论著·公共卫生智库

弗雷明汉脂肪变性指数与成年人胆结石病的关联性分析:一项基于NHANES的横断面研究

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[摘要] **目的** 探讨弗雷明汉脂肪变性指数(Framingham Steatosis Index, FSI)与胆结石病风险的关联强度,以评估其作为风险标志物和简易筛查工具的潜力。**方法** 通过一项横断面研究,纳入美国国家健康与营养调查数据库2017—2020周期中5 705名成年人数据。采用复杂抽样加权的多因素logistic回归,评估FSI(作为连续变量及四分位数分组)与胆结石风险的关联;利用限制性立方样条与阈值效应分析探讨非线性关系;通过交互与亚组分析考察效应修饰;并采用多种敏感性分析验证结果的稳健性。**结果** 完全调整logistic回归模型显示FSI与胆结石风险呈显著正向关联(*OR*=1.31,95%*CI*:1.20~1.44,*P*<0.001);与FSI最低四分位组相比,最高四分位组的胆结石风险显著升高(*OR*=3.67,95%*CI*:2.21~6.09,*P*<0.001)。限制性立方样条分析提示FSI与胆结石病之间存在非线性关系(*P* for nonlinear=0.031),风险阈值拐点为-0.27。敏感性分析验证了上述正向关联的稳健性。**结论** FSI水平升高与胆结石患病风险呈显著正向关联,提示其具有作为社区及临床便捷代谢综合指标的潜力,可用于快速识别胆结石高危人群。**对策** 建议公共卫生部门考虑将FSI指标纳入成人胆结石病风险筛查体系,在中国人群做前瞻性验证后,利用阈值在社区层面快速识别胆结石高风险、低风险的个体,优化筛查资源分配;制定并推广针对体质量、血脂、血压、血糖的综合指南,通过加强公众教育、完善监测,最终实现对高危人群的早期预警和精准干预,降低疾病负担。

[关键词] 弗雷明汉脂肪变指数;胆石症;脂肪肝;横断面研究;国家健康和营养检查调查

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Association between the Framingham steatosis index and gallstone disease in adults: A cross-sectional study based on NHANES

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[**Abstract**] Objective To investigate the association between Framingham steatosis index (FSI) and the risk of gallstone disease in order to evaluate its potential as a risk marker and simple screening tool.

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Methods A cross-sectional study was conducted on 5 705 adults subjected from the 2017-2020 cycle of the US National Health and Nutrition Examination Survey (NHANES). A complex sampling-weighted multivariable logistic regression model was employed to assess the association between FSI (treated as both a continuous variable and in quartiles) and gallstone risk. Restricted cubic spline (RCS) and threshold effect analyses were utilized to explore nonlinear relationships. Interaction and subgroup analyses were performed to examine potential effect modifiers, and multiple sensitivity analyses were applied to verify the robustness of the findings. **Results** The fully adjusted logistic regression model showed a significant positive association between FSI and gallstone risk (*OR*=1.31, 95%*CI*: 1.20 to 1.44, *P*<0.001). Compared with the low FSI quartile, the high quartile had a significantly increased risk (*OR*=3.67, 95%*CI*: 2.21 to 6.09, *P*<0.001). Restricted cubic spline analysis suggested a nonlinear relationship between FSI and gallstone disease (*P* for nonlinear=0.031), with an inflection point at −0.27. Sensitivity analyses confirmed the robustness of the positive association. **Conclusion** Elevated FSI levels are significantly positively correlated with the risk of gallstone disease, suggesting its potential as a convenient metabolic composite indicator in community and clinical settings for the rapid identification of high-risk individuals. **Countermeasures** It is recommended that public health authorities should consider taking FSI into screening program for adult gallstone risk. Following prospective validation in Chinese populations, its threshold value could be utilized for rapid community-based risk stratification (high-*vs* low-risk), thereby optimizing the allocation of screening resources. Furthermore, comprehensive guidelines targeting body weight, blood lipids, blood pressure, and blood glucose should be developed and promoted. Strengthening public education and enhancing surveillance should be conducted to achieve the ultimate goals of early warning, precise intervention, and reduction of disease burden for high-risk populations.

