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儿童期体质指数与妊娠期高血压的潜在因果关系： 孟德尔随机化研究

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【摘要】 目的 采用孟德尔随机化(MR)方法探讨儿童期体质指数(BMI)与妊娠期高血压(GH)的潜在因果关系。**方法** 从全基因组关联研究(GWAS)数据库获取儿童期BMI数据集(ID: ebi-a-GCST90002409)和GH数据集(ID: finn-b-O15_HYPTENSPREG), 其中儿童期BMI数据集的样本量为39 620例, 包括8 173 382个单核苷酸多态性(SNP); GH数据集的样本量为123 579例, 包括16 379 784个SNP。本研究采用逆方差加权法(IVW)、MR-Egger回归、加权中位数法、简单模式法、加权模式法分析儿童期BMI与GH的潜在因果关系。采用Cochran Q检验评估各SNP间的统计学异质性, 采用MR-Egger回归的截距项、MR-PRESSO检验及漏斗图分析SNP的水平多效性, 采用留一法评估单个SNP对IVW分析结果的影响。**结果** 本研究共筛选出16个与儿童期BMI高度相关的SNP, 剔除rs2076308(回文SNP)、rs17817449(离群值)、rs61765651(离群值)后, 最终纳入13个与儿童期BMI高度相关的SNP。IVW分析结果显示, 儿童期BMI升高是GH的危险因素[OR=1.29, 95%CI (1.09~1.53), $P<0.01$]; 且MR-Egger回归、加权中位数法、简单模式法、加权模式法分析的 β 值与IVW分析的 β 值方向一致。Cochran Q检验结果显示, 与儿童期BMI高度相关的SNP间不存在统计学异质性($P=0.47$)。MR-Egger回归的截距项、MR-PRESSO检验、漏斗图分析结果均显示, 与儿童期BMI高度相关的SNP不存在水平多效性。留一法分析结果显示, 剔除单个SNP后, MR分析结果无明显改变。**结论** 儿童期BMI升高是GH的危险因素。

【关键词】 高血压, 妊娠性; 体质指数; 儿童; 孟德尔随机化分析**【中图分类号】** R 714.246 **【文献标识码】** A DOI: 10.12114/j.issn.1008-5971.2024.00.095

Potential Causal Relationship between Childhood BMI and Gestational Hypertension: a Mendelian Randomization Study

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【Abstract】 Objective To analyze the potential causal relationship between childhood body mass index (BMI) and gestational hypertension (GH) through Mendelian randomization (MR) method. **Methods** The childhood BMI dataset (ID: ebi-a-GCST90002409) and GH dataset (ID: finn-b-O15_HYPTENSPREG) were obtained from the genome-wide association study (GWAS) database. The sample size of the childhood BMI dataset was 39 620, including 8 173 382 single nucleotide polymorphisms (SNPs). The sample size of GH dataset was 123 579, including 16 379 784 SNPs. In this study, inverse variance weighting (IVW), MR-Egger regression, weighted median method, simple model method and weighted model method were used to analyze the potential causal relationship between childhood BMI and GH. Cochran Q test was used to evaluate the statistical heterogeneity among SNPs. The intercept term of MR-Egger regression, MR-PRESSO test and funnel plot were used to analyze the level pleiotropy of SNPs. The effect of single SNPs on IVW analysis results was evaluated by leave-one-out method. **Results**

A total of 16 SNPs highly correlated with childhood BMI were screened in this study. After excluding rs2076308 (palindrome SNP), rs17817449 (outlier) and rs61765651 (outlier), 13 SNPs highly correlated with childhood BMI were finally included. IVW analysis results showed that increased childhood BMI was a risk factor for GH [OR=1.29, 95%CI (1.09-1.53), $P<0.01$]. The β values of MR-Egger regression, weighted median method, simple mode method and weighted mode method were consistent with the β value of IVW. The results of Cochran Q test showed that there was no statistical heterogeneity among SNPs highly correlated with childhood BMI ($P=0.47$). The results of intercept term of MR-Egger regression, MR-PRESSO test and funnel plot analysis showed that there was no level pleiotropy in SNPs highly correlated with childhood BMI. The results of leave-one-out analysis showed that there was no significant change in MR analysis results after removing a single SNP. **Conclusion** Increased

childhood BMI is a risk factor for GH.

