

C反应蛋白 - 甘油三酯 - 葡萄糖指数与帕金森病相关性的加权横断面研究：基于NHANES数据库的分析

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收稿日期: 2026年7月14日; 录用日期: 2026年8月8日; 发布日期: 2026年8月18日

摘要

目的: 探讨C反应蛋白 - 甘油三酯 - 葡萄糖指数(CTI)与帕金森病(PD)之间的关联。方法: 基于NHANES数据库, 纳入12,291名参与者并进行复杂抽样加权分析。将CTI分别作为连续变量和三分位分组变量纳入加权Logistic回归模型, 采用限制性立方样条(RCS)评估剂量 - 反应关系, 同时采用ROC曲线比较CTI、TyG和CRP对PD的区分效能。结果: 纳入样本加权后代表1,033,961,743名人群, PD加权患病率为1.15%。随着CTI三分位升高, PD加权患病率由T1组0.72%升至T3组1.71%。在完全调整模型中, CTI作为连续变量时与PD患病可能性升高相关(OR = 1.79, 95% CI: 1.23~2.60, P = 0.003); 与T1 (5.2~8.01)组相比, T3 (8.81~13.11)组PD患病可能性较高(OR = 2.00, 95% CI, 1.01~4.00, P = 0.049), 趋势检验P = 0.003。RCS分析提示CTI与PD之间呈正向线性关联(非线性检验P = 0.118)。ROC分析显示, CTI、TyG和CRP区分PD的AUC分别为0.636、0.558和0.574。亚组分析显示总体关联稳定(OR = 1.87, 95% CI: 1.41~2.50, P < 0.001), 年龄分层存在交互作用(交互作用检验P = 0.003)。结论: 在NHANES加权人群中, 较高CTI与PD患病可能性升高相关, 与TyG和CRP相比, CTI对PD具有相对更好的区分效能。

关键词

C反应蛋白 - 甘油三酯 - 葡萄糖指数, 帕金森病, NHANES, 胰岛素抵抗, 慢性炎症

Association between the C-Reactive Protein-Triglyceride-Glucose Index and Parkinsonism: A Weighted Cross-Sectional Study Based on the NHANES Database

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文章引用: 范梦露, 张超辉, 孙中武. C 反应蛋白-甘油三酯-葡萄糖指数与帕金森病相关性的加权横断面研究: 基于NHANES 数据库的分析[J]. 临床医学进展, 2026, 16(8): 1459-1468. DOI: 10.12677/acm.2026.1682923

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Received: July 14, 2026; accepted: August 8, 2026; published: August 18, 2026

Abstract

Objective: To investigate the association between the C-reactive protein-triglyceride-glucose index (CTI) and Parkinsonism (PD). **Methods:** Based on the NHANES database, 12,291 participants were included and analyzed using complex sampling weights. CTI was included in weighted logistic regression models both as a continuous variable and as a tertile-based categorical variable. Restricted cubic spline (RCS) analysis was used to evaluate the dose-response relationship. Receiver operating characteristic (ROC) curves were used to compare the discriminatory performance of CTI, TyG, and CRP for PD. **Results:** The weighted sample represented 1,033,961,743 individuals, and the weighted prevalence of PD was 1.15%. With increasing CTI tertiles, the weighted prevalence of PD increased from 0.72% in T1 to 1.71% in T3. In the fully adjusted model, CTI as a continuous variable was associated with increased odds of PD (OR = 1.79, 95% CI: 1.23~2.60, P = 0.003). Compared with the T1 group (5.2~8.01), the T3 group (8.81~13.11) had higher odds of PD (OR = 2.00, 95% CI: 1.01~4.00, P = 0.049), with a P value for trend of 0.003. RCS analysis suggested a positive linear association between CTI and PD (P for nonlinearity = 0.118). ROC analysis showed that the AUC values of CTI, TyG, and CRP for discriminating PD were 0.636, 0.558, and 0.574, respectively. Subgroup analysis showed a stable overall association (OR = 1.87, 95% CI: 1.41~2.50, P < 0.001), with an interaction by age stratification (P for interaction = 0.003). **Conclusion:** In the weighted NHANES population, higher CTI was associated with increased odds of Parkinsonism. Compared with TyG and CRP, CTI showed relatively better discriminatory performance for PD.

