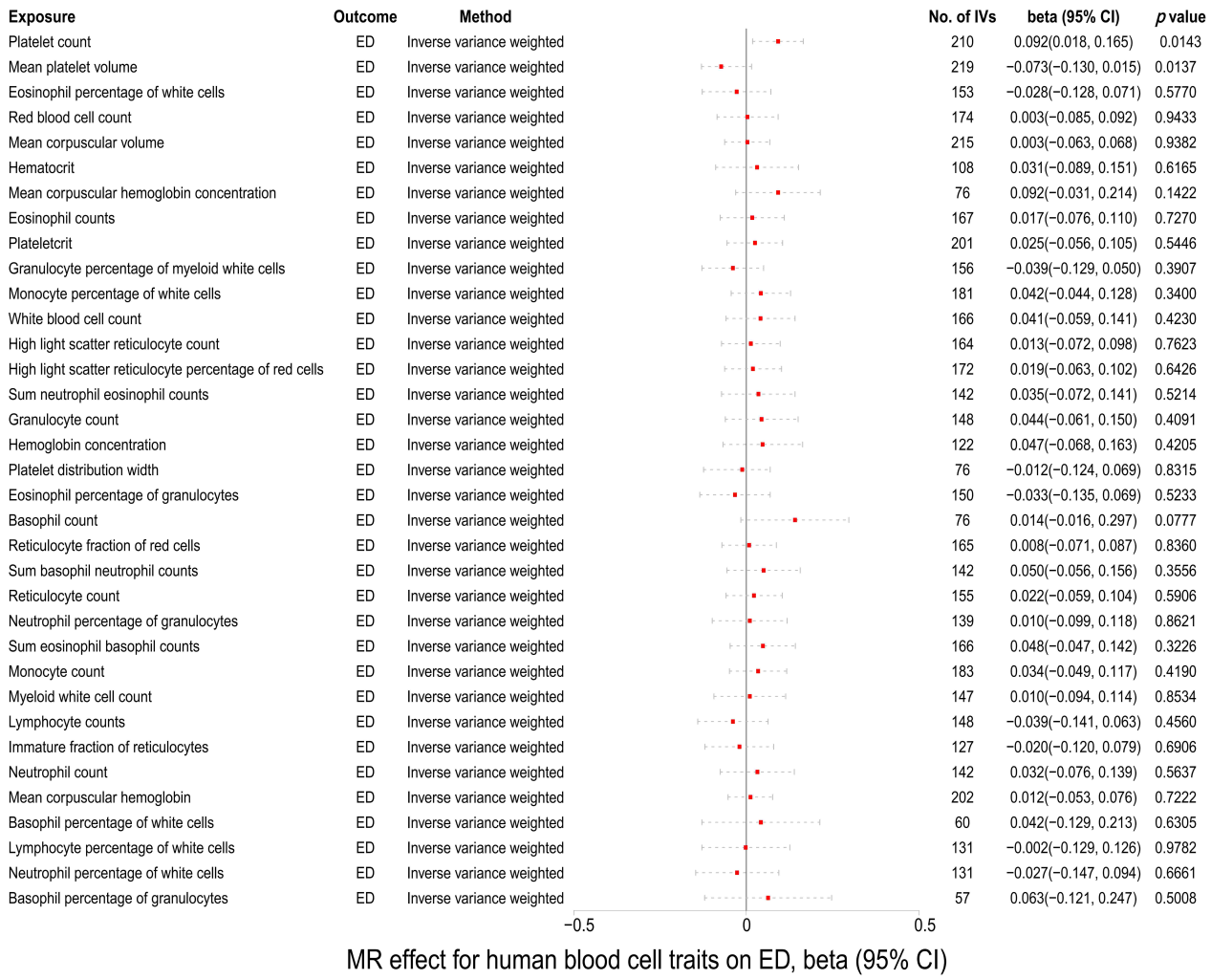


FIGURE 12. The forest plot of Mendelian randomization estimates for 35 HBC traits on erectile dysfunction. ED, erectile dysfunction. CI, confidence interval; OR, odds ratio; IVs, the number of instrumental variables. Error bars represent 95% CI.