【Key words】 Hypertension, pregnancy-induced; Body mass index; Child; Mendelian randomization analysis

妊娠期高血压疾病指孕妇妊娠20周后出现的血压升高,并伴有蛋白尿、水肿等症状的一种妊娠并发症,其包括妊娠期高血压(gestational hypertension, GH)、子痫前期、子痫、慢性高血压并发子痫前期和妊娠合并慢性高血压,其不仅影响孕妇健康,还可能对胎儿发育产生不利影响^[1]。研究表明, GH的发生与多种因素相关,如孕妇年龄、体质量、生活方式及遗传因素等^[2]。体质指数(body mass index, BMI)是评估个体健康状况的重要指标之一,尤其是儿童和青少年时期BMI。研究表明,儿童期BMI与其成年后多种疾病发生相关,如心血管疾病、糖尿病和癌症^[3]。但目前关于儿童期BMI与其GH发生风险间的关系尚未明确。孟德尔随机化(Mendelian randomization, MR)是利用遗传变异作为工具变量,通过选择与暴露因素相关的遗传变异来模拟一种随机对照试验的效果,从而揭示暴露因素与结局的因果关系^[4]。本研究采用MR方法探讨儿童期BMI与GH的潜在因果关系,现报道如下。

1 对象与方法

1.1 研究设计

采用MR方法,以儿童期BMI为暴露因素, GH为结局,分析儿童期BMI与GH的因果关系。

1.2 数据来源

从全基因组关联研究(genome wide association study, GWAS)数据库(<https://gwas.mrcieu.ac.uk/>)获取儿童期BMI数据集(ID: ebi-a-GCST90002409)和GH数据集(ID: finn-b-O15_HYPTENSPREG),其中儿童期BMI数据集的样本量为39 620例,包括8 173 382个单核苷酸多态性(single nucleotide polymorphism, SNP); GH数据集的样本量为123 579例,其中GH患者7 686例、健康对照者115 893例,包括16 379 784个SNP。

1.3 筛选工具变量

(1)筛选与儿童期BMI高度相关的SNP作为工具变量,即 $P < 1.0 \times 10^{-8}$ 。(2)排除连锁不平衡的SNP,设置区域宽度为10 000、 $r^2=0.01$;采用函数harmonise_data去除具有中间等位基因频率的回文SNP。(3)排除弱工具变量,以 F 值 >10 表示弱工具变量偏倚风险较低, F 值的计算公式为: $F \text{ 值} = [(n-k-1)/k] \times [R^2/(1-R^2)]$,其中 n 为样本量、 k 为SNP数量、 R^2 为每个SNP解释的方差比例^[5]。(4)剔除离群值:采用MR-PRESSO法识别SNP的离群值^[6]。

1.4 MR分析过程

应用R 4.3.1软件中的“TwoSample MR包”进行MR分析,具体步骤如下:(1)MR方法:本研究采用逆方

差加权法(inverse variance weighting, IVW)^[7]、MR-Egger回归^[8]、加权中位数法^[9]、简单模式和加权模式分析儿童期BMI与GH的因果关系,若各SNP间无统计学异质性和水平多效性,则以IVW分析结果为主^[10]。

(2)统计学异质性:应用Cochran Q 检验评估各SNP间是否存在统计学异质性,以 $P \leq 0.05$ 提示存在统计学异质性^[11]。(3)水平多效性:采用MR-Egger回归的截距项、MR-PRESSO检验及漏斗图分析SNP的水平多效性,若截距项与0相比无统计学意义,表明SNP不存在水平多效性;MR-PRESSO检验结果显示, $P > 0.05$ 提示SNP不存在水平多效性;漏斗图分析结果显示,SNP左右分布基本对称,提示SNP不存在明显水平多效性。

(4)敏感性分析:采用留一法评估单个SNP对IVW分析结果的影响,若剔除单个SNP后IVW分析结果无明显改变,提示该SNP对IVW分析结果无明显影响^[12]。

2 结果

2.1 工具变量

本研究共筛选出16个与儿童期BMI高度相关的SNP,剔除rs2076308(回文SNP)、rs17817449(离群值)、rs61765651(离群值)后,最终纳入13个与儿童期BMI高度相关的SNP,见表1。

2.2 MR分析结果

IVW分析结果显示,儿童期BMI升高是GH的危险因素[$OR=1.29$, 95%CI (1.09 ~ 1.53), $P < 0.01$];且MR-Egger回归、加权中位数法、简单模式、加权模式分析的 β 值与IVW分析的 β 值方向一致,见图1~2。

Cochran Q 检验结果显示,与儿童期BMI高度相关的SNP间不存在统计学异质性($P=0.47$)。MR-Egger回归的截距项分析结果显示,与儿童期BMI高度相关的SNP不存在水平多效性($P=0.49$);MR-PRESSO检验结果显示,与儿童期BMI高度相关的SNP不存在水平多效性($P=0.53$);漏斗图分析结果显示,与儿童期BMI高度相关的SNP左右分布基本对称,提示与儿童期BMI高度相关的SNP无明显水平多效性,见图3。留一法分析结果显示,剔除单个SNP后,MR分析结果无明显改变,见图4。

