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邻苯二甲酸酯暴露与高密度脂蛋白相关炎症指标异常的关联性研究

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[摘要] **目的** 探讨尿邻苯二甲酸酯代谢物与高密度脂蛋白胆固醇(high-density lipoprotein-cholesterol, HDL-C)相关的4个炎症指标(LHR、MHR、NHR、PHR)的关联,并解释其可能的生物学机制。**方法** 采用美国全国健康和营养调查(national health and nutrition examination survey,NHANES)的4 573名成年参与者,对邻苯二甲酸酯和炎症指标进行广义线性模型(generalized linear model, GLM)、限制性立方样条(restricted cubic spline,RCS)和加权分位数和(weighted quantile sum,WQS)回归分析,分别探讨邻苯二甲酸酯单暴露和混合暴露与HDL-C炎症指标的潜在关联。**结果** 9种尿邻苯二甲酸酯代谢物均与至少一个炎症指标存在显著正向关联($P<0.05$),1种代谢物(MEP)和炎症指标(LHR)存在负向关联,部分暴露代谢物和结局炎症指标存在非线性关联。对每个结局炎症指标,WQS回归显示不同邻苯二甲酸酯代谢物具有不同的权重贡献。亚组分析结果表明在不同性别、年龄、BMI人群中,邻苯二甲酸酯与HDL-C相关炎症指标的关联结果存在差异。**结论** 邻苯二甲酸酯暴露和HDL-C相关炎症指标存在关联,但需进一步研究揭示其潜在机制。

[关键词] 邻苯二甲酸酯;高密度脂蛋白胆固醇;新型炎症指标
[中图法分类号] R12;R364.5;R446.12 [文献标志码] A

Association between phthalates and high-density lipoprotein-related inflammatory indicators

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[**Abstract**] Objective To investigate the association of urinary phthalate metabolites with 4 high-density lipoprotein-cholesterol(HDL-C) -related inflammatory indicators [lymphocyte/HDL-C ratio (LHR), monocyte/HDL-C ratio (MHR), neutrophil/HDL-C ratio (NHR), and platelet/HDL-C ratio (PHR)], and to explain their possible biological mechanisms. Methods The 4 573 adult participants from the National Health and Nutrition Examination Survey (NHANES) were subjected, and then generalized linear regression (GLM), restricted cubic spline (RCS), and weighted quantile sum (WQS) regressions were performed to explore the potential associations of phthalates mono-exposures and mixed exposures, respectively, with the HDL-C-related inflammation metrics. Results Nine urinary phthalate metabolites were significantly positively associated with at least 1 inflammatory marker, while 1 metabolite (MEP) showed a negative association with an inflammatory indicator (LHR). Some exposure metabolites showed a nonlinear association with outcome inflammatory indicators. WQS regression revealed varying weight contributions of individual metabolite to

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each inflammatory outcome. Subgroup analyses indicated differential association effects of phthalates with HDL-C-related inflammatory metrics across gender, age, and BMI populations. **Conclusion** There are associations between phthalate exposure and HDL-C-related inflammation indicators, but further studies are needed to reveal the underlying mechanisms.

[**Key words**] phthalates; high-density lipoprotein cholesterol; novel inflammatory indicators

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炎症是心血管疾病、呼吸系统疾病、代谢性疾病、神经退行性疾病、癌症等多种重大疾病发生发展的核心过程[1]。在这一过程中,慢性炎症与代谢紊乱往往并存且相互促进,以动脉粥样硬化为典型代表,其发展过程中同时受到全身炎症状态和局部脂质沉积的影响[2]。近年,基于免疫细胞和高密度脂蛋白胆固醇(High-density lipoprotein cholesterol,HDL-C)比值的新型血液学参数(如淋巴细胞/HDL-C比值LHR、单核细胞/HDL-C比值MHR、中性粒细胞/HDL-C比值NHR、血小板/HDL-C比值PHR)因其能同时反映炎症状态和代谢功能,已成为评估疾病风险的有力工具[3]。上述复合参数在Ⅱ型糖尿病[4]、宫颈癌[5]、缺血性脑卒中[6]、主动脉夹层和动脉瘤[7]等疾病中展现出良好的预测和预后评估能力,较传统单一指标更具临床价值。

环境污染物可能刺激机体发生炎症激活和脂质代谢紊乱等反应[8],从而增加疾病风险或加速疾病进程。邻苯二甲酸酯(Phthalates,PAEs)是应用最广泛的增塑剂,大量存在于塑料、个人护理产品和医疗设备中[9]。一项调查研究显示90%研究对象的尿液样本中检出多种邻苯二甲酸酯代谢物[10]。这种广泛存在性加剧了其潜在健康威胁。PAEs作为一种内分泌干扰化学物,具有生殖毒性、发育毒性和致癌性[11],可导致女性生育能力降低或胎儿早产[12],干扰男性甲状腺激素水平[13]并损害雄性生殖系统功能[14],以及增加儿童气道炎症和哮喘风险[15,16]。最新研究表明,PAEs诱导的炎症可能是其致病机制之一[17]。然而,目前尚不清楚PAEs是否会影响HDL-C相关炎症指标,以及这种影响的程度如何。由于缺乏定量证据,难以全面评估PAEs暴露对炎症状态和代谢功能的综合影响,从而可能低估其对人群健康的潜在风险。

