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· 母亲妊娠期不良因素对儿童生长发育影响专栏 ·

母亲孕前体质量指数和孕早期血脂与学龄前儿童超重肥胖风险的关联

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【摘要】 目的 探究母亲孕前体质量指数(BMI)与学龄前儿童超重肥胖风险的关联, 以及母亲孕早期血脂在孕前 BMI 与儿童超重肥胖风险之间的中介作用, 为学龄前儿童肥胖预防策略的制定提供科学依据。**方法** 基于 2018 年 6 月—2022 年 9 月北大-通州前瞻性出生队列研究, 纳入 1 292 对母子, 将学龄前儿童 3 岁时 BMI-*Z* 评分>1 定义为 3 岁时有超重肥胖风险组(n=173), ≤1 定义为无超重肥胖风险组(n=1 119)。应用多因素 Logistic 回归分析母亲孕前 BMI、孕早期血脂[总胆固醇(TC)、甘油三酯(TG)、高密度脂蛋白胆固醇(HDL-C)、低密度脂蛋白胆固醇(LDL-C)、TC/HDL-C、TG/HDL-C、LDL-C/HDL-C]与 3 岁儿童超重肥胖风险的关联, 探究孕早期血脂在孕前 BMI 与 3 岁儿童超重肥胖之间的中介效应。**结果** 有超重肥胖风险组和无超重肥胖风险组儿童母亲孕前 BMI 水平、孕早期 LDL-C 及 TC/HDL-C、LDL-C/HDL-C 差异均有统计学意义(χ^2/Z 值分别为 19.01, 2.48, 2.48, 2.71, P 值均<0.05)。多因素 Logistic 回归分析结果显示, 母亲孕前 BMI 升高, 孕早期 LDL-C、TC/HDL-C、LDL-C/HDL-C 升高均会增加 3 岁儿童超重肥胖的发生风险(OR 值分别为 1.09, 1.42, 1.49, 1.60, P 值均<0.05)。母亲孕早期 LDL-C、TC/HDL-C、LDL-C/HDL-C 在孕前 BMI 与 3 岁儿童超重肥胖风险之间的中介效应均有统计学意义(P 值均<0.05), 中介效应占比分别为 7.3%, 10.2%, 23.5%。**结论** 母亲孕早期高血脂在孕前肥胖与学龄前儿童肥胖之间有部分中介作用, 母亲孕前肥胖和孕早期高血脂均是学龄前儿童肥胖的风险因素。

【关键词】 母亲; 人体质量指数; 血脂异常; 超重; 肥胖症; 回归分析; 儿童, 学龄前

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Association between body mass index during pre-pregnancy and maternal lipid levels during early pregnancy with the risk of overweight and obesity in preschool children

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【Abstract】 Objective To analyze the relationship between body mass index(BMI) during pre-pregnancy, maternal lipid levels during early pregnancy and childhood overweight and obesity, as well as the mediating role of maternal lipid levels during early pregnancy in pre-pregnancy BMI and childhood overweight and obesity, providing scientific evidence for developing obesity prevention strategies in preschool children. **Methods** Using data from Peking University Birth Cohort in Tongzhou (PKUBC-T) collected between June 2018 and September 2022, the study included 1 292 mother-child pairs. Participants were stratified into two groups based on children's BMI-*Z* scores at age 3: an overweight/obesity risk group (BMI-*Z*>1, n=173) and a non-overweight/obesity risk group (BMI-*Z*≤1, n=1 119). Multivariate Logistic regression was conducted to analyze the associations between pre-pregnancy BMI, maternal lipid levels[total cholesterol(TC), triglyceride(TG), high density lipoprotein cholesterol(HDL-C), low density lipoprotein cholesterol(LDL-C), TC/HDL-C, TG/HDL-C, LDL-C/HDL-C] during early pregnancy and childhood overweight and obesity. The mediating effect of maternal lipid levels during early pregnancy on pre-pregnancy BMI and childhood overweight and obesity was further explored. **Results** There were statistically significant differences in pregnancy BMI levels, early pregnancy blood LDL-C, TC/HDL-C, LDL-C/HDL-C levels between the overweight and obesity risk group and the non overweight and obesity risk group (χ^2/Z=19.01, 2.48, 2.48, 2.71, all P<0.05). Multivariate Logistic regression analysis showed that pre-pregnancy BMI, LDL-C, TC/HDL-C and LDL-C/HDL-C in early pregnancy were significantly associated with childhood overweight and obesity (OR=1.09, 1.42, 1.49, 1.60, all P<0.05). LDL-C, TC/HDL-C and LDL-C/HDL-C in early pregnancy played a significant mediating role on pre-pregnancy BMI and childhood obesity and the mediating effects accounted for 7.3%, 10.2%, 23.5% of the total effects, respectively (all P<0.05). **Conclusions** Maternal hyperlipidemia during early pregnancy partially mediated the association between pre-pregnancy obesity and childhood obesity. Both pre-pregnancy obesity and maternal hyperlipidemia during early pregnancy are risk factors for obesity in preschool children.

