

· 临床研究 ·

## 肥胖共患中枢性性早熟女童的脂质组学分析

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**[摘要]** 目的: 通过脂质组学分析技术, 系统筛选儿童肥胖共患中枢性性早熟(childhood obesity comorbid with central precocious puberty, CO-CPP)的潜在生物标志物, 并探索差异脂质联合疾病相关临床指标应用于CO-CPP早期识别和预警的可行性, 为临床实践提供新依据。方法: 选取2024年1月—2025年6月首次就诊于南京医科大学附属淮安第一医院儿科内分泌门诊的6~8岁肥胖女童20例, 根据是否合并中枢性性早熟(central precocious puberty, CPP)或外周性性早熟(peripheral precocious puberty, PPP)分为CO-CPP组(10例)和肥胖共患外周性性早熟(childhood obesity comorbid with peripheral precocious puberty, CO-PPP)组(10例)。比较两组一般临床资料, 采集血清样本进行非靶向脂质组学分析。筛选差异脂质后开展受试者工作特征(receiver operating characteristic, ROC)曲线分析, 进一步结合临床指标通过二元Logistic回归构建联合预测模型, 并开展联合ROC分析评估预测效能。结果: 脂质组学分析共鉴定出42种差异有统计学意义的脂质分子, 其中神经酰胺(ceramide, Cer)、磷脂酰胆碱(phosphatidylcholine, PC)表达上调, 磷脂酰乙醇胺(phosphatidylethanolamine, PE)表达下调。Cer、PC、PE单独预测CO-CPP的ROC曲线下面积(area under the curve, AUC)分别为0.810、0.798、0.834, 均展现出良好的判别效能( $P$ 均 $< 0.05$ )。Cer联合基础黄体生成素(luteinizing hormone, LH)的预测模型AUC可达0.970。结论: CO-CPP女童体内与青春期发育相关的关键脂质Cer、PC表达上调, PE表达下调, 上述脂质或可作为CO-CPP的潜在生物学标志物。Cer联合基础LH的判别效能优于单一脂质指标, 具有较好的临床应用潜力。

**[关键词]** 肥胖; 性早熟; 共病; 脂质组学; 儿童**[中图分类号]** R725.8**[文献标志码]** A**[文章编号]** 1007-4368(2026)06-864-09**doi:** 10.7655/NYDXBNSN260112

### Lipidomics analysis of childhood obesity comorbid with central precocious puberty

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**[Abstract]** **Objective:** This study employed lipidomics analysis to systematically screen potential biomarkers of childhood obesity comorbid with central precocious puberty (CO-CPP), and explored the feasibility of combining these biomarkers with disease-related clinical indicators to provide new evidence for early identification and warning of CO-CPP. **Methods:** A total of 20 obese female children aged 6 to 8 years who first visited the Pediatric Endocrinology Clinic of the Affiliated Huai'an No. 1 People's Hospital of Nanjing Medical University between January 2024 and June 2025 were enrolled. They were divided into the CO-CPP group ( $n=10$ ) and the comorbidity of childhood obesity comorbid with peripheral precocious puberty (CO-PPP) group ( $n=10$ ) based on the presence of central precocious puberty (CPP) or peripheral precocious puberty (PPP). General clinical data were compared between the two groups, and serum samples were collected for non-targeted lipidomics analysis. Differential lipids were screened using receiver operating characteristic (ROC) curve analysis, and a combined predictive model was constructed with clinical indicators via binary logistic regression, followed by further combined ROC analysis. **Results:** Lipidomics analysis identified 42 lipid molecules with significant differences. Among them, the expression of ceramide (Cer) and phosphatidylcholine (PC) were up-regulated, while the expression of phosphatidylethanolamine (PE) was down-regulated. The area under the curve (AUC) of ROC for predicting CO-CPP by Cer, PC, and PE alone was 0.810, 0.798, and 0.834, respectively, all of which showed good discriminative efficacy (all  $P < 0.05$ ). The

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AUC of the combined prediction model of Cer and the basal level of luteinizing hormone (LH) was 0.970. **Conclusion:** In girls with CPP, the expressions of Cer and PC, the key lipids associated with pubertal development, are up-regulated, while the expression of PE is down-regulated. These lipids may serve as potential biological markers for CPP. The discriminative efficacy of Cer combined with basal LH is superior to that of single lipid indicators, showing good potential for clinical application.

[Key words] obesity; precocious puberty; comorbidity; lipidomics; children

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肥胖症是一种日益在全球范围内凸显的慢性代谢性疾病<sup>[1-2]</sup>,其病理机制已从单一的营养过剩表型演变为涉及遗传、环境与行为的多因素交互作用模型<sup>[3-4]</sup>。肥胖与儿童内分泌发育异常相关<sup>[5]</sup>,且肥胖儿童发生中枢性性早熟(central precocious puberty, CPP)的风险显著高于正常体重儿童<sup>[6-7]</sup>。肥胖女童的CPP风险相对于男童更高,可能与性二态性因素有关<sup>[7]</sup>。此外,肥胖合并维生素D缺乏的儿童性早熟风险进一步增加<sup>[8]</sup>。患有外周性性早熟(peripheral precocious puberty, PPP)的儿童若未及时干预,长期代谢紊乱如高胰岛素血症、瘦素抵抗等疾病状态可能激活促性腺激素释放激素(gonadotropin-releasing hormone, GnRH)神经元进展为CPP<sup>[9-11]</sup>。这表明肥胖可能通过胰岛素抵抗、脂肪因子紊乱及下丘脑-垂体-性腺轴(hypothalamic-pituitary-gonadal axis, HPGA)激活等多种机制加速性发育<sup>[12]</sup>。

