四川大学学报（医学版） 2024，55（3）：566－573
J Sichuan Univ（Med Sci） doi: 10.12182/20240560106

在线全文

高雄激素血症检测指标与子痫前期的遗传因果性研究*

林婵余[1]， 陈静波[2]， 赵晓苗[1,2△]

1. 广东药科大学（广州 510006）；2. 广东省人民医院（广州 510000）

【摘要】 目的 运用双样本孟德尔随机化（two sample Mendelian randomization, 2SMR）方法，揭示高雄激素血症的临床检测指标与子痫前期的因果关联。**方法** 利用来自英国生物银行队列的全基因组关联研究（genome-wide association study, GWAS）数据，分析雄激素指数的相关单核苷酸多态性（single nucleotide polymorphism, SNP）位点〔包括总睾酮（total testosterone, TT）、生物可利用睾酮（bioavailable testosterone, BIOT）和性激素结合球蛋白（sex hormone binding globulin, SHBG）〕。同时，使用芬兰数据库中关于子痫前期和原发性高血压并发子痫前期的GWAS数据统计SNP位点。采用5种遗传因果性分析方法（包括随机效应逆方差加权法等）推测因果关系，并通过敏感性分析评估异质性和位点多效性。**结果** 根据遗传变异工具变量筛选标准，筛选出与雄激素指标TT、BIOT、SHBG具有统计学显著相关的186、127、262个SNP位点作为遗传工具变量。孟德尔随机化（Mendelian randomization, MR）分析未发现TT、BIOT、SHBG水平与子痫前期及原发性高血压并发子痫前期发病风险之间存在因果关系。其中，SHBG在与子痫前期MR分析中显示异质性（Cochran's Q检验，P=0.01），BIOT在与原发性高血压并发子痫前期MR分析中显示位点多效性，其他工具变量未显示显著异质性或多效性。**结论** MR分析结果表明，目前的遗传预测证据不支持TT、BIOT、SHBG水平与子痫前期以及原发性高血压并发子痫前期之间存在因果关系。

【关键词】 睾酮 子痫前期 孟德尔随机化分析

Genetic Causation Analysis of Hyperandrogenemia Testing Indicators and Preeclampsia

LIN Chanyu[1], *CHEN Jingbo*[2], *ZHAO Xiaomiao*[1,2△]. 1. *Guangdong Pharmaceutical University*, Guangzhou 510006, China; 2. *Reproductive Center of Guangdong Provincial People's Hospital*, Guangzhou 510000, China

△ Corresponding author, E-mail: zhaoxmiao@163.com

【Abstract】 Objective Some epidemiological studies have shown that pregnant women who develop preeclampsia (PE) have elevated levels of testosterone in their maternal plasma compared to women with normal blood pressure during pregnancy, revealing a potential association between hyperandrogenism in women and PE. To explore the causal relationship between hyperandrogenism and PE, this study selected total testosterone (TT), bioavailable testosterone (BIOT), and sex hormone binding globulin (SHBG) as exposure factors and PE and chronic hypertension with superimposed PE as disease outcomes. Two-sample Mendelian randomization (MR) analyses were used to genetically dissect the causal relationships between the three exposure factors (TT, BIOT, and SHBG) and the outcomes of PE and chronic hypertension with superimposed PE. **Methods** Two independent genome-wide association study (GWAS) databases were used for the two-sample MR analysis. In the GWAS data of female participants from the UK Biobank cohort, single nucleotide polymorphisms (SNPs) associated with TT, BIOT, and SHBG were analyzed, involving 230 454, 188 507, and 188 908 samples, respectively. GWAS data on PE and chronic hypertension with superimposed PE from the Finnish database were used to calculate SNP, involving 3 556 PE cases and 114 735 controls, as well as 38 cases of chronic hypertension with superimposed PE and 114 735 controls. To meet the assumptions of instrumental relevance and independence in MR analysis, SNPs associated with exposure were identified at the genome-wide level (P<5.0×10^{-8}), and those in linkage disequilibrium interference were excluded based on clustering thresholds of R^2<0.001 and an allele distance greater than 10 000 kb. Known confounding factors, including previous PE, chronic kidney disease, chronic hypertension, diabetes, systemic lupus erythematosus, or antiphospholipid syndrome, were also identified and the relevant SNPs were removed. Finally, we extracted the outcome data based on the exposure-related SNPs in the outcome GWAS, integrating exposure and outcome data, and removing palindromic sequences. Five genetic causal analysis methods, including inverse variance-weighted method (IVW), MR-Egger regression, weighted median method, simple mode method, and weighted mode method, were used to infer causal relationships. In the IVW, it was assumed that the selected SNPs satisfied the three assumptions and provided the most ideal estimate of the effect. IVW was consequently used as the primary analysis method in this study. Considering the potential heterogeneity among the instrumental