【Keywords】 Mothers; Body mass index; Dyslipidemias; Overweight; Obesity; Regression analysis; Child, preschool

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儿童肥胖已成为全球性的公共卫生问题,学龄前期儿童肥胖会增加学龄期乃至成人期多种代谢性疾病、心血管疾病的发生风险[1]。较多证据证实母亲孕前超重肥胖可增加儿童超重肥胖的发生风险[2-4],也有研究提示母亲孕早期血脂升高是儿童肥胖发生的危险因素[5]。有研究发现总胆固醇(total cholesterol, TC)/高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)、甘油三酯(triglyceride, TG)/HDL-C、低密度脂蛋白胆固醇(low density lipoprotein cholesterol, LDL-C)/HDL-C 等血脂比值指标能更全面地反映脂质代谢情况,其对心血管疾病、糖尿病等疾病的预测价值明显优于单一血脂指标[6-8]。本研究基于前瞻性出生队列数据,在分析母亲孕前体质量指数(body mass index, BMI)与学龄前儿童超重肥胖关联的基础上,综合应用血脂及其比值指标分析母亲孕早期血脂与儿童超重肥胖风险的关联,及其在孕前 BMI 与儿童超重肥胖间的中介作用,为学龄前儿童肥胖的预防策略制定提供科学依据。

1　对象与方法

1.1　对象　研究对象来自北大-通州出生队列,队列纳入标准为过去半年居住在北京市通州区,孕周在 13^{+6} 周以内,计划在北京市通州区妇幼保健院建档、产检及分娩,年龄 18~49 岁的孕妇[9]。该队列在 2018 年 6 月—2019 年 1 月招募孕妇,到 2022 年 9 月完成 3 岁儿童的随访工作。本研究选取队列中在北京市通州区妇幼保健院分娩单胎活产且无出生缺陷,并已经随访到子代 3 岁的 1 816 对母子,排除孕前 BMI、孕早期血脂、子代 3 岁时体检数据缺失的母子对,最终共纳入 1 292 对母子进行分析。本研究获得北京大学伦理审查委员会的批准(批准号:IRB00001052-19032),研究纳入的母子对均签署知情同意书。

1.2　方法　通过问卷收集孕妇人口学特征,即出生日期、民族、文化程度、家庭年收入、职业、孕前身高、孕前体重、孕晚期体重等,根据孕前身高和孕前体重计算孕前 BMI,并依据国家卫生行业标准[10],将孕妇分为孕前低体重(BMI<18.5 kg/m^2)、体重正常(18.5~<24.0 kg/m^2)、超重(24.0~<28.0 kg/m^2)、肥胖(≥28.0 kg/m^2)。从医疗记录和分娩记录获取孕妇疾病诊断、末次月经日期、分娩日期、分娩方式、产次,胎儿性别、出生体重等信息。妊娠不足 37 周发生分娩定义为早产[11]。利用全自动生化分析仪进行孕早期(孕 14 周以内)空腹静脉血的 TC、TG、HDL-C、LDL-C 检测。在子代随访中获取子代 3 岁时的身高和体重,根据世界卫生组织 2006 年 5 岁以下儿童生长发育标准[12],计算子代 3 岁时的 BMI-Z 评分,BMI-Z 评分>1 即定义为该儿童有超重肥胖风险。