传统CPP的诊断依赖金标准GnRH刺激试验<sup>[13]</sup>,但该方法存在显著局限性:①需连续抽取3次或更多次血液样本,增加患儿身心压力及家长经济负担;②漏诊率高;③相关辅助检查如骨龄测定、盆腔超声及MRI存在设备依赖和操作复杂等问题。目前尚无具有临床实用价值的特异性生物标志物,导致早期筛查与精准分型困难<sup>[14]</sup>,故探索表观遗传标记等新型筛查技术成为儿科内分泌学关键课题。

组学技术发展推动多组学整合分析用于疾病精准诊疗。代谢物的异常波动揭示了疾病状态下的代谢紊乱<sup>[15-16]</sup>,而脂质凭借其在生物膜构成、能量代谢调节及病理生理过程中的多重核心功能成为关键研究对象<sup>[17]</sup>。脂质组学聚焦于脂质的结构解析与功能阐释,正逐步揭示其在疾病发生发展中的深层机制<sup>[18]</sup>。

本研究旨在通过脂质组学分析,筛选有助于肥胖共患中枢性性早熟(childhood obesity comorbid with central precocious puberty, CO-CPP)诊断的潜在生物标志物,并探索其与性早熟相关临床指标联合构建预测模型,评估其用于CO-CPP早期识别与预测的价值。

## 1 对象和方法

### 1.1 对象

本研究选取2024年1月—2025年6月间首次就诊于南京医科大学附属淮安第一医院儿科内分泌门诊的20例6~8岁肥胖女童,根据患有CPP或PPP分为CO-CPP组( $n=10$ )和肥胖共患外周性性早熟(childhood obesity comorbid with peripheral precocious puberty, CO-PPP)组( $n=10$ ),其中PPP在本研究中均为单纯性乳房发育。纳入标准:①符合肥胖诊断标准的女童。肥胖定义为个体体重指数(body mass index, BMI)超过性别和年龄分层的BMI参考标准;②确诊为CPP和PPP的女童。CPP、PPP诊断根据GnRH激发试验结果、盆腔超声、骨龄及生长速率,标准参考《中枢性性早熟诊断与治疗专家共识(2022)》<sup>[19]</sup>;③就诊前未接受任何药物治疗。排除标准:①合并中枢神经系统异常及其他继发性疾病(如先天性肾上腺皮质增生症、麦克纳-阿尔布雷特综合征、原发性甲状腺功能减退症及普拉德-威利综合征等)的CPP女童;②既往使用过影响HPGA的药物;③依从性差。本研究经南京医科大学附属淮安第一医院伦理委员会批准(批件号:KY-2024-344-01),符合《赫尔辛基宣言》要求患儿父母均知情同意。

### 1.2 方法

#### 1.2.1 临床数据收集

身高、体重、BMI由专业人员测量,年龄别身高Z评分(height-for-age Z-score, HAZ)、年龄别体重Z评分(weight-for-age Z-score, WAZ)和年龄别BMI Z评分(body mass index-for-age Z-score, BAZ)由WHO AnthroPlus(版本1.0.4)软件计算。骨龄指数(bone age index, BAI)=(骨龄-实际年龄)/实际年龄。乳房分期依据坦纳标准。血清基础促性腺激素(gonadotropin, Gn)、雌二醇(estradiol, E2)、催乳素(prolactin, PRL)、胰岛素样生长因子1(insulin-like growth factor 1, IGF-1)水平用罗氏(日本)电化学发光免疫分析仪检测。采用中华05法判断骨龄(bone age, BA)。子

子宫容积(uterine volume, UV)、卵巢容积(ovarian volume, OV)、卵泡数目(number of follicles, NOF)、子宫长度(uterine length, UL)由专业的超声医师评估。

受试女童禁食12 h后,于上午8:00在安静状态下采集静脉血。刺激试验前测定基础血清Gn水平,随后给予醋酸曲普瑞林(0.1 mg/瓶)。注射剂量为2.5  $\mu\text{g}/\text{kg}$ ,最大剂量为100  $\mu\text{g}$ 。分别于注射前及注射后30、60、90 min采集静脉血2 mL,采用免疫化学发光法测定血清Gn水平。其余血清-80  $^{\circ}\text{C}$ 保存。

### 1.2.2 脂质组学

样本提取:血清经4  $^{\circ}\text{C}$ 解冻,取50  $\mu\text{L}$ 加入150  $\mu\text{L}$ 提取试剂,于摇床1 500 r/min涡旋混匀20 min,随后转移至96孔板,4  $^{\circ}\text{C}$ 下2 200 g离心10 min。过滤后滤液采用 $\text{C}^{18}$ 正/负离子模式检测分析。质控(quality control, QC)样本由等量混合样品制备。检测时样本序列随机分布, QC样本均匀穿插其中。