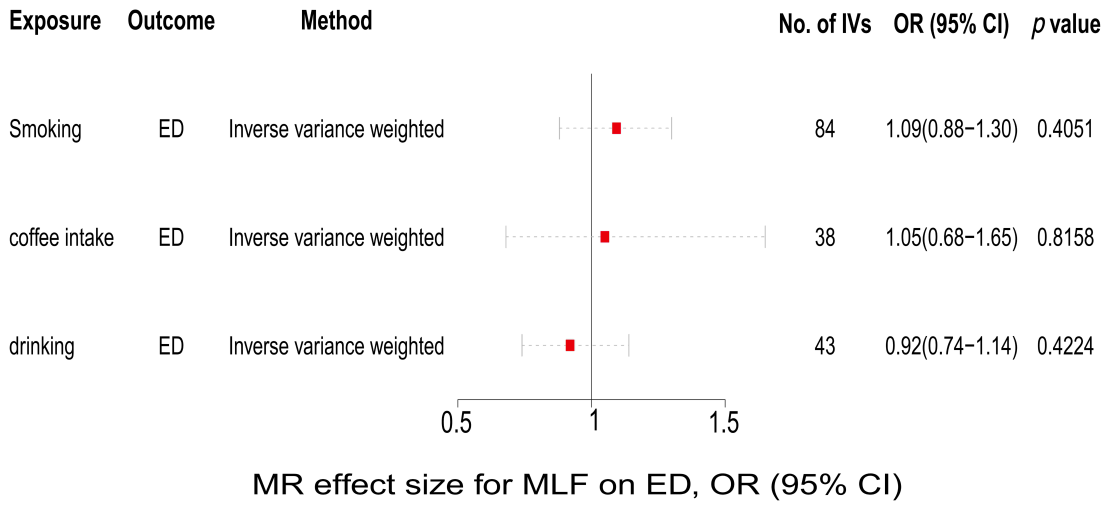


FIGURE 13. Univariable MR results for the effects of modifiable lifestyle factors on ED. The forest plot of MR estimates for modifiable lifestyle factors on ED. MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; IVs, the number of instrumental variables; ED, erectile dysfunction; CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism. MLF: Modifiable lifestyle factors.

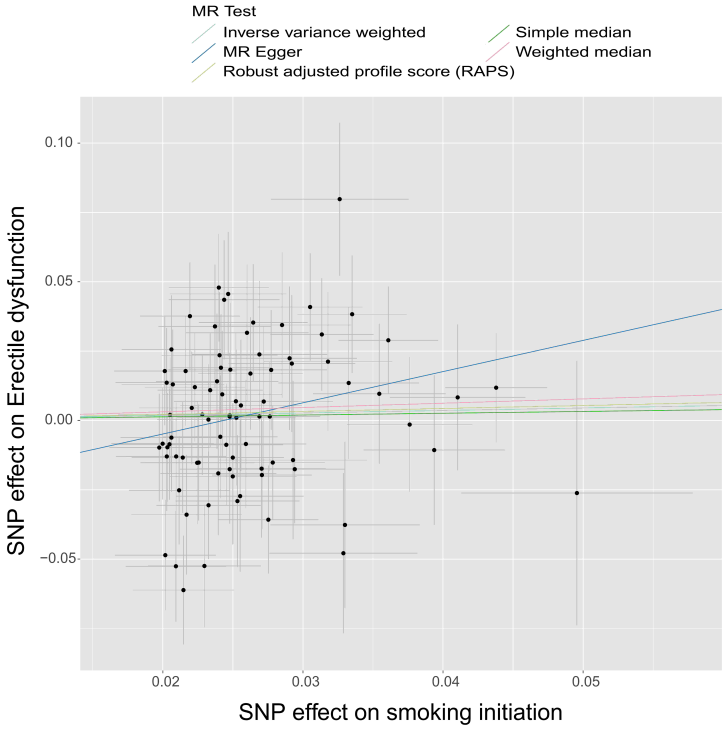


FIGURE 14. Univariable MR results for the effects of modifiable lifestyle factors on ED. Each point represents the SNP effects on smoking initiation and ED. MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; IVs, the number of instrumental variables; ED, erectile dysfunction; CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism.

