



非糖尿病成人中有机磷农药暴露与胰岛素抵抗的 关联及交互作用研究

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【摘要】 目的 探究非糖尿病成人中有机磷农药多种代谢物与胰岛素抵抗的关联及交互作用。方法 基于2003–2018年美国国家健康和营养调查(National Health and Nutrition Examination Survey, NHANES), 共计纳入3 395名研究对象, 经自然对数转换后, 采用多元线性回归、限制性立方样条以及分位数加权和回归模型, 分别评估尿液中有机磷农药代谢物与胰岛素抵抗的单独效应与混合暴露效应, 重点探索甲基类代谢物与乙基类代谢物的交互作用。其中, 胰岛素抵抗指标包括甘油三酯葡萄糖(triglyceride-glucose, TyG)指数、甘油三酯葡萄糖-体质量指数(triglyceride-glucose-body mass index, TyG-BMI)、甘油三酯葡萄糖-腰高比(triglyceride-glucose-waist-height ratio, TyG-WHtR)和甘油三酯葡萄糖-腰围(triglyceride-glucose-waist circumference, TyG-WC)。结果 在自然对数尺度下, 除二甲基硫代磷酸酯(dimethyl thiophosphate, DMTP)外, 其余各有机磷农药代谢物浓度与TyG-BMI均呈现正向关联且具有统计学意义($P < 0.05$), 其中甲基类(Σ DMAP)、乙基类(Σ DEAP)、总暴露(Σ DAP)的 β 值及95%置信区间(confidence interval, CI)分别为0.004 1(95%CI: 0.000 5 ~ 0.007 7)、0.006 4(95%CI: 0.002 2 ~ 0.010 5)、0.006 0(95%CI: 0.001 8 ~ 0.010 2)。上述关系大多呈线性($P_{\text{overall}} < 0.05$, $P_{\text{non-linearity}} > 0.05$)。甲基类与乙基类代谢物可能存在协同作用, 但该关系并不显著。有机磷农药代谢物混合暴露与TyG-BMI、TyG-WC、TyG-WHtR均存在正向关联, 其中二乙基二硫代磷酸酯(diethyl dithiophosphate, DEDTP)权重在不同胰岛素抵抗指标下占比均超过50%。结论 有机磷农药的摄入可能会导致胰岛素抵抗评估指标上升, 增加了胰岛素抵抗的风险, 代谢物之间的交互作用可能进一步加剧这一效应。

【关键词】 有机磷酸酯类 胰岛素抵抗 代谢组 回归分析

A Study of the Association and Interaction Between Organophosphorus Pesticide Exposure and Insulin Resistance in Non-diabetic Adults

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【Abstract】 Objective To explore the association and interaction between multiple organophosphorus pesticide metabolites and insulin resistance in non-diabetic adults. **Methods** Based on data from the National Health and Nutrition Examination Survey (NHANES) conducted in the United States from 2003 to 2018, a total of 3 395 research subjects were included. After natural logarithmic transformation, multiple linear regression, restricted cubic spline, and quantile-weighted regression models were used to separately evaluate the individual and combined exposure effects of urinary organophosphorus pesticide metabolites on insulin resistance. The analysis focused on exploring the interaction between methyl-type and ethyl-type metabolites. Indicators of insulin resistance included the triglyceride-glucose (TyG) index, triglyceride-glucose-body mass index (TyG-BMI), triglyceride-glucose-waist-to-height ratio (TyG-WHtR), and triglyceride-glucose-waist circumference (TyG-WC). **Results** On the natural logarithmic scale, except for dimethylthiophosphate (DMTP), the concentrations of all other organophosphorus pesticide metabolites were positively correlated with TyG-BMI and reached statistical significance ($P < 0.05$). The β values and 95% CI for the methyl group (Σ DMAP), ethyl group (Σ DEAP), and total exposure (Σ DAP) were 0.004 1 (95% CI: 0.000 5–0.007 7), 0.006 4 (95% CI: 0.002 2–0.010 5), and 0.006 0 (95% CI: 0.001 8–0.010 2), respectively. Most of these relationships were linear ($P_{\text{overall}} < 0.05$, $P_{\text{non-linearity}} > 0.05$). There may be a synergistic effect between the methyl and ethyl group metabolites, but this relationship was not significant. Mixed exposure to organophosphorus pesticide metabolites was positively correlated with TyG-BMI, TyG-WC, and TyG-WHtR. The weight of diethyl dithiophosphate (DEDTP) accounted for more than 50% in different insulin

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resistance indicators. **Conclusion** The intake of organophosphorus pesticides may increase indicators used to assess insulin resistance, raising the risk of insulin resistance. Interactions between metabolites may further worsen this effect.

[Key words] Organophosphates Insulin resistance Metabolome Regression analysis

有机磷农药(organophosphorus pesticides, OPPs)作为全球农业生产中最常用的杀虫剂之一^[1-3],其环境残留问题及对人类健康的潜在影响已引发广泛关注^[4]。有机磷农药可通过食物链进入人体,并在体内代谢转化为二甲烷基磷酸酯和二乙烷基磷酸酯等多种代谢物^[5]。OPPs原型及其代谢产物可能干扰内分泌系统进而影响人体代谢健康^[6]。胰岛素抵抗(insulin resistance, IR)是代谢综合征^[7]和2型糖尿病^[8]的核心病理生理机制。即使在非糖尿病患者中,IR也与心血管疾病^[9-11]、高血压^[12]等慢性疾病风险密切相关。目前关于OPPs暴露与IR关联的研究较少,且存在一定局限性。一方面,多数研究仅关注农药原型或单一特异性代谢物^[13-14],而忽略了OPPs半衰期较短的特点,难以反映慢性暴露效应或难以全面评估该类农药的整体健康影响^[13,15]。另一方面,现有研究多聚焦于单一代谢物与IR的关系,而现实中人群往往同时暴露于多种OPPs的混合物,这些农药可能通过共同的生物学途径(如氧化应激、炎症反应等)协同影响胰岛素敏感性。因而,有必要深入探究不同农药特征基团可能产生的联合生物学效应,为复杂环境暴露下的健康风险评估提供科学依据。此外,在研究方法上,尽管甘油三酯葡萄糖(triglyceride-glucose, TyG)指数已被广泛用于IR评估,但这一单一指标可能难以全面反映IR的复杂性,尤其是在考虑肥胖程度和脂肪分布等影响因素时。