LC-MS/MS检测:样品在Vanquish超高效液相色谱仪与Q Exactive四极杆-轨道阱高分辨质谱仪联用系统上检测,脂质经反相色谱分离后以正/负离子( $\text{ESI}^+/\text{ESI}^-$ )模式分析。色谱检测使用Acquity<sup>TM</sup> BEH  $\text{C}^{18}$ 柱(柱温40  $^{\circ}\text{C}$ ),洗脱液A为60%乙腈水、B为10%乙腈异丙醇,5 min冲洗平衡,流速0.3 mL/min。质谱采用加热电喷雾离子源,负离子模式优化用20%+30%阶梯归一化碰撞能量。

组学分析:用XCalibur Quan Browser提取总离子流图曲线下面积(area under the curve, AUC)作脂质定量信息, R/Python编程行显著性检验与分类分析;以差异倍数(fold change, FC) $\geq 1.2$ 筛差异脂质,获得上调/下调种类数量,供后续主成分分析(principal component analysis, PCA)、聚类及相关分析。

### 1.3 统计学方法

数据分析采用SPSS 27.0软件。定性信息以构成比表示,卡方检验用于两组比较。符合正态分布的连续变量以均值 $\pm$ 标准差( $\bar{x} \pm s$ )表示,独立样本两组比较采用 $t$ 检验。相关性分析采用Pearson相关分析。非正态分布的连续变量以中位数(四分位数)[ $M(P_{25}, P_{75})$ ]表示,比较采用Man-Whitney  $U$ 检验,相关性分析采用Spearman秩相关分析。绘制受试者工作特征(receiver operating characteristic, ROC)曲线。 $P < 0.05$ 为差异有统计学意义。

## 2 结果

### 2.1 一般临床资料比较

两组女童在HAZ、BA、BAI、E2、OV、UV、身高、

体重、黄体生成素(luteinizing hormone, LH)基础值、卵泡刺激素(follicle-stimulating hormone, FSH)基础值及空腹血糖(fasting plasma glucose, FPG)方面的差异均具有统计学意义( $P$ 均 $< 0.05$ )。年龄、总胆红素(total bilirubin, TBIL)、胰岛素(insulin, INS)及甘油三酯(triglyceride, TG)等指标的差异均无统计学意义。其中两组肥胖患儿BMI均未超过同年龄同性别儿童BMI的第97百分位,属于轻度肥胖( $P > 0.05$ ,表1)。

### 2.2 脂质组学分析

脂质定量值跨多数量级平滑连续稳定、质量优,可用于后续分析。箱线图示样本组中位数、四分位距及须线范围高度一致,脂质丰度分布同质。以QC样本脂质响应强度相对标准差(relative standard deviation, RSD) $\leq 30\%$ 过滤,剔除RSD $> 30\%$ 脂质保证统计稳定,仅6.4%脂质因RSD过高被剔除(图1)。

脂质组学共鉴定出1 880种高置信度脂质,涉及神经酰胺(ceramide, Cer)、磷脂酰胆碱(phosphatidylcholine, PC)、磷脂酰乙醇胺(phosphatidylethanolamine, PE)等不同脂质分类(图2A)。分析脂质定量值相关性显示,CO-PPP组内重复性及一致性较高,CO-CPP组虽稍分散,整体仍呈较高水平正相关(图2B)。

采用 $\text{FC} \geq 1.2$ 和显著性水平( $P < 0.05$ )的双重筛选标准,鉴定出42种具有统计学显著性的差异脂质,包括18种上调脂质和24种下调脂质(图3A、B)。下调脂质以蓝色标记,上调脂质以红色标记,无差异脂质以灰色标记。

通过相关性分析评估了差异脂质之间的代谢关联性。红色表示正相关,蓝色表示负相关;颜色越深,相关性程度越高(图4)。

脂质组学结果显示,Cer、PC、PE这三类差异脂质或为潜在的CO-CPP生物标志物。与其他组别相比,CO-CPP组PC、Cer水平增加以及PE水平降低。ROC分析示PC、PE的AUC分别为0.798和0.834(图5)。

### 2.3 Cer与临床指标的联合分析

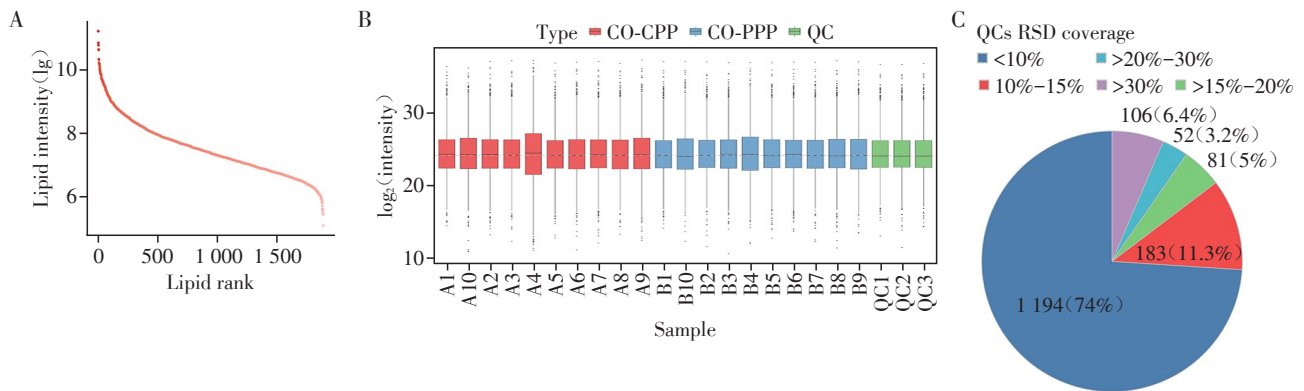
Cer与LH基础值、INS呈正相关且具有统计学意义( $P < 0.05$ ),相关系数分别为0.52和0.46,与FSH基础值等其余指标的相关性无统计学意义( $P > 0.05$ ,表2)。

