2026, 51(2) DOI:10.11817/j.issn.1672-7347.2025.250010

·COMPLEX LIVER DISEASE MECHANISMS AND PRECISION DIAGNOSIS AND TREATMENT·
·复杂肝病机制与精准诊疗·

导 读

肝脏是物质代谢、炎症调控与损伤修复的核心器官，乙醇、代谢紊乱、病毒感染、药物及遗传等多重因素交织，共同构成我国慢性肝病的复杂疾病谱。随着代谢相关脂肪性肝病(既往也称为非酒精性脂肪性肝病)、酒精相关性肝病、药物性肝损伤及遗传性肝病发病率持续攀升，临床对肝病的病因溯源、机制阐释、精准分型与个体化干预提出更高要求。《中南大学学报(医学版)》本期特设《复杂肝病机制与精准诊疗》专题，集中刊发系列原创研究与临床报道，系统覆盖代谢性肝病、酒精相关性肝病、药物性肝损伤、遗传性肝病及重症肝衰竭等关键领域，旨在串联基础机制、临床诊疗与转化研究，为复杂肝病的规范化、精准化防治提供学术支撑与实践指引。

本专题成果兼具机制深度与临床价值：在代谢性肝病领域，研究采用孟德尔随机化方法证实甘油三酯葡萄糖指数与代谢相关脂肪性肝病存在因果关联，为代谢风险分层与早期筛查提供遗传学依据；在酒精相关性肝病方向，系统阐述组蛋白去乙酰化酶家族在脂质代谢、炎症与纤维化中的调控作用，明确该家族各亚型及Sirtuins家族作为治疗靶点的潜力，为靶向药物研发提供理论框架；在药物性肝损伤方向，对比中药与西药致肝损伤的机制差异、诊断标志物与干预策略，解析氧化应激、线粒体功能障碍、免疫激活等核心通路，同时报道司美格鲁肽诱发慢加急性肝衰竭的罕见病例，为高危人群用药安全提供警示；针对疑难重症，报道乙型肝炎后肝硬化合并血色病诱发肝衰竭的诊疗实践，强调铁过载作为“二次打击”因素的致病意义，提出慢性肝病合并不明原因肝损伤时应将血色病纳入鉴别诊断。

这些研究立足临床痛点，融合流行病学、分子机制、临床病例与方法学创新，既揭示了肝病进展的关键通路，也建立了可落地的诊疗思路。期望本专题能推动基础研究与临床实践深度融合，促进多学科协作，助力我国复杂肝病防治水平提升，为实现早筛、早诊、精准干预提供新思路与新策略。

(中南大学湘雅二医院药学部　颜苗教授，
中南大学湘雅二医院消化内科、中南大学湘雅二医院桂林医院消化内科　谭玉勇副主任医师)

甘油三酯–葡萄糖指数与非酒精性脂肪性肝病因果关系的孟德尔随机化研究

王轶娜[1]，陈元国[2]，王鸯[1]，陈露[3]，尹美龙[2]，肖晓[1]，黄晶[1]，邝晶洁[4]，李亚勇[2]

[1. 中南大学湘雅二医院老年医学科，长沙 410011；2. 中南大学湘雅三医院急诊医学科，长沙 410013；
3. 海南医科大学附属海南医院，海南省人民医院老年医学中心(医疗保健中心)，海口 571199；
4. 中国人民解放军联勤保障部队第九二一医院干部病房，长沙 410003]

收稿日期(Date of reception)：2025-01-14
第一作者(First author)：王轶娜，Email: wangyina@csu.edu.cn, ORCID: 0000-0002-0402-1795
通信作者(Corresponding author)：李亚勇，副主任医师，Email: liyy999@csu.edu.cn, ORCID: 0000-0001-7092-0302
基金项目(Foundation item)：湖南省自然科学基金(2023JJ30786)。This work was supported by the Natural Science Foundation of Hunan Province, China (2023JJ30786).
开放获取(Open access)：本文遵循知识共享许可协议，允许第三方用户按照署名-非商业性使用-禁止演绎4.0(CC BY-NC-ND 4.0)的方式，在任何媒介以任何形式复制、传播本作品(https://creativecommons.org/licenses/by-nc-nd/4.0/)。

©Journal of Central South University (Medical Science). All rights reserved.

［摘 要］**目的：**非酒精性脂肪性肝病(non-alcoholic fatty liver disease，NAFLD)已成为严重影响人类健康的重要公共卫生问题。本研究采用双样本孟德尔随机化(Mendelian randomization，MR)法，分析甘油三酯-葡萄糖(triglyceride-glucose，TyG)指数与NAFLD之间的因果关系，旨在探索TyG指数对NAFLD的潜在影响。**方法：**TyG指数的全基因组关联分析(genome-wide association study，GWAS)汇总数据来源于基于UK Biobank的已发表研究，NAFLD的GWAS汇总数据来源于IEU Open GWAS数据库。使用逆方差加权(inverse-variance weighted，IVW)法作为主要分析方法，并辅以加权中位数(weighted median，WM)法和MR-Egger法，以进一步探讨TyG指数与NAFLD之间的因果关系。采用Cochran's *Q*检验评估数据异质性；通过MR-Egger法检验水平多效性，并应用MR多效性残差和与异质性检验(MR pleiotropy residual sum and outlier，MR-PRESSO)法进行离群值检验及异常数据剔除。此外，采用留一法验证结果的稳健性，绘制漏斗图评估结果的可靠性。最后，应用MR Steiger方向性检验，确保因果关系的合理性。**结果：**MR-PRESSO法检测到离群值(rs2081687；rs483082)，予以剔除后，IVW法分析结果显示TyG指数与NAFLD呈显著正相关(*OR*=1.798，95% *CI* 1.466~2.207，*P*=1.904E-08)，WM法(*OR*=1.621，95% *CI* 1.144~2.296，*P*=0.007)和MR-Egger法(*OR*=1.630，95% *CI* 1.153~2.304，*P*=0.006)显示的因果关系与IVW法一致。相关方法未检测到异质性和水平多效性，留一法亦未检测到对结果影响大的单核苷酸多态性(single nucleotide polymorphism，SNP)，漏斗图基本对称，支持结果的稳健性和可靠性。MR Steiger方向性检验未发现反向因果的SNP。**结论：**TyG指数与NAFLD之间存在因果关系，TyG指数升高可增加NAFLD的发生风险，且没有证据证明二者存在反向关联，该结论可为探究NAFLD的潜在风险因素及制订有效预防策略提供参考。