Keywords**C-Reactive Protein-Triglyceride-Glucose Index, Parkinsonism, NHANES, Insulin Resistance, Chronic Inflammation**

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<http://creativecommons.org/licenses/by/4.0/>**Open Access****1. 引言**

帕金森病(PD)是一类以运动症状和非运动症状为主要表现的神经退行性疾病,其发生发展受到年龄、遗传易感性、代谢状态、炎症反应和氧化应激等多种因素共同影响[1]-[3]。我国 PD 的年龄标准化发病率从 1990 年的 12.8/10 万上升至 2021 年的 24.3/10 万,呈现显著增长趋势,预计到 2030 年,我国 PD 患病人数将增加至约 508 万例,这一趋势对个人和社会都带来显著影响[4]。

既往研究显示,非糖尿病 PD 患者中胰岛素抵抗异常的患病率可达 58.4% [5];以甘油三酯-葡萄糖(triglyceride-glucose, TyG)指数为代表的胰岛素抵抗替代指标,亦被证实与 PD 发生风险及认知损害相关[6]-[8]。另一方面,系统综述与 Meta 分析表明,PD 患者外周血及脑脊液 C 反应蛋白(C-reactive protein,

CRP)水平升高,提示炎症反应在PD病理过程中具有重要作用[9],且基线CRP升高还与PD患者较差预后相关[10]。C反应蛋白-甘油三酯-葡萄糖指数(C-reactive protein-triglyceride-glucose index, CTI)是整合CRP与TyG信息的复合指标,可同时反映炎症负荷和胰岛素抵抗状态[11][12]。近年来研究发现,CTI与高血压人群卒中风险以及心血管-肾脏-糖尿病共病进展显著相关,且其风险分层能力优于CRP或TyG等单一指标[13][14]。鉴于炎症和胰岛素抵抗分别代表PD相关病理生理的重要维度,CTI可能较单一指标更全面地反映PD相关的代谢-炎症负荷。

然而,目前关于CTI与PD之间关系的直接证据仍然有限。因此,本研究基于NHANES数据库进行复杂抽样加权分析,评估CTI与PD患病之间的关联,旨在为PD的临床预防和干预策略的制定提供依据。

2. 资料与方法

2.1. 数据来源与研究对象

本研究基于NHANES公开数据开展横断面分析。NHANES采用分层、多阶段、概率抽样设计,可通过复杂抽样权重推断非机构化居民的人群水平结果。根据本地分析数据,本研究纳入同时具有PD状态、CTI、复杂抽样设计变量及主要协变量信息的12,291名参与者,其中PD病例139例;加权后代表1,033,961,743名人群。排除标准包括:(1)年龄<40岁($n=65,064$);(2)CTI数据缺失($n=23,961$)。本研究使用公开去标识化数据,不涉及个人隐私信息,原始调查已通过NCHS伦理审查并获得参与者知情同意。

2.2. CTI的定义

$CTI = 0.412 \times \ln(CRP [mg/L]) + \ln[TG (mg/dL) \times FPG (mg/dL)/2]$,并按三分位分为T1 (5.2~8.01)、T2 (8.01~8.81)和T3 (8.81~13.11)组。

2.3. 帕金森病的评估

PD的诊断基于一种或多种专门用于治疗PD的药物处方。在NHANES数据库中,某些药物的使用通过调查回答进行评估。由于数据收集有限,并非所有用于治疗PD的药物都能纳入。因此,NHANES数据库仅包含这些药物的部分,如卡比多巴、恩他卡朋、左旋多巴、阿曼达定、普拉克索和溴克里普汀[15][16]。只有当患者报告使用一种或多种指定药物时,才被归类为PD;否则,他们被归类为非PD参与者[17]。

2.4. 临床资料收集及分组

本研究选择与PD潜在相关的因素作为协变量包括年龄、性别、教育水平、贫困收入比(PIR)、BMI、收缩压、HbA1c、LDL、HDL、ALT、AST、尿酸、肌酐、高血压、心血管疾病、吸烟和饮酒状态。

