孟德尔随机化探索凝血功能与妊娠期糖尿病的因果关系

曾凡英[1,2]，沈平[2]，郭伟杰[3]，何国琳[1△]

1. 四川大学华西第二医院 产科 出生缺陷与相关妇儿疾病教育部重点实验室（成都 610041）；

2. 四川大学华西空港医院 妇产科（成都 610200）；3. 澳门大学健康科学学院 生物医学科学系（澳门 999078）

【摘要】 目的 采用双样本孟德尔随机化（Mendelian randomization, MR）探究凝血功能〔血管性血友病因子（von Willebrand factor, vWF）、血管性血友病因子裂解酶（a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13, ADAMTS13）、活化部分凝血活酶时间（activated partial thromboplastin time, APTT）、凝血因子8（coagulation factor Ⅷ, FⅧ）、凝血因子11（coagulation factor ⅪⅠ, FⅪ）、凝血因子7（coagulation factor Ⅶ, FⅦ）、凝血因子10（coagulation factor Ⅹ, FⅩ）、内源性凝血酶生成潜能（endogenous thrombin potential, ETP）、血浆纤溶酶原激活抑制剂1（plasminogen activator inhibitor-1, PAI-1）、蛋白C（protein C）、纤溶酶（plasmin）〕与妊娠期糖尿病之间的因果关联，为凝血功能与妊娠期糖尿病发病关联提供遗传学证据支持。方法 通过R包TwoSampleMR（v 0.5.6）对IEU OpenGWAS数据库进行访问，获取妊娠期糖尿病GWAS摘要统计数据。采用逆方差加权法（inverse-variance weighted method, IVW）、MR-Egger法、加权中位数法（weighted median method, WM）对11种凝血功能指标与妊娠期糖尿病之间的因果关联进行MR分析。结果 本研究利用GWAS妊娠期糖尿病汇总统计数据（包含5 687例病例和117 892例对照）进行MR分析，发现基因预测的血浆FⅧ水平与妊娠期糖尿病风险降低存在因果关系〔IVW：比值比（odds ratio, OR）= 0.28，95%置信区间（confidence interval, CI）：0.10～0.75，$P<0.001$；WM: OR=0.30，95%CI: 0.09～0.98，$P<0.001$〕，其他凝血功能指标与妊娠期糖尿病风险未存在因果关系（$P>0.05$）。结论 血浆FⅧ水平与GDM风险存在因果关系，此发现突显了妊娠期间凝血功能和葡萄糖代谢之间的复杂相互作用，但这一发现还需进一步地深入探索。

【关键词】 孟德尔随机化 凝血功能 妊娠期糖尿病

Exploring the Causal Relationship Between Coagulation Function and Gestational Diabetes Mellitus Through Mendelian Randomization *ZENG Fanying*[1,2], *SHEN Ping*[2], *GUO Weijie*[3], *HE Guolin*[1△]. 1. *Key Laboratory of Birth Defects and Related Diseases of Women and Children of the Ministry of Education*, *Department of Obstetrics and Gynecology*, *West China Second University Hospital*, *Sichuan University*, Chengdu 6100041, China; 2. *West China Airport Hospital*, *Sichuan University*, Chengdu 610200, China; 3. *Department of Biomedical Sciences*, *Faculty of Health Sciences*, *University of Macau*, Taipa 999078, Macau SAR, China

△ Corresponding author, E-mail: heguolin19@163.com

【Abstract】 **Objective** To explore the causal association between coagulation function, including von Willebrand factor (vWF), a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13), activated partial thromboplastin time (aPTT), coagulation factor Ⅷ (FⅧ), coagulation factor Ⅺ (FⅪ), coagulation factor Ⅶ (FⅦ), coagulation factor Ⅹ (FⅩ), endogenous thrombin potential (ETP), plasminogen activator inhibitor-1 (PAI-1), protein C, and plasmin, and gestational diabetes mellitus (GDM) using two-sample two-way Mendelian randomization (MR), and to provide genetic evidence for the association between coagulation function and the pathogenesis of GDM. **Methods** The IEU OpenGWAS database was accessed using the R package TwoSampleMR (v 0.5.6) to obtain the statistical data of the genome-wide association study (GWAS) summary of GDM. MR analysis of the causal association between 11 coagulation function and GDM was performed by the inverse-variance weighted method (IVW), the MR-Egger method, and the weighted median method (WM). **Results** In this study, the GWAS summary statistics of GDM (covering 5 687 cases and 117 892 controls) were used for MR analysis. It was found that there was a causal relationship between the predicted plasma FⅧ level and the risk for GDM (IVW: [odds ratio, OR]=0.28, 95% confidence interval [CI]: 0.10-0.75, $P<0.001$; WM: OR=0.30, 95% CI: 0.09-0.98, $P<0.001$). There was no causal relationship between other coagulation function and the risk for GDM ($P>0.05$). **Conclusion** There is a significant causal relationship between the plasma FⅧ level and the risk for GDM. This finding highlights the complex interaction between coagulation function and glucose metabolism during pregnancy, but further research on this finding is warranted.