[**Key words**] Framingham steatosis index; cholelithiasis; fatty liver; cross-sectional studies; National Health and Nutrition Examination Survey

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胆结石病(gallstone disease, GSD)是一种常见的消化系统疾病,其发病率在不同地区和人群差异显著。流行病学调查显示,美国和欧洲成年人的胆结石患病率为5%~25%,在美洲印第安人中可高达70%,而亚洲人群中则相对较低[1-3]。多数胆结石患者的临床表现常为无症状,但3%~8%的患者可能出现胆绞痛、胆囊炎、胆管炎甚至胰腺炎等严重并发症,这些并发症不仅严重影响患者生活质量,还显著加重了医疗负担[4-5]。此外,胆结石也是胆囊癌的重要危险因素之一,其潜在的公共健康危害不容忽视[6]。

胆结石的发生机制复杂,主要涉及胆固醇在合成、胆汁结晶和分泌过程[7],同时与年龄、性别、肥胖、糖尿病、胰岛素抵抗(insulin resistance, IR)及非酒精性脂肪肝病(nonalcoholic fatty liver disease, NAFLD)等密切相关[8-9]。其中,肥胖尤其是腹型肥胖,被认为是胆结石的危险因素。然而,传统的肥胖评价指标如体质指数(body mass index, BMI),在反映脂肪组织的实际分布及代谢活性方面存在一定局限性。近年来,一些新兴的脂肪分布与代谢功能指标,如体圆指数(body roundness index, BRI)、内脏脂肪指数和内脏脂肪代谢评分等逐渐受到关注,研究者试图探讨这些指标与胆结石风险之间的潜在关联[10-11],以期为胆结石的管理和风险预测提供更多证据。

在此背景下,弗雷明汉脂肪变性指数(Framingham Steatosis Index, FSI)作为一种整合多维度临床信息的脂肪相关指数,被用于代谢性疾病风险的评估。它是一种结合年龄、性别、BMI、血压、糖尿病状态、TG、ALT、AST等临床常规指标,用于预测肝脂肪变性的综合评分工具[12]。相较于肝脂肪变性指数和脂肪肝指数等传统模型,FSI被证实在预测NAFLD方

面具有更高的准确性[13-14]。近年来,有研究将FSI与心血管疾病、慢性肾脏疾病等的发生风险相关联[15-16],但目前尚缺乏系统性研究评估FSI与胆结石风险之间的关系。这一研究空白限制了对FSI在胆结石风险评估及临床应用价值的深入认识。

鉴于NAFLD与胆结石在发病机制上存在高度重叠性,如IR、脂质代谢紊乱和内脏脂肪堆积[11],有理由推测FSI可能与胆结石风险密切相关。因此,本研究基于美国国家健康与营养调查(National Health and Nutrition Examination Survey, NHANES)数据库,开展一项以人群为基础的横断面研究,旨在系统评估FSI与GSD风险之间的关联性强弱及其在不同人群中的差异,为深入理解GSD提供新的视角。

1 资料与方法

1.1 研究人群

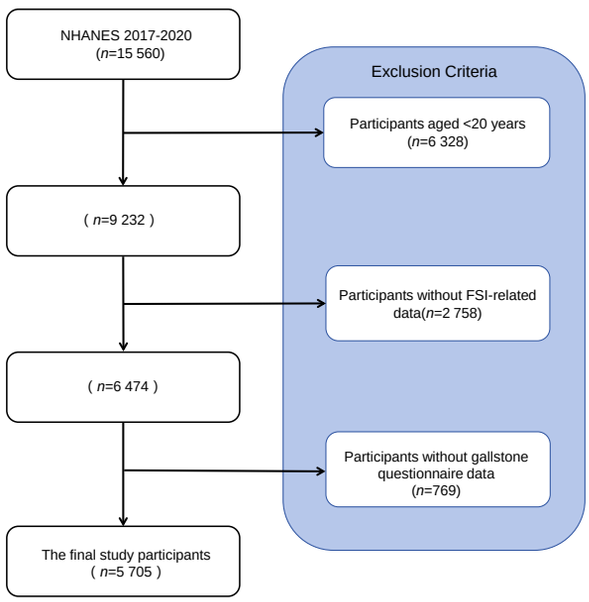
NHANES数据库旨在评估美国成人及儿童的健康和营养状况,提供全国性健康数据。鉴于胆结石资料的可用性,本研究选取了2017-2020年期间NHANES收集的数据,涵盖了人口学特征、体格检查、实验室检测及问卷调查信息。所有调查均获得国家健康统计中心伦理委员会批准(伦理号:Protocol#98-12),所有参与者均签署知情同意书,确保数据采集符合伦理规范。