［**关键词**］甘油三酯-葡萄糖指数；非酒精性脂肪性肝病；因果关系；孟德尔随机化；全基因组关联分析；风险

Causal relationship between the triglyceride-glucose index and non-alcoholic fatty liver disease: A Mendelian randomization study

WANG Yina[1], CHEN Yuanguo[2], WANG Yang[1], CHEN Lu[3], YIN Meilong[2], XIAO Xiao[1], HUANG Jing[1], KUANG Jingjie[4], LI Yayong[2]

[1. Department of Geriatrics, Second Xiangya Hospital, Central South University, Changsha 410011; 2. Department of Emergency, Third Xiangya Hospital, Central South University, Changsha 410013; 3. Center of Geriatrics (Medical Care Center), Hainan General Hospital, Hainan Affiliated Hospital, Hainan Medical University, Haikou 571199; 4. Cadre Ward, 921 Hospital, the People's Liberation Army Joint Logistics Support Force, Changsha 410003, China]

ABSTRACT

Objective: Non-alcoholic fatty liver disease (NAFLD) has become a major public health issue that seriously affects human health. This study aims to employ a two-sample Mendelian randomization (MR) approach to investigate the causal relationship between the triglyceride-glucose (TyG) index and NAFLD, aiming to explore the potential impact of the TyG index on NAFLD.

Methods: Summary-level data for the TyG index were obtained from published genome-wide association study (GWAS) based on the UK Biobank, while GWAS summary data for NAFLD were retrieved from the IEU Open GWAS database. The inverse-variance weighted (IVW) method was used as the primary analysis, complemented by the weighted median (WM) method and the MR-Egger regression to further assess the causal relationship. Cochran's *Q* test was used to evaluate heterogeneity. Horizontal pleiotropy was assessed using MR-Egger regression, and the MR pleiotropy residual sum and outlier (MR-PRESSO) method was applied to detect and remove outliers. Leave-one-out analysis was conducted to assess the robustness of the results, and funnel plots were generated to

©Journal of Central South University (Medical Science). All rights reserved.

evaluate reliability. Finally, MR Steiger directionality tests were performed to confirm the validity of the causal direction.

Results: The MR-PRESSO method identified outliers (rs2081687 and rs483082), which were excluded. After removal, IVW analysis showed that the TyG index was significantly positively associated with NAFLD (*OR*=1.798, 95% *CI* 1.466 to 2.207, *P*=1.904E-08). Consistent results were observed using the WM method (*OR*=1.621, 95% *CI* 1.144 to 2.296, *P*=0.007) and the MR-Egger method (*OR*=1.630, 95% *CI* 1.153 to 2.304, *P*=0.006). No significant heterogeneity or horizontal pleiotropy was detected. Leave-one-out analysis showed that no single nucleotide polymorphism (SNP) had a substantial influence on the results. Funnel plots were generally symmetrical, supporting the robustness and reliability of the findings. MR Steiger directionality tests did not detect any evidence of reverse causality.

Conclusion: This MR study suggests a causal relationship between the TyG index and NAFLD. Elevated TyG index levels are associated with an increased risk of NAFLD, with no evidence supporting reverse causation. These findings provide a reference for identifying potential risk factors for NAFLD and developing effective prevention strategies.

KEY WORDS triglyceride-glucose index; non-alcoholic fatty liver disease; causal relationship; Mendelian randomization; genome-wide association study; risk

非酒精性脂肪性肝病(non-alcoholic fatty liver disease，NAFLD)是指在排除过量饮酒和其他肝病(如病毒性肝炎、自身免疫性肝病等)的前提下，由于肝脏脂肪过度积聚所致的代谢性肝损伤，常伴有胰岛素抵抗(insulin resistance，IR)及遗传易感性。重症患者可进展为肝硬化，甚至肝细胞癌[1]，且容易并发其他代谢性疾病或心脑血管疾病[2-5]。根据一项系统综述[6]，在全球范围内，NAFLD的患病率在过去30年间增长超过50%，从1990—2006年的25.3%上升到2016—2019年的38.2%。中国NAFLD患病率接近30%，已成为当前最常见的慢性肝病[7]。近年来，代谢功能障碍在NAFLD发生和发展中的核心作用逐渐被认识。2023年，国际专家共识[8]提出“代谢功能障碍相关脂肪性肝病(metabolic dysfunction-associated steatotic liver disease，MASLD)”这一新命名，旨在更准确地反映该病与全身代谢紊乱的密切关系。MASLD的诊断标准包括影像学或组织学证实的肝脏脂肪变性，且至少合并以下代谢异常中的1项：肥胖、2型糖尿病、高血压、高甘油三酯血症或低高密度脂蛋白胆固醇血症[8]。与传统定义的NAFLD患者相比，MASLD患者通常表现出更显著的IR、更高的肝纤维化风险及心血管事件风险[9]。随着生活方式和饮食结构的改变，NAFLD/MASLD的患病率预计将持续上升，该疾病已成为重要的公共卫生问题。因此，早期识别并进行有效干预，对于阻止NAFLD/MASLD的进展具有重要意义。

近年来，甘油三酯-葡萄糖(triglyceride-glucose，TyG)指数被广泛认为是一种评估IR的新型可靠指标。该指数通过计算空腹甘油三酯和空腹血糖乘积的对数值得出，不仅较传统指标更契合代谢相关脂肪性肝病(metabolic associated fatty liver disease，MAFLD)中“高甘油三酯+高空腹血糖”的核心代谢异常，且具有操作简便、成本低廉、易于推广等优势，已成为临床与流行病学研究中的常用工具[10]。荟萃分析[11]研究了TyG指数与NAFLD风险之间的剂量反应关系，发现TyG指数可能是NAFLD传统风险因素之外的一个新的独立风险因素，但尚无足够证据证实两者之间存在因果关系。

孟德尔随机化(Mendelian randomization，MR)法作为揭示因果关系的新型流行病学方法，利用受孕时遗传变异的随机分配特性，其研究设计与随机对照试验(randomized controlled trial，RCT)类似。MR法不仅能有效避免反向因果关系及混杂因素所致的偏倚，而且无需投入RCT般大量的人力、物力和时间，亦不受伦理问题限制，堪称一种天然、高效的“RCT”，在疾病病因学探索中得到了广泛应用[12-14]。鉴于此，本研究基于全基因组关联分析(genome-wide association study，GWAS)公开数据库，采用双样本MR法，旨在探索TyG指数对NAFLD的潜在因果效应，为临床制订NAFLD相关预防策略提供参考依据。

©Journal of Central South University (Medical Science). All rights reserved.