2.5. 统计学分析

所有分析均考虑NHANES复杂抽样设计,采用相应的MEC检查权重、分层变量和聚类变量进行加权。连续变量根据分布特征以均值(标准差)或中位数(四分位数)表示,分类变量以加权频数和百分比表示;组间比较分别采用加权方差分析或加权 χ^2 检验。采用加权Logistic回归模型评估CTI与PD之间的关联,报告比值比(OR)及95%置信区间(95% CI)。构建三个逐步调整模型:Model 1为未调整模型;Model 2调整年龄、性别和BMI;Model 3进一步调整教育水平、贫困收入比(PIR)、收缩压、HbA1c、LDL、HDL、ALT、AST、尿酸、肌酐、高血压、心血管疾病、吸烟和饮酒状态。采用RCS评估CTI与PD之间的剂量-反应关系及非线性趋势,并采用ROC曲线比较CTI、TyG和CRP对PD的区分效能。

为了评估结果的稳健性,进一步按年龄、教育水平、PIR、BMI、高血压、心血管疾病、吸烟、饮酒和性别进行亚组分析,并计算交互作用 P 值。所有统计分析均使用 R 软件(版本 4.5.1),双侧 $P < 0.05$ 认为差异具有统计学意义。

3. 结果

3.1. 研究对象基线特征

本研究共纳入 12,291 名参与者,其中 PD 病例 139 例。加权后代表 1,033,961,743 名人群,总体 PD 加权患病率为 1.15%。随着 CTI 三分位升高,BMI、收缩压、HbA1c、LDL、尿酸、NLR、SIRI 和 CTI 本身整体呈升高趋势,而 HDL 呈下降趋势($P < 0.001$)。PD 加权患病率从 Q1 (5.2~8.01)组 0.72%升至 Q2 (8.01~8.91)组 1.08%和 Q3 (8.81~13.11)组 1.71%,组间差异具有统计学意义($P = 0.010$),见表 1。

Table 1. Baseline characteristics of the study population

表 1. 研究人群基线特征

	总人群 (N = 1,033,961,743)	T1 (N = 372,218,206)	T2 (N = 336,537,581)	T3 (N = 325,205,956)	P 值
连续变量					
年龄(岁)	55.00 (47.00~66.00)	53.00 (46.00~63.00)	57.00 (48.00~68.00)	57.00 (49.00~66.00)	<0.001
BMI (kg/m ²)	28.10 (24.63~32.34)	25.42 (22.84~28.85)	28.50 (25.45~32.33)	31.07 (27.35~35.96)	<0.001
SBP (mmHg)	124.00 (114.00~138.00)	120.00 (110.00~134.00)	126.00 (114.00~140.00)	128.00 (118.00~140.00)	<0.001
HbA1c (%)	5.50 (5.30~5.80)	5.40 (5.20~5.60)	5.50 (5.30~5.80)	5.70 (5.40~6.30)	<0.001
LDL-C (mg/dL)	119.00 (96.00~143.00)	116.00 (94.00~138.00)	121.00 (97.00~145.00)	121.00 (96.00~149.00)	<0.001
AST (U/L)	23.00 (19.00~27.00)	23.00 (20.00~27.00)	23.00 (20.00~27.00)	22.00 (18.00~27.00)	0.001
ALT (U/L)	21.00 (17.00~28.00)	21.00 (16.00~26.00)	21.00 (17.00~28.00)	23.00 (17.00~31.00)	<0.001
UA (mg/dL)	5.40 (4.50~6.40)	5.00 (4.20~5.90)	5.60 (4.70~6.50)	5.80 (4.90~6.80)	<0.001
Scr (mg/dL)	0.85 (0.71~1.00)	0.85 (0.70~1.00)	0.88 (0.73~1.00)	0.84 (0.70~1.00)	0.006
HDL-C (mg/dL)	52.00 (43.00~64.00)	60.00 (49.00~72.00)	51.00 (43.00~62.00)	45.00 (38.00~54.00)	<0.001
分类变量					
性别					0.301
男	491,584,374 (47.54%)	172,929,440 (46.46%)	164,265,953 (48.81%)	154,388,981 (47.47%)	
女	542,377,370 (52.46%)	199,288,766 (53.54%)	172,271,628 (51.19%)	170,816,976 (52.53%)	
教育程度					<0.001
高中以下	189,130,999 (18.29%)	57,921,998 (15.56%)	61,980,689 (18.42%)	69,228,312 (21.29%)	
高中毕业	260,606,335 (25.20%)	80,562,407 (21.64%)	90,211,515 (26.81%)	89,832,414 (27.62%)	
大学及以上	584,224,409 (56.50%)	233,733,801 (62.79%)	184,345,377 (54.78%)	166,145,231 (51.09%)	
PIR					<0.001
低(≤1.3)	217,809,789 (21.07%)	62,261,730 (16.73%)	70,992,589 (21.09%)	84,555,471 (26.00%)	
中(1.3~3.5)	330,883,218 (32.00%)	110,672,148 (29.73%)	108,932,601 (32.37%)	111,278,468 (34.22%)	
高(>3.5)	485,268,736 (46.93%)	199,284,328 (53.54%)	156,612,391 (46.54%)	129,372,017 (39.78%)	