1.3　质量控制　由经培训的专职人员协助研究对象完成调查问卷,核查人员每日检查所有问卷的填写或录入完整度。问卷经检查合格后进行数据录入和储存,一致性检验后复核原始问卷,核查问卷录入的准确性。从医疗记录和分娩记录导出的数据均采用电子录入,单录入后由专门质控人员核对,数据采集系统为电子化系统。血脂水平的检测有统一的操作流程和严格的质量控制措施。检测过程同时检测质控样本,当质控样检测值均在样本检测均值 $\bar{x}\pm2s$ 范围内,则认为该批次的样本检测结果在控。

1.4　统计学分析　应用 R 4.2.2 软件进行数据分析,计量资料采用 Shapiro-Wilk 检验及 QQ 图法进行正态性检验,母亲分娩年龄、孕前 BMI、儿童出生体重满足正态分布,采用($\bar{x}\pm s$)描述,使用 t 检验进行组间比较;母亲孕早期血脂及其比值指标不满足正态分布,采用 $M(P_{25}, P_{75})$ 描述,使用 Wilcoxon 秩和检验进行组间比较。计数资料采用频数和百分比描述,使用 χ^2 检验进行组间比较。关联分析采用多因素 Logistic 回归模型,纳入回归模型的协变量分为混杂因素和其他重要影响因素两类。基于既往相关文献[4],母亲分娩年龄为混杂因素,母亲产次、儿童性别、儿童出生体重为其他重要影响因素;并根据儿童性别进行分层分析,排除母亲早产、妊娠期糖尿病、妊娠期高血压的母子对进行敏感性分析,检验关联结果的稳定性。

R 软件中的“mediation”包用非参数 Bootstrap 法检验中介效应,适用于广义线性回归模型分析[13]。先使用 Logistic 回归模型计算自变量、中介变量对因变量的效应,若效应有统计学意义,则进行下一步分析,输出间接效应、直接效应及中介效应占总效应的比例。检验水准 $\alpha=0.05$。

2　结果

2.1　研究对象的基本特征　纳入的 1 292 母子对中,有 173 名(13.39%)儿童 3 岁时有超重肥胖风险。有、无超重肥胖风险组儿童母亲孕前 BMI 和子代体重分别为(23.52±3.84) kg/m^2,(3.53±0.51) kg;(22.30±3.34) kg/m^2,(3.35±0.45) kg,差异均有统计学意义(t 值分别为 3.93,4.44,P 值均<0.05)。两组母亲分娩年龄分别为(30.25±3.73,30.46±3.95)岁,差异无统计学意义($t=-0.68$,$P>0.05$)。

两组儿童母亲孕前 BMI 水平分类、孕早期 LDL-C 及 TC/HDL-C、LDL-C/HDL-C 差异均有统计学意义(P 值均<0.05)。超重肥胖风险组男、女童占比分别为 51.45%(89 名)、48.55%(84 名),无超重肥胖风险组占比分别为 50.04%(560 名)、49.96%(559 名),差

异无统计学意义($\chi^2=0.07$, $P>0.05$)。见表 1~2。

表 1 不同组别儿童母亲孕早期血脂指标比较[$M(P_{25},P_{75})$]

Table 1 Comparison of early pregnancy blood lipid indicators among different groups of mothers[$M(P_{25},P_{75})$]

组别	人数	TC/(mmol·L^{-1})	TG/(mmol·L^{-1})	HDL-C/(mmol·L^{-1})	LDL-C/(mmol·L^{-1})	TC/HDL-C	TG/HDL-C	LDL-C/HDL-C
有超重肥胖风险	173	4.07(3.62,4.53)	1.08(0.86,1.46)	1.63(1.44,1.87)	2.36(1.99,2.76)	2.38(2.10,2.85)	0.66(0.49,0.91)	1.34(1.14,1.76)
无超重肥胖风险	1 119	3.97(3.57,4.45)	1.07(0.85,1.37)	1.72(1.48,1.93)	2.21(1.88,2.63)	2.33(2.03,2.70)	0.62(0.47,0.84)	1.29(1.05,1.63)
Z 值		1.41	0.96	−1.86	2.48	2.48	1.49	2.71
P 值		0.16	0.34	0.06	0.01	0.01	0.14	0.01