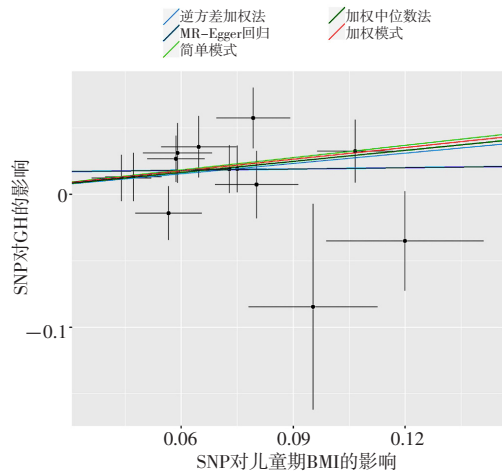
3 讨论

一项哥本哈根的回顾性队列研究纳入49 600例7~45岁的参与者,结果显示,儿童期BMI升高与GH[$RR=1.66$, 95%CI (1.42 ~ 1.94)]和先兆子痫[$RR=1.57$, 95%CI (1.46 ~ 1.70)]发生风险升高有关^[13]。一项纳入985名澳大利亚女性的队列研究结果显示,儿童期超重与GH发生风险升高相关[$RR=1.66$, 95%CI (1.07 ~ 2.52)]^[14]。上述研究提示儿童期BMI

表1 与儿童期BMI高度相关的SNP
Table 1 SNP highly associated with childhood BMI

SNP	效应等位基因	其他等位基因	儿童期BMI				GH				F值
			SE	β 值	P值	效应等位基因频率	SE	β 值	P值	效应等位基因频率	
rs11676272	G	A	<0.01	0.07	2.37E^{-21}	NA	0.01	0.01	0.28	0.41	152.40
rs12042908	G	A	<0.01	-0.05	2.77E^{-14}	NA	0.01	-0.02	0.12	0.49	112.11
rs12641981	T	C	<0.01	0.04	4.19E^{-08}	NA	0.01	0.01	0.48	0.47	86.54
rs13107325	T	C	0.01	0.09	3.51E^{-08}	NA	0.07	-0.08	0.27	0.01	86.68
rs41279738	G	T	0.02	0.11	1.30E^{-08}	NA	0.03	-0.03	0.35	0.05	89.49
rs4477562	T	C	0.01	0.08	8.29E^{-13}	NA	0.02	0.00	0.77	0.13	113.61
rs543874	G	A	<0.01	0.07	1.62E^{-15}	NA	0.02	0.05	0.01	0.17	127.63
rs56133711	A	G	<0.01	0.05	2.00E^{-10}	NA	0.02	-0.01	0.48	0.24	100.50
rs571312	A	C	<0.01	0.05	2.00E^{-10}	NA	0.02	0.03	0.16	0.18	100.24
rs62500888	G	A	<0.01	-0.04	6.91E^{-10}	NA	0.01	-0.01	0.47	0.36	92.14
rs7138803	A	G	<0.01	0.07	7.12E^{-20}	NA	0.01	0.01	0.29	0.38	146.01
rs7199285	T	C	0.01	-0.06	1.34E^{-10}	NA	0.02	-0.03	0.12	0.17	94.94
rs939584	T	C	0.01	0.10	8.85E^{-26}	NA	0.02	0.03	0.17	0.83	168.58