基于此,本研究旨在探讨一般人群中OPPs暴露与IR的关联性,特别关注OPPs甲基化(Σ DMP)和乙基化代谢物(Σ DEAP)对IR的潜在交互作用。为提高研究结果的可靠性和全面性,本研究采用多维度评估体系:引入甘油三酯葡萄糖-体质量指数(triglyceride-glucose-body mass index, TyG-BMI)^[16]、甘油三酯葡萄糖-腰高比(triglyceride-glucose-waist-height ratio, TyG-WHtR)^[17]和甘油三酯葡萄糖-腰围(triglyceride-glucose-waist circumference, TyG-WC)^[18]等复合指标,从不同角度综合评价OPPs暴露与IR的关系。

1 资料与方法

1.1 研究对象与设计

本研究数据来自美国疾病控制和预防中心开展的一项有关美国人口健康和营养状况的全国性调查(National Health and Nutrition Examination Survey, NHANES)。该

调查通过个人访谈、标准化体格检查和生物样本收集数据。本研究在2003–2018年NHANES的6轮横断面调查数据基础上,纳入18岁及以上的非糖尿病成年人中测定了尿液中农药暴露量的子样本。

为保证研究质量,本研究制定以下纳入标准:①调查时年龄 ≥ 18 岁;②非糖尿病的个体(既往不患糖尿病,目前不服用胰岛素)。排除标准:①患严重疾病、传染病患者及特殊生理状况者(中风、心脏病、肾病等严重疾病,乙肝、丙肝,孕妇);②结局变量缺失者(无空腹血糖测量信息、无胰岛素测量信息、空腹血糖 < 3.5 mmol/L);③暴露完全缺失者(OPPs暴露完全缺失);④无效应答者(任何协变量“拒绝回答”或“不知道”)。最终分析数据集中的样本量为3395人。研究对象筛选流程图见图1。

NHANES调查已获得美国国家卫生统计中心研究伦理审查委员会批准。所有参与者均提供了愿意参与研究的书面同意书。

1.2 有机磷农药暴露评估

NHANES研究通过固相萃取-高耦合同位素稀释-超高效液相色谱-串联质谱法^[19]测定人体尿液中的烷基磷酸酯类(dialkyl phosphates, DAPs)代谢物,作为OPPs的监测指标。DAPs是OPPs进入人体后的主要代谢产物^[4,5],能够综合反映OPPs的暴露情况,现已成为评估人体OPPs暴露水平的重要生物标志物。本研究选择两类六种主要DAPs代谢物作为暴露指标:①二甲基系代谢物,包括二甲基磷酸酯(dimethyl phosphate, DMP)、二甲基硫代磷酸酯(dimethyl thiophosphate, DMTP)、二甲基二硫代磷酸酯(dimethyl dithiophosphate, DMDTP);②二乙基系代谢物,包括二乙基磷酸酯(diethyl phosphate, DEP)、二乙基硫代磷酸酯(diethyl thiophosphate, DETP)、二乙基二硫代磷酸酯(diethyl dithiophosphate, DEDTP),上述代谢物单位均为ng/mL。

为了便于与其他研究进行比较并同时调查多种OPPs的暴露情况增加统计效能,本研究进一步考虑DMP、DMTP和DMDTP三种二甲基代谢物的总和 Σ DMP(ng/mL),DEP、DETP和DEDTP三种二乙基代谢物的总和 Σ DEAP(ng/mL),以及 Σ DMP和 Σ DEAP的总和——总代谢物 Σ DAP(ng/mL)。

1.3 胰岛素抵抗结局评估

本研究以TyG指数、TyG-BMI、TyG-WHtR、TyG-WC

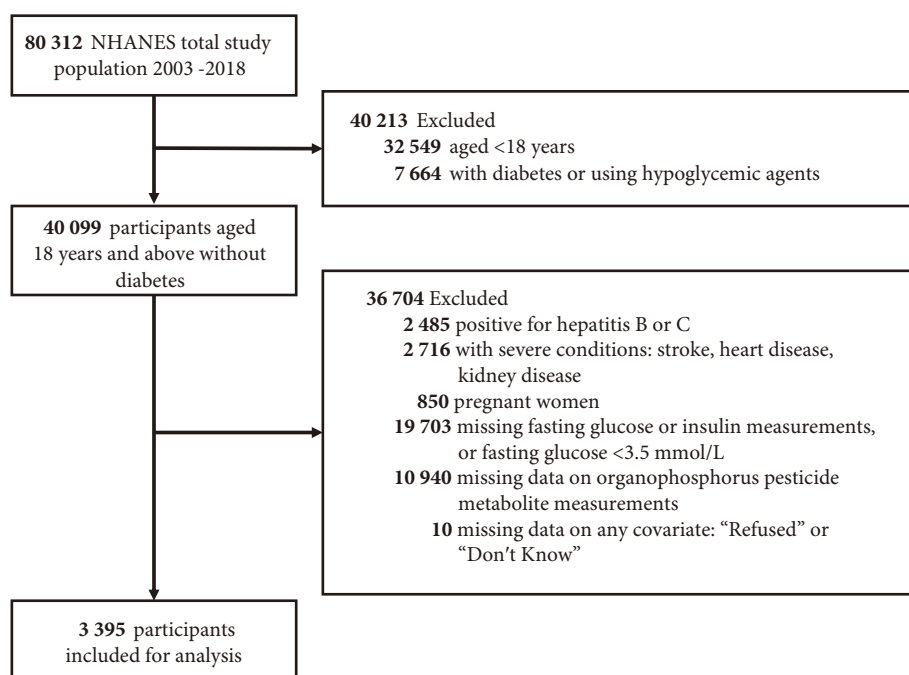


图 1 研究对象筛选流程图

Fig 1 Research subject screening flowchart

作为结局指标。

TyG指数与高胰岛素-正常血糖钳夹试验(IR评估的黄金标准)的相关性强且在不同人群中的变异性较低^[20]。当前研究已证实肥胖与IR相关^[21],其结合肥胖指标:体质指数(BMI)、腰围、腰高比衍生出TyG-BMI、TyG-WC、TyG-WHtR三种指标。衍生指标在心血管疾病、IR预测等方面通常比TyG指数具有更强的诊断效能^[22-23]。