* 国家自然科学基金（No. 82271661）资助

△ 通信作者，E-mail: zhaoxmiao@163.com

出版日期：2024-05-20

variables, random-effects IVW was used for MR analysis. The results were interpreted using odds ratios (OR) and the corresponding 95% confidence interval (CI) to explain the impact of exposure factors on PE and chronic hypertension with superimposed PE. If the CI did not include 1 and had a *P* value less than 0.05, the difference was considered statistically significant. Sensitivity analysis was conducted to assess heterogeneity and pleiotropy. Heterogeneity was examined using Cochran's *Q* test, and pleiotropy was assessed using MR-Egger intercept analysis. Additionally, leave-one-out analysis was conducted to examine whether individual SNPs were driving the causal associations. To further validate the findings, MR analyses were performed using the same methods and outcome variables, but with different exposure factors, including waist-to-hip ratio adjusted for BMI (WHRadjBMI) and 25-hydroxyvitamin D levels, with MR results for WHRadjBMI and PE serving as the positive controls and MR results for 25-hydroxyvitamin D levels and PE as the negative controls. **Results** According to the criteria for selecting genetic instrumental variables, 186, 127, and 262 SNPs were identified as genetic instrumental variables significantly associated with testosterone indicators TT, BIOT, and SHBG. MR analysis did not find a causal relationship between the TT, BIOT, and SHBG levels and the risk of developing PE and chronic hypertension with superimposed PE. The IVW method predicted that genetically predicted TT (OR [95% CI]=1.018 [0.897-1.156], *P*=0.78), BIOT (OR [95% CI]=1.11 [0.874-1.408], *P*=0.392), and SHBG (OR [95% CI]=0.855 [0.659-1.109], *P*=0.239) were not associated with PE. Similarly, genetically predicted TT (OR [95% CI]=1.222 [0.548-2.722], *P*=0.624), BIOT (OR [95% CI]=1.066 [0.242-4.695], *P*=0.933), and SHBG (OR [95% CI]=0.529 [0.119-2.343], *P*=0.402) were not significantly associated with chronic hypertension with superimposed PE. Additionally, MR analysis using the MR-Egger method, weighted median method, simple mode method, and weighted mode method yielded consistent results, indicating no significant causal relationship between elevated testosterone levels and PE or chronic hypertension with superimposed PE. Heterogeneity was observed for SHBG in the analysis with PE (Cochran's *Q* test, *P*=0.01), and pleiotropy was detected for BIOT in the analysis with PE (MR-Egger intercept analysis, *P*=0.014), suggesting that the instrumental variables did not affect PE through BIOT. Other instrumental variables did not show significant heterogeneity or pleiotropy. Leave-one-out analysis confirmed that the results of the MR analysis were not driven by individual instrumental variables. Consistent with previous MR studies, the results of the control MR analyses using WHRadjBMI and 25-hydroxyvitamin D levels supported the accuracy of the MR analysis approach and the methods used in this study. **Conclusion** The MR analysis results suggest that current genetic evidence does not support a causal relationship between TT, BIOT, and SHBG levels and the development of PE and chronic hypertension with superimposed PE. This study suggests that elevated testosterone may be a risk factor for PE but not a direct cause.