ROC曲线分析提示Cer的AUC为0.810。选取部分与肥胖、CPP相关临床指标与Cer指标行联合预测,ROC曲线分析显示,LH基础值+Cer联合预测CO-CPP的AUC为0.970(表3),高于上述其他单一

表1 CO-CPP组与CO-PPP组基本信息比较

Table 1 Comparison of basic information between the CO-CPP group and CO-PPP group

Variable	CO-CPP(n=10)	CO-PPP(n=10)	Test Statistics	P
Age(years, $\bar{x} \pm s$ )	7.38 $\pm$ 0.62	7.12 $\pm$ 0.65	$t=2.093$	0.051
Height(cm, $\bar{x} \pm s$ )	136.39 $\pm$ 6.96	127.75 $\pm$ 4.43	$t=3.310$	0.004
HAZ[ $M(P_{25}, P_{75})$ ]	2.04(1.09, 2.60)	0.97(0.16, 1.86)	$z=-1.965$	0.049
Weight(kg, $\bar{x} \pm s$ )	38.74 $\pm$ 4.35	35.17 $\pm$ 3.08	$t=2.119$	0.048
WAZ( $\bar{x} \pm s$ )	2.56 $\pm$ 0.49	2.50 $\pm$ 0.69	$t=0.210$	0.836
BMI(kg/m <sup>2</sup> , $\bar{x} \pm s$ )	20.74 $\pm$ 1.92	21.58 $\pm$ 2.17	$t=-0.918$	0.371
BAZ( $\bar{x} \pm s$ )	2.11 $\pm$ 0.52	2.49 $\pm$ 0.79	$t=-1.272$	0.220
BA[years, $M(P_{25}, P_{75})$ ]	10.25(8.98, 11.0)	8.45(6.80, 8.80)	$z=-3.053$	0.002
BAI[ $M(P_{25}, P_{75})$ ]	0.33(0.18, 0.40)	0.18(0.06, 0.25)	$z=-2.427$	0.015
IGF-1(ng/mL, $\bar{x} \pm s$ )	273.11 $\pm$ 111.87	208.80 $\pm$ 52.62	$t=1.645$	0.117
LH[IU/L, $M(P_{25}, P_{75})$ ]	1.14(0.32, 4.00)	0.13(0.06, 0.27)	$z=-3.408$	<0.001
FSH[IU/L, $M(P_{25}, P_{75})$ ]	3.35(2.30, 5.99)	1.68(0.52, 2.80)	$z=-2.117$	0.034
E2[pg/mL, $M(P_{25}, P_{75})$ ]	13.65(8.55, 41.50)	4.97(2.80, 15.78)	$z=-1.965$	0.046
OV[mL, $M(P_{25}, P_{75})$ ]	4.08(2.44, 5.72)	2.26(1.35, 3.18)	$z=-2.192$	0.029
PRL[ng/mL, $M(P_{25}, P_{75})$ ]	10.66(6.34, 15.30)	9.01(5.54, 18.53)	$z=0.000$	1.000
UV(mL, $\bar{x} \pm s$ )	2.84 $\pm$ 1.05	1.11 $\pm$ 0.61	$t=4.496$	<0.001
FPG(mmol/L, $\bar{x} \pm s$ )	5.18 $\pm$ 0.47	4.66 $\pm$ 0.53	$t=2.270$	0.036
TG[mmol/L, $M(P_{25}, P_{75})$ ]	0.82(0.59, 1.29)	0.64(0.53, 0.82)	$z=-1.209$	0.226
ALT[U/L, $M(P_{25}, P_{75})$ ]	13.00(5.00, 21.00)	12.00(2.60, 21.40)	$z=-0.303$	0.762
AST[U/L, $M(P_{25}, P_{75})$ ]	20.30(15.60, 25.00)	21.60(18.20, 25.00)	$z=-0.756$	0.450
INS[pmol/L, $M(P_{25}, P_{75})$ ]	114.45(55.70, 147.25)	63.05(43.90, 85.27)	$z=-1.663$	0.096
TBIL[ $\mu$ mol/L, $M(P_{25}, P_{75})$ ]	7.80(5.40, 10.20)	7.90(5.00, 10.80)	$z=-0.113$	0.910



A: Quantitative intensity sequencing analysis. B: Distribution of lipid quantification values. C: The proportion of response intensity RSD corresponding to spectral peaks in the quality control sample, with the purple portion excluded.