【Key words】 Mendelian randomization Coagulation factors Gestational diabetes mellitus

妊娠期糖尿病(gestational diabetes mellitus, GDM)是一种常见代谢障碍性疾病,与孕期不良妊娠结局密切相关[1-2]。同时GDM孕妇及其子代也面临患糖尿病、肥胖以及早发心血管疾病等风险。据统计,全球每年有超过一百万的孕妇被诊断为GDM,且这一数字还在持续增长,在某些发达国家GDM的发病率已高达10%至20%,而在亚洲和中东的部分地区,这一比例甚至高达到25%至30%[3-6]。早期发现并干预GDM可改善母儿妊娠结局,减轻社会经济负担。尽管不同国家和地区采取了多样化的筛查和管理方案,但由于GDM病因复杂和诊断标准多样化,使其早期预防和干预仍是一个挑战。

GDM的发病机制涉及多种因素,包括胰岛素抵抗、胰岛素分泌不足及妊娠期胰岛素代谢异常等[7-8]。近期研究强调了血清中凝血因子在GDM发生和发展中的潜在作用。怀孕期间血液系统会发生显著变化,以适应血流动力学和凝血功能的变化,这一过程可能与GDM的发生密切相关[9-12]。研究发现,凝血酶原活性物质、纤维蛋白原以及D-二聚体等凝血因子的异常水平与GDM的发生和预后存在关联[9-12]。例如,在一项队列研究中发现,GDM患者可能同时存在高凝状态和高纤溶状态[13]。然而,目前对于GDM中这些凝血因子的确切作用和潜在机制仍缺乏全面的研究。

传统的观察性研究常受到混杂变量和反向因果关系的限制,难以明确因果关系。在此背景下,孟德尔随机化(Mendelian randomization, MR)提供了一种新颖的研究方法[14]。通过利用自然发生的遗传变异作为代理,类似于随机对照试验的方式,MR有助于更准确地确定因果关系[15]。这种方法不仅可以提供宝贵的见解,还可能为GDM的研究和临床管理开辟新的路径。深入理解这些关系对于制定针对这种日益流行的疾病的有效诊断和治疗策略至关重要。因此本研究拟通过MR探索凝血功能与GDM的因果关系,为凝血功能与GDM发病关联提供遗传学证据支持。