续表

吸烟					<0.001
从不	509,770,368 (49.30%)	197,751,262 (53.13%)	171,997,439 (51.11%)	140,021,668 (43.06%)	
曾经	330,209,568 (31.94%)	109,796,293 (29.50%)	107,978,466 (32.09%)	112,434,809 (34.57%)	
当前	193,981,807 (18.76%)	64,670,652 (17.37%)	56,561,676 (16.81%)	72,749,480 (22.37%)	
饮酒					0.057
否	258,811,495 (25.03%)	88,564,284 (23.79%)	89,577,529 (26.62%)	80,669,682 (24.81%)	
是	775,150,249 (74.97%)	283,653,922 (76.21%)	246,960,052 (73.38%)	244,536,275 (75.19%)	
高血压					<0.001
无	513,537,047 (49.67%)	231,209,896 (62.12%)	155,788,682 (46.29%)	126,538,468 (38.91%)	
有	520,424,697 (50.33%)	141,008,310 (37.88%)	180,748,898 (53.71%)	198,667,488 (61.09%)	
CVD					<0.001
无	906,794,505 (87.70%)	340,056,726 (91.36%)	294,742,902 (87.58%)	271,994,876 (83.64%)	
有	127,167,239 (12.30%)	32,161,480 (8.64%)	41,794,678 (12.42%)	53,211,080 (16.36%)	
PD					0.010
无	1,022,096,204 (98.85%)	369,545,045 (99.28%)	332,916,999 (98.92%)	319,634,160 (98.29%)	
有	11,865,539 (1.15%)	2,673,161 (0.72%)	3,620,582 (1.08%)	5,571,796 (1.71%)	

注：连续变量以中位数(P25~P75)表示，组间比较采用 Kruskal-Wallis H 检验；分类变量以加权例数(加权百分比)表示，组间比较采用 Rao-Scott χ^2 检验。BMI = 体质指数；SBP = 收缩压；HbA1c = 糖化血红蛋白；LDL-C = 低密度脂蛋白胆固醇；HDL-C = 高密度脂蛋白胆固醇；AST = 天冬氨酸氨基转移酶；ALT = 丙氨酸氨基转移酶；UA = 尿酸；Scr = 血清肌酐；PIR = 家庭收入贫困比；CVD = 心血管疾病；PD = 帕金森病。

3.2. CTI 与 PD 的关联

加权 Logistic 回归结果显示，CTI 升高与 PD 患病可能性升高相关。以连续变量纳入时，Model 1、Model 2 和 Model 3 中的 OR 分别为 1.47 (95% CI: 1.13~1.92, P = 0.004)、1.46 (95% CI: 1.09~1.97, P = 0.013) 和 1.79 (95% CI: 1.23~2.60, P = 0.003)。在三分位分析中，T3 组在完全调整模型中相较 T1 组的 OR 为 2.00 (95% CI: 1.01~4.00, P = 0.049)，趋势检验 P = 0.003，见表 2。限制性立方样条模型显示，随着 CTI 增加，PD 患病可能性呈逐渐升高趋势；非线性检验 P = 0.118，提示两者之间更符合线性剂量 - 反应关系(图 1)。

Table 2. Multivariate logistic regression analysis of CTI and PD
表 2. CTI 与 PD 的多因素 Logistic 回归分析

CTI	模型 1		模型 2		模型 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
变化 1 个 SD	1.47 (1.13~1.92)	0.004	1.46 (1.09~1.97)	0.013	1.79 (1.23~2.60)	0.003
T1	Reference		Reference		Reference	
T2	1.36 (0.73~2.51)	0.328	1.22 (0.61~2.45)	0.521	1.30 (0.67~2.51)	0.435
T3	2.10 (1.18~3.75)	0.013	1.91 (1.05~3.48)	0.035	2.00 (1.01~4.00)	0.049
趋势性检验		0.004		0.011		0.003