基于上述背景,本研究旨在通过探讨尿液中邻苯二甲酸酯代谢物浓度与4种HDL-C相关炎症指标(LHR、MHR、NHR、PHR)的关联性,揭示环境污染物影响健康的可能的新型炎症标志物,为心血管疾病等炎症相关疾病的早期预防提供新靶点,也为制定邻苯二甲酸酯暴露限值政策提供科学依据。

1 材料和方法

1.1 研究设计和人群

本研究数据来源于美国国家健康和营养调查(national health and nutrition examination survey,NHANES)。NHANES采用多阶段分层概率抽样方法,通过入户访谈、移动检查中心体检和生物样本检测(每个周期随机抽取1/3子样本)收集全美代表性数据。本研究基于2005~2018年7个调查周期(n=70 190),筛选出≥20岁的美国成年人,排除妊娠妇女及关键变量缺失者,最终纳入4 573名研究对象进行横断面分析。本研究使用的NHANES数据已获得美国国家卫生统计中心(NCHS)研究伦理审查委员会批准,所有参与者在调查前均签署书面知情同意书。由于分析仅涉及去标识化的公开数据,因此无须额外伦理审查。本研究的纳排标准如图1所示。

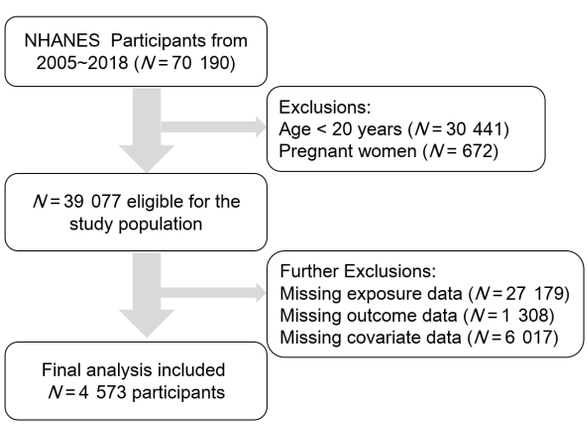


图1 研究对象纳入与排除标准

Figure 1 Inclusion and exclusion criteria for participants

1.2 尿邻苯二甲酸酯代谢物测定

本研究选取2005年至2018年可及的尿邻苯二甲酸酯代谢物数据,排除检出率小于90%的代谢物,最终共有10种代谢物纳入分析,包括邻苯二甲酸单(羧基异壬酯)(MCNP),邻苯二甲酸单(羧基异辛酯)

(MCOP),邻苯二甲酸单-2-乙基-5-羧基戊基酯(MECPP),邻苯二甲酸单丁酯(MnBP),邻苯二甲酸单(3-羧丙基)酯(MCPP),邻苯二甲酸单乙酯(MEP),邻苯二甲酸单(2-乙基-5-羟基己基)酯(MEHHP),邻苯二甲酸单异丁酯(MiBP),邻苯二甲酸单(2-乙基-5-氧代)酯(MEOHP),邻苯二甲酸单苄酯(MBzP)。

NHANES采用高效液相色谱-电喷雾电离-串联质谱(HPLC-ESI-MS/MS)测定尿邻苯二甲酸酯代谢物水平。对于低于检测限(LOD)的测量值,NHANES建议将其替换为 LOD/$\sqrt{2}$再纳入分析中。鉴于不同个体间的尿液浓缩情况不同,将邻苯二甲酸酯代谢物水平除以肌酐浓度,得出μg/g肌酐的代谢物最终测量值,以调整邻苯二甲酸酯代谢物水平。计算公式:$\text{尿PAEs校正浓度}\left(\mu g/g\right)=\frac{\text{尿PAEs}\left(ng/mL\right)}{\text{尿肌酐}\left(mg/dL\right)}\times 100$。调整后的代谢物水平多呈偏态分布,因此采用自然对数转换后的调整值进行分析。

1.3 高密度脂蛋白胆固醇相关的炎症标志物测定

LHR、MHR、NHR 和 PHR 是通过 NHANES 数据库中完整血细胞计数数据计算得出,包括淋巴细胞计数(LYM,10^3 cells/uL)、单核细胞计数(MON,10^3 cells/μL)、中性粒细胞计数(NEU,10^3 cells/μL)、血小板计数(PLT,10^3 cells/μL)和高密度脂蛋白胆固醇(HDL-C,mg/dL)。计算公式如下:LHR=LYM/HDL-C,MHR=MON/HDL-C,NHR=NEU/HDL-C,PHR=PLT/HDL-C。此外,由于变量呈偏态分布,采取自然对数转换以满足正态分布。