本研究中,首先排除年龄<20岁的参与者(n=6 328)。随后,排除缺乏BMI、TG、AST、ALT、碱性磷酸酶(alkaline phosphatase, ALP)、γ-谷氨酰转肽酶(gamma-glutamyl transpeptidase, GGT)、空腹血糖、糖化血红蛋白、高血压、吸烟与饮酒情况等实验室及问卷数据的2 758例。另排除因缺乏胆结石相关资料诊断信息者769例。最终共纳入5 705名符合条件的参与者(图1)。本研究采用完整案例分析法,所有在关键变量上存在缺失的参与者均未被纳入最终分析。

1.2 外部验证人群

为验证本研究主要发现在独立人群中的稳健性,补充建立外部验证样本集。该样本集的数据来源于河南中医药大学第一附属医院的住院患者电子病历系统。研究方案获得该院伦理委员会批准(伦理批件号:2025HL-28),并获得豁免知情同意,检索了2025年1月至2025年10月期间住院且完成腹部超声检查的患者名单。

根据腹部超声检查报告将患者分为"存在胆结石"与"未见胆结石"两类。在每一类人群中,分别采用简单随机抽样的方法。排除标准包括:①年龄<20岁;



NHANES: national health and nutrition examination survey; FSI: Framingham steatosis index

图1 研究人员筛选流程图

Figure 1 Flowchart of participant selection

②关键协变量(如FSI计算所需指标等)缺失者。FSI的计算方法与NHANES主分析保持完全一致。最终共纳入750名研究对象(其中胆结石患者230名,非胆结石患者520名),构成了一个独立的医院基础病例对照验证样本集,用于重复主要分析。

1.3 FSI公式计算

本研究采用了LONG等[12]提出的FSI公式。具体计算方法如下:FSI=-7.981+0.011×年龄(岁)-0.146×性别(女性=1,男性=0)+0.173×BMI(kg/m^2)+0.007×TG(mg/dL)+0.593×高血压(是=1,否=0)+0.789×糖尿病(是=1,否=0)+1.1×ALT:AST比率≥1.33(是=1,否=0)。

1.4 协变量评估

人口统计数据,包括年龄、性别、种族、教育程度、贫困收入比(poverty-income ratio, PIR)及婚姻状况等,均通过标准化问卷调查收集。教育水平分为3类:低于高中学历、高中或同等学力、高中以上学历。PIR分为3个层次,即低水平(<1.30)、中等水平(1.30~3.50)、高水平(>3.50)[17]。婚姻状况分为已婚/同居、离婚/分开居住/丧偶、从未结婚;行为及其他健康相关变量包括吸烟、饮酒、糖尿病状态和高血压状态。吸烟状况分为从未吸烟者、过去吸烟者或当前吸烟者。累积吸烟量≤100支香烟的参与者被归类为从未吸烟者;累积吸烟量>100支但当前不吸烟的为过去吸烟

者;而累积吸烟量>100支且回答“您当前是否吸烟?”为“是”的被归类为当前吸烟者。饮酒行为分类为:当前饮酒者和非当前饮酒者(包括既往饮酒者和从未饮酒者)。根据自报问卷,当前饮酒者是指过去12个月内每月至少饮酒1次的参与者。