注：模型 1：未调整模型；模型 2：调整年龄、性别、BMI；模型 3：调整年龄、性别、BMI、教育水平、PIR、SBP、HbA1c、LDL-C、HDL-C、ALT、AST、UA、Scr、高血压、CVD、吸烟、饮酒。

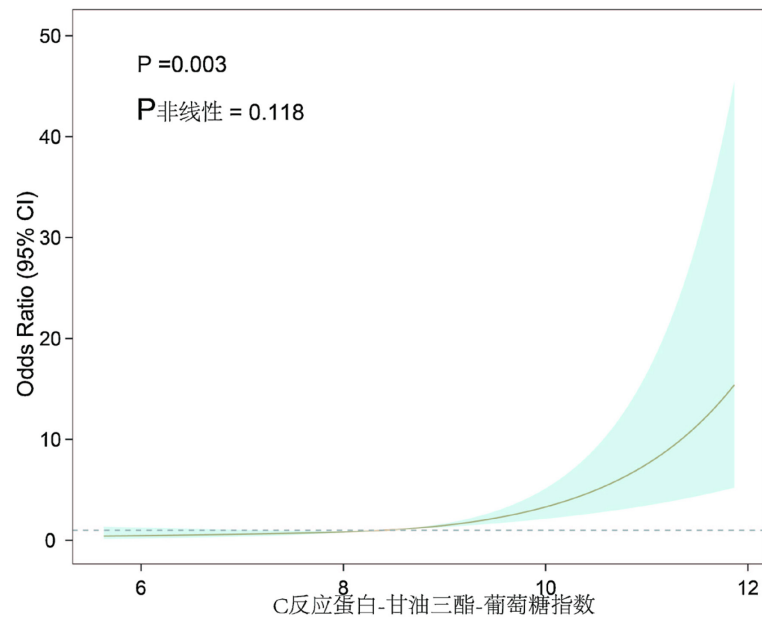


Figure 1. Dose-response relationship between serum CTI and PD
图 1. 血清 CTI 与 PD 的剂量 - 反应关系

3.3. ROC 曲线分析

ROC 曲线分析显示(图 2), CTI、TyG 和 CRP 区分 PD 的 AUC 分别为 0.636 (95% CI: 0.587~0.680)、0.558 (95% CI: 0.507~0.608)和 0.574 (95% CI: 0.524~0.624)。其中, CTI 的 AUC 最高。

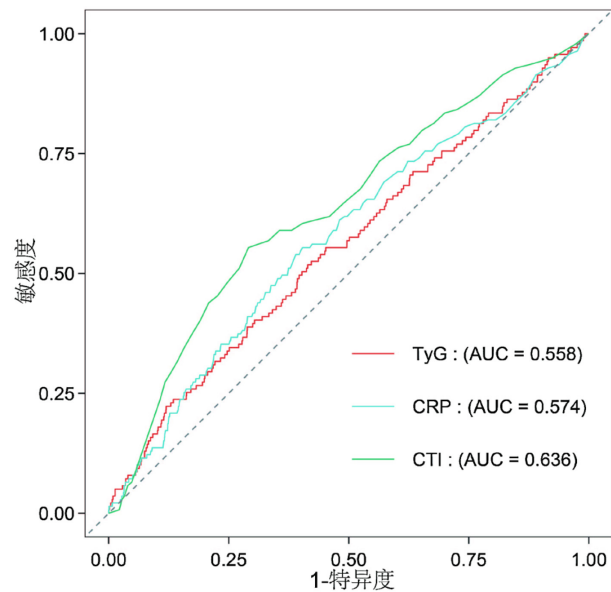


Figure 2. ROC curve of serum CTI predicting PD
图 2. 血清 CTI 预测 PD 的 ROC 曲线

3.4. 亚组分析

亚组分析显示(图 3), 在大多数亚组中 CTI 升高与 PD 的相关性呈一致正相关($P > 0.05$)。交互作用仅

显示年龄分层存在显著的交互作用($P = 0.003$), 在年龄 < 60 岁人群中关联更强($OR = 2.71$, 95% CI: 1.87~3.92, $P < 0.001$)。