1 资料与方法

1.1 研究设计

MR法利用遗传变异作为工具变量(instrumental variable，IV)来研究TyG指数与NAFLD的因果关系。根据MR法的加强流行病学观察性研究报告(Strengthening the Reporting of Observational Studies in Epidemiology using MR，STROBE-MR)指南[15]，需满足以下3个关键性假设：1)作为IV的单核苷酸多态性(single nucleotide polymorphism，SNP)与暴露(TyG指数)密切相关；2)IV与结局(NAFLD)之间没有直接关系，仅通过暴露影响结局；3)IV与混杂因素无关。

1.2 数据的来源与IV的筛选

暴露(TyG指数)数据来源于基于英国生物样本库(UK Biobank)的已发表的GWAS数据，最终纳入273 368名具有遗传数据的欧洲裔样本，年龄为40~69岁。已剔除中途退出者、缺失基因型或基因型性别与自报性别不符者、性染色体异常个体、近亲样本、非欧洲血统者、TyG相关变量(甘油三酯及葡萄糖)超出均数±3倍标准差的极端值者，以及患有糖尿病和脂蛋白代谢紊乱等可能影响血糖与血脂水平的个体。

结局(NAFLD)数据来源于IEU Open GWAS数据库，共纳入778 614名欧洲裔受试者，包括8 434例NAFLD患者和770 180例对照，涉及6 784 388个SNP。为控制偏倚、确保结果有效性，暴露与结局数据分别来源于不同的GWAS数据库，且无样本重叠。这有助于提高因果关联结论的可信度，使其更接近真实的生物学因果关系，而非统计学假象。

在MR分析中，为确保IV与暴露因素的关联强度，以$P<10^{-8}$为筛选标准，选择与暴露因素(TyG指数)显著相关的SNPs作为IV。由于体重指数和血压作为NAFLD的重要危险因素，与TyG指数密切相关[4-5]，这与MR的独立性和排他性假设相违背，因此本研究排除了与体重指数、血压等代谢性状显著相关的位点。为保证独立性，本研究设置阈值参数($r^2<0.01$，kb=10 000)来去除连锁不平衡的影响；为评估IV与TyG的关联强度，避免弱IV偏移，纳入统计量$F>10$的SNP($F=\beta^2/SE^2$)。

经上述流程筛选，获得192个与TyG指数显著相关的SNP。在NAFLD的GWAS数据中提取这些SNP，以$P<5\times10^{-8}$为标准，剔除与结局显著关联的位点，并剔除等位基因不匹配及回文结构SNP。剔除MR多效性残差和与异质性检验(MR pleiotropy residual sum and outlier，MR-PRESSO)法检出的2个离群值(rs2081687、rs483082)。最终，经解除连锁不平衡、去除混杂控制、筛选F值、调整等位基因及剔除离群值后，共纳入139个SNP作为IV(图1；附图1，https://doi.org/10.57760/sciencedb.xbyxb.00188)。

1.3 MR分析

采用双样本MR法探究TyG指数与NAFLD的因果关系，以逆方差加权(inverse-variance weighted，IVW)法为主要分析方法，由于异质性检验$P=0.146$(见2.2敏感性分析)，提示无明显异质性，故采用固定效应模型。同时，辅以加权中位数(weighted median，WM)法和MR-Egger回归法作为补充分析方法，以评估结果的稳健性与可靠性。

在假设所有SNP均为有效IV的前提下，IVW法可提供最精确的因果效应估计值[16]。WM法对异常值不敏感，即使超过50%的SNP无效时，仍能提供相对稳定的因果估计[17]；MR-Egger法允许IV存在水平多效性，可在存在共线性的情况下进行因果估计，但其估计精度相对较低[18]。

上述分析使用R4.3.3软件中的TwoSampleMR(版本0.6.0)、MendelianRandomization(版本0.8.0)和MRPRESSO软件包(版本1.0)进行，检验水准$\alpha=0.05$。

1.4 敏感性分析

通过异质性检验、水平多效性检验和留一法进行敏感性分析。Cochran's Q统计量用于检测异质性，若$P<0.05$，则表示结果具有异质性[19]；MR-Egger截距法和MR-PRESSO法可用于检验水平多效性。通过截距值，可评估遗传变异是否通过除暴露因素外的其他途径对结果产生影响，当$P<0.05$时，表明存在水平多效性[20-21]；MR-PRESSO法进行离群值检测并剔除离群值，还可检测IVW线性回归中的异常值并删除异常值以提供校正的MR估计，作为IVW法的补充，可加强阳性结果的稳健性[22-23]；留一法通过依次剔除单个SNP，再计算剩余SNPs的合并效应值，探讨是否存在单个SNP驱动因果关联，如果剔除单个SNP后对MR分析影响较大，则表明MR分析受单个IV的干扰[24]；使用漏斗图检测结果偏倚。最后，使用MR Steiger进行方向性检验。

2 结 果

2.1 MR分析

MR研究结果表明，TyG指数与NAFLD之间存在正向因果关系。IVW法结果显示，TyG指数升高增加NAFLD的发生风险(OR=1.798，95% CI 1.466~2.207，P=1.903E-08)。WM法(OR=1.621，95% CI 1.144~2.296，P=0.007)、MR-Egger法(OR=1.630，95% CI 1.153~2.304，P=0.006)及MR-PRESSO法(OR=1.799，95% CI 1.466~2.207，P=1.903E-07)显示了相似的因果关系。散点图(图2)和森林图(图3)均显示基因预测的TyG是NAFLD的危险因素。

©Journal of Central South University (Medical Science). All rights reserved.