根据美国糖尿病协会的标准,糖尿病的诊断基于以下任-标准:空腹血糖≥126 mg/dL、糖化血红蛋白≥6.5%、自我报告的临床医师诊断为糖尿病或正在使用胰岛素/开始药物治疗降低血糖[18]。高血压定义为收缩压≥130 mmHg或(和)舒张压≥85 mmHg,或自报高血压诊断或正在接受降压药物治疗。

1.5 统计学分析

本研究所有统计分析均基于复杂抽样嵌套设计并进行加权处理,以确保结果能够代表全国人群。数据的提取、合并、清理与分析均通过R软件(版本4.4.1)以及决策链软件(版本1.1.5.8,杭州猿通信息科技有限公司)完成。所有统计检验均为双侧检验,P值<0.05认为差异具有统计学意义。

在正式分析前,首先对主要变量FSI进行异常值检测,采用箱线图方法识别并剔除FSI的异常值(定义为高于第三四分位数加1.5倍四分位距或低于第一四分位数减1.5倍四分位距的数据点),以减少极端值对建模结果的影响。

对于连续型变量,首先采用Kolmogorov-Smirnov检验评估其正态分布性,Levene检验用于方差齐性的判断。若变量符合正态分布且方差齐性,采用独立样本t检验进行组间比较,结果以$\bar{x}\pm s$表示。若变量不符合正态分布或不满足方差齐性,则采用Wilcoxon秩和检验,结果以$M(P_{25},P_{75})$表示。对于分类变量,采用卡方检验进行组间比较;若当任一单元格期望频数<5时,则采用Fisher精确检验。分类变量结果以例(%)表示。

为评估FSI与胆结石患病风险的关联,构建了多因素Logistic回归模型。模型1为未调整模型;模型2在模型1基础上调整了人口统计学变量,包括性别、年龄、种族、教育水平、PIR及婚姻状况;模型3在模型2基础上进一步纳入高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)、ALP、GGT、血压状态、血糖状态、吸烟状况和饮酒状况等潜在混杂因素。FSI按四分位数进行分组,以最低四分位组为参考,报告各模型下的OR及95%CI。

为探讨FSI与胆结石风险之间的剂量-反应关系,进一步采用限制性立方样条(restricted cubic spline, RCS)模型拟合非线性趋势,关于RCS模型节点的选择,采用了基于赤池信息准则(Akaike information criterion, AIC)的自动化算法来确定最优节点数(本研究中最终确定的节点数为3)。此外,进行交互与亚组分析,以评估不同人群特征对FSI与胆结石关联的修饰效应。进一步采用多种敏感性分析以验证结果稳健性,包括分别剔除FSI极端值(<2%或>99%分位值)及采用不同分组策略(如三分位分组)进行重复分析。

2 结果

2.1 基线特征

胆结石组的FSI、年龄和ALP水平均高于非胆结石组(Z=12.51,P<0.001;Z=11.03,P<0.001;Z=6.56,P<0.001)。就种族构成而言,胆结石组非西班牙裔白人的比例更高(χ^2=24.12,P=0.003)。婚姻状况方面,胆结石组已婚或同居者比例亦高于非胆结石组(χ^2=24.25,P=0.002)。此外,胆结石组高血压和糖尿病患病率均明显高于对照组(χ^2=25.00,P<0.001;χ^2=69.56,P<0.001)。表明胆结石患者在代谢负担及慢性病患病率方面呈现出更为不利的基线特征(表1)。本研究所有连续变量均不符合正态分布(表2),因此组间连续变量的比较采用非参数检验。

2.2 FSI与胆结石之间的关联

在未调整协变量的模型1中,当FSI作为连续变量,与胆结石患病风险呈正相关(OR=1.29,95%CI:1.24~1.35,P<0.001)。在调整性别、年龄、种族、教育、婚姻状况等人口学变量的模型2中,正相关依然存在(OR=1.32,95%CI:1.22~1.43,P<0.001)。在进一步调整GGT、ALP、HDL-C、高血压状态、糖尿病状态、吸烟状态及饮酒状况等混杂因素的模型3中,FSI与胆结石风险之间的正相关依然稳健(OR=1.31,95%CI:1.20~1.44,P<0.001)。