图1 CO-CPP组与CO-PPP组脂质定量分析比较

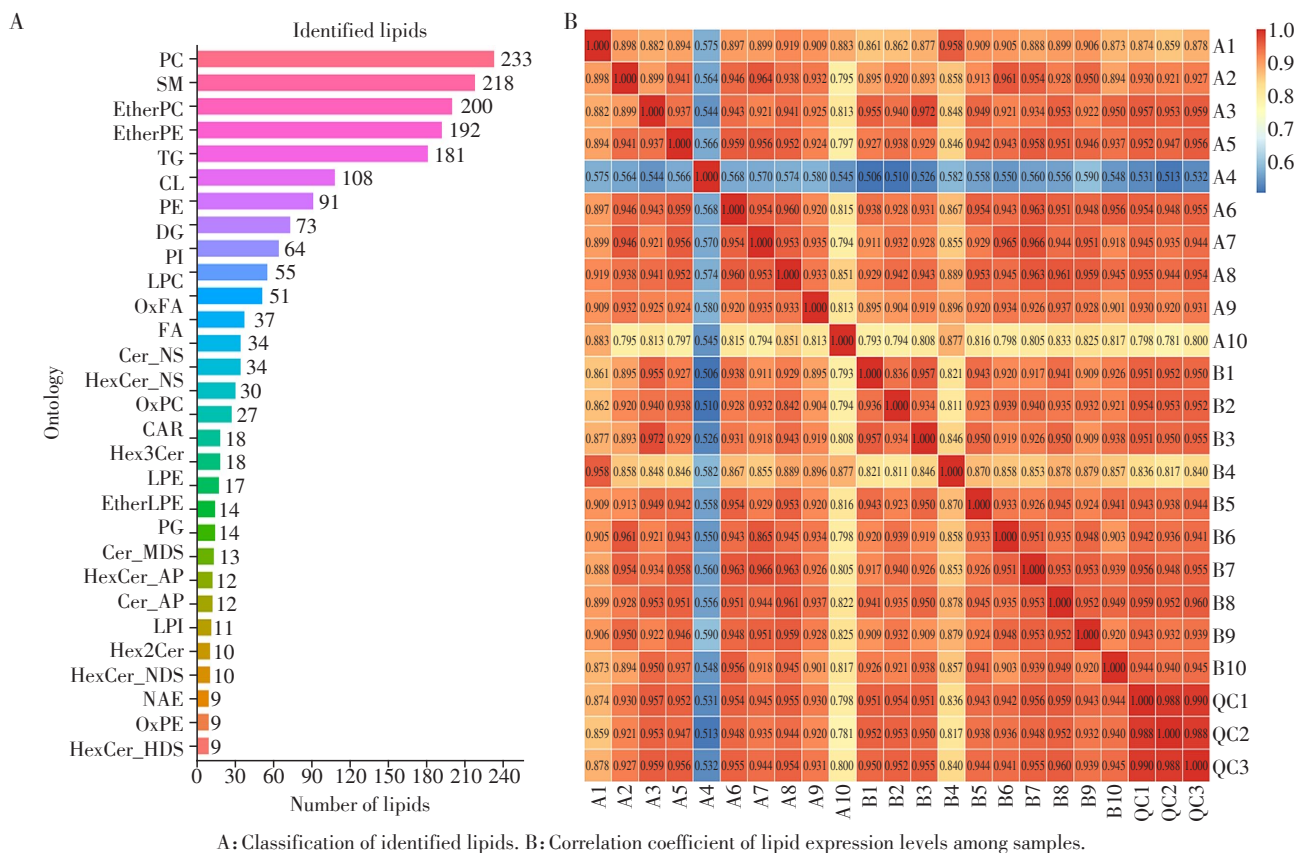
Figure 1 Comparison of lipid quantitative analysis between the CO-CPP group and CO-PPP group

指标及联合指标的AUC,提示判别效能提升。

选取Cer与LH基础值行二元Logistic回归分析显示Omnibus检验显著性水平 $P < 0.001$ , Nagelkerke  $R^2$ 为0.807, Hosmer-Lemeshow检验 $P$ 值0.773,提示该模型整体显著,拟合效果良好,但变量系数提示无统计学意义( $P > 0.05$ ,表4)。