1.4 统计分析

首先进行描述性统计以分析人口学特征分布和暴露代谢物的水平。连续变量以均值±标准差(正态分布)或中位数和几何均数(对数正态分布)表示,分类变量以频数(百分比)表示。采用t检验和卡方检验进行组间比较,以评估不同性别组参与者的基本特征差异;采用 Spearman's 秩相关系数研究邻苯二甲酸酯代谢物浓度之间的相关性,以初步评估其共暴露模式及潜在协同效应。本研究使用广义线性回归(GLM)探索单个邻苯二甲酸酯代谢物与炎症生物标志物之间的关联,并采用限制性立方样条(RCS,节点数5)检验暴露与结局间的非线性关联,以避免遗漏暴露和结局间的潜在复杂关系。由于人体日常暴露多为混合暴露且尿邻苯二甲酸酯代谢物间具有较强的相关性,采用加权分位数和(WQS)回归探索10种代谢物混合暴露与炎症指标的关联并计算单个化合物对混合物整体效应的贡献权重。对数转换的炎症结局指标及肌酐标准化邻苯二甲酸酯代谢物浓度用于所有回归模型,调整的协变量数据主要通过入户访谈问卷提取,包括年龄、性别、种族、教育程度、家庭收入贫困比(PIR)、职业、体质指数(BMI,kg/m^2)、吸烟、饮酒量、饮食类型、高血压、糖尿病。本研究在观察性研究报告规范(STROBE)的指导下进行,所有分析和图表绘制均采用R4.4.2版本进行,以双侧检验P<0.05为具有统计学显著性。

2 结果

2.1 参与者基线特征

表1描述了4 573名参与者的基线特征。本次分析中包含2 458名男性和2 115名女性,男性参与者更可能暴露于烟草和酒精摄入,且相较于女性,男性患有高血压和糖尿病的比率更大。体质指数的分布表明男性的肥胖率高于女性,但重度肥胖者女性多于男性。

2.2 尿邻苯二甲酸酯代谢物和血细胞计数分布

表2显示了尿邻苯二甲酸酯代谢物和血细胞计数分布,图2显示了10种经尿肌酐调整后的代谢物秩相关系数,可见其中MECPP和MEHHP,MECPP和MEOHP,MEHHP和MEOHP的相关度较高,均达到0.92及以上。

2.3 个体尿邻苯二甲酸酯代谢物和炎症标志物水平关联性分析

2.3.1 尿邻苯二甲酸酯代谢物单暴露线性回归分析 广义线性回归分析结果显示个体尿邻苯二甲酸酯代谢物和炎症标志物水平存在普遍的正向关联。其中,MnBP、MCOP、MCPP等代谢物与HDL-C相关炎症指标的关联尤为突出。本研究探索到LHR与MnBP、MEHHP、MiBP等多种邻苯二甲酸酯代谢物存在显著正向关联,但与MEP呈负向关系;MHR与MCOP、MnBP等暴露代谢物存在正向关联;NHR和PHR分别与MCPP、MECPP等代谢物水平呈正向关联。关联结果见图3。

2.3.2 尿邻苯二甲酸酯代谢物与炎症指标的非线性关联分析 通过限制性立方样条(RCS)模型对40个PAEs-炎症指标的关联进行分析,发现17个模型的总体关联检验显著(overall association test,P<0.05),在这17个显著关联中,9个(53%)尿PAEs-炎症指标关系表现出显著的非线性效应(非线性检验P<0.05)。此外,在GLM中未检测到显著关联的暴露-结局模型中,2个在RCS模型中表现出显著的非线性效应

表1 参与者的基线特征

Table 1 Baseline characteristics of participants

	All	Male	Female	*P*
	N=4 573	*N*=2 458	*N*=2 115	
Age (Year)	42.6±14.0	42.8±14.1	42.5±13.9	0.420
Education attainment				<0.001
Less than high school	763 (16.7%)	477 (19.4%)	286 (13.5%)	
High school graduate	1 009 (22.1%)	569 (23.1%)	440 (20.8%)	
Above high school	2 801 (61.3%)	1 412 (57.4%)	1 389 (65.7%)	
PIR				0.451
<1.3	1 043 (22.8%)	544 (22.1%)	499 (23.6%)	
1.31~3.5	1 669 (36.5%)	899 (36.6%)	770 (36.4%)	
>3.5	1 861 (40.7%)	1 015 (41.3%)	846 (40.0%)	
Smoking				<0.001
Yes	1 826 (39.9%)	1 114 (45.3%)	712 (33.7%)	
No	2 747 (60.1%)	1 344 (54.7%)	1 403 (66.3%)	
Alcohol consumption				<0.001
Non-drinker	1 236 (27.0%)	482 (19.6%)	754 (35.7%)	
Light	1 448 (31.7%)	965 (39.3%)	483 (22.8%)	
Moderate	812 (17.8%)	340 (13.8%)	472 (22.3%)	
Heavy	1 077 (23.6%)	671 (27.3%)	406 (19.2%)	
Dietary types				<0.001
Normal	3 938 (86.1%)	2 179 (88.6%)	1 759 (83.2%)	
Low calorie diet	400 (8.8%)	162 (6.6%)	238 (11.3%)	
Low fat diet	69 (1.5%)	38 (1.6%)	31 (1.5%)	
Low salt diet	32 (0.7%)	17 (0.7%)	15 (0.7%)	
Low sugar diet	8 (0.2%)	5 (0.2%)	3 (0.1%)	
Other special diet	126 (2.8%)	57 (2.3%)	69 (3.3%)	
BMI (kg/m^2)				<0.001
<25	1 328 (29.0%)	645 (26.2%)	683 (32.3%)	
25~30	1 515 (33.1%)	937 (38.1%)	578 (27.3%)	
>30	1 730 (37.8%)	876 (35.6%)	854 (40.4%)	
Hypertension				<0.001
Yes	2 047 (44.8%)	1 228 (50.0%)	819 (38.7%)	
No	2 526 (55.2%)	1 230 (50.0%)	1 296 (61.3%)	
Diabetes				0.005
Yes	520 (11.4%)	310 (12.6%)	210 (9.9%)	
No	4 053 (88.6%)	2 148 (87.4%)	1 905 (90.1%)	