1 资料与方法

1.1 研究设计

MR分析必须满足3个关键假设。第一个假设是遗传变量应与暴露显著相关,第二个假设是作为暴露工具变量提取的遗传变异与其他混杂因素无关,第三个假设是遗传变异对结局的影响只能通过暴露作用,而不能通过其他因素影响[16-17]。图1描述了本研究的总体设计。本研究采用MR设计,利用双样本设计探讨血清凝血功能指标与GDM之间的因果关系。血清凝血功能指标被定义为暴露因素,其中包括血管性血友病因子(von Willebrand factor, vWF)、血管性血友病因子裂解酶(a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13, ADAMTS13)、活化部分凝血活酶时间(activated partial thromboplastin time, APTT)、凝血因子8(coagulation factor Ⅷ, FⅧ)、凝血因子11(coagulation factor ⅩⅠ, FⅩⅠ)、凝血因子7(coagulation factor Ⅶ, FⅦ)、凝血因子10(coagulation factor Ⅹ, FⅩ)、内源性凝血酶生
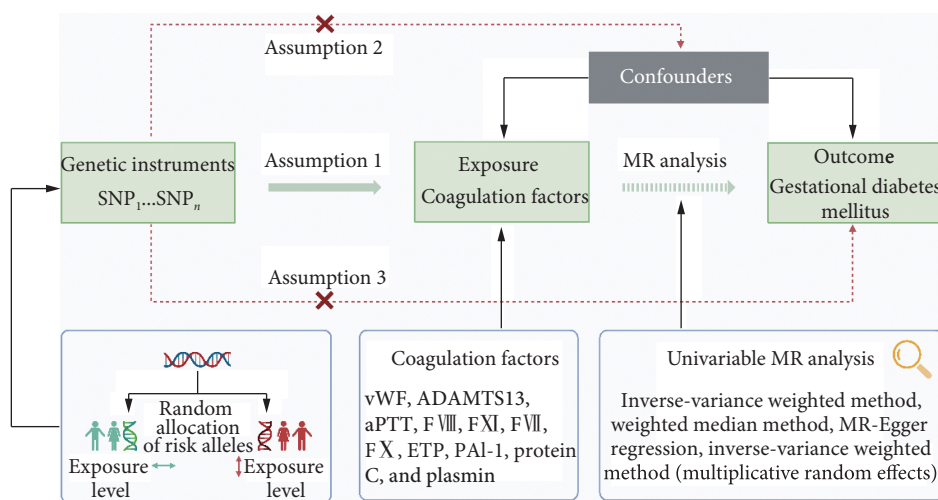

图1 研究的总设计图
Fig 1 Overall design of the study

vWF: von Willebrand factor; ADAMTS13: a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13; APTT: activated partial thromboplastin time; FⅦ: coagulation factor Ⅶ; FⅧ: coagulation factor Ⅷ; FⅩ: coagulation factor Ⅹ; FⅩⅠ: coagulation factor ⅩⅠ; ETP: endogenous thrombin potential; PAI-1: plasminogen activator inhibitor-1.

成潜能（endogenous thrombin potential, ETP）、血浆纤溶酶原激活抑制剂1（plasminogen activator inhibitor-1, PAI-1）、蛋白C（protein C）、纤溶酶（plasmin）。结局变量为是否患有GDM。

1.2　数据来源

不同凝血功能指标的数据来源于各自的全基因组关联研究（genome-wide association study, GWAS）[17-23]。FinnGen队列的妊娠期糖尿病GWAS摘要统计数据可通过R包TwoSampleMR（v 0.5.6）对IEU OpenGWAS数据库进行访问[24-25]。其中凝血功能指标的数据来源于不同的私人研究，数据来源人群为各自研究招募人群；GDM的数据来源于芬兰生物银行的长期随访人群数据，二者之间的人群重叠很少。表1中详细列示了各项研究的数据来源，凝血功能指标的原始数据能够从相关文献中获得。

1.3　工具变量

为了确保暴露因素与结局变量相互独立且高度相关，我们选择了全基因组中意义显著的单核苷酸多态性（single nucleotide polymorphism, SNP）作为工具变量，以千人全基因组项目提供的全基因组信息为基准，设置凝血因子具有全基因组意义的P值阈值为<5×10^{-7}，连锁不平衡参数（r^2）设置为0.001，遗传窗口设定为10 000 kb，从不同凝血因子的数据中筛选出无连锁效应的工具变量。

1.4　MR分析

本研究采用逆方差加权法（inverse-variance weighted method, IVW）、MR-Egger法、加权中位数法（weighted median method, WM）进行孟德尔随机化分析[25]。统计强度F值设定为>10[26]，计算公式为（Beta/SE）^{2}。

1.5　异质性检验、敏感性分析和多效性分析

异质性检验采用IVW法和MR-Egger法[25-26]。当检验P值<0.05时，表示SNPs之间存在异质性；P值>0.05则表示不存在异质性。敏感性分析采用逐一排除法，以探讨单个SNPs对因果关联的影响。多效性分析则利用MR pleiotropy test函数，当检验P值<0.05时，表示存在多效性；P值>0.05则表示不存在多效性。