【Key words】 Testosterone　Preeclampsia　Mendelian randomization analysis

子痫前期(preeclampsia, PE)作为一种妊娠期的严重并发症,在我国的发病率约为4.2%[1],全球每年约7万名孕产妇和50万名婴儿因此死亡[2],是导致母亲和围产儿死亡的重要原因之一。先兆子痫幸存者的预期寿命缩短,中风、心血管疾病和糖尿病的风险增加,而先兆子痫妊娠的胎儿发生早产、围产期死亡、神经发育迟缓以及心血管和代谢疾病的风险增加[3]。因此,亟须开展PE的早筛早防治研究,保障高危人群的母子健康。

一些流行病学研究显示,与血压正常的妊娠相比,并发PE的妊娠期母体血浆睾酮水平有所升高[4-5]。然而既往研究多为观察性研究且样本量有限,易受到混杂因素和反向因果关系的干扰[6],因此其结果缺乏准确性和可靠性,且鲜有文献提及雄激素与PE之间是否存在因果关系。孟德尔随机化(Mendelian randomization, MR)利用与暴露显著相关的单核苷酸多态性(single nucleotide polymorphism, SNP)作为工具变量(instrumental variable, IVs),每个SNP都模仿一个独立的随机对照试验来揭示暴露与结局之间的因果关系。这种方法消除了潜在的环境或社会混杂因素以及反向因果关系的影响,可以提供更有力、更准确的证据[7]。此外,双样本孟德尔随机化(two sample Mendelian randomization, 2SMR)分析基于两个独立的全基因组关联研究(genome-wide association study, GWAS)数据库,利用大样本量和增强的统计能力进行分析,从而提供更有说服力的因果关系证据。目前有许多研究以PE作为结局进行MR分析[8-15]。然而,尚无研究通过MR分析探讨高雄激素血症检测指标与PE之间的因果关系。

本研究选择了高雄激素血症常用检测指标总睾酮(total testosterone, TT)、生物可利用睾酮(bioavailable testosterone, BIOT)、性激素结合球蛋白(sex hormone binding globulin, SHBG)作为暴露因素,PE、原发性高血压并发子痫前期(chronic hypertension with superimposed preeclampsia , CH-PE)作为疾病结局,采用2SMR分析从遗传角度分别解析TT、BIOT和SHBG三种暴露因素与PE和CH-PE之间的因果关系。此外,为了进一步验证研究结果,本研究分别使用体重指数调整后的腰臀比

(WHRadjBMI)和25-羟基维生素D水平作为暴露因素,PE作为结局进行阳性和阴性对照分析,并同时探讨这两种暴露因素与CH-PE之间是否存在因果关系。

1 资料与方法

1.1 数据来源

采用英国生物银行队列中女性参与者的GWAS数据,以研究雄激素与PE之间的关联。汇总2020年RUTH等[16]发表的数据,统计临床雄激素指标包括TT、BIOT以及SHBG显著相关的SNP位点,分别涉及230 454、188 507、189473例样本。使用欧洲生物信息学研究所中WHRadjBMI和25-羟基维生素D水平的GWAS汇总数据来计算对照分析中暴露相关的SNP位点。使用芬兰数据库中PE和CH-PE的GWAS汇总数据来计算疾病相关的SNP位点。这些数据分别涉及3 556个PE病例和114 735个对照,以及38个CH-PE病例和114 735个对照。所使用的暴露GWAS和结局GWAS数据均源自欧洲人群,以减少人群分层的问题。GWAS的详细信息参见资源附件中附表S1。

1.2 工具变量选择

工具变量需要满足 3 个条件假设:①相关性假设:IVs与暴露因素高度相关;②独立性假设:IVs不能与混杂因素相关联;③排他性假设:暴露因素是IVs影响结局的唯一途径[17]。

为满足相关性假设,本研究在全基因组水平($P<5.0\times10^{-8}$)上确定与暴露相关的SNP[14];随后,以聚类阈值为$R^2<0.001$、等位基因距离大于10 000 kb的标准排除连锁不平衡的干扰[6]。为满足独立性假设,根据DIMITRIADIS等[18]的研究,既往PE、慢性肾病、原发性高血压、糖尿病、系统性红斑狼疮或抗磷脂综合征被认为是PE发病的高危因素。此外,基于PE作为结局的MR研究中,发现类风湿关节炎[14]、WHRadjBMI[11]、尿白蛋白/肌酐比值[9],以及甲烷短菌[8]与PE之间存在正向的因果关系。通过搜索PhenoScanner数据库[19](http://www.phenoscanner.medschl.cam.ac.uk),剔除在全基因组显著性水平($P<5.0\times10^{-8}$)上与上述潜在混杂因素相关的SNP,将其保存为暴露数据。随后,用F值($F=\mathrm{Beta}^2/\mathrm{SE}^2$)来评价弱工具变量效应,$F$值>10的工具变量被认为是强工具变量[20]。最后,在结局GWAS中根据暴露相关SNP提取结局数据,整合暴露数据和结局数据,并剔除回文SNP序列。