(MECPP-NHR 和 MEHHP-NHR)。图4展示了部分非线性关联的RCS拟合曲线(仅展示总体关联和非线性关联检验均显著的结果),多数尿PAEs对炎症指标的影响表现为先降后升的趋势。

2.3.3 尿邻苯二甲酸酯代谢物混合暴露分析 WQS回归分析显示10种代谢物混合暴露与4种炎症指标均存在正向关联(表3),图5显示了混合暴露中各代谢物的相对权重分布。在10种邻苯二甲酸酯代谢物与LHR的关联效应中,MiBP,MEHHP,MBzP贡献的权重最大,而在混合代谢物与MHR和NHR的关联效应中,MBzP和MCOP分别占主导地位,在PHR中,MECPP和MBzP是导致与混合代谢物正关联的主要化学物。

2.4 亚组分析

分别对性别、年龄(≤65岁、>65岁)、BMI(<25 kg/m^2、≥25 kg/m^2、≥30 kg/m^2)进行分层GLM分析。男性和

表2 尿邻苯二甲酸酯代谢物和血细胞计数分布

Table 2 Distribution of urinary phthalate metabolites and blood cell counts

Variables	Detection Rate(%)	Geometric Mean(GM)	First Quartile(Q1)	Median(M)	Third Quartile(Q3)
HDL-C/(mg/dL)	/	50.90	42.00	51.00	62.00
LYM/(10^3cells/uL)	/	2.12	1.70	2.10	2.60
MON/(10^3cells/uL)	/	0.54	0.40	0.50	0.60
NEU/(10^3cells/uL)	/	3.96	3.10	3.90	5.00
PLT/(10^3cells/uL)	/	243.89	209.00	243.00	286.00
LHR	/	0.05	0.03	0.04	0.06
MHR	/	0.01	0.01	0.01	0.01
NHR	/	0.09	0.06	0.08	0.11
PHR	/	4.86	3.75	4.87	6.17
UCR/(mg/dL)	/	104.66	69.00	120.00	176.00
MCNP/(ng/mL)	96.16	2.67	1.10	2.20	4.40
MCOP/(ng/mL)	98.76	10.44	3.50	8.10	22.90
MECPP/(ng/mL)	99.85	16.55	6.70	14.50	32.60
MnBP/(ng/mL)	98.62	12.60	5.90	12.90	25.70
MCPP/(ng/mL)	91.83	2.35	0.80	1.80	4.00
MEP/(ng/mL)	99.79	64.17	20.20	55.00	178.01
MEHHP/(ng/mL)	99.48	11.20	4.20	9.80	22.10
MiBP/(ng/mL)	98.36	7.83	3.70	7.90	14.90
MEOHP/(ng/mL)	99.26	7.08	2.70	6.00	13.17
MBzP/(ng/mL)	98.05	5.52	2.00	5.04	11.70

HDL-C: high-density lipoprotein cholesterol; LYM: lymphocyte count; MON: monocyte count; NEU: neutrophil count; PLT: platelet count; LHR: lymphocyte to HDL-C ratio; MHR: monocyte to HDL-C ratio; NHR: neutrophil to HDL-C ratio; PHR: platelet to HDL-C ratio; UCR: urinary creatinine; MCNP: mono(carboxyisononyl) phthalate; MCOP: mono(carboxyisooctyl) phthalate; MECPP: mono-2-ethyl-5-carboxypentyl phthalate; MnBP: mono-n-butyl phthalate; MCPP: mono(3-carboxypropyl) phthalate; MEP: mono-ethyl phthalate; MEHHP: mono (2-ethyl-5-hydroxyhexyl) phthalate; MiBP: mono-isobutyl phthalate; MEOHP: mono (2-ethyl-5-oxohexyl) phthalate; MBzP: mono-benzyl phthalate