2　结果

2.1　工具变量的选择

通过系统地检索不同GWAS的结果，筛选出与11种凝血功能指标（包括vWF、ADAMTS13、aPTT、FⅧ、FⅪ、FⅦ、FⅩ、ETP、PAI-1、蛋白C和纤溶酶）相关的显著SNP，以此来探究这些因子对GDM的潜在因果影响。首先，我们在相应的GWAS研究中保留了与每种暴露表型显著相关的SNP（P<5×10^{-7}）。随后，采用基于连锁不平衡（LD）的聚类方法，我们筛选了与LD无关的SNP（r^2阈值=0.1，窗口大小=10 000 kb）。关键在于，SNP对暴露的影响和对结果的影响应归因于同一等位基因。在数据协调过程中，具有不一致等位基因的模糊SNP以及具有无法纠正的模糊链的回文SNP被排除。因此，最终用于两

表 1　不同GWAS数据的信息
Table 1　Information on different GWAS data

Variable	Study	Source type	Sample size	Ancestry
Exposure				
ADAMTS13	MA Q[17]	Independent research	2 304	European
aPTT	TANG W[21]	Independent research	9 240	European
ETP	ROCANIN-ARJO A[20]	Independent research	1 967	European
FⅦ	De VRIES P S[22]	Independent research	27 495	European
FⅧ	SABATER-LLEAL M[24]	Independent research	29 573	European
FⅩ	SUN B B[23]	Independent research	3 301	European
FⅪ	SUHRE K[19]	Independent research	997	European
PAI-1	HUANG J[18]	Independent research	19 599	European
Plasmin	SUN B B[23]	Independent research	3 301	European
Protein C	TANG W[21]	Independent research	8 048	European
vWF	SABATER-LLEAL M[24]	Independent research	42 256	European
Outcome				
GDM	FinnGen	Biobanking data	210 870	European

All abbreviations are explained in the note to Fig 1.

样本MR分析中的工具变量SNP数量小于等于附表1所列数量,分析所用的SNP详情数量见附图1。为评估每个工具变量的强度,我们计算了每个工具暴露关联的F统计量。在本研究中,所有F统计量均远>10,表明这些SNP是强有力的工具变量。

2.2　凝血功能指标与GDM的因果关系

我们利用芬兰生物银行第五轮的GWAS妊娠期糖尿病汇总统计数据(包含5 687例病例和117 892例对照)进行MR分析,以估计11种凝血功能指标对GDM风险的因果影响,MR分析采用的IVW模型、MR-Egger模型、WM模型以及IVW随机效应模型(IVW-MRE)。研究结果显示,基因预测的血浆FⅧ水平与GDM风险降低存在因果关系〔IVW: 比值比(odds ratio, OR)=0.28, 95%置信区间(confidence interval, CI): 0.10 ~ 0.75, $P<0.001$; WM: OR=0.30, 95%CI: 0.09 ~ 0.98, $P<0.001$〕,指出长期较高的血浆FⅧ水平是GDM的保护因素。然而,未发现其他凝血功能指标与GDM风险存在因果关系($P>0.05$)。因果关系的主要测定结果见图2,因果关系的补充测定结果见表2。
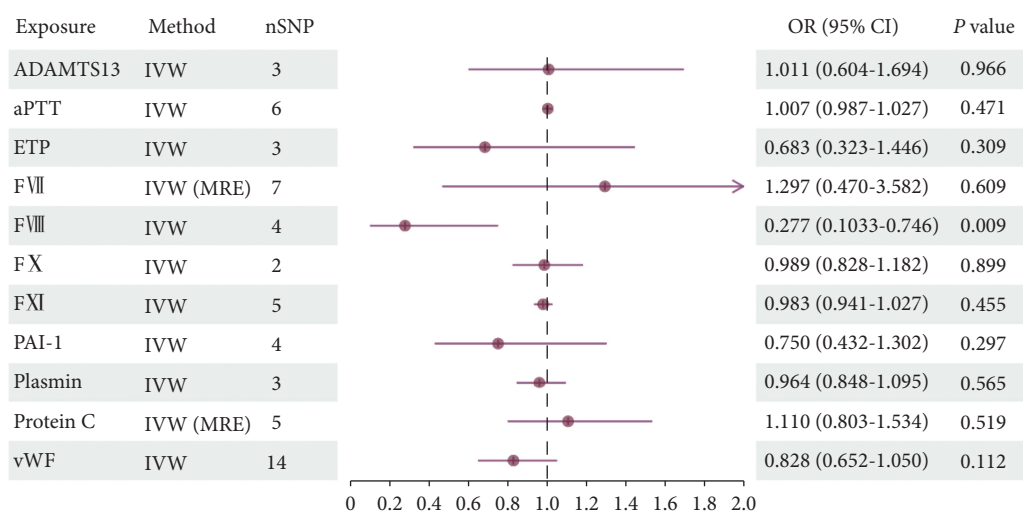
Exposure	Method	nSNP		OR (95% CI)	P value
ADAMTS13	IVW	3		1.011 (0.604-1.694)	0.966
aPTT	IVW	6		1.007 (0.987-1.027)	0.471
ETP	IVW	3		0.683 (0.323-1.446)	0.309
FⅦ	IVW (MRE)	7		1.297 (0.470-3.582)	0.609
FⅧ	IVW	4		0.277 (0.1033-0.746)	0.009
FX	IVW	2		0.989 (0.828-1.182)	0.899
FXI	IVW	5		0.983 (0.941-1.027)	0.455
PAI-1	IVW	4		0.750 (0.432-1.302)	0.297
Plasmin	IVW	3		0.964 (0.848-1.095)	0.565
Protein C	IVW (MRE)	5		1.110 (0.803-1.534)	0.519
vWF	IVW	14		0.828 (0.652-1.050)	0.112