将FSI以四分位数分组后,以Q1组为参考,在完全调整模型中,Q4组(OR=3.67,95%CI:2.21~6.09,P<0.001)风险仍显著升高。此外,趋势性检验(P for trend<0.001)显示FSI与胆结石风险之间存在显著的剂量-反应关系(表3)。

为进一步探讨FSI与胆结石风险之间的关系,本研究采用RCS评估FSI与GSD风险之间的剂量反应关系。结果显示,FSI与GSD风险之间存在统计学显著的关联(P for overall<0.001),且该关联呈现非线性趋势(P for non-linearity=0.031),见图2。风险变化的拐点大致位于FSI=-0.27,当FSI低于该拐点时,胆结石风险随FSI的升高迅速增加(OR=1.48,95%CI:1.15~1.89,P<0.001);而当FSI超过该拐点后,风险曲线有所减弱

表1 参与者的基线特征[$M(P_{25},P_{75})$,例(%)]

Table 1 Baseline characteristics of participants [$M(P_{25},P_{75})$, n(%)]

Variable	Overall (n=5 705)	Non-gallstone group (n=5 106)	Gallstone group (n=599)	Z/χ^2	P
Age/years	51.00(36.00,64.00)	50.00(35.00,63.00)	59.00(45.00,70.00)	11.03	<0.001
Gender				119.50	<0.001
Male	2 814.00(49.33)	2 392.00(46.85)	422.00(70.45)		
Female	2 891.00(50.67)	2 714.00(53.15)	177.00(29.55)		
Race				24.12	0.003
Mexican American	668.00(11.71)	589.00(11.54)	79.00(13.19)		
Non-Hispanic black	1 425.00(24.98)	1 317.00(25.79)	108.00(18.03)		
Non-Hispanic white	2 242.00(39.30)	1 963.00(38.44)	279.00(46.58)		
Other race	1 370.00(24.01)	1 237.00(24.23)	133.00(22.20)		
Education level				1.41	0.493
Less than high school	888.00(15.57)	789.00(15.45)	99.00(16.53)		
High school	1 384.00(24.26)	1 231.00(24.11)	153.00(25.54)		
Some college or above	3 433.00(60.18)	3 086.00(60.44)	347.00(57.93)		
Martial status				24.25	0.002
Married/Cohabitating	3 364.00(58.97)	2 992.00(58.60)	372.00(62.10)		
Divorced/Widowed/Separated	1 276.00(22.37)	1 118.00(21.90)	158.00(26.38)		
Never married	1 065.00(18.67)	996.00(19.51)	69.00(11.52)		
PIR				7.35	0.025
<1.3	1 516.00(26.57)	1 365.00(26.73)	151.00(25.21)		
1.3~3.5	2 257.00(39.56)	1 990.00(38.97)	267.00(44.57)		
>3.5	1 932.00(33.87)	1 751.00(34.29)	181.00(30.22)		
FSI	−0.94(−2.11,0.39)	−1.04(−2.20,0.29)	−0.18(−1.23,0.94)	12.51	<0.001
GGT/(U/L)	21.00(15.00,33.00)	21.00(15.00,33.00)	22.00(15.00,34.00)	1.00	0.315
ALP/(U/L)	73.00(61.00,89.00)	73.00(60.00,88.00)	79.00(65.00,97.00)	6.56	<0.001
HDL-C/(mg/dL)	51.00(42.00,62.00)	51.00(42.00,62.00)	50.00(42.00,60.00)	−0.87	0.384
HTN				25.00	<0.001
No	2 970.00(52.06)	2 716.00(53.19)	254.00(42.40)		
Yes	2 735.00(47.94)	2 390.00(46.81)	345.00(57.60)		
Diabetes				69.56	<0.001
No	4 549.00(79.74)	4 149.00(81.26)	400.00(66.78)		
Yes	1 156.00(20.26)	957.00(18.74)	199.00(33.22)		
Smoking status				18.28	<0.001
Current smoker	1 093.00(19.16)	987.00(19.33)	106.00(17.70)		
Former smoker	1 509.00(26.45)	1 307.00(25.60)	202.00(33.72)		
Never smoked	3 103.00(54.39)	2 812.00(55.07)	291.00(48.58)		
Drinking status				33.41	<0.001
No	1 212.00(21.24)	1 030.00(20.17)	182.00(30.38)		
Yes	4 493.00(78.76)	4 076.00(79.83)	417.00(69.62)		