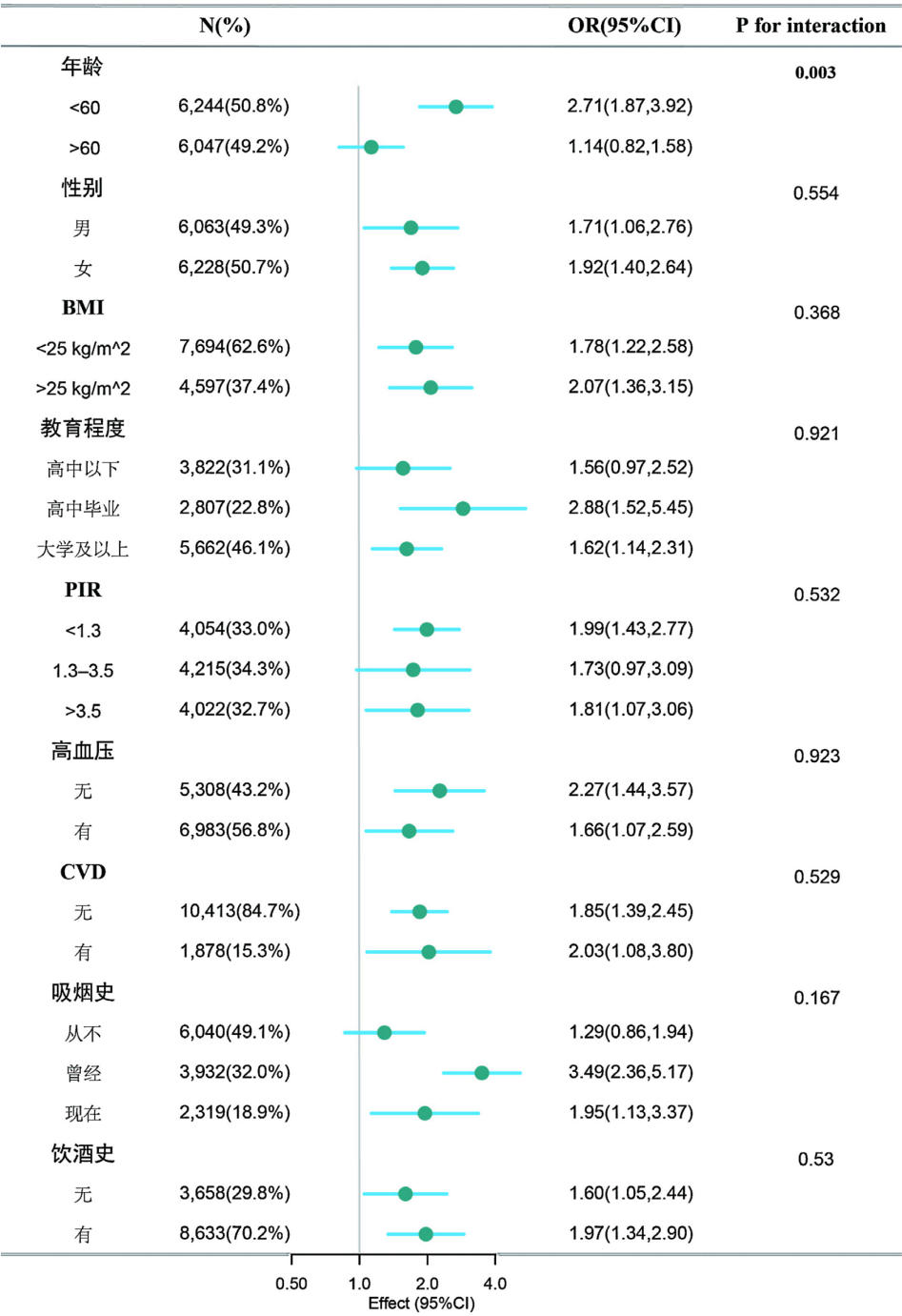


Figure 3. Subgroup analysis of the relationship between CTI and PD
图 3. CTI 与 PD 关系的亚组分析

4. 讨论

本研究基于 NHANES 复杂抽样加权数据提供了关于 CTI 与中老年人群 PD 之间关联的证明, CTI 升

高与 PD 患病可能性增加显著相关,即使在完全调整协变量后这种关系仍然显著,同时,本研究显示 CTI 与 PD 的关联优于 TyG、CRP。此外,亚组分析和交互作用分析证明了 CTI 与 PD 之间的关系一致性。