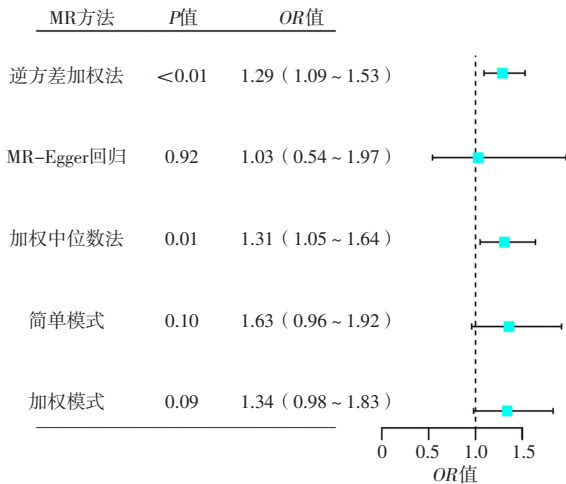
注: SNP=单核苷酸多态性, BMI=体质指数, GH=妊娠期高血压。



注: SNP=单核苷酸多态性, GH=妊娠期高血压, BMI=体质指数。

图1 儿童期BMI与GH因果关系的散点图

Figure 1 Scatter plots of the relationship between childhood BMI and GH



注: MR=孟德尔随机化。

图2 MR分析结果的森林图

Figure 2 Forest plot of MR analysis results

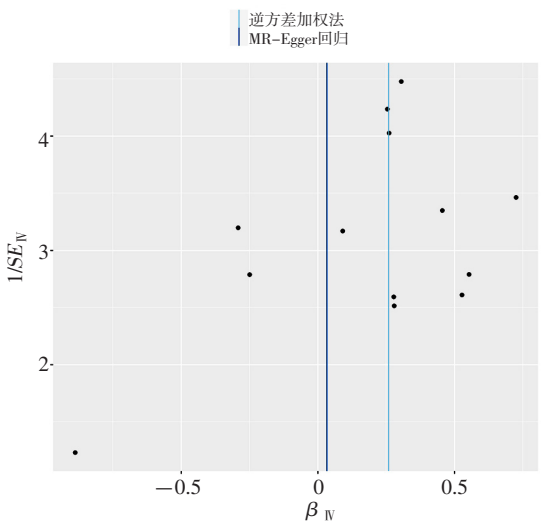


图3 与儿童期BMI高度相关的SNP的漏斗图

Figure 3 Funnel diagram of SNP highly associated with childhood BMI

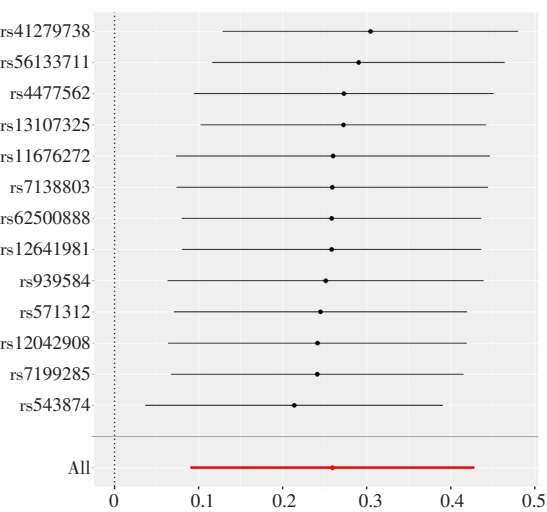


图4 留一法分析结果

Figure 4 Leave-one-out analysis results

升高与成年后GH相关。

本研究采用MR方法探讨了儿童期BMI与GH的潜在因果关系, IVW分析结果显示, 儿童期BMI升高是GH的危险因素, 且MR-Egger回归、加权中位数法、简单模式、加权模式分析的 β 值与IVW分析的 β 值方向一致, 因与儿童期BMI高度相关的SNP间无统计学异质性和水平多效性, 故以IVW分析结果为主。分析儿童期BMI升高增加GH发生风险的原因可能如下: (1) 肥胖儿童常伴随胰岛素抵抗, 这不仅增加了2型糖尿病的发生风险, 也可能导致血管功能异常和内皮功能损伤, 而这些均是GH发生的关键因素^[15]。(2) 肥胖与慢性低度炎症状态有关, 而炎症因子水平升高可能导致血管炎症反应和内皮功能障碍, 进而增加GH发生风险^[16]。(3) 肥胖可影响激素(如性激素、胰岛素、皮质醇等)平衡, 而这些激素变化可能影响血压调节功能。(4) 肥胖儿童常存在不良饮食习惯且缺乏运动, 这也会增加GH发生风险^[17]。因此, 预防儿童超重或肥胖可能为预防GH提供新的思路。

4 结论

综上所述, 儿童期BMI升高是GH的危险因素。但本研究仍存在一定局限性: (1) 数据主要来自GWAS数据库(欧洲血统人群), 故本研究结果在其他种族和人群中的普适性有待进一步证实。(2) GWAS数据库未提供纳入人群腰围、身高、腰臀比等相关特征信息, 而这些数据对于分类和提高研究结果的准确性具有重要作用。

作者贡献: 邢影进行文章的构思与设计, 研究的实施与可行性分析, 数据收集、整理、分析, 结果分析与解释, 负责撰写、修订论文; 罗小平负责文章的质量控制及审校, 并对文章整体负责、监督管理。

本文无利益冲突。

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(收稿日期: 2023-11-17; 修回日期: 2024-03-21)

(本文编辑: 谢武英)