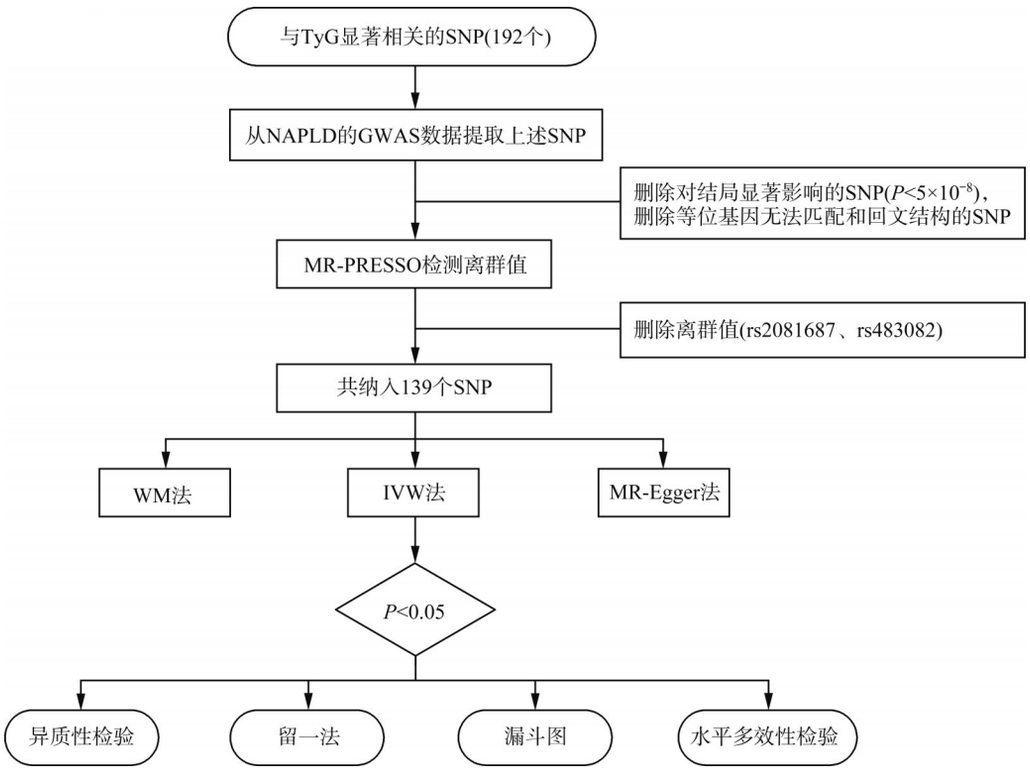


图1　MR分析流程图

Figure 1　MR analysis flowchart

MR: Mendelian randomization; TyG: Triglyceride-glucose; SNP: Single nucleotide polymorphism; NAFLD: Non-alcoholic fatty liver disease; GWAS: Genome-wide association study; MR-PRESSO: MR pleiotropy residual sum and outlier; IVW: Inverse-variance weighted; WM: Weighted median.

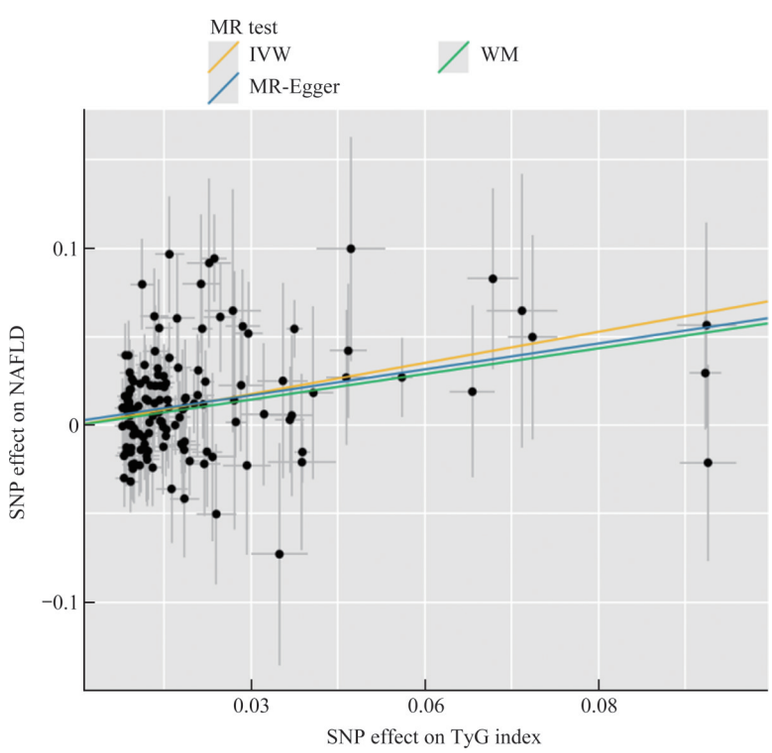


图2　MR分析散点图

Figure 2　MR analysis scatter plot

©Journal of Central South University (Medical Science). All rights reserved.