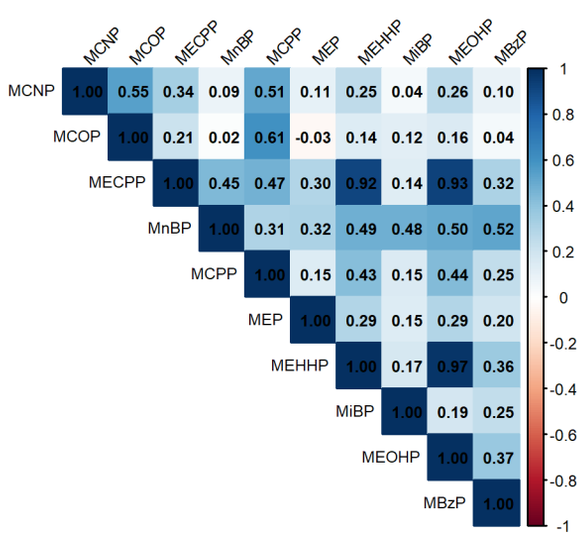
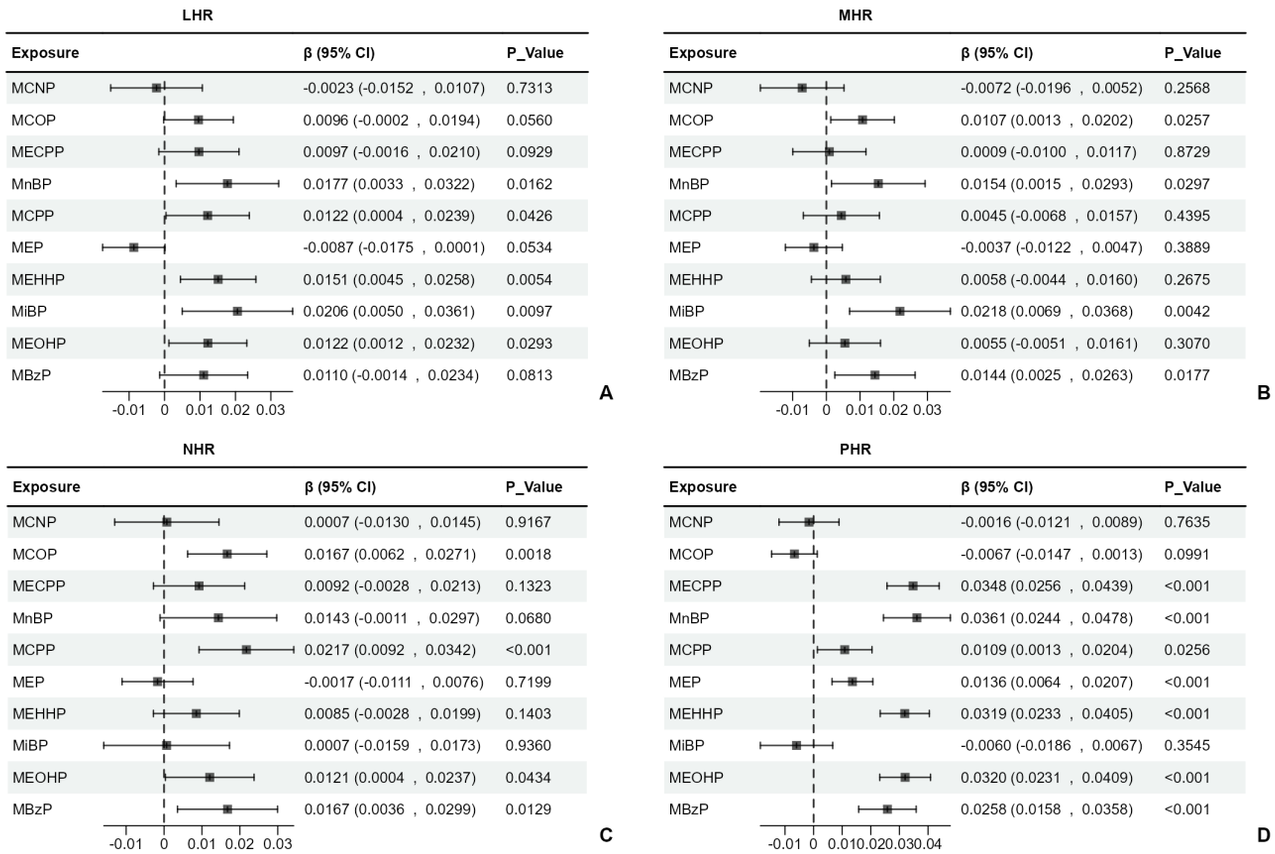


图2 尿邻苯二甲酸酯代谢物秩相关系数

Figure 2 Spearman's rank correlation coefficients of urinary phthalate metabolites