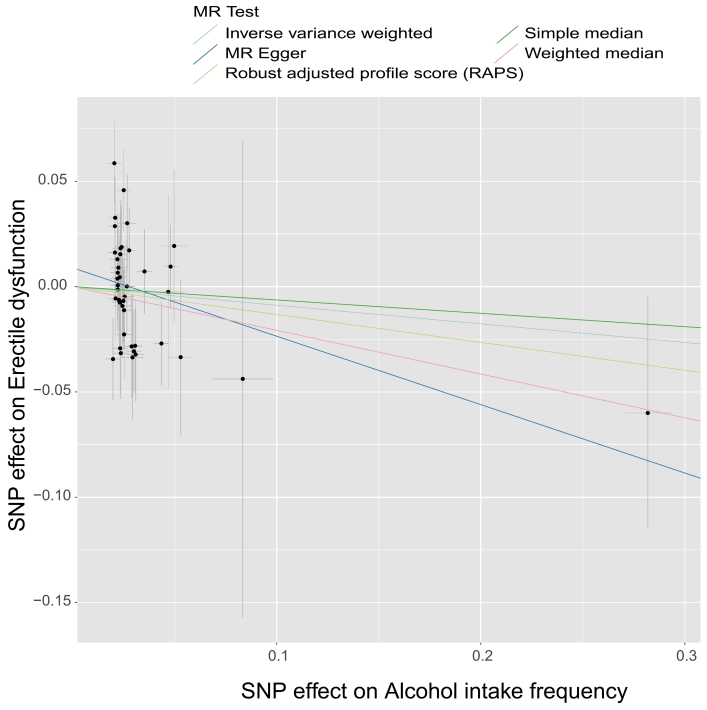


FIGURE 15. Univariable MR results for the effects of modifiable lifestyle factors on ED. Each point represents the SNP effects on Alcohol intake frequency (drinking) and ED. MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; IVs, the number of instrumental variables; ED, erectile dysfunction; CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism.