计算公式如下: $TyG\ index = \ln(\text{空腹甘油三酯} \times \text{空腹血糖} / 2)$, 式中, 甘油三酯和血糖的单位均为mg/dL。 $TyG-BMI = TyG\ index \times BMI$, $TyG-WC = TyG\ index \times WC$, $TyG-WHtR = TyG\ index \times WHtR$, 式中, BMI单位为kg/m², WC单位为cm。

1.4 统计学方法

1.4.1 有机磷农药暴露浓度校正

本研究首先对浓度低于其检测限(LOD)的暴露, 由LOD除以 $\sqrt{2}$ 替代^[15], 对于协变量和肌酐的缺失值利用R语言mice包进行多重插补。再基于O'Brien提出的肌酐标准化方法调整暴露生物标志物浓度, 以校正尿液稀释效应对生物标志物浓度测量的影响^[24]。具体而言, 构建包含性别、年龄、种族和BMI的尿肌酐预测模型, 得出个体尿肌酐浓度的预测值与观察值的比率, 并将DAPs浓度测量值除以该比率, 从而得到肌酐校正后的DAPs浓度^[25]。由于DAPs浓度呈右偏分布, 为加强暴露与结局数据正态性, 对DAPs与结局指标同时进行自然对数转换。

1.4.2 调查对象基本特征分析

本研究采用卡方检验或t检验评估参与者基本特征, 对不同性别进行组间比较, 观察其差异是否有统计学意义, 使用Spearman方法分析六种OPPs之间的相关性。

1.4.3 有机磷农药暴露与胰岛素抵抗的关联分析

使用多元线性回归分别探究各DAPs与IR指标之间的线性关联, 再将暴露划分为三分位数分类变量, 从而验证连续性分析结果的稳健性, 同时避免极端值或非线性关系对结果的干扰。通过亚组分析探究这种线性关联在不同性别、年龄组间的差异。

为讨论两类不同烷基代谢物的交互效应, 本研究同时考虑①连续型暴露的交互作用效应值; ②基于浓度中位数分层的离散化暴露, 分别在既定暴露(如 $\Sigma DMAP$)的不同层级上运行其他暴露(如 $\Sigma DEAP$)的回归模型, 采用似然比检验获取层间差异的P值; ③将暴露离散化为二分类变量后, 将两个二分类变量纳入模型, 获取交互项系数 $\beta_{交互项}$, 其中 $\beta_{交互项}$ 即为加性交互效应值^[26]。

通过绘制限制性立方样条评估各DAPs与各IR指标的非线性关系, 在暴露浓度的5%、35%、65%、95%分位点处设置4个节点, 从而验证线性关联结果, 并获得浓度-反应曲线的变化趋势。最后构建加权分位数和回归模型(WQS)^[27]探究DAPs联合暴露对IR的影响。

1.4.4 协变量定义

根据以往文献确定了潜在的混杂因素, 其中性别、年

龄、种族、文化程度、婚姻状况、家庭贫困收入比(poverty income ratio, PIR)、体力活动、NHANES周期等数据通过直接访谈获得。文化程度分为三个等级,即低水平(高中以下)、中等水平(高中)、高水平(大学及以上)。PIR为家庭收入与贫困线之间的比率,根据PIR水平分为低($PIR < 1.3$)、中($1.3 \leq PIR < 1.5$)、高收入($PIR \geq 3.5$)^[28]。BMI(kg/m^2)分为BMI < 25 、 $25 \leq \text{BMI} < 30$ 、BMI ≥ 30 。体力活动根据自我报告的活动强度分为四个类别(无、中等、剧烈、其他)。是否吸烟通过自我报告或血清可替宁浓度 $\geq 0.015 \text{ ng/mL}$ 认为吸烟,否则认为不吸烟^[29]。饮酒通过自我报告的每日饮酒杯数(杯)分为不、轻度(男性 < 3 , 女性 < 2)、中($3 \leq \text{男性} < 4$, $2 \leq \text{女性} < 3$)、重度($4 \leq \text{男性}$, $3 \leq \text{女性}$)。能量摄入(kcal/day)分为较低(男性 < 2000 , 女性 < 1600)、正常($2000 \leq \text{男性} \leq 3000$, $1600 \leq \text{女性} \leq 2400$)、较高(男性 > 3000 , 女性 > 2400)^[30]。高血压患者定义为三次血压测量的平均收缩压(systolic blood pressure, SBP)和舒张压(diastolic blood pressure, DBP)达到以下标准者:SBP $\geq 140 \text{ mmHg}$ 或DBP $\geq 90 \text{ mmHg}$ ($1 \text{ mmHg} = 0.133 \text{ kPa}$);或由医生诊断的自报高血压;或自报使用抗高血压药物^[12]。

所有的统计分析均使用R软件(版本4.4.3)进行,双尾 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 研究对象基本特征

遵循纳入排除标准,本研究最终纳入3 395名符合条件的研究对象,其中1 670名男性与1 725名女性,平均年龄为43.76岁,性别、年龄、文化程度、婚姻状况、BMI、体力活动、饮酒、吸烟、能量摄入在男性、女性群体的分布差异有统计学意义($P < 0.05$)。详见网络资源附件附表1。

2.2 有机磷农药生物标志物

附图1显示6种DAPs均呈现出右偏分布,且普遍存在正相关,其中DMP与DMTP的相关性最强($r = 0.697$),其次是DMTP与DMDTP($r = 0.650$),DEDTP与其他各暴露物均未呈现出明显相关性($r < 0.03$)。附图1见网络资源附件。

2.3 有机磷农药与胰岛素抵抗的线性回归分析

2.3.1 整体多元线性回归分析结果

结果见表1。在调整所有协变量后,针对TyG-BMI指标,除DMTP外,其余暴露生物标志物浓度与其均存在正相关($P < 0.05$),DEDTP与TyG-WC、TyG-WHtR存在正相关($P < 0.05$)。需特别说明的是,由于DAPs与各IR指标均被自然对数转换,故 β 值较小。将各DAPs按照三分位数划分后,可以看到 ΣDMAP 的Q2组($\beta = 0.0111$, 95%CI:

$0.0006 \sim 0.0216$, $P = 0.04$), ΣDEAP 的Q3组($\beta = 0.0142$, 95%CI: $0.0033 \sim 0.0250$, $P = 0.01$), ΣDAP 的Q2组($\beta = 0.0118$, 95%CI: $0.0012 \sim 0.0223$, $P = 0.03$)和Q3组($\beta = 0.0148$, 95%CI: $0.0040 \sim 0.0256$, $P < 0.01$)与TyG-BMI呈正相关。值得注意的是,不同分位数组间存在的效应值差异提示OPPs与TyG-BMI指标可能存在非线性关系。