女性对邻苯二甲酸酯的反应存在显著差异,在女性人群中,MiBP和MnBP与炎症结局指标正相关,而MCOP、MEP与炎症结局指标负相关;在男性人群中,MEOHP、MnZP、MCPP等多种PAEs代谢物均与结局指标呈正向关联,未观察到显著负相关。通过年龄分层分析,发现年龄≤65岁的人群中MnZP、MiBP、MEOHP、MCOP与多个炎症结局指标之间存在显著关联,而年龄>65岁的人群中未观察到显著关联,提示年轻人群对邻苯二甲酸酯更为敏感。不同BMI人群对邻苯二甲酸酯暴露的反应也不尽相同,BMI<25 kg/m^{2}的人群中,MCOP、MnBP、MiBP、MnZP等暴露指标与炎症指标的正向关联较为显著;25≤BMI<30 kg/m^{2}的人群中,MCNP、MCOP与炎症指标呈负向关联;BMI≥30 kg/m^{2}的人群中,MCPP与LHR、NHR、PHR呈正相关。



All results were adjusted for age, sex, race, education level, family income-to-poverty ratio, occupation, BMI, smoking, alcohol consumption, dietary type, hypertension, and diabetes.

图3 PAEs和炎症指标的广义线性回归分析

Figure 3 Generalized linear regression analysis of PAEs and inflammatory markers

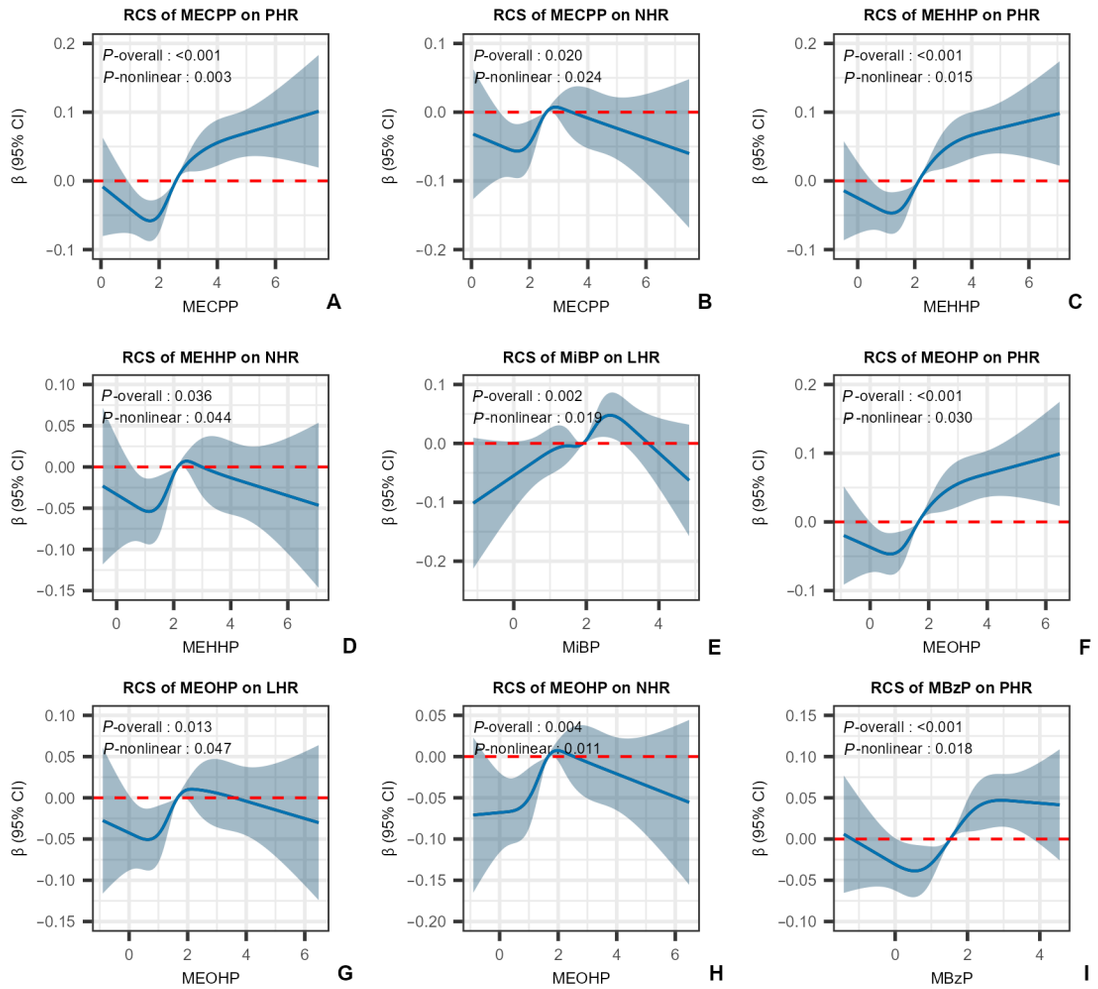
2.5 敏感性分析

为调整NHANES多阶段复杂抽样的权重,更好地反映总体人口的真实分布,本研究进行加权广义线性回归分析。在加权回归后,MEHHP、MiBP、MEOHP和LHR的正向关联依旧存在,但与MHR所有关联不再具有统计学显著性;NHR尚和MCOP、MCPP存在正向关联;PHR指标除MCPP之外,其余代谢物的关联仍稳定存在。总体而言,加权前后分析结果和方向较为一致,均表明PAEs与HDL-C相关炎症指标升高呈正相关,从而保证了本次研究结果的稳健性。加权广义线性回归采用survey包进行分析,权重调整为三分之一环境子样本权重/8。