### 3 讨论

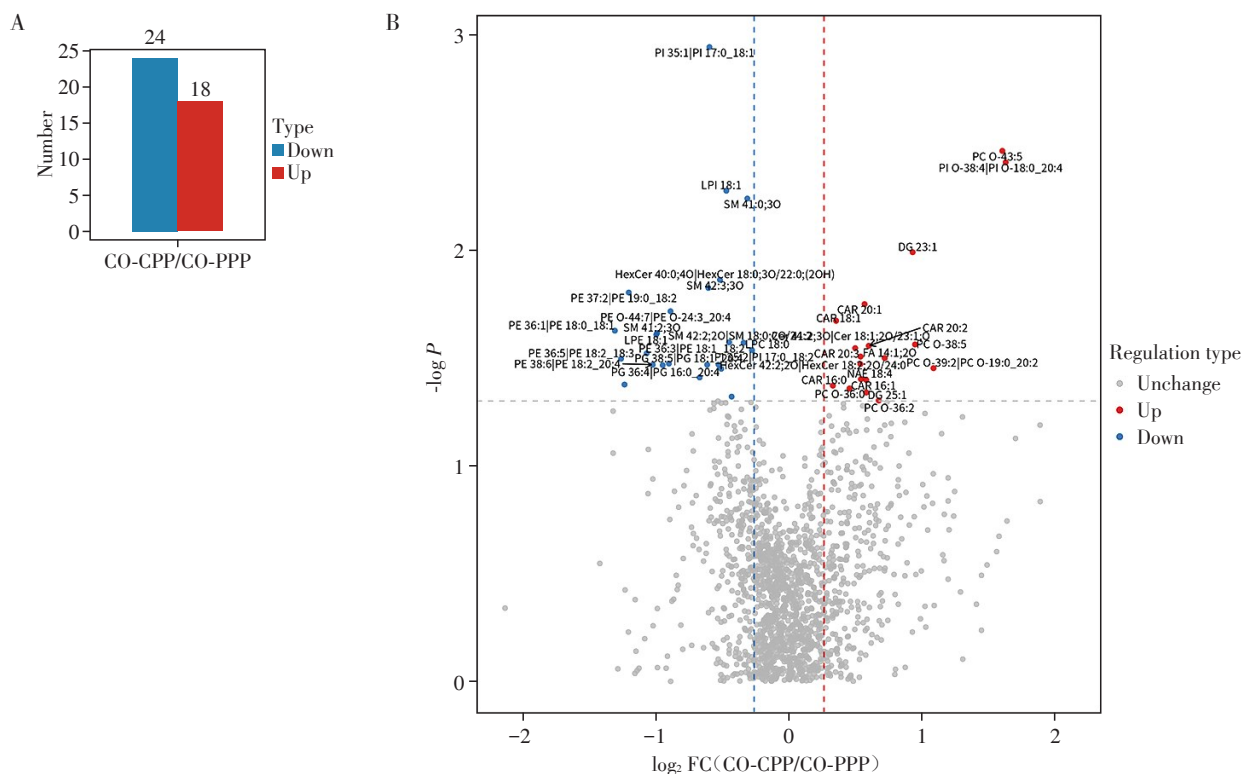
近半个世纪以来,随着全球经济的快速发展及饮食结构的变化,儿童肥胖率持续攀升<sup>[2]</sup>。大量流行病学及临床研究证实,肥胖是儿童发生CPP的重要独立危险因素之一<sup>[6-7]</sup>。揭示二者共病的生物学



A: Classification of identified lipids. B: Correlation coefficient of lipid expression levels among samples.

图2 CO-CPP组与CO-PPP组的脂质分类及相关性分析

Figure 2 Lipid classification and correlation analysis between the CO-CPP group and the CO-PPP group



A: Differences in lipid quantity. B: Volcano plot of lipid differences.

图3 CO-CPP组与CO-PPP组组间差异脂质数量柱状图及火山图

Figure 3 Column chart and volcano plot of lipid quantity differences between the CO-CPP group and the CO-PPP group

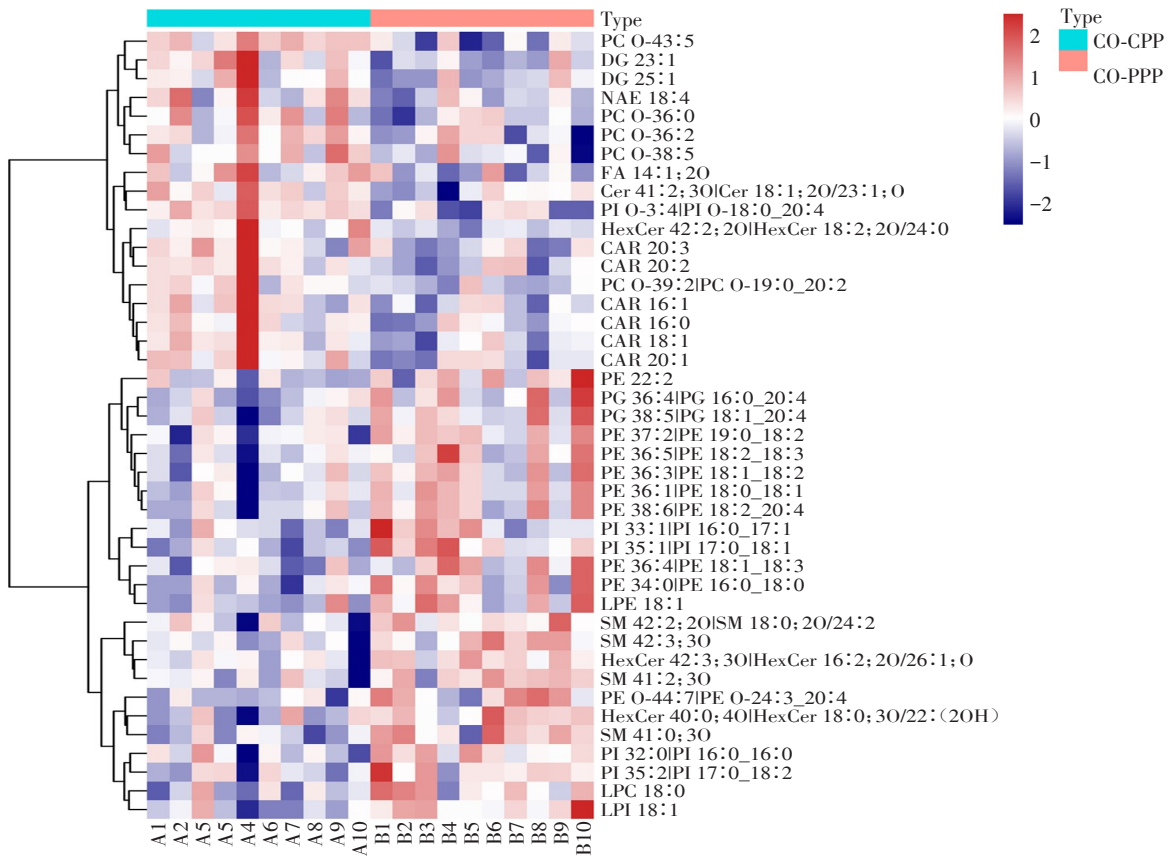
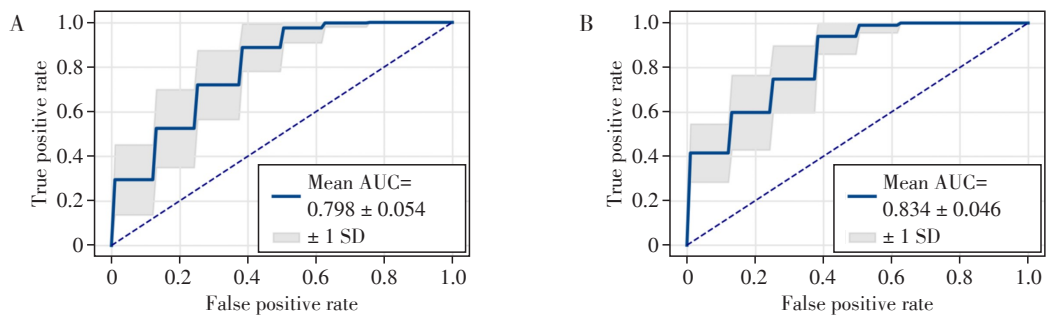