1.3 2SMR分析方法

本研究运用了多种MR分析方法,包括随机效应逆方差加权法(inverse variance weighted, IVW)、MR-Egger回归法、加权中位数法(weighted median, WM)、简单模式法以及加权模式法[21]。随机效应IVW法假设所选取的SNP满足三大条件假设,提供了最理想的效应估计值。MR-Egger回归法的计算过程与随机效应IVW法类似。不同之处在于MR-Egger回归法假设所有SNP都是无效的IVs,并通过回归截距来估计无效工具变量的影响。然而,无效的IVs会降低MR-Egger法的统计能力。其次,如果50%以上的IVs是有效的,那么WM法可以提供准确的估计结果。此外,简单模式法将具有相似因果效应值的SNP进行分簇,将最大SNP簇的因果效应估计值作为最后的因果效应估计值。加权模式法的过程与简单模式法相似,但为每个SNP分配权重。基于随机效应IVW法比其他4种方法检验效能更高,因此本研究采取随机效应IVW法作为主效分析,将TT、BIOT、SHBG与PE、CH-PE分别进行MR分析,共进行6次MR分析。为了进一步验证研究结果,我们使用了相同的方法和结局变量以及不同的暴露因素(WHRadjBMI和25-羟基维生素D水平)进行了4次MR分析,其中WHRadjBMI与PE的MR结果作为阳性对照,25-羟基维生素D水平与PE的MR结果作为阴性对照。结果用比值比(odds ratio, OR)值以及相应的95%置信区间(confidence interval, CI)来解释暴露因素对PE、CH-PE的影响。如果置信区间不包含1,并且$P<0.05$,则表明差异有统计学意义,即高雄激素血症检测指标中的TT、BIOT、SHBG与PE或CH-PE之间存在显著关联,若随机效应IVW法、MR-Egger法等5种方法的结果一致,则结论将更加可靠。

1.4 敏感性分析

本研究采用Cochran's Q统计量进行异质性检验,$P<0.05$为差异有统计学意义。采用MR-Egger截距分析来进行多效性检验,$P<0.05$为差异有统计学意义,表明工具变量存在多效性,即工具变量不通过暴露因素影响结局,这表明结果的可靠性受到了多效性的影响。此外,本研究采用留一法检验是否存在单个SNP驱动因果关联。

2 结果

2.1 工具变量筛选结果

过滤掉不符合在全基因组水平($P<5.0\times10^{-8}$)与暴露相关的SNP,排除存在连锁不平衡的SNP位点,TT、BIOT、SHBG所有SNP中分别有235、156、351个SNP满足相关性假设。经过剔除高血压、糖尿病、类风湿性关节炎等混杂因素相关SNP后,TT、BIOT、SHBG所有SNP中分别有213、138、302个SNP被认定满足独立性假设。

TT的SNP的F值范围是23.65 ~ 1 194.13,BIOT的SNP的F值范围是25.44 ~ 1 060.35,SHBG的SNP的F值范围

是20.76 ~ 1 318.22, 均大于10, 因此不存在弱工具变量。

最后, 整合暴露数据和结局数据, 并剔除回文SNP序列, 本研究筛选了186个SNP作为TT的IVs, 127个SNP作为BIOT的IVs, 以及262个SNP作为SHBG的IVs, 见表1。

表 1　遗传工具变量筛选过程

Table 1　Genetic instrumental variable selection process

Exposure	Associated with exposure (P<5.0×10^{-8})	After excluding LD	Independent of confounding factors	IVs
TT	30 223	235	213	186
BIOT	15 823	156	138	127
SHBG	53 178	351	302	262

TT: total testosterone; BIOT: bioavailable testosterone; SHBG: sex hormone-binding globulin; LD: linkage disequilibrium; IVs: instrumental variable.