3 讨论

本研究基于NHANES研究2005~2018年调查数据,从单暴露和混合暴露两方面报告了多种尿邻苯二甲酸酯代谢物与HDL-C相关的4种炎症指标水平之间的统计学关联。对于每一个炎症结局指标,探索了不同PAEs代谢物的效应贡献权重的差异。结果表明,暴露于邻苯二甲酸酯可能会导致HDL-C相关炎症标志物水平升高。性别、年龄、和BMI的差异能够影响邻苯二甲酸酯和炎症因子水平的关联。

本研究为首次对邻苯二甲酸酯暴露与HDL-C相关炎症标志物间关联的探索性分析。既往传统炎症指标研究的结果与本研究结果较为一致,为本研究观察到的PAEs与HDL-C相关炎症指标的关联提供了潜在的生物学合理性。有研究观察到尿邻苯二甲酸酯代谢物与C反应蛋白(CRP)[18]和白细胞计数(WBC)等常见炎症指标呈正相关[19],在近年来发现的新型炎症指标如全身免疫炎症指数(SII)[20]、血小板与淋巴细胞比值(PLR)、中性粒细胞与淋巴细胞比值(NLR)等[21],也有相关研究证据支持。既往研究中邻苯二甲酸酯与炎症指标在不同亚组中的关联也存在差异,这



All results were adjusted for age, sex, race, education level, family income-to-poverty ratio, occupation, BMI, smoking, alcohol consumption, dietary type, hypertension, and diabetes

图4 尿PAEs和HDL-C相关炎症指标的非线性关联

Figure 4 Nonlinear associations between urinary PAEs and HDL-C-related inflammatory markers

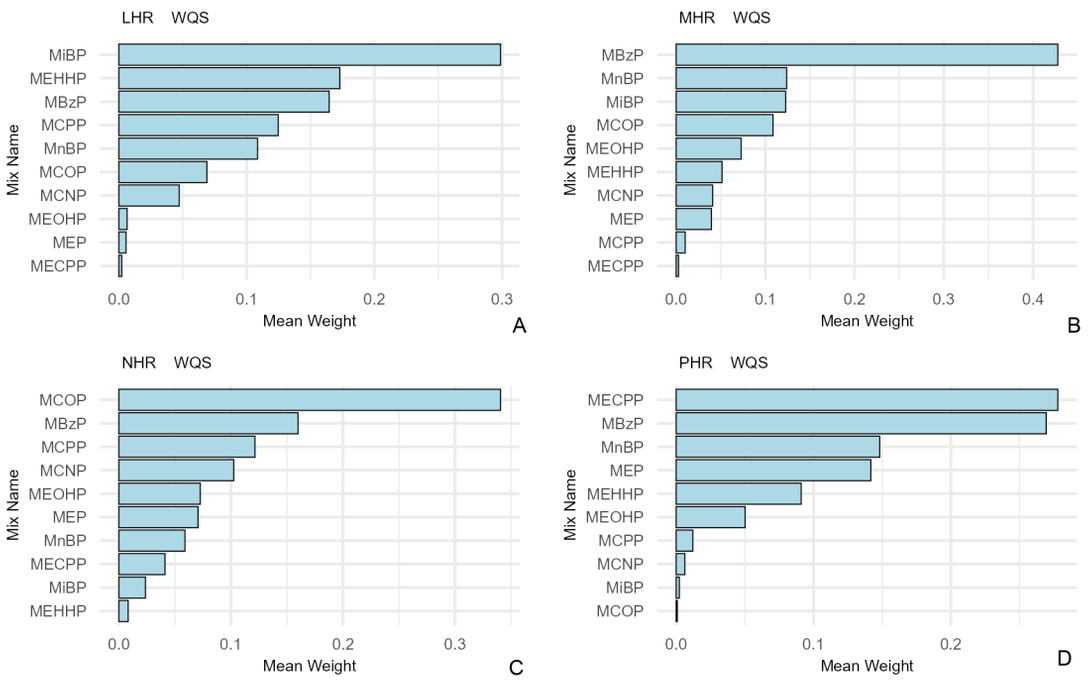
表3 混合暴露代谢物与炎症指标的WQS指数系数

Table 3 WQS index coefficients between mixed exposure metabolites and inflammatory markers