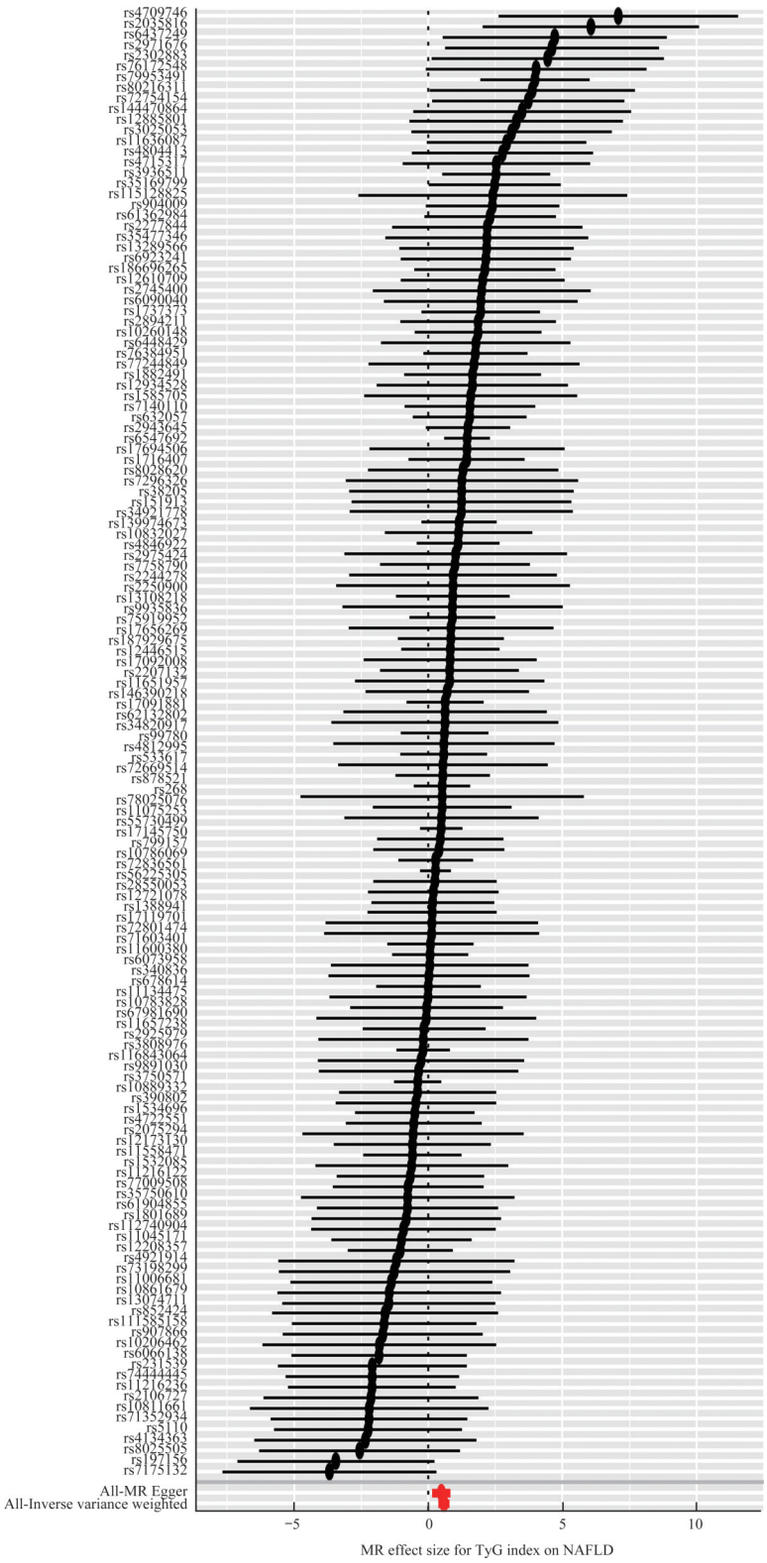


图3 MR分析结果森林图

Figure 3 Forest plot of MR analysis results

2.2 敏感性分析

在TyG指数与NAFLD因果关系的MR研究中，MR-PRESSO分析检测到2个异常的IV(rs2081687、rs483082)。剔除这2个离群值后，异质性检验显示纳入的SNP之间无明显异质性(IVW法，P=0.146；MR Egger法，P=0.139)；MR-Egger回归截距检验(P=0.489)和MR-PRESSO全局检验(P=0.146)均表明TyG指数与NAFLD之间的因果估计未受水平多效性的显

©Journal of Central South University (Medical Science). All rights reserved.

著干扰。留一法敏感性分析结果显示，逐一剔除单个SNP后，因果关系估计值未发生显著变化，进一步支持了结果的稳健性(图4)。漏斗图显示SNP分布基本对称，提示不存在明显的多效性偏倚，MR分析估计结果较为可靠(图5)。MR Steiger方向性检验未发现存在反向因果关系的SNP(附图2，https://doi.org/10.57760/sciencedb.xbyxb.00188)。