此外, 本研究还筛选了WHRadjBMI以及25-羟基维生素D水平的IVs, 具体过程可参见资源附件中附表S2。

2.2　孟德尔随机化分析结果

TT、BIOT、SHBG与PE的随机效应IVW法分析结果显示: 遗传预测的TT与PE〔OR(95%CI)= 1.018(0.897 ~ 1.156), P= 0.78〕的发病无关; 遗传预测的BIOT与PE〔OR(95%CI)= 1.11(0.874 ~ 1.408), P= 0.392〕的发病无关; 遗传预测的SHBG与子痫前期〔OR(95%CI)= 0.855(0.659 ~ 1.109), P= 0.239〕的发病无关。随机效应IVW法分析结果表明高雄激素血症检测指标中的TT、BIOT、SHBG与PE之间没有显著的因果关联。

TT、BIOT、SHBG与CH-PE的随机效应IVW法分析结果显示: 遗传预测的TT与CH-PE〔OR(95%CI)= 1.222(0.548 ~ 2.722), P= 0.624〕的发病无关; 遗传预测的BIOT与CH-PE〔OR(95%CI)= 1.066(0.242 ~ 4.695), P= 0.933〕的发病无关; 遗传预测的SHBG与CH-PE〔OR(95%CI)= 0.529(0.119 ~ 2.343), P= 0.402〕的发病无关。随机效应IVW法分析结果表明高雄激素血症检测指标中的TT、BIOT、SHBG与CH-PE之间没有显著的因果关联。

由图1 ~ 图4可知, 本研究利用MR-Egger法、WM法、简单模式法以及加权模式法分析高雄激素血症检测指标

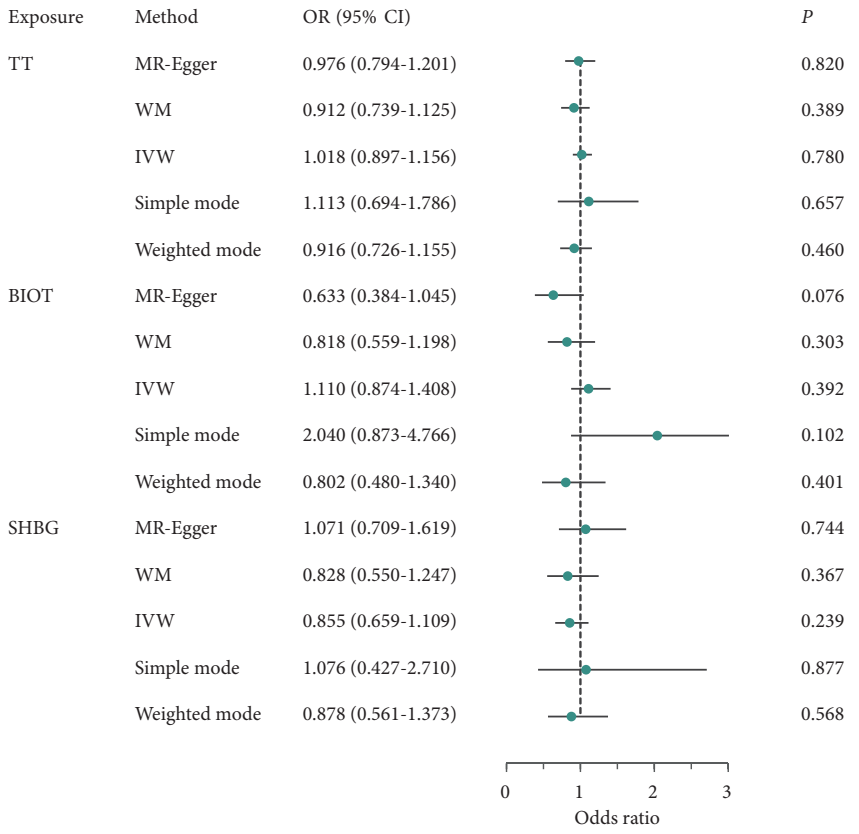

图 1　TT、BIOT、SHBG与PE的MR效应值

Fig 1　MR effect values of TT, BIOT, SHBG, and PE

TT: total testosterone; BIOT: bioavailable testosterone; SHBG: sex hormone-binding globulin; IVW: inverse variance weighted; WM: weighted median.