2.3.2 亚组分析

本部分探究了 ΣDMAP 、 ΣDEAP 、 ΣDAP 与4种IR指标在不同性别、不同年龄组间的差异,分别在男性/女性、18~60岁/60岁以上分层运行模型,并调整所有协变量。在其他变量保持一定水平的情况下,在女性、年龄18~60岁中 ΣDEAP 每增加一个对数单位,TyG-BMI会分别增加0.0064个对数单位(95%CI: $0.0002 \sim 0.0125$)、0.0077个对数单位(95%CI: $0.003 \sim 0.0125$)。在男性、年龄18~60岁中 ΣDAP 每增加一个对数单位,TyG-BMI会分别增加0.0064个对数单位(95%CI: $0.0007 \sim 0.0120$)、0.0063个对数单位(95%CI: $0.0014 \sim 0.0112$),上述结果均有统计学意义($P < 0.05$)。除上述结果外,其余结果均无统计学意义。详见网络资源附件附表2。

2.4 二甲基代谢物与二乙基代谢物交互效应的探究

表2显示 ΣDMAP 与 ΣDEAP 在调整所有协变量的情况下,不同IR结局指标下的分层交互效应以及连续型交互效应。 ΣDMAP 与 ΣDEAP 的关联通常在暴露物浓度较高的百分位数中增加,例如在TyG指数指标结局下,在低浓度的 ΣDEAP 中, ΣDMAP 每增加1个对数单位,TyG指数相应增加0.0006个对数单位;在高浓度的 ΣDEAP 中, ΣDMAP 每增加1个对数单位,TyG指数相应增加0.0020个对数单位。尽管当前 ΣDMAP 与 ΣDEAP 的相互作用对各IR结局指标的影响无统计学意义,但在较高浓度的分层暴露中,其效应估计值越大的趋势保持一致,连续型交互、加性交互效应的效应值其统计学意义均不显著。

2.5 限制性立方样条曲线分析

综合上述研究结果,各DAPs与TyG-BMI指标呈现出较强的关联性。本研究使用限制性立方样条模型,图2展示了各DAPs与TyG-BMI的剂量-反应关系,其中暴露物浓度与结局指标均做ln对数变换,结果显示各DAPs与TyG-BMI没有明显的非线性关系,但DETP、DEDTP在整体上呈现出与TyG-BMI有正相关趋势($P_{\text{overall}} < 0.05$),DMDTP对TyG-BMI的影响呈现出先上升后下降的趋势($P_{\text{overall}} < 0.05$)。其余暴露物虽然在曲线上与TyG-BMI呈现正向趋势,但并无统计学意义。