0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0

图 2　孟德尔随机化主要分析结果

Fig 2　Mendelian randomization primary analysis results

All abbreviations are explained in the note to Fig 1. nSNP: the number of single nucleotide polymorphisms.

2.3　异质性分析与敏感性分析结果

在血浆FⅧ和GDM之间的MR分析中,未检测到显著的异质性或多效性($P>0.05$)。大多数其他检测结果也未显示出异质性或多效性,所有异质性分析结果见表3,水平多效性分析的结果见表4。然而,在血浆FⅦ和PAI-1与GDM的MR分析中,检测到了异质性的存在。因此,本研究选择报告IVW随机效应模型的检测结果。具体详细结果见图2。敏感性分析显示,在逐一排除法中未发现对因果关联估计值有显著影响的SNP,具体结果见图3。

3　讨论

本研究通过MR分析,旨在阐明多种凝血功能指标与GDM发病间的潜在因果关系。本研究对与这些凝血功能指标相关的遗传变异进行了严格的检验,从而提出了有关GDM发病机制的重要见解。主要发现强调了血浆FⅧ水平与GDM发生之间的因果关系,结果具有统计学差异。尽管先前的流行病学研究已暗示血液高凝状态与GDM间存在潜在联系[9-12],但本研究通过MR方法,为血浆FⅧ作为GDM发展的因果因素提供了有力证据。此发现凸显了妊娠期间凝血功能和葡萄糖代谢之间的复杂相互作用,值得进一步探索其机制基础。

本研究发现血浆FⅧ在血液凝固过程中扮演着重要角色,并且其在GDM发病机制中的作用相对复杂。GDM是妊娠期间出现的糖尿病类型,其主要表现为胰岛素抵抗和胰岛β细胞功能障碍[27-30]。妊娠期间,母体产生的激素,如胎盘生乳素、雌激素和孕激素等,可能导致对胰岛素的敏感性下降,增加GDM患病风险。FⅧ主要在肝脏合成,是血液凝固关键蛋白,与vWF结合,在凝血级联反应中发挥作用[31-33]。近年来的研究表明,FⅧ也可能参与调节炎症反应和内皮功能,与胰岛素抵抗和糖尿病发病机制相关[31-33]。一种可能的机制是FⅧ通过影响内皮细胞功能,间接调节胰岛素信号传导,因内皮功能障碍是胰岛素抵抗的关键因素之一[31-32, 34]。FⅧ可能通过调节血管内皮细胞活性,改善内皮功能,从而降低胰岛素抵抗,减少GDM风险。另一机制可能涉及炎症反应,炎症是GDM发病的重要因素[33, 35]。FⅧ可能通过调节免疫细胞