Outcome	β_{wqs}	95% *CI*	*P*
LHR	0.037 8	(0.013 4~0.062 2)	0.002 4
MHR	0.031 6	(0.009 3~0.054 0)	0.005 6
NHR	0.026 2	(0.000 4~0.052 0)	0.046 7
PHR	0.064 9	(0.047 5~0.082 4)	<0.001

可能源于PAEs的内分泌干扰作用。人体生理学和内源性激素水平因性别和年龄而不同,可能会影响机体与内分泌干扰物的相互作用[22]。有研究表明,邻苯二甲酸酯可能通过抗雄激素作用[23]、干扰甲状腺激素功能并影响脂肪代谢[24]等机制,使得PAEs暴露与炎症指标的关联在不同人群中表现出差异性。但本研究未观察到PAEs在老年人中的特殊效应,可能与该亚组的样本量较小有关。为更全面地了解PAEs对不同人群炎症指标的影响和潜在机制,需要更大的人群研究和动物实验以进一步调查。

毒理学研究揭示,PAEs暴露激活NF-κB/NLRP3通路[25]或TRPA1-p38 MAPK通路[26],加剧氧化应激和炎症反应;PAEs的内分泌干扰特性可能导致体内各激素失衡,从而导致炎症因子水平升高[27];除炎症激活机制外,PAEs暴露可通过增加活性氧水平,从而增加线粒体-溶酶体破坏的趋势,导致细胞凋亡或坏死,或介导细胞内铁稳态失调以触发铁死亡[28],进而发展为炎症反应。炎症可进一步通过促进血管内皮损伤、免疫细胞浸润、脂质沉积等,驱动动脉粥样硬化进展



All results were adjusted for age, gender, race, education level, family income-to-poverty ratio, occupation, BMI, smoking, alcohol consumption, dietary type, hypertension, and diabetes

图5 PAEs代谢物混合暴露相对权重分布

Figure 5 Relative weight distribution of mixed exposure to PAE metabolites

并诱发心血管事件[29]。

PAEs可通过干扰脂质代谢影响心血管风险。HDL-C具有抗炎、抗氧化和免疫调节等心血管保护作用[30, 31],其功能受损会导致炎症标志物水平升高。研究表明,PAEs通过以下途径影响脂质代谢:①PAEs显著改变了胆固醇代谢途径和氧化还原过程,抑制参与胆固醇外排的基因表达[32];②干扰甲状腺激素功能,影响甲状腺激素对脂质代谢的双重调节作用[33];③PAEs通过抑制JAK2/STAT5通路导致肝细胞脂质积累[34],并影响脂肪细胞分化[35]。上述机制可共同调整血液中HDL-C的水平,导致HDL-C相关的炎症指标水平的改变。这些改变可导致HDL-C水平降低及其抗炎功能受损,进而促进动脉粥样硬化发展。临床研究发现,HDL-C相关炎症指标与心血管事件风险显著相关,如MHR升高与心血管风险增加显著相关[36],且能独立预测急性冠脉综合征患者的远期预后[37];NHR和脑卒中的不良预后相关[38],并与冠状动脉疾病严重程度呈非线性关联[39];PHR和脑卒中的发生率及心血管死亡率存在正向关联[40]等。以上关联均彰显了HDL-C相关炎症指标在心血管风险评估中的关键作用,提示PAEs暴露可能通过此通路增加心血管疾病风险。这一发现具有重要的临床和公共卫生学意义:在临床层面,HDL-C相关炎症指标可为PAEs暴露人群的心血管等疾病风险早期筛查提供客观依据,并有助于制定个体化的干预策略;在公共卫生领域,将为环境污染物健康风险评估提供新的生物标志物体系,并为制定基于循证医学的PAEs暴露限值标准提供科学依据。

本研究尚存在一定的局限性。首先,本研究为横断面调查,无法确认邻苯二甲酸酯暴露与HDL-C相关炎症指标的因果关系,需要进一步的纵向研究以更有效地揭示因果关系的方向;其次,NHANES数据库仅提供美国人群的健康信息,外推至亚洲人群时需要额外的研究证据支持,且鉴于邻苯二甲酸酯在中国人群的广泛暴露,急需在中国人群中进行相关流行病学调查验证。邻苯二甲酸酯与HDL-C相关炎症指标间的关系值得在更详细的分子流行病学研究中进一步探索,尤其是在潜在敏感的亚组中。

本研究结果表明,单个或联合暴露于邻苯二甲酸酯代谢物与HDL-C相关炎症指标之间存在潜在关联,性别、年龄、BMI在PAEs暴露和炎症反应中存在差异。邻苯二甲酸酯可能通过影响HDL-C功能或诱导炎症反应等机制影响心血管健康,但仍需要进一步的研究来更深入地阐明这些关联产生的潜在过程及其对公

共卫生的潜在影响。未来的研究应继续探索邻苯二甲酸酯暴露的长期健康影响和潜在机制,为心血管疾病和其它炎症相关疾病的预防和干预提供新思路。

利益冲突 本文所有作者声明不存在利益冲突

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