2.6 加权分位数和回归分析

本研究构建WQS模型综合考虑DAPs混合物联合暴

表 1 尿液中有机磷农药暴露与胰岛素抵抗指数之间关联的线性回归分析

Table 1 Linear regression analysis of the association between urinary organophosphorus pesticide exposure and insulin resistance index								
Chemicals	TyG index		TyG-BMI		TyG-WC		TyG-WHtR	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
DMP								
Continuous	0.0006 (−0.0010-0.0022)	0.45	0.0035 (0.0004-0.0066)	0.03	0.0014 (−0.0015-0.0043)	0.35	0.0010 (−0.0018-0.0038)	0.50
Q1	Ref.		Ref.		Ref.		Ref.	
Q2	0.0009 (−0.0053-0.0072)	0.77	0.0061 (−0.0061-0.0183)	0.33	0.0000 (−0.0114-0.0114)	1.00	−0.0022 (−0.0134-0.0089)	0.69
Q3	0.0020 (−0.0038-0.0077)	0.51	0.0109 (−0.0004-0.0222)	0.06	0.0037 (−0.0069-0.0143)	0.49	0.0026 (−0.0077-0.0130)	0.62
DMTP								
Continuous	0.0003 (−0.0013-0.0019)	0.72	0.0025 (−0.0006-0.0057)	0.12	−0.0006 (−0.0035-0.0024)	0.71	−0.0009 (−0.0038-0.0020)	0.54
Q1	Ref.		Ref.		Ref.		Ref.	
Q2	0.0013 (−0.004-0.0067)	0.62	0.0096 (−0.001-0.0201)	0.08	0.0031 (−0.0068-0.0130)	0.54	0.0022 (−0.0075-0.0118)	0.66
Q3	0.0031 (−0.0025-0.0088)	0.28	0.0095 (−0.0016-0.0205)	0.09	0.0026 (−0.0078-0.013)	0.62	0.0013 (−0.0088-0.0115)	0.80
DMDTP								
Continuous	0.0017 (−0.0003-0.0037)	0.09	0.0055 (0.0016-0.0095)	< 0.01	0.0020 (−0.0017-0.0057)	0.29	0.0019 (−0.0016-0.0055)	0.29
Q1	Ref.		Ref.		Ref.		Ref.	
Q2	−0.0024 (−0.0085-0.0036)	0.43	0.0083 (−0.008-0.0201)	0.17	0.0024 (−0.0086-0.0135)	0.67	0.0028 (−0.0081-0.0136)	0.62
Q3	0.0031 (−0.0034-0.0097)	0.35	0.0155 (0.0028-0.0283)	0.02	0.0083 (−0.0037-0.0203)	0.18	0.0075 (−0.0042-0.0192)	0.21
ΣDMAP								
Continuous	0.0008 (−0.001-0.0027)	0.38	0.0041 (0.0005-0.0077)	0.03	0.0007 (−0.0027-0.0041)	0.67	0.0002 (−0.0031-0.0035)	0.90
Q1	Ref.		Ref.		Ref.		Ref.	
Q2	0.0011 (−0.0042-0.0065)	0.68	0.0111 (0.0006-0.0216)	0.04	0.0056 (−0.0043-0.0154)	0.27	0.0036 (−0.006-0.0133)	0.46
Q3	0.0030 (−0.0026-0.0086)	0.29	0.0090 (−0.0019-0.020)	0.11	0.0035 (−0.0068-0.0138)	0.50	0.0030 (−0.0071-0.0131)	0.56
DEP								
Continuous	0.0004 (−0.0013-0.0020)	0.66	0.0038 (0.0007-0.007)	0.02	0.0017 (−0.0013-0.0047)	0.26	0.0014 (−0.0015-0.0043)	0.34
Q1	Ref.		Ref.		Ref.		Ref.	
Q2	0.0020 (−0.0046-0.0086)	0.56	0.0035 (−0.0094-0.0165)	0.59	0.0017 (−0.0104-0.0139)	0.78	0.0018 (−0.0101-0.0137)	0.77
Q3	−0.0008 (−0.0069-0.0054)	0.81	0.0093 (−0.0028-0.0213)	0.13	0.0015 (−0.0098-0.0127)	0.80	0.0016 (−0.0094-0.0126)	0.78
DETP								
Continuous	−0.0001 (−0.0024-0.0022)	0.94	0.0062 (0.0017-0.0106)	< 0.01	0.0013 (−0.0029-0.0055)	0.54	0.0011 (−0.0029-0.0052)	0.59
Q1	Ref.		Ref.		Ref.		Ref.	
Q2	0.0024 (−0.0034-0.0082)	0.42	0.0124 (0.0011-0.0238)	0.03	0.0088 (−0.0019-0.0195)	0.11	0.0092 (−0.0012-0.0197)	0.08
Q3	−0.0009 (−0.0072-0.0055)	0.78	0.0136 (0.0012-0.0261)	0.03	0.0033 (−0.0083-0.0150)	0.57	0.0024 (−0.0090-0.0137)	0.69
DEDTP								
Continuous	0.0078 (−0.0014-0.0169)	0.10	0.1035 (0.0860-0.1211)	< 0.01	0.0640 (0.0474-0.0806)	< 0.01	0.0607 (0.0445-0.0770)	< 0.01
Q1	Ref.		Ref.		Ref.		Ref.	
Q2	0.0016 (−0.0053-0.0086)	0.64	0.0293 (0.0157-0.0429)	< 0.01	0.0173 (0.0045-0.0301)	< 0.01	0.0171 (0.0046-0.0296)	< 0.01
Q3	0.0041 (−0.0072-0.0154)	0.48	0.0648 (0.0428-0.0868)	< 0.01	0.0381 (0.0175-0.0588)	< 0.01	0.0384 (0.0182-0.0586)	< 0.01
ΣDEAP								
Continuous	0.0002 (−0.0019-0.0023)	0.86	0.0064 (0.0022-0.0105)	< 0.01	0.0021 (−0.0018-0.0060)	0.30	0.0016 (−0.0022-0.0054)	0.41
Q1	Ref.		Ref.		Ref.		Ref.	
Q2	0.0012 (−0.0043-0.0068)	0.67	0.0065 (−0.0043-0.0174)	0.24	0.0034 (−0.0068-0.0135)	0.51	0.0011 (−0.0088-0.0111)	0.82
Q3	−0.0013 (−0.0069-0.0042)	0.64	0.0142 (0.0033-0.0250)	0.01	0.0045 (−0.0056-0.0147)	0.38	0.0032 (−0.0067-0.0132)	0.52
ΣDAP								
Continuous	0.0009 (−0.0013-0.0030)	0.44	0.0060 (0.0018-0.0102)	< 0.01	0.0009 (−0.0031-0.0048)	0.66	0.0006 (−0.0032-0.0045)	0.75
Q1	Ref.		Ref.		Ref.		Ref.	
Q2	0.0020 (−0.0034-0.0074)	0.46	0.0118 (0.0012-0.0223)	0.03	0.0054 (−0.0045-0.0153)	0.28	0.0031 (−0.0065-0.0128)	0.53
Q3	0.0034 (−0.0021-0.0089)	0.22	0.0148 (0.0040-0.0256)	< 0.01	0.0052 (−0.0049-0.0154)	0.31	0.0048 (−0.0051-0.0147)	0.34

β : regression coefficient; DMP: dimethyl phosphate; DMTP: dimethyl thiophosphate; DMDTP: dimethyl dithiophosphate; ΣDMAP: Sum of dimethyl metabolites; DEP: diethyl phosphate; DETP: diethyl thiophosphate; DEDTP: diethyl dithiophosphate; ΣDEAP: Sum of diethyl metabolites; ΣDAP: Sum of dimethyl and diethyl metabolites; TyG: triglyceride glucose; TyG-WC: triglyceride glucose-waist circumference; TyG-BMI: triglyceride glucose-body mass index; TyG-WHtR: triglyceride glucose-waist-to-height ratio; Q1: quartile 1; Q2: quartile 2; Q3: quartile 3. Models were adjusted for sex, age, race, education level, marital status, poverty income ratio (PIR), physical activity, body mass index (BMI), smoking, drinking, energy intake, hypertension, and NHANES cycle. Estimates in bold indicate that the association is statistically significant ($P < 0.05$).

露与4种IR指标的关联, 结果见表3。在完全调整的模型中, OPPs的联合暴露与TyG-BMI、TyG-WC、TyG-WHtR的关联均呈正相关($P < 0.05$), 其WQS回归指数分别为0.0317 (95%CI: 0.0177 ~ 0.0457)、0.0241 (95%CI: 0.0105 ~ 0.0378)、0.0224 (95%CI: 0.0098 ~ 0.0351)。图3显示调整协变量后WQS模型中各DAPs的权重,

表 2 甲基类与乙基类交互作用的结果

Table 2 The result of interaction between sums of dimethyl metabolites (Σ DMAp) and sums of diethyl metabolites (Σ DEAP)

	TyG index			TyG-BMI			TyG-WC			TyG-WHtR		
	Estimates	95% CI	P	Estimates	95% CI	P	Estimates	95% CI	P	Estimates	95% CI	P
Σ DMAp												
$\leq 50\% \Sigma$ DEAP	0.0006	-0.0023-0.0035	0.60	0.0006	-0.0050-0.0062	0.99	0.0004	-0.0050-0.0058	0.81	0.0008	-0.0045-0.0062	0.88
$> 50\% \Sigma$ DEAP	0.0020	-0.0008-0.0048	0.60	0.0030	-0.0024-0.0083	0.99	0.0034	-0.0017-0.0085	0.81	0.0029	-0.0022-0.0081	0.88
Σ DEAP												
$\leq 50\% \Sigma$ DMAp	-0.0019	-0.0052-0.0014	0.90	0.0038	-0.0027-0.0104	0.81	-0.0002	-0.0065-0.0060	0.74	-0.0002	-0.0064-0.0060	0.81
$> 50\% \Sigma$ DMAp	-0.0010	-0.0042-0.0022	0.90	0.0025	-0.0034-0.0084	0.81	0.0017	-0.0041-0.0074	0.74	0.0013	-0.0044-0.0070	0.81
Continuous interaction	0.0009	-0.0006-0.0024	0.25	-0.0003	-0.0033-0.0026	0.84	0.0003	-0.0026-0.0032	0.84	-0.0001	-0.0030-0.0027	0.93
Additive interaction	0.0010	-0.0082-0.0102	0.84	0.0026	-0.0153-0.0205	0.78	-0.0009	-0.0182-0.0163	0.91	0.0013	-0.0158-0.0183	0.88

The abbreviations are explained in the note to Table 1. Models were adjusted for sex, age, race, education level, marital status, poverty income ratio (PIR), physical activity, body mass index (BMI), smoking, drinking, energy intake, hypertension, and NHANES cycle.