一方面, Hogg 等发现,非糖尿病 PD 患者中存在较高比例的未识别胰岛素抵抗,提示代谢异常在 PD 人群中并不少见[5]。随后, Chang 等在全国队列中进一步报道, TyG 每升高 1 个单位, PD 发生风险增加 6.2% (HR = 1.062, 95% CI 1.007~1.119) [6]。此外, Cao 等和 Cheng 等的研究均表明,较高 TyG 不仅与 PD 患者认知功能下降相关,还与更高的认知障碍风险及纹状体多巴胺能损伤有关,提示胰岛素抵抗可能不仅参与 PD 的发生,也与疾病进展和非运动症状演变密切相关[7][8]。另一方面,炎症标志物 CRP 在 PD 中的作用同样受到广泛关注。Qiu 等的 Meta 分析纳入 23 项病例对照研究后发现, PD 患者血清和脑脊液 CRP 水平均显著高于健康对照,支持外周及中枢炎症激活参与 PD 病理过程[9]。Sawada 等进一步发现,较高基线 CRP 与 PD 患者更差的生存预后相关, CRP 每升高 2 倍,全因死亡风险增加 29% (HR = 1.29, 95% CI 1.10~1.52) [10]。这些研究共同表明,炎症和代谢异常均在 PD 病理过程中发挥重要作用。与上述证据相一致,本研究进一步提示,将 CRP 与 TyG 整合形成的复合指标 CTI, ROC 分析显示, CTI 的 AUC 高于 CRP 和 TyG,值得注意的是,尽管 CTI 的 AUC 高于 TyG 和 CRP,提示其相较单一代谢或炎症指标具有更高的区分度,但其 AUC 绝对值仅为 0.636,整体鉴别效能仍然有限。因此, CTI 目前不宜被解释为具有临床筛查或诊断价值的工具,而更应被定位为一个与 PD 患病状态相关的候选生物标志物。其是否能够用于 PD 风险分层、早期识别或临床预测模型构建,仍需在前瞻性队列和外部验证研究中进一步评估。

CTI 由 CRP 与 TyG 构成,其中 TyG 是公认的胰岛素抵抗替代指标,因此 CTI 升高提示机体存在更明显的代谢紊乱与炎症负荷[13][14][18]。一方面,胰岛素在中枢神经系统中具有神经营养和神经保护作用,胰岛素抵抗可通过削弱胰岛素信号转导,导致线粒体功能障碍、氧化应激增强、自噬受损及 α -突触核蛋白异常聚集,从而促进多巴胺能神经元变性[3][19]。另一方面,慢性炎症也是 PD 的重要病理基础,持续激活的小胶质细胞和星形胶质细胞可释放多种促炎细胞因子和氧化应激介质,加重神经元损伤,并与 α -突触核蛋白聚集形成恶性循环[20][21]。因此, CTI 作为整合炎症与胰岛素抵抗信息的复合指标,可能较单一指标更全面地反映 PD 相关的代谢-炎症异常,这为其与 PD 的显著关联提供了潜在的生物学解释。

亚组分析显示,年龄分层存在显著交互作用, CTI 与 PD 的关联在相对低龄人群中更为明显。这一结果可能提示,在低龄人群中, CTI 所反映的代谢-炎症负荷对 PD 的相对贡献更易显现;而在高龄人群中,由于年龄本身是 PD 最主要的危险因素,且常伴随更明显的衰老相关神经退行、炎症重塑及多重共病负担, CTI 的独立关联可能被部分弱化[2][3][22]-[24]。

综上,本研究基于 NHANES 加权数据发现 CTI 升高与 PD 患病可能性增加相关,且其区分效能优于 TyG 和 CRP;该关联在多数亚组中方向一致,提示代谢异常与系统性炎症可能共同与 PD 相关。需要特别指出的是,首先, NHANES 为横断面数据,无法明确 CTI 升高与 PD 发生之间的时间先后关系,因此不能排除反向因果的可能。PD 本身及其治疗过程可能通过影响活动量、营养状态、体重变化、脂质代谢、胰岛素敏感性及炎症水平,进而改变 CTI 所反映的代谢表型[25][26]。其次,本研究基于 NHANES 数据,而我国人群在遗传背景、生活方式等方面存在显著差异,因此,研究结果在我国人群中的应用需谨慎。未来仍需前瞻性队列研究和机制研究进一步验证 CTI 在 PD 风险评估和早期干预中的潜在价值。

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