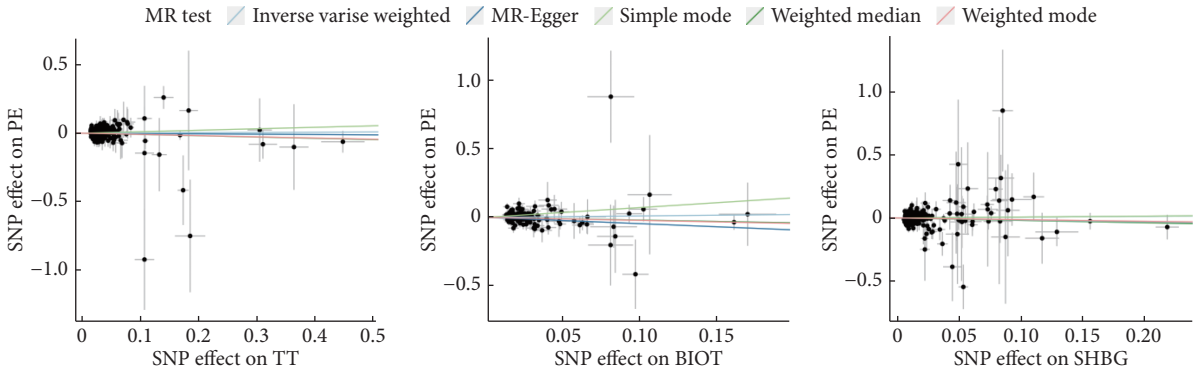

图 2 TT、BIOT、SHBG与PE的MR分析散点图

Fig 2 Scatter plots of MR analysis of TT, BIOT, SHBG, and PE

TT: total testosterone; BIOT: bioavailable testosterone; SHBG: sex hormone-binding globulin; SNP: single nucleotide polymorphism; PE: preeclampsia.

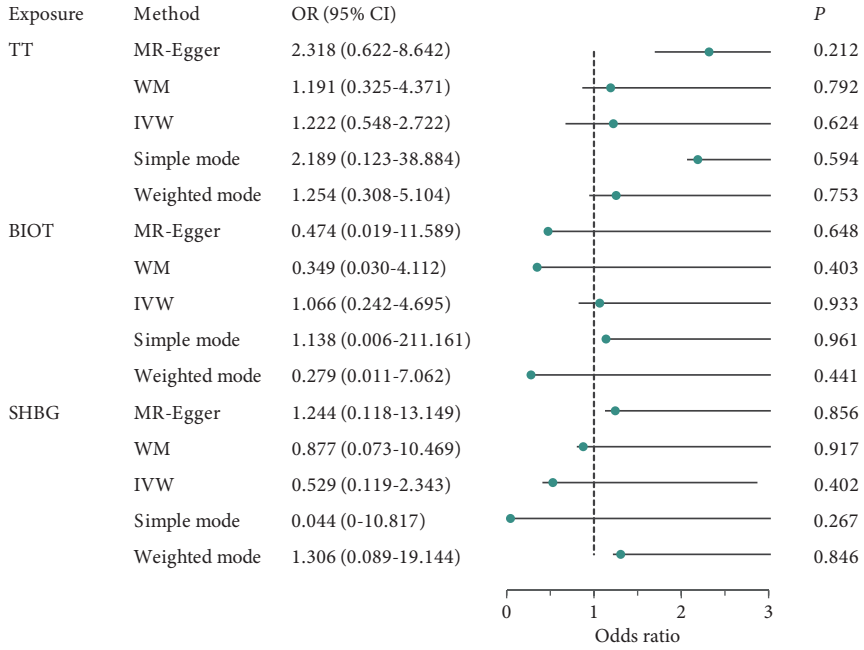

图 3 TT、BIOT、SHBG与CH-PE的MR效应值

Fig 3 MR effect values of TT, BIOT, SHBG, and CH-PE

TT: total testosterone; BIOT: bioavailable testosterone; SHBG: sex hormone-binding globulin; IVW: inverse variance weighted; WM: weighted median.