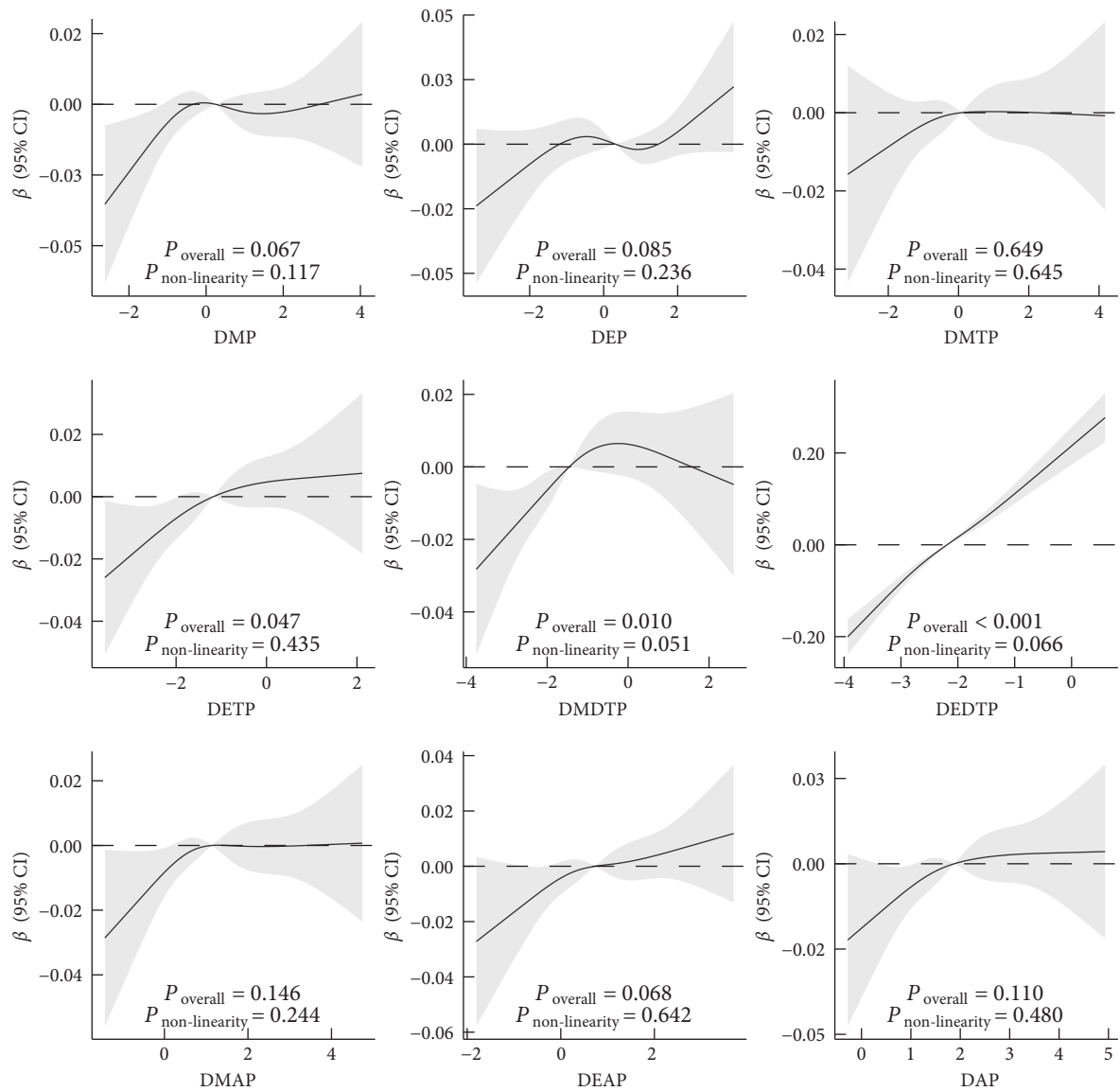


图 2 有机磷农药与TyG-BMI的剂量-反应曲线

Fig 2 The dose-response curve of organophosphorus pesticides and TyG-BMI

The abbreviations are explained in the note to Table 1. Models were adjusted for sex, age, race, education level, marital status, poverty income ratio (PIR), physical activity, body mass index (BMI), smoking, drinking, energy intake, hypertension, and NHANES cycle.

表 3 有机磷农药WQS回归指数与胰岛素抵抗指标的关系
Table 3 The relationship between the regression index of organophosphorus pesticide WQS and indicators of insulin resistance

IR index (ln)	β	95% CI	P
TyG			
Model I	0.0017	-0.0017-0.0050	0.33
Model II	-0.0005	-0.0076-0.0067	0.89
TyG-BMI			
Model I	-0.0123	-0.0268-0.0014	0.08
Model II	0.0317	0.0177-0.0457	< 0.01
Tyg-WC			
Model I	-0.0128	-0.0228--0.0028	0.01
Model II	0.0241	0.0105-0.0378	< 0.01
TyG-WHtR			
Model I	-0.0071	-0.0163-0.0020	0.13
Model II	0.0224	0.0098-0.0351	<0.01

The abbreviations are explained in the note to Table 1. Model I is unadjusted for covariates; Model II adjusts for sex, age, race, education level, marital status, poverty income ratio (PIR), physical activity, body mass index (BMI), smoking, drinking, energy intake, hypertension, and NHANES cycle.