表 2 不同组别儿童母亲基本特征比较

Table 2 Comparison of demographic characteristics distribution among different groups

组别	人数	孕前 BMI 水平				早产		产次		妊娠期糖尿病	妊娠期高血压
		低体重	正常	超重	肥胖	是	否	初产妇	经产妇		
有超重肥胖风险组	173	12(6.94)	91(52.60)	45(26.01)	25(14.45)	10(5.78)	163(94.22)	104(60.12)	69(39.88)	63(36.42)	12(6.94)
无超重肥胖风险组	1 119	99(8.85)	720(64.34)	228(20.38)	72(6.43)	51(4.56)	1 068(95.44)	673(60.14)	446(39.86)	382(34.14)	78(6.97)
χ^2 值		19.01				0.26		<0.01		0.25	<0.01
P 值		<0.01				0.61		1.00		0.62	1.00

注:( )内数字为构成比或患病率/%。

2.2 *母亲孕前 BMI 与儿童超重肥胖风险的关联* 多因素 Logistic 回归分析结果显示,母亲孕前 BMI 和 BMI 水平分类均会影响 3 岁儿童的超重肥胖发生风险。在校正混杂因素(母亲分娩年龄、产次、儿童性别、儿童出生体重)后,母亲孕前 BMI 与儿童 3 岁时超重肥胖风险呈正相关($OR=1.09$, 95%$CI=1.04\sim1.14$, $P<0.05$)。母亲孕前体重正常、超重、肥胖的子代 3 岁时存在超重肥胖风险的比例分别为 11.22%(91/811),16.48%(45/273),25.77%(25/97)。母亲孕前肥胖的儿童 3 岁时存在超重肥胖风险的概率是体重正常者的 2.78 倍($OR=2.78$, 95%$CI=1.64\sim4.61$, $P<0.05$)。

根据儿童性别分层分析,在校正混杂因素(母亲分娩年龄、产次,儿童性别、儿童出生体重)后,Logistic 回归分析结果显示,母亲孕前 BMI 与男童 3 岁时超重肥胖风险呈正相关($OR=1.08$, 95%$CI=1.01\sim1.15$),母亲孕前肥胖的男童 3 岁时发生超重肥胖风险的概率是体重正常者的2.43倍($OR=2.43$, 95%$CI=1.13\sim4.97$);母亲孕前 BMI 与女童 3 岁时超重肥胖风险呈正相关($OR=1.10$, 95%$CI=1.03\sim1.17$),母亲孕前肥胖的女童 3 岁时发生超重肥胖风险的概率是体重正常者的 3.22 倍($OR=3.22$, 95%$CI=1.52\sim6.54$)(P 值均<0.05)。男、女童组的关联结果差异无统计学意义($P_{交互作用}>0.05$)。排除母亲早产和患有妊娠期代谢性疾病(妊娠期糖尿病或妊娠期高血压)的母子对,母亲孕前 BMI 与儿童 3 岁时超重肥胖风险呈正相关($OR=1.08$, 95%$CI=1.01\sim1.16$),母亲孕前肥胖的儿童 3 岁时发生超重肥胖风险的概率是体重正常者的 2.43 倍($OR=2.43$, 95%$CI=1.00\sim5.62$)(P 值均<0.05)。

2.3 *母亲孕早期血脂与儿童超重肥胖风险的关联* Logistic 回归模型结果显示,在校正混杂因素(母亲分娩年龄、产次、儿童性别、儿童出生体重)后,母亲孕早期 LDL-C、TC/HDL-C、LDL-C/HDL-C 均与儿童 3 岁时超重肥胖风险呈正相关[OR 值(95%CI)分别为1.42(1.07~1.87)、1.49(1.11~1.99)、1.60(1.15~2.22),P 值均<0.05]。儿童性别分层后,母亲孕早期血脂与 3 岁男、女童组的关联结果差异无统计学意义($P_{交互作用}>0.05$)。排除母亲早产和患有妊娠期代谢性疾病(妊娠期糖尿病或妊娠期高血压)的母子对,母亲孕早期 LDL-C/HDL-C 与儿童 3 岁时超重肥胖的风险呈正相关($OR=1.71$, 95%$CI=1.04\sim2.78$, $P<0.05$)。