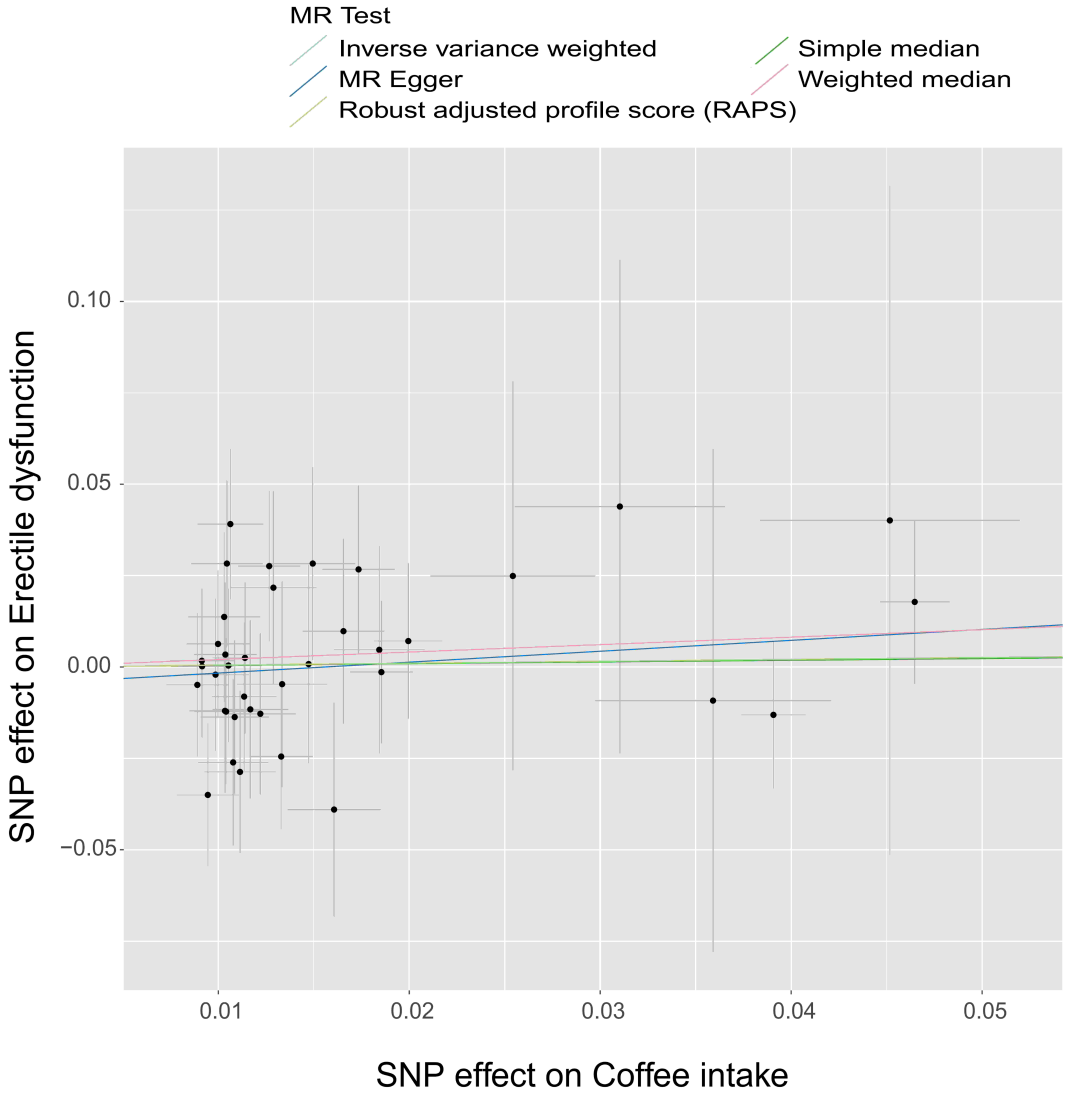


FIGURE 16. Univariable MR results for the effects of modifiable lifestyle factors on ED. Each point represents the SNP effects on coffee intake and ED. MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; IVs, the number of instrumental variables; ED, erectile dysfunction; CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphism.

to improve treatments for those affected [66, 67]; (2) the strong relationship between mood disorders and metabolic syndrome (obesity and dyslipidemia, *etc*.) [65, 68, 69], the intricate interplay between mental stress (MS) and metabolic syndrome is reflected by the association between MS and vascular endothelial damage, a condition that may underlie the development of ED [70–72]. Although positive psychological emotions, including happiness and subjective well-being, have been found to have a mitigating effect on depressive symptoms [19], it appears that their impact is limited as they do not appear to be effective in improving ED. Furthermore, our findings suggest that individuals with negative psychological traits such as major depression, irritability and neuroticism may be at a higher risk for developing ED, our findings are in agreement with prior investigations, corroborating the veracity of previous scientific work in this area [73, 74]. The evidence gleaned from our study serves to augment the existing pool of clinical data and provides greater insight into the therapeutic potential of IM for treating ED.

A unified conclusion regarding the causality between HBC traits and ED among related studies, including ours, has not yet been reached. In the intricate web of human health and disease, the role of platelets has been a subject of great interest and exploration. A study involving 230 patients has shed new light on the potential link between platelet traits and ED. The study found that 130 patients with ED had significantly higher MPV and platelet count than the 100 control patients, highlighting the potential role of platelets in the pathogenesis of ED [75]. In the intricate web of human health and disease, the role of platelets has been a subject of great interest and exploration. Our MR analysis supported platelet traits, including MPV and platelet count, as potential risk factors for ED. Although heterogeneity was not found after Cochrane's Q-test in the IVW analysis, the results of multivariable MR did not provide evidence for a causal relationship between platelet traits and ED. Despite this, there is growing evidence to suggest that platelets play a significant role in the development of ED, particularly in vasculogenic ED. Platelets have been implicated