图4 CO-CPP组与CO-PPP组代谢关联性热图

Figure 4 Heat map of metabolic association between the CO-CPP group and CO-PPP group



A: ROC curve of PC. B: ROC curve of PE.

图5 PC、PE的ROC曲线图

Figure 5 ROC curves of PC and PE

机制,对于制定精准的预防及干预策略至关重要。近年来,Cer在肥胖儿童性早熟发病机制中的调控作用日益成为该领域的研究焦点<sup>[20]</sup>,但目前对于肥胖与CPP共病的内在分子联系,尤其是脂质代谢层面的机制,报道仍较少。本研究采用非靶向脂质组学技术,对CO-CPP组与CO-PPP组的患儿血清样本进行了初步分析。

本研究发现 Cer 在 CO-CPP 组表达明显高于 CO-PPP 组。与直接调控 GnRH 神经元的吻素不同, Cer 以独特非经典模式调控下丘脑介导的青春期发

育:经室旁核(paraventricular nucleus, PVN)与卵巢交感神经支配构成非典型神经-内分泌轴<sup>[21]</sup>。Heras等<sup>[21]</sup>的动物模型证实了处于高营养状态下的雌性大鼠表现出性成熟提前,下丘脑 Cer 整体含量显著升高。对瘦型雌性大鼠进行脑室内干预注射不同物质会产生不同的表型:神经酰胺酶 C6 可增加 Cer 合成并加速性成熟,而使用多球菌素持续阻断 Cer 产生则延迟效果。通过检测腹腔神经节与卵巢中交感神经标志物即去甲肾上腺素(norepinephrine, NE)及其代谢物3-甲氧基-4-羟基苯基乙二醇(3-methoxy-

表2 Cer与临床指标的相关性分析

Table 2 Correlation analysis between Cer and clinical indicators

Indicator	$r_s$	$P$
LH	0.52	0.02
INS	0.46	0.04
FSH	0.22	0.36
OV	0.09	0.68
UV	0.36	0.11
E2	0.41	0.08
TG	0.19	0.43
TBIL	0.20	0.42
BA	0.38	0.10
BAI	0.22	0.36

表3 单一指标及联合指标预测CO-CPP的ROC曲线

Table 3 ROC curves for single and combined indicators in the prediction of CO-CPP

Indicator	AUC(95%CI)	Cutoff value	$P$
Cer	0.810(0.620-1.000)	6.98	0.010
LH	0.950(0.860-1.000)	0.32	0.001
INS	0.720(0.484-0.956)	92.50	0.090
TG	0.660(0.403-0.917)	0.83	0.226
TBIL	0.515(0.253-0.777)	6.80	0.910
LH+Cer	0.970(0.902-1.000)	-	<0.001
INS+Cer	0.820(0.634-1.000)	-	0.016
TG+Cer	0.820(0.629-1.000)	-	0.016
TBIL+Cer	0.810(0.618-1.000)	-	0.019

表4 Cer、基础LH与CO-CPP女童的二元Logistic回归分析

Table 4 Bivariate logistic regression analysis of Cer, basal LH in CO-CPP girls

Variable	Coefficient	Omnibus test	Nagelkerke $R^2$	Hosmer-Lemeshow test	$P$
Constant	-80.552	$P<0.001$	0.807	$P=0.773$	0.264
LH	23.866	$P<0.001$			0.165
Cer	10.599	$P<0.001$			0.287