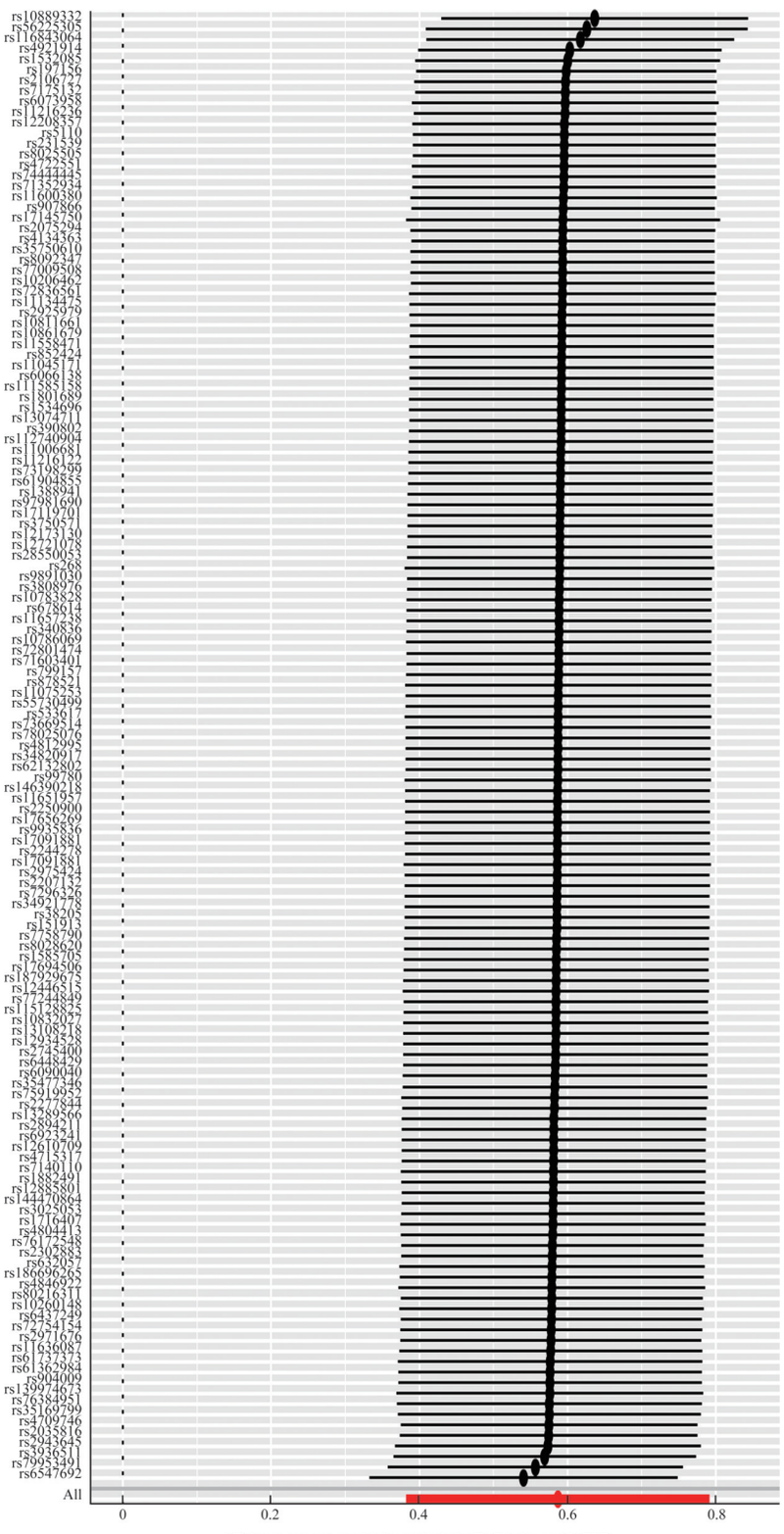


图4　留一法结果

Figure 4　Result of leave one method

©Journal of Central South University (Medical Science). All rights reserved.

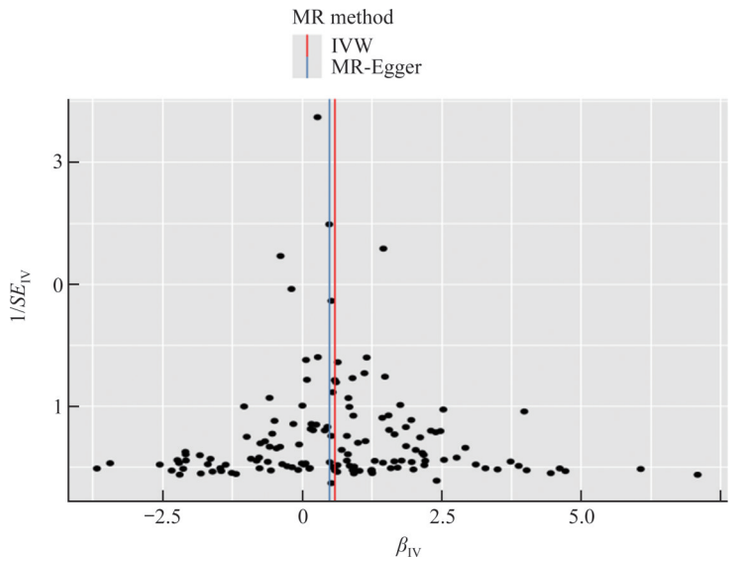


图5 MR分析结果漏斗图

Figure 5 Funnel plot of MR analysis results

3 讨 论

尽管TyG指数作为IR的新型标志物已在多种代谢性疾病中得到广泛研究，但现有证据多来自观察性研究，其与NAFLD之间的因果关系尚未充分阐明。本研究采用双样本MR法，基于GWAS数据库及IEU Open GWAS数据库的公开数据，探讨了TyG指数与NAFLD之间的潜在因果关系。结果显示，遗传预测的TyG指数升高显著增加NAFLD的发生风险，敏感性分析进一步验证了结果的稳健性与可靠性。这一发现从遗传学角度为TyG指数与IR、肝脏脂肪蓄积及相关代谢紊乱之间的关联提供了因果推断证据，进一步明确了TyG指数在NAFLD病因学中的作用。此外，如前所述，随着对代谢紊乱与肝损伤关系的认识不断深入，NAFLD正逐渐被修订为MASLD[8]。尽管本研究主要基于NAFLD表型进行分析，但其涉及的代谢机制探索同样适用于MASLD。因此，本研究不仅填补了TyG指数与NAFLD因果关系方面的研究空白，也为未来基于MASLD命名体系的早期筛查、风险评估及干预策略制订提供了遗传学依据。

既往流行病学研究普遍认为，TyG指数可作为IR的简便替代指标。与传统的胰岛素抵抗指数(homeostasis model assessment of insulin resistance，HOMA-IR)相比，TyG指数不受空腹胰岛素检测条件限制，具有更高的可重复性[25-28]。Zeng等[29]在中国非糖尿病人群中发现，TyG指数与NAFLD呈显著正相关。一项横断面研究[30]提示，纤维化患者的TyG指数及其相关衍生指标，包括甘油三酯-葡萄糖-体重指数、甘油三酯-葡萄糖-腰围指数及甘油三酯-葡萄糖-腰围身高比指数等，均显著高于对照组[30]。经多变量校正后，TyG指数仍为独立危险因素，且随TyG指数升高，肝纤维化风险呈递增趋势。上述结果表明，TyG指数不仅可能与NAFLD的患病风险相关，还可能反映肝脏脂肪沉积程度及肝纤维化进展风险，进一步支持了IR在NAFLD发生与发展中的关键作用，也提示TyG指数有望成为临床上预测NAFLD发生与发展风险的有效指标。

从机制角度看，TyG指数所反映的“高甘油三酯+高空腹血糖”状态实质上是IR的代谢表征。研究[31-33]表明，IR可通过促进脂肪组织游离脂肪酸外流、增强肝脏脂肪酸摄取和去饱和作用，导致肝细胞内脂滴堆积。脂肪酸过载可激活线粒体氧化应激与内质网应激，诱发脂毒性损伤及炎症反应[34-36]。近年研究[37-39]发现，TyG指数升高还与肝脏氧化还原稳态失衡、Kupffer细胞激活及肿瘤坏死因子(tumor necrosis factor，TNF)-α、白细胞介素(interleukin，IL)-6等炎症因子水平升高密切相关，从而进一步加剧肝细胞凋亡及纤维化形成。此外，TyG指数与代谢综合征、动脉僵硬度、心血管疾病等共病存在显著关联，提示其未来可作为评估全身代谢紊乱状态的潜在指标[40-42]。

本研究亦存在一定局限性。首先，纳入MR分析的样本来源于欧洲人群数据库，考虑到不同种族间可能存在遗传差异，本研究结论能否推广至其他人群尚需进一步验证。其次，由于本研究基于GWAS

©Journal of Central South University (Medical Science). All rights reserved.