in the formation of clots that can lead to blockages in the cavernosal walls, thereby reducing blood flow and impairing erectile function. Furthermore, platelets have been shown to secrete mediators that increase oxidative stress during erection, further exacerbating the pathogenesis of ED. As we continue to explore the complex interplay between platelets and ED, let us strive to uncover new insights into the pathogenesis of this debilitating condition, and pave the way for new treatments and therapies that can improve the lives of millions of affected individuals [76]. Our study did not provide evidence for a causal relationship between other HBC traits (*i.e.*, red cell and white cell components) in the ED, although an association between them and ED cannot be excluded. Therefore, more studies with a larger sample size are needed for more robust evidence.

Smoking, coffee intake, and drinking are all modifiable lifestyle factors of ED. A previous study had showed that smoking and drinking were important risk factors for ED. In the realm of human health and wellness, the intricacies of the male physiology have been a subject of great interest and exploration. A cross-sectional survey of 8367 Australian men between the ages of 16 and 59 has revealed new insights into the impact of lifestyle factors on ED. The adjusted odds ratios for ED were found to be 1.39 (95% CI 1.05 to 1.83, p = 0.02) for those who smoked more than 20 cigarettes per day. These findings underscore the importance of recognizing the harmful effects of smoking on male sexual health. However, there is hope. The survey also revealed that moderate alcohol consumption, defined as 1–4 drinks per day, can significantly reduce the likelihood of having ED. These results offer a glimmer of light amidst the darkness, and suggest that there are lifestyle changes that can be made to positively impact male sexual health. Let us continue to explore the complex interplay between lifestyle and male physiology, and strive to uncover new ways to promote health and wellbeing [77]. However, our study did not discover a casual association between smoking, drinking and ED. It is unclear if drinking coffee has any effect on urological conditions like ED, despite previous studies suggesting that coffee may have benefits for chronic diseases. More research is needed to understand this relationship. Mykoniatis *et al.* [78] discovered that coffee intake could be beneficial to ED patients, of which caffeine might have a positive effect [78, 79]. A large prospective cohort study of 51,529 individuals discovered that coffee intake was not associated with ED occurrence [79]. The study did not find a clear link between coffee and ED, but there might be a weak and non-linear relationship between them. More research is needed to understand this potential connection.

The major strengths of the present study are the MR design and the considerable number of ED cases. Moreover, all the recruited participants in the GWAS were of European origin, excluding the interference of bias in population stratification.

Some limitations of this study should be acknowledged. It is difficult to tell apart the causes of vasculogenic ED and neurogenic ED. However, most cases of ED in the western world are thought to be due to problems with blood vessels. But, ED can have multiple causes and involve both physical and psychological factors. Moreover, one potential issue is that the criteria for determining whether a psychological trait is positive or negative may not be clear or universally agreed upon. Psychological traits are complex and multifaceted, and there is no widely accepted framework for categorizing them as either positive or negative. According to the current literature, we strived for more objective and culturally sensitive approaches to evaluating psychological traits. Due to the lack of adequate literature support, we could rely on subjective judgments when evaluating and categorizing these traits. This subjective categorization might lead to bias.

5. Conclusions

We have established a causal link between HBP and ED, and we have also found evidence suggesting a causal relationship between IM and ED. HBP and IM could be independent risk factors, but the mechanism of the association between them and ED remains to be discovered. Moreover, it seems that positive psychological traits may not necessarily reduce the incidence of ED, despite the fact that negative psychology might lead to ED.

AVAILABILITY OF DATA AND MATERIALS

The summary statistics performed in this study can be obtained upon request from the Open GWAS database (https://gwas.mrcieu.ac.uk/).

AUTHOR CONTRIBUTIONS

ZS, JH and YPL—drafted the manuscript. HS, ZQF, STS, PL, BX—contributed to the data analysis and manuscript revision. ZW—supervised the whole research and is responsible for the integrity of data analysis. All authors contributed to the article and approved the submitted version.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

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FUNDING

This research received no external funding.

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/1707273346819735552/attachment/Supplementary%20material.zip.

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