4-hydroxyphenylglycol, MHPG),发现雌鼠出生后第25天NE/MHPG比值水平升高,提示早期交感神经激活,第29天则显著下降,反映卵巢已成熟。选择性阻断PVN的Cer合成过程可完全阻断卵巢成熟过程,确证PVN-Cer通路为该调控轴的关键。肥胖儿童中,过量的游离脂肪酸(free fatty acid, FFA)可作为Cer合成的底物,通过从头合成途径促进Cer的合成<sup>[22]</sup>,这可能是Cer介导CPP的关键基础。另一种Cer合成途径是鞘磷脂经鞘磷脂酶分解为Cer,其过程可被肿瘤坏死因子- $\alpha$ (tumor necrosis factor-alpha,

TNF- $\alpha$ )等炎症信号激活<sup>[23]</sup>。TNF- $\alpha$ 是一种主要由免疫细胞分泌的促炎细胞因子,在肥胖患者外周血中呈显著高表达<sup>[24]</sup>,通过干扰胰岛素信号转导级联介导胰岛素抵抗的发生,是肥胖相关代谢紊乱的关键介导因子之一<sup>[23,25-27]</sup>。有研究表明,患有胰岛素抵抗的患者组织中Cer的水平远超正常,例如2型糖尿病患者骨骼肌细胞中Cer水平显著升高<sup>[28-29]</sup>。在利拉鲁肽治疗期间,患者血浆Cer浓度显著降低,提示该药物可能通过调控Cer代谢改善糖代谢紊乱<sup>[30]</sup>。另有研究表明,抑制Cer的生物合成或激活其降解途径(如酸性Cer酶过表达)可有效改善胰岛素信号转导效率<sup>[31]</sup>。因此,在肥胖状态下,FFA蓄积与慢性炎症可分别驱动Cer的生物合成,致使Cer异常蓄积,加剧代谢紊乱。己糖神经酰胺(hexosylceramide, HexCer)是Cer的下游糖基化衍生物,研究提示,在肥胖状态下,HexCer向Cer转化过程可能加速,导致Cer积累和HexCer相对减少。这种连贯的代谢反应变化直接促进胰岛素抵抗、炎症和心血管疾病风险升高<sup>[32-33]</sup>。本研究中,CO-CPP组的Cer含量显著高于对照组,表现为Cer 41:2;30|Cer 18:1;20/23:1;0增加,且HexCer 42:3;30|HexCer 16:2;20/26:1;0和HexCer 40:0;40|HexCer 18:0;30/22:0;(20H)明显减少,提示Cer合成增加,结果与已知理论一致<sup>[21-22]</sup>。

本研究还发现,CO-CPP组PC含量高于对照组,PE含量低于对照组,且CO-CPP组PC/PE比值升高。PC和PE是细胞膜的主要磷脂成分。既往研究表明,肥胖和2型糖尿病患者的血清中PC水平显著升高,且与胰岛素敏感性呈负相关,通过诱导肌细胞膜Cer积累加剧胰岛素抵抗<sup>[28]</sup>;PE合成酶Pcyt2杂合缺失的小鼠可表现为肥胖、胰岛素抵抗<sup>[34]</sup>。上述代谢异常均可促进CPP的发生。此外,另有研究显示,内源性大麻素(endogenous cannabinoid, eCB)系统与Kisspeptin密切相关,其活性分子对GnRH神经元起抑制作用<sup>[10,35-38]</sup>。磷脂酶D(phospholipase D, PLD)参与催化eCB活性分子形成过程<sup>[39]</sup>,活性下降可抑制eCB活性分子生成。PC、PE含量及比值变化提示PLD通路活性受到抑制,可能导致eCB系统对GnRH神经元抑制减弱而引起CPP,与已知研究结果一致<sup>[10,35,39]</sup>,但具体机制待扩大样本量后进一步研究阐明。

鉴于Cer在肥胖及CPP发病过程中均发挥重要作用,本研究将其确立为核心研究对象。Cer的ROC曲线分析显示其AUC值为0.810,表明其是区

分两组的良好指标。LH基础值+Cer联合预测CO-CPP的AUC为0.970,高于LH基础值、Cer单一指标及Cer与其他临床指标联合的AUC,提示判别效能提升。二元Logistic回归分析得到相关数据提示该模型整体显著,拟合效果良好,结合两个指标联合预测可提升判别效能,考虑影响不显著( $P > 0.05$ )可能与样本较少有关。

上述发现可能有助于阐明CO-CPP的发病机制,为CO-CPP的诊断提供潜在生物标志物,并为探索生物标志物与CPP相关临床指标联合构建预测模型提供方案。本研究存在若干局限性:首先,研究未纳入正常女孩对照组,限制了结果的可比性与普适性。其次,样本量少,结论稳健性需大样本验证。第三,未控制饮食等混杂因素,可能干扰结论。

总之,本研究对患有CO-CPP和CO-PPP的女童开展了探索性脂质组学分析,结果显示两组脂质组成有显著差异,初步识别若干可能相关的关键脂质并尝试构建LH基础值与Cer联合预测CO-CPP的初步模型,或为后续研究提供参考。

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所有作者声明无利益冲突。

#### Conflict of Interests:

All authors declare that there is no conflict of interests.

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#### Author's Contributions:

CHEN Guanyu was responsible for conceptual design, literature search, data processing, and initial draft writing; ZHANG Zekai was responsible for conceptual design and sample collection; GONG Yuan and JIANG Ting were responsible for sample collection and data organization; LIU Jin and TANG Yongquan were responsible for literature search and data organization; ZHOU Wendie was responsible for conceptual design, paper review, and guidance.

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