DEDTP在不同指标中都占主导地位,其权重均大于50%。在不同结局指标中, TyG指数中权重较大的是DEDTP (59.78%)和DMDTP(11.62%); TyG-BMI中权重较大的是DEDTP(77.04%)和DETP(8.37%); TyG-WC中权重较大的是DEDTP(77.48%)和DMP(10.56%); TyG-WHtR中权重较大的是DEDTP(80.21%)和DMDTP(10.44%)。

2.7 敏感性分析

在TyG-BMI指标的相关讨论中,将BMI纳入协变量,可能存在过度调整的风险。为完善结果的稳定性,本部分针对TyG-BMI分析中的协变量仅纳入性别、年龄、种族、教育水平、婚姻状况、PIR、体力活动、吸烟情况、饮酒情况、能量摄入、高血压、NHANES周期。

由表4可见,在线性关系探索中, DMDTP($\beta=0.0088$, 95%CI: 0.0012 ~ 0.0164, $P=0.02$)、DEDTP($\beta=0.0088$, 95% CI: 0.3251 ~ 0.3853, $P<0.01$)与TyG-BMI有关联且具有统计学意义。在WQS分析中, OPPs的联合暴露与TyG-BMI在不调整BMI后呈现正相关($\beta=0.1266$, 95%CI: 0.1008 ~ 0.1525, $P<0.01$), 且效应值相较调整BMI时更大。

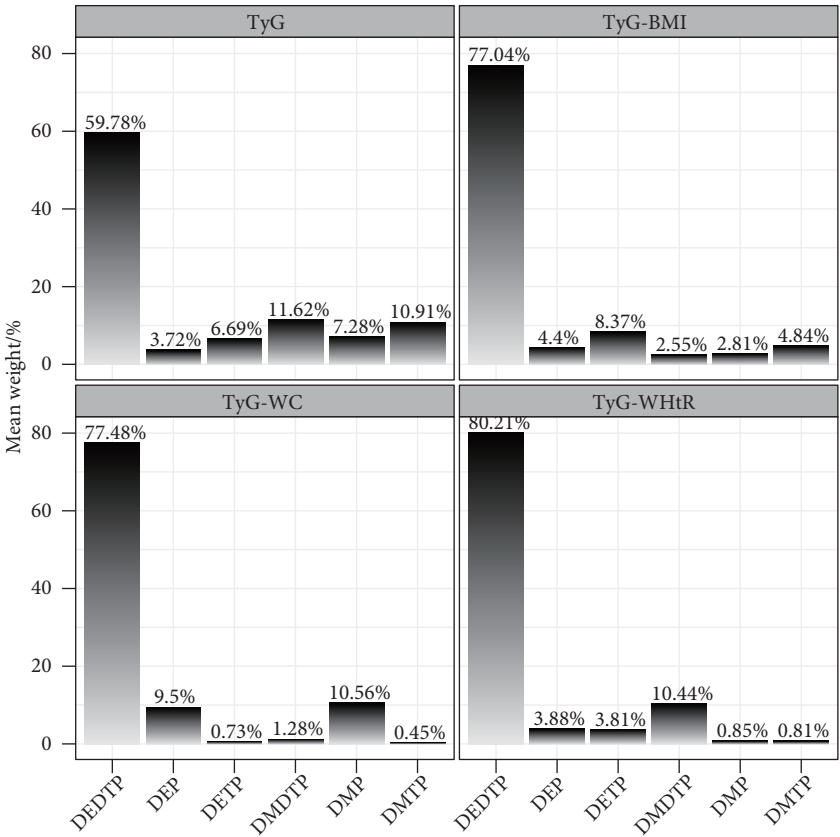


图 3 WQS模型回归指数中每种DAPs的权重

Fig 3 The weights of each DAP in the regression index of the WQS model

The abbreviations are explained in the note to Table 1. The model adjusts for sex, age, race, education level, marital status, poverty income ratio (PIR), physical activity, body mass index (BMI), smoking, drinking, energy intake, hypertension, and NHANES cycle.

表 4 有机磷农药代谢物与TyG-BMI多元线性回归补充结果

Table 4 Supplementary results of the multiple linear regression analysis of organophosphorus pesticide metabolites and TyG-BMI

Chemicals (Continuous)	TyG-BMI	
	β (95% CI)	P
DMP	0.000 2 (−0.005 8-0.006 2)	0.95
DMTP	0.000 6 (−0.005 5-0.006 8)	0.84
DMDTP	0.008 8 (0.001 2-0.016 4)	0.02
Σ DMAP	−0.000 2 (−0.007 2-0.006 8)	0.94
DEP	0.002 5 (−0.003 6-0.008 6)	0.42
DETP	0.005 9 (−0.002 8-0.014 5)	0.18
DEDTP	0.355 2 (0.325 1-0.385 3)	< 0.01
Σ DEAP	0.005 6 (−0.002 4-0.013 7)	0.17
Σ DAP	0.000 9 (−0.007 2-0.009 1)	0.81

The abbreviations are explained in the note to Table 1. Models were adjusted for sex, age, race, education level, marital status, poverty income ratio (PIR), physical activity, smoking, drinking, energy intake, hypertension, and NHANES cycle.

由图4可见, DMP、DEP、DMDTP、DEDTP与TyG-BMI可能具有非线性关联($P_{\text{non-linearity}} < 0.05$)。综上, 不调整BMI与调整BMI的两部分分析结果效应值略有不同, 但效应方向均为正。

3 讨论

本研究基于NHANES数据, 在3 395名非糖尿病成年人中探讨OPP与IR的相关性。研究发现OPP暴露与IR指标呈正向关联, 且甲基类与乙基类代谢物的联合暴露可能加剧这一风险。结果显示在未分组的情况下, 多种OPP暴露与TyG-BMI呈正相关, 除此以外DEDTP与TyG-WC、TyG-WHtR也呈现正相关, 在亚组分析中这种风险在年龄为18~60岁相对更高, 并通过限制性立方样