汇总数据，缺乏个体层面信息，无法控制年龄、性别等潜在混杂因素对NAFLD发病率的影响。此外，TyG指数用于预测NAFLD的具体阈值尚未明确，未来需开展更精细的研究以提供更精确的估计。

作者贡献声明：王轶娜、李亚勇　论文设计与修改；陈元国、王鸯、陈露　数据分析，论文撰写；尹美龙、肖晓、黄晶、邝晶洁　数据采集。所有作者阅读并同意最终的文本。

利益冲突声明：作者声称无任何利益冲突。

参考文献

[1] Raza S, Rajak S, Upadhyay A, et al. Current treatment paradigms and emerging therapies for NAFLD/NASH[J]. Front Biosci, 2021, 26(2): 206-237. https://doi.org/10.2741/4892.

[2] Wang M, Zhou BG, Zhang Y, et al. Association between non-alcoholic fatty liver disease and risk of stroke: a systematic review and meta-analysis[J]. Front Cardiovasc Med, 2022, 9: 812030. https://doi.org/10.3389/fcvm.2022.812030.

[3] Polyzos SA, Kechagias S, Tsochatzis EA. Review article: non-alcoholic fatty liver disease and cardiovascular diseases: associations and treatment considerations[J]. Aliment Pharmacol Ther, 2021, 54(8): 1013-1025. https://doi.org/10.1111/apt.16575.

[4] Mantovani A, Petracca G, Beatrice G, et al. Non-alcoholic fatty liver disease and risk of incident chronic kidney disease: an updated meta-analysis[J]. Gut, 2022, 71(1): 156-162. https://doi.org/10.1136/gutjnl-2020-323082.

[5] Chung GE, Cho EJ, Yoon JW, et al. Nonalcoholic fatty liver disease increases the risk of diabetes in young adults: a nationwide population-based study in Korea[J]. Metabolism, 2021, 123: 154866. https://doi.org/10.1016/j.metabol.2021.154866.

[6] Younossi ZM, Golabi P, Paik JM, et al. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review[J]. Hepatology, 2023, 77(4): 1335-1347. https://doi.org/10.1097/HEP.0000000000000004.

[7] Li J, Zou B, Yeo YH, et al. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999-2019: a systematic review and meta-analysis[J]. Lancet Gastroenterol Hepatol, 2019, 4(5): 389-398. https://doi.org/10.1016/S2468-1253(19)30039-1.

[8] Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature [J]. J Hepatol, 2023, 79(6): 1542-1556. https://doi.org/10.1016/j.jhep.2023.06.003.

[9] Targher G, Valenti L, Byrne CD. Metabolic dysfunction-associated steatotic liver disease[J]. N Engl J Med, 2025, 393(7): 683-698. https://doi.org/10.1056/nejmra2412865.

[10] Tahapary DL, Pratisthita LB, Fitri NA, et al. Challenges in the diagnosis of insulin resistance: Focusing on the role of HOMA-IR and tryglyceride/glucose index[J]. Diabetes Metab Syndr, 2022, 16(8): 102581. https://doi.org/10.1016/j.dsx.2022.102581.

[11] Ling Q, Chen J, Liu X, et al. The triglyceride and glucose index and risk of nonalcoholic fatty liver disease: a dose-response meta-analysis[J]. Front Endocrinol, 2023, 13: 1043169. https://doi.org/10.3389/fendo.2022.1043169.

[12] Richmond RC, Davey Smith G. Mendelian randomization: concepts and scope[J/OL]. Cold Spring Harb Perspect Med, 2022, 12(1): a040501[2025-01-01]. https://doi.org/10.1101/cshperspect.a040501.

[13] Burgess S, Davey Smith G, Davies NM, et al. Guidelines for performing Mendelian randomization investigations: update for summer 2023[J]. Wellcome Open Res, 2023, 4: 186. https://doi.org/10.12688/wellcomeopenres.15555.3.

[14] Zuber V, Grinberg NF, Gill D, et al. Combining evidence from Mendelian randomization and colocalization: Review and comparison of approaches[J]. Am J Hum Genet, 2022, 109(5): 767-782. https://doi.org/10.1016/j.ajhg.2022.04.001.

[15] Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the reporting of observational studies in epidemiology using mendelian randomisation (STROBE-MR): explanation and elaboration[J/OL]. BMJ, 2021, 375: n2233 [2025-01-01]. https://doi.org/10.1136/bmj.n2233.

[16] Taschler B, Smith SM, Nichols TE. Causal inference on neuroimaging data with Mendelian randomisation[J]. Neuroimage, 2022, 258: 119385. https://doi.org/10.1016/j.neuroimage.2022.119385.

[17] Bowden J, Holmes MV. Meta-analysis and Mendelian randomization: a review[J]. Res Synth Methods, 2019, 10(4): 486-496. https://doi.org/10.1002/jrsm.1346.

[18] Li J, Bai H, Qiao H, et al. Causal effects of COVID-19 on cancer risk: a Mendelian randomization study[J/OL]. J Med Virol, 2023, 95(4): e28722[2025-01-01]. https://doi.org/10.1002/jmv.28722.

[19] Wu K, Li A, Liu L, et al. Inflammatory bowel disease and cardiovascular disease: a two-sample Mendelian randomization analysis[J]. Front Cardiovasc Med, 2022, 9: 927120. https://doi.org/10.3389/fcvm.2022.927120.

[20] Verbanck M, Chen CY, Neale B, et al. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases[J]. Nat Genet, 2018, 50(5): 693-698. https://doi.org/10.1038/s41588-018-0099-7.

[21] Yazdanpanah M, Yazdanpanah N, Gamache I, et al. Metabolome-wide Mendelian randomization for age at menarche and age at natural menopause[J]. Genome Med, 2024, 16(1): 69. https://doi.org/10.1186/s13073-024-01322-7.