表 2　MR分析的补充结果
Table 2　Supplement results of the MR analysis

Exposure	Outcome	Method	nSNP	Beta	Sandard error	P
ADAMTS13	GDM	MR Egger	3	−0.096	0.802	0.924
ADAMTS13	GDM	WM	3	0.016	0.279	0.953
ADAMTS13	GDM	IVW (MRE)	3	0.011	0.037	0.763
aPTT	GDM	MR Egger	6	0.013	0.021	0.582
aPTT	GDM	WM	6	0.007	0.012	0.536
aPTT	GDM	IVW (MRE)	6	0.007	0.007	0.341
ETP	GDM	MR Egger	3	−0.443	1.031	0.742
ETP	GDM	WM	3	−0.438	0.425	0.303
ETP	GDM	IVW (MRE)	3	−0.381	0.141	0.007
FⅦ	GDM	MR Egger	7	0.097	0.723	0.898
FⅦ	GDM	WM	7	0.083	0.215	0.698
FⅦ	GDM	IVW	7	0.260	0.508	0.609
FⅧ	GDM	MR Egger	4	−0.383	2.600	0.896
FⅧ	GDM	WM	4	−1.207	0.592	0.041
FⅧ	GDM	IVW (MRE)	4	−1.285	0.294	0.001
FⅩ	GDM	IVW (MRE)	2	−0.011	0.089	0.899
FⅪ	GDM	MR Egger	5	0.036	0.073	0.650
FⅪ	GDM	WM	5	−0.011	0.026	0.660
FⅪ	GDM	IVW (MRE)	5	−0.017	0.013	0.198
PAI-1	GDM	MR Egger	4	−0.224	1.667	0.905
PAI-1	GDM	WM	4	−0.287	0.227	0.207
PAI-1	GDM	IVW (MRE)	4	−0.288	0.276	0.297
Plasmin	GDM	MR Egger	3	0.021	0.106	0.875
Plasmin	GDM	WM	3	−0.043	0.069	0.537
Plasmin	GDM	IVW (MRE)	3	−0.037	0.043	0.396
Protein C	GDM	MR Egger	5	−0.021	0.275	0.944
Protein C	GDM	WM	5	0.062	0.057	0.277
Protein C	GDM	IVW	5	0.104	0.162	0.519
vWF	GDM	MR Egger	14	−0.177	0.161	0.294
vWF	GDM	WM	14	−0.188	0.114	0.100
vWF	GDM	IVW (MRE)	14	−0.189	0.119	0.112

All abbreviations are explained in the note to Fig 1. nSNP: the number of single nucleotide polymorphisms.

活性或减少炎症介质的释放, 降低炎症水平, 减轻胰岛素抵抗, 降低GDM风险。总之, FⅧ可能通过改善内皮功能和调节炎症反应, 间接影响胰岛素抵抗和β细胞功能, 从而在一定程度上降低GDM的发病风险。然而, 这一领域还需更多研究来阐明具体的分子机制和生物学路径。

尽管本研究的发现具有说服力, 但仍存在一些局限性。首先, MR假设遗传变异与混杂因素无关, 但这一假设可能并非总是成立。残留混杂或多效性可能导致因果效应估计的偏差。其次, 虽然本研究的分析聚焦于一系列凝血功能指标, 但其他未测量的变量或相互作用可能也会影响GDM的病因。最后, 由于本研究人群主要集中在欧洲人群中, 不同人种间的基因分布差异显著, 因此本

表3 MR异质性分析的结果

Table 3 Results of the MR heterogeneity analysis

Exposure	Outcome	Method	Q	Q_df	P
ADAMTS13	GDM	MR Egger	0.021	1	0.885
ADAMTS13	GDM	IVW	0.041	2	0.980
aPTT	GDM	MR Egger	2.779	4	0.595
aPTT	GDM	IVW	2.869	5	0.720
ETP	GDM	MR Egger	0.277	1	0.598
ETP	GDM	IVW	0.281	2	0.869
FⅦ	GDM	MR Egger	38.662	5	0.000
FⅦ	GDM	IVW	39.592	6	0.000
FⅧ	GDM	MR Egger	0.934	2	0.627
FⅧ	GDM	IVW	1.059	3	0.787
FⅩ	GDM	IVW	2.277	1	0.131
FⅪ	GDM	MR Egger	0.753	3	0.861
FⅪ	GDM	IVW	1.347	4	0.853
PAI-1	GDM	MR Egger	6.821	2	0.033
PAI-1	GDM	IVW	6.826	3	0.078
Plasmin	GDM	MR Egger	0.460	1	0.498
Plasmin	GDM	IVW	0.918	2	0.632
Protein C	GDM	MR Egger	33.023	3	0.000
Protein C	GDM	IVW	36.946	4	0.000
vWF	GDM	MR Egger	15.878	12	0.197
vWF	GDM	IVW	15.898	13	0.255

All abbreviations are explained in the note to Fig 1.