2.4 *母亲孕早期血脂在孕前 BMI 与子代超重肥胖风险间的中介作用* 调整母亲分娩年龄、产次、儿童性别、儿童出生体重等协变量,中介效应模型结果表明,孕前 BMI 升高,可使孕早期 LDL-C、TC/HDL、LDL-C/HDL 升高,进而提高 3 岁儿童发生超重肥胖的风险,中介效应占比分别为 7.3%,10.2%,23.5%。

3 讨论

本研究结果显示,母亲孕前 BMI 升高、孕早期血脂升高均为 3 岁儿童超重肥胖的风险因素。多项队列研究已阐明母亲孕前 BMI 升高会引起子代超重肥胖的发生风险[2-4]。有研究应用单一血脂指标探究孕早期血脂与子代肥胖的关联,发现母亲孕早期血脂升高会引起子代 3 岁 BMI-Z 评分的升高、11~12 岁 BMI、胸围、体脂百分比的升高[5,14]。另有研究发现血脂比值升高与体重增加的正向关联[15-16]。虽然尚未见研究探究母亲孕期血脂比值指标与儿童肥胖的关系,但是目前有少量研究用血脂比值指标衡量孕期血脂[17-18],其中一项中国福建的研究发现孕早期 TC/HDL-C、TG/HDL-C 升高会增加妊娠期糖尿病的发生风险[17]。而既往研究已证实妊娠期糖尿病会提高子

代超重肥胖的发病风险[19]。本研究也发现母亲孕早期血脂在孕前 BMI 与 3 岁儿童超重肥胖之间存在部分中介作用。虽然既往尚无研究定量分析母亲孕期血脂在孕前 BMI 与儿童肥胖之间的中介作用,但一项荷兰的出生队列研究提示孕前超重肥胖的母亲,孕期血脂肪酸含量更高,分娩出的子代出生体重更重[20],研究结论与本研究相似。提示儿童超重肥胖的预防关口可提前至母亲备孕期、孕早期,母亲应在孕前维持适宜体重,重视孕期血脂的监测与控制。

母亲孕前 BMI、孕早期血脂对儿童肥胖的影响机制尚不清楚。孕前超重肥胖的孕妇宫内有更多的葡萄糖和脂肪酸,糖脂的过度暴露可能会引起胎儿脂肪细胞生成增加、脂肪组织发育异常[21];此外,孕前超重肥胖孕妇的肥胖易感基因会遗传给子代,都可能增加子代出生后发生超重肥胖的风险[22]。孕早期血脂升高意味着母体代谢异常,可能引起胎儿宫内的胰岛素抵抗,进而引起子代肥胖[23];且孕早期血脂升高也可能通过影响胎儿与生长发育相关基因的甲基化水平,进而影响子代生长发育[24]。母亲孕早期血脂在孕前 BMI 与子代肥胖间的部分中介作用,原因可能为孕前超重肥胖的孕妇,常伴有脂联素水平降低及胰岛素抵抗[25],影响孕妇孕期脂代谢水平,进而通过宫内暴露、表观遗传等方式影响儿童肥胖。

本研究综合应用血脂及其比值指标衡量孕早期血脂水平,基于前瞻性出生队列数据深入分析母亲孕前 BMI、孕早期血脂与 3 岁儿童超重肥胖的关联。但本研究存在一些局限性:(1)仅纳入北京市通州区的人群,未来可将研究人群拓展至更广范围,对研究结论进行验证;(2)研究仅用 BMI-*Z* 评分衡量儿童 3 岁时的超重肥胖风险,未来可结合胸围、腰围、体脂百分比等指标更全面地衡量儿童肥胖。

综上所述,母亲孕早期高血脂在孕前肥胖与学龄前儿童肥胖之间有部分中介作用,母亲孕前肥胖和孕早期高血脂都是学龄前儿童肥胖的风险因素,未来在开展学龄前儿童肥胖防控时要关注具有这些危险因素的儿童群体。

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