[22] Park JK, Bafna S, Forrest IS, et al. Phenome-wide Mendelian randomization study of plasma triglyceride levels and 2600 disease traits[J/OL]. eLife, 2023, 12: e80560[2025-01-01]. https://doi.org/10. 7554/eLife.80560.

[23] Xiao Z, Wang Z, Zhang T, et al. Bidirectional Mendelian

©Journal of Central South University (Medical Science). All rights reserved.

randomization analysis of the genetic association between primary lung cancer and colorectal cancer[J]. J Transl Med, 2023, 21(1): 722. https://doi.org/10.1186/s12967-023-04612-7.

[24] Jia L, Lv W, Liang L, et al. The causal effect of reproductive factors on breast cancer: a two-sample Mendelian randomization study[J]. J Clin Med, 2023, 12(1): 347. https://doi.org/10.3390/jcm12010347.

[25] Park HM, Lee HS, Lee YJ, et al. The triglyceride-glucose index is a more powerful surrogate marker for predicting the prevalence and incidence of type 2 diabetes mellitus than the homeostatic model assessment of insulin resistance[J]. Diabetes Res Clin Pract, 2021, 180: 109042. https://doi.org/10.1016/j.diabres.2021.109042.

[26] Nevárez-Sida A, Guerrero-Romero F. The triglycerides and glucose index: a cost-effectiveness analysis compared with the homeostatic model assessment for insulin resistance[J]. Value Health Reg Issues, 2023, 37: 49-52. https://doi.org/10.1016/j.vhri.2023.05.001.

[27] Son DH, Lee HS, Lee YJ, et al. Comparison of triglyceride-glucose index and HOMA-IR for predicting prevalence and incidence of metabolic syndrome[J]. Nutr Metab Cardiovasc Dis, 2022, 32(3): 596-604. https://doi.org/10.1016/j.numecd.2021.11.017.

[28] Lopez-Jaramillo P, Gomez-Arbelaez D, Martinez-Bello D, et al. Association of the triglyceride glucose index as a measure of insulin resistance with mortality and cardiovascular disease in populations from five continents (PURE study): a prospective cohort study[J/OL]. Lancet Healthy Longev, 2023, 4(1): e23-e33[2025-01-01]. https://doi.org/10.1016/S2666-7568(22)00247-1.

[29] Zeng P, Cai X, Yu X, et al. Markers of insulin resistance associated with non-alcoholic fatty liver disease in non-diabetic population[J]. Sci Rep, 2023, 13(1): 20470. https://doi.org/10.1038/s41598-023-47269-4.

[30] Yang B, Gong M, Zhu X, et al. Correlation between liver fibrosis in non-alcoholic fatty liver disease and insulin resistance indicators: a cross-sectional study from NHANES 2017-2020[J]. Front Endocrinol, 2025, 16: 1514093. https://doi.org/10.3389/fendo.2025.1514093.

[31] Zhao J, Wu Y, Rong L, et al. Anti-lipolysis induced by insulin in diverse pathophysiologic conditions of adipose tissue[J]. Diabetes Metab Syndr Obes, 2020, 13: 1575-1585. https://doi.org/10.2147/DMSO.S250699.

[32] Yin X, Guo X, Liu Z, et al. Advances in the diagnosis and treatment of non-alcoholic fatty liver disease[J]. Int J Mol Sci, 2023, 24(3): 2844. https://doi.org/10.3390/ijms24032844.

[33] Kabeer SW, Sharma S, Sriramdasu S, et al. microRNA-721 regulates gluconeogenesis via KDM2A-mediated epigenetic modulation in diet-induced insulin resistance in C57BL/6J mice [J]. Biol Res, 2024, 57(1): 27. https://doi.org/10.1186/s40659-024-00495-0.

[34] Ziolkowska S, Binienda A, Jabłkowski M, et al. The interplay between insulin resistance, inflammation, oxidative stress, base excision repair and metabolic syndrome in nonalcoholic fatty liver disease[J]. Int J Mol Sci, 2021, 22(20): 11128. https://doi.org/10.3390/ijms222011128.

[35] Guo X, Yin X, Liu Z, et al. Non-alcoholic fatty liver disease (NAFLD) pathogenesis and natural products for prevention and treatment[J]. Int J Mol Sci, 2022, 23(24): 15489. https://doi.org/10.3390/ijms232415489.

[36] Allameh A, Niayesh-Mehr R, Aliarab A, et al. Oxidative stress in liver pathophysiology and disease[J]. Antioxidants, 2023, 12(9): 1653. https://doi.org/10.3390/antiox12091653.

[37] Sakurai Y, Kubota N, Yamauchi T, et al. Role of insulin resistance in MAFLD[J]. Int J Mol Sci, 2021, 22(8): 4156. https://doi.org/10.3390/ijms22084156.

[38] Zhang J, Liu Q, He J, et al. Novel therapeutic targets in liver fibrosis[J]. Front Mol Biosci, 2021, 8: 766855. https://doi.org/10.3389/fmolb.2021.766855.

[39] Zhao YQ, Deng XW, Xu GQ, et al. Mechanical homeostasis imbalance in hepatic stellate cells activation and hepatic fibrosis[J]. Front Mol Biosci, 2023, 10: 1183808. https://doi.org/10.3389/fmolb.2023.1183808.

[40] Gounden V, Devaraj S, Jialal I. The role of the triglyceride-glucose index as a biomarker of cardio-metabolic syndromes [J]. Lipids Health Dis, 2024, 23(1): 416. https://doi.org/10.1186/s12944-024-02412-6.

[41] Cui C, Liu L, Zhang T, et al. Triglyceride-glucose index, renal function and cardiovascular disease: a national cohort study [J]. Cardiovasc Diabetol, 2023, 22(1): 325. https://doi.org/10.1186/s12933-023-02055-4.

[42] Zhou H, Ding X, Lan Y, et al. Multi-trajectories of triglyceride-glucose index and lifestyle with Cardiovascular Disease: a cohort study[J]. Cardiovasc Diabetol, 2023, 22(1): 341. https://doi.org/10.1186/s12933-023-02076-z.

(责任编辑 郭征)

©Journal of Central South University (Medical Science). All rights reserved.