表4 MR水平多效性分析的结果

Table 4 Results of the MR pleiotropy analysis

Exposure	Outcome	Egger_intercept	Standard error	P
ADAMTS13	GDM	0.006	0.042	0.911
aPTT	GDM	−0.006	0.021	0.779
ETP	GDM	0.004	0.057	0.960
FⅦ	GDM	0.012	0.034	0.743
FⅧ	GDM	−0.020	0.057	0.758
FⅩ	GDM	NA[*]	NA	NA
FⅪ	GDM	−0.025	0.032	0.497
PAI-1	GDM	−0.004	0.097	0.972
Plasmin	GDM	−0.027	0.039	0.621
Protein C	GDM	0.033	0.054	0.593
vWF	GDM	−0.001	0.009	0.905

[*] The results of the horizontal pleiotropy analysis contain NA values for certain coagulation factors due to the limited number of instrumental variables (only 2). This makes it difficult to generate a horizontal pleiotropy shift, thus making it impossible to conduct horizontal pleiotropy testing for these factors. NA: not available. All abbreviations are explained in the note to Fig 1.

研究的结果可能难以推广到东亚人群。未来的研究需要结合更广泛的遗传标记和临床参数,以全面了解GDM的发病机制。
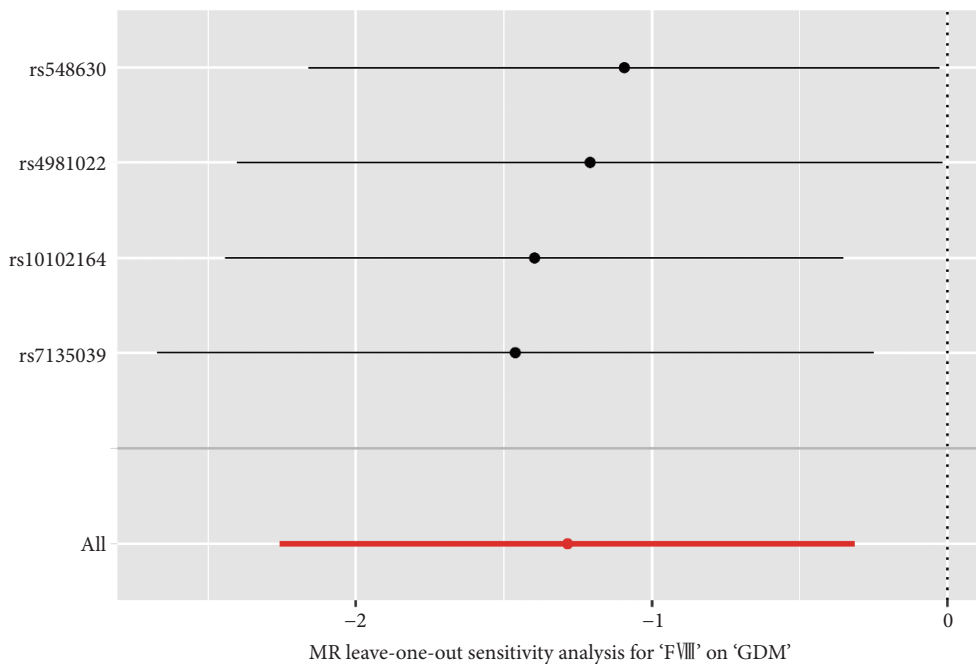
综上所述,血浆FⅧ水平与GDM发生存在统计学显著的因果关系,妊娠期间的凝血功能和糖代谢之间存在

图3 留一法分析的结果

Fig 3 Results of the leave-one-out analysis

复杂的相互作用, 但此发现还需进一步地深入探索研究。

* * *

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Author Contribution　ZENG Fanying is responsible for conceptualization, formal analysis, methodology, software, visualization, writing--original draft, and writing--original draft. SHEN Ping is responsible for investigation and project administration. GUO Weijie is responsible for conceptualization and data curation. HE Guolin is responsible for formal analysis, funding acquisition, methodology, software, visualization, writing--original draft, and writing--original draft. 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

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