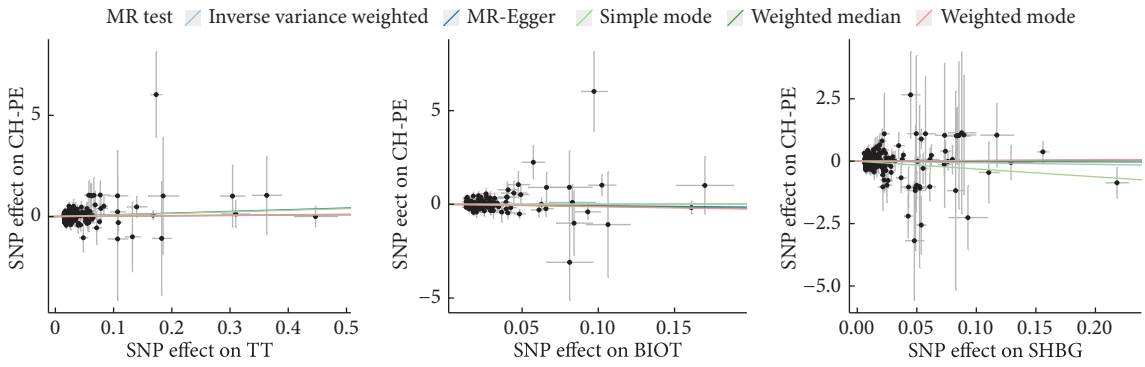

图 4 TT、BIOT、SHBG与CH-PE的MR分析散点图

Fig 4 Scatter plots of MR analysis of TT, BIOT, SHBG, and CH-PE

TT: total testosterone; BIOT: bioavailable testosterone; SHBG: sex hormone-binding globulin; SNP: single nucleotide polymorphism; CH-PE: chronic hypertension with superimposed preeclampsia.

与PE以及CH-PE的因果关系,结果一致表明高雄激素血症检测指标中的TT、BIOT、SHBG与PE以及CH-PE之间没有显著的因果关联。

正如预期,阳性对照中,MR结果显示遗传预测的WHRadjBMI与PE风险相关〔OR(95%CI)= 1.291(1.047 ~ 1.593), *P*= 0.017〕; 对于阴性对照,MR结果显示遗传预测的25-羟基维生素D水平与PE风险无关〔OR(95%CI)= 1.017(0.819 ~ 1.263), *P*= 0.879〕; 见资源附件中附图S1、S2。MR结果显示遗传预测的WHRadjBMI与CH-PE风险无关〔OR(95%CI)= 1.145(0.35 ~ 3.746), *P*= 0.823〕,遗传预测的25-羟基维生素D水平与CH-PE风险无关〔OR(95%CI)= 2.165(0.588 ~ 7.976), *P*= 0.246〕,WHRadjBMI和25-羟基维生素D水平与CH-PE的MR结果参见资源附件中附图S3、附图S4。

2.3　敏感性分析结果

SHBG与PE的Cochran's *Q*检验结果表明SHBG与PE的MR分析中所使用的SNP存在异质性(*P*< 0.05),由于随机效应IVW法选取了随机效应模型,其结果依然具有可靠性。TT、BIOT与PE和TT、BIOT、SHBG与CH-PE的Cochran's *Q*检验结果均提示SNP之间不存在异质性(*P*> 0.05),见表2。

表 2　敏感性分析

Table 2　Sensitivity analysis

Outcome	Exposure	*P* for heterogeneity test	*P* for pleiotropy test
PE	TT	0.769	0.615
	BIOT	0.078	0.014
	SHBG	0.01	0.169
CH-PE	TT	0.906	0.231
	BIOT	0.120	0.576
	SHBG	0.679	0.361

TT: total testosterone; BIOT: bioavailable testosterone; SHBG: sex hormone-binding globulin; PE: preeclampsia; CH-PE: chronic hypertension with superimposed preeclampsia.

BIOT与PE的MR-Egger截距分析结果表明BIOT与PE的MR分析中所使用的SNP存在多效性(*P*< 0.05),即工具变量不通过BIOT而影响PE的发生。TT、SHBG与PE和TT、BIOT、SHBG与CH-PE的MR-Egger截距分析结果均提示不存在多效性(*P*> 0.05),见表2。通过留一法验证,MR分析的结果不受单个工具变量的干扰,见资源附件中附图S5 ~ 附图S10。

WHRadjBMI、25-羟基维生素D水平与PE、CH-PE的MR分析并未出现多效性。具体敏感性分析结果参见资源附件中附表S3,留一法验证结果参见资源附件中附图S11 ~ 附图S14。