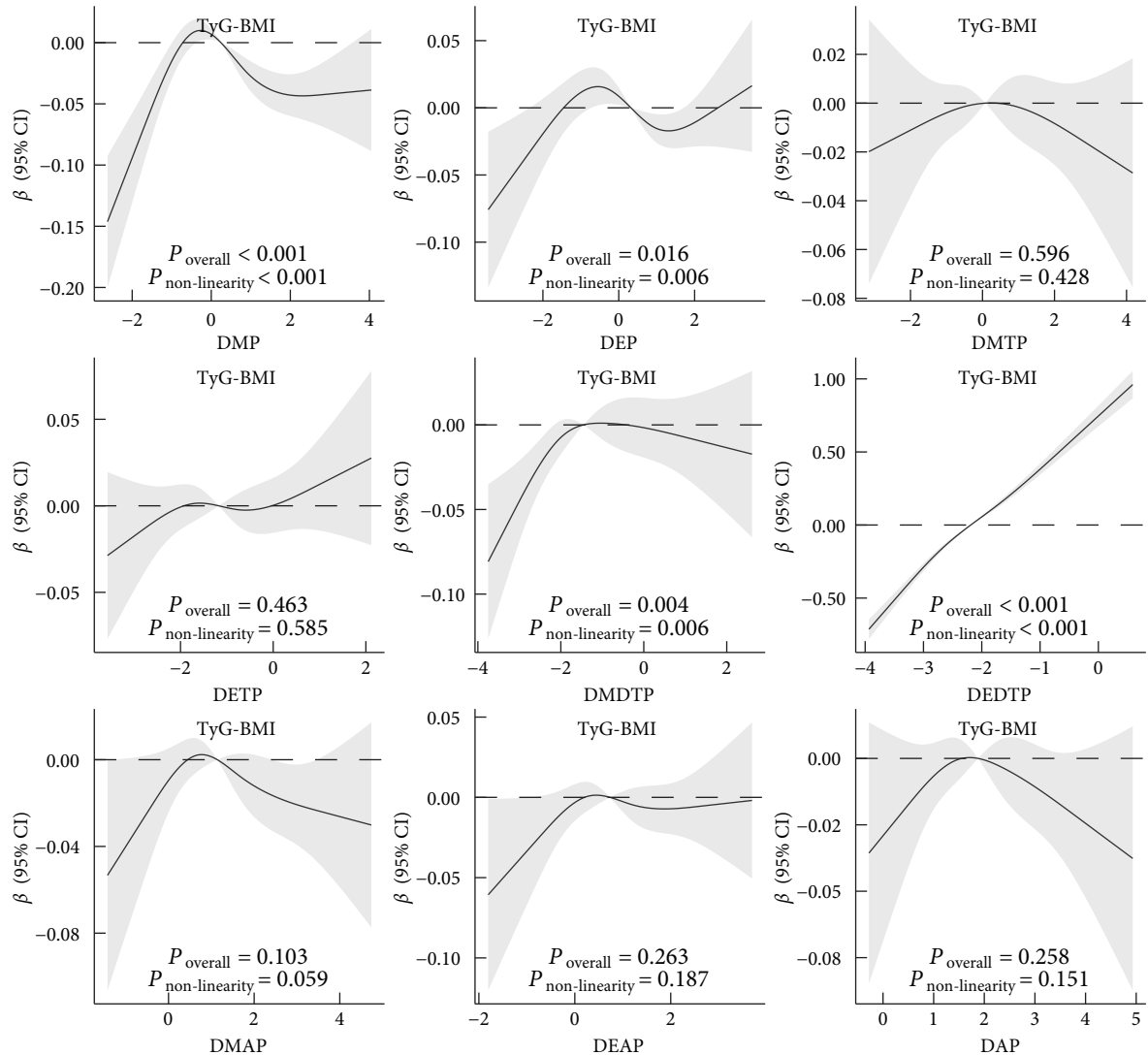


图 4 有机磷农药与TyG-BMI剂量-反应曲线补充结果

Fig 4 Supplementary results of the dose-response curve for organophosphorus pesticides and TyG-BMI

The abbreviations are explained in the note to Table 1. Models were adjusted for sex, age, race, education level, marital status, poverty income ratio (PIR), physical activity, smoking, drinking, energy intake, hypertension, and NHANES cycle.

条绘制出的剂量-反应曲线证实了这种正向性。交互分析结果显示,二甲基类代谢物与二乙基类代谢物在固定分层上,虽然效应估计值大于0,但统计意义并不显著,可能是由于两类农药代谢物同时存在不同的特征基团。WQS结果进一步显示OPPs的联合暴露对TyG-BMI、TyG-WC、TyG-WHtR均有正向风险。

既往研究发现OPPs暴露会增加IR的风险,其中老年人易感人群,可能的机制是OPPs通过破坏肠道屏障完整性、增加脂多糖入血引发低度炎症,最终导致IR^[14],此外,老年人由于慢性低水平的炎症反应^[31],更有可能出现空腹血糖受损,造成IR^[13]。值得注意的是,一项泰国的研究在农药喷洒者和普通人群中,没有观察到有机磷酸酯农药暴露与IR之间存在显著关联^[32],这与本研究发现存在差异,可能是因为IR的评价指标不同,同时该研究的研究对象主要来自泰国本地居民,最终分析样本量为285人,其样本量远小于本研究。

本研究观察到TyG-BMI指标的相关研究结果更为显著。已有研究表明OPPs可能损害肠道完整性,引发低度炎症,并使得人体获得更多脂肪且具有较低的胰岛素敏感性^[14]。另一方面,有研究指出脂肪组织分解引起的游离脂肪酸水平升高会促使肥胖受试者的空腹高胰岛素血症,因此肥胖患者可能会更容易产生IR^[21],而BMI是反映全身性肥胖的核心指标,进一步支持BMI相关指标的敏感性,故在一定程度上TyG-BMI可能成为更适合的IR预测指标。

本研究的主要局限性是横断面研究设计,只能在有限的解释能力下探索暴露与结果之间的关系。此外由于NHANES数据设计结构,本研究仅纳入常见的6种OPPs代谢物,未能考虑到更全面的代谢物组成,其次由于DEDTP代谢物的检出率较低,其相关结果需谨慎解释。最后,现有文献指出根据农药施用强度指标(PAI)的警戒线为7 kg/hm²,中国属于高强度农药施用国家(PAI约为10.35 kg/hm²),而美国属于低强度农药施用国家(PAI约为2.46 kg/hm²),整体上中国人群的膳食结构^[33]与农药施用强度^[34]与美国具有明显差异,亟需本土队列验证。

综上,本研究发现OPPs体内浓度增加与IR的评估指标(如TyG指数、TyG-BMI、TyG-WC、TyG-WHtR)上升存在关联,农药代谢物种类之间的交互作用可能进一步加剧这一效应,为非糖尿病人群早期代谢风险防控提供新证据。未来需通过前瞻性队列验证因果关联,并结合代谢组、肠道菌群等多组学技术深入解析不同农药的联合作用所致的生物学效应,在不同种族及暴露场景下验证结论,以完善农药暴露的健康风险评估体系。

* * *

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