3　讨论

通过2SMR分析,本研究旨在探究高雄激素血症检测指标中的TT、BIOT和SHBG水平与PE、CH-PE之间的遗传因果关联。结果显示,尽管由于多效性的存在,BIOT与PE之间的因果关系存在不确定性,然而,基于遗传预测的TT和SHBG与PE之间没有显著的因果关联,TT、BIOT和SHBG与CH-PE之间也没有明显的因果关系。因此,本研究未能发现高雄激素血症检测指标中的TT、BIOT和SHBG水平对PE和CH-PE的发生具有直接的因果作用。

对照MR分析显示,本研究MR结果支持遗传预测的WHRadjBMI与PE风险相关,这与VENKATESH等[11]的2SMR研究一致。观察性研究的荟萃分析表明,25-羟基维生素D浓度与PE之间存在负相关[22]。然而,本研究MR结果与MAGNUS等[15]的MR研究结果一致,未发现遗传预测的25-羟基维生素D水平与PE之间存在因果关联。本研究对照MR分析结果与既往报道的MR研究一致,证实了本研究中所采用的MR分析流程和方法的准确性。该一致性进一步加强了对于高雄激素血症检测指标与PE之间缺乏因果关系这一结论的可信度。

当前,PE的确切病因仍有争议,但多因素、多通路共同参与PE的发生已成为普遍共识。其中,胎盘缺陷与子宫螺旋动脉重塑失败被认为是PE发病机制的关键[23]。螺旋动脉重塑失败可引发母体血管狭窄和胎盘相对缺血,但介导这一过程的分子机制尚未明确。GOPALAKRISHNAN等[24]的研究显示,妊娠大鼠中睾酮水平的升高可导致子宫动脉血流量减少、血流阻力指数上升,桡动脉和螺旋动脉直径和长度、胎盘动脉分支数和脐动脉直径均减小,甚至出现胎盘缺氧,这一结果与螺旋动脉重塑失败的表现颇为相似。然而,该研究并未明确阐述雄激素破坏螺旋动脉重塑的具体机制。CHINNATHAMBI等[25]的研究将妊娠大鼠的母体睾酮水平升高至人类先兆子痫中的睾酮水平,可导致妊娠大鼠全身动脉压升高。以上研究结果结合本研究结果提示,雄激素可能是PE发病的高危因素之一,但并非导致PE的直接诱因。雄激素可能是PE病理胎盘的一种代偿性变化,而这种代偿性变化可能导致母体血流动力学调节失衡。这一观点仍需进一步深入研究证实。

本研究创新地采用MR进行分析,该方法可有效克服潜在的混杂因素和反向因果关系的影响。此外,暴露因素数据与结局数据来自不同的队列,且涵盖足够数量的样本,暴露因素和结局之间的人群重叠率较低。本研究

也存在一定的局限性。首先,BIOT与PE的MR分析中出现多效性,导致该分析结果无效。其次,纳入的数据未进行年龄分层分析,研究结果可能存在一定的偏倚。第三,本研究数据来自欧洲人群,研究结果是否适用于其他人群有待进一步证实。

综上所述,人群中遗传预测证据表明TT、BIOT、SHBG的浓度与PE以及CH-PE之间不存在因果关系,该结果提示雄激素可能是PE发病的高危因素之一,但并非导致PE的直接诱因。

* * *

作者贡献声明 林婵余负责数据审编、正式分析、调查研究、研究方法、软件、验证、可视化和审读与编辑写作,陈静波负责监督指导、初稿写作和审读与编辑写作,赵晓苗负责论文构思、经费获取、研究项目管理、提供资源和监督指导。所有作者已经同意将文章提交给本刊,且对将要发表的版本进行最终定稿,并同意对工作的所有方面负责。

Author Contribution LIN Chanyu is responsible for data curation, formal analysis, investigation, methodology, software, validation, visualization, and writing--review and editing. CHEN Jingbo is responsible for supervision, writing--original draft, and writing--review and editing. ZHAO Xiaomiao is responsible for conceptualization, funding acquisition, project administration, resources, and supervision. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

利益冲突 所有作者均声明不存在利益冲突

Declaration of Conflicting Interests All authors declare no competing interests.

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（2024 – 01 – 19收稿, 2024 – 05 – 02修回）

编辑　余　琳