PIR: Poverty-to-income ratio; FSI: Framingham steatosis index; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase; HDL-C: High-density lipoprotein cholesterol; HTN: Hypertension

表2 连续变量正态性检验结果

Table 2 Results of normality test for continuous variables

Variable	*D*	*P*
Age	4.75	<0.001
FSI	2.58	<0.001
HDL-C	6.49	<0.001
ALP	7.11	<0.001
GGT	21.09	<0.001

FSI: Framingham steatosis index; HDL-C: High-density lipoprotein cholesterol; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase

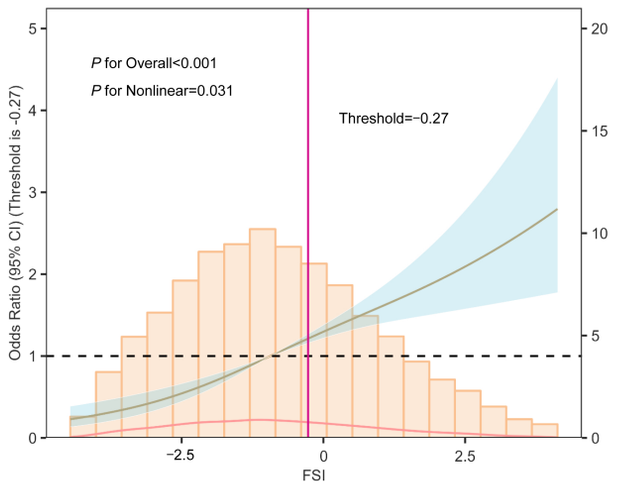
(*OR*=1.04,95%*CI*:0.96~1.13,*P*=0.306),提示当FSI达到一定水平后,其对胆结石风险的边际影响有所降低,见表4。

2.3 交互与亚组分析

为进一步探讨FSI与胆结石病风险关联在不同人群中的异质性,本研究进行了交互与亚组分析(表5)。结果显示,在所纳入的变量中,年龄、性别、教育程度、PIR、种族、婚姻状况、BMI、吸烟及饮酒状况与FSI之间均未观察到显著的交互作用(*P* for interaction>0.05)。FSI与胆结石风险的正向关联在多数亚组中均存在。尽管关联强度在各亚组间存在一定的数值差异,但这些差异均无统计学意义。

2.4 敏感性分析

为验证研究结果的稳健性,本研究进行多项敏感性分析。首先,分别剔除FSI低于第2百分位数和高于第99百分位数的极端值后重新构建多因素加权logistic回归模型。结果显示,无论是否剔除极端值,FSI与GSD风险的正向关联均保持显著,完全调整模型中,剔除前数据(*OR*=1.31,95%*CI*:1.20~1.44,*P*<0.001);剔除低于第2百分位后(*OR*=1.30,95%*CI*:1.18~1.44,*P*<0.001);剔除高于第99百分位后(*OR*=1.29,95%*CI*:1.16~1.43,*P*<0.001)(表6);并展示了分别剔除FSI低于第2百分位和高于第99百分位的极端值后,将FSI按四分位数分组,重新进行多因素逻辑回归的结果(表7、8)。



CI: Confidence interval; FSI: Framingham steatosis index

图2 FSI与胆结石病风险之间的剂量-反应关系

Figure 2 Dose-response relationship between FSI and risk of gallstone disease

将FSI按三分位数分组进行分析,结果显示,与Q1组相比,Q2、Q3组的胆结石风险依次升高(完全调整模型:Q2组(*OR*=1.76,95%*CI*:1.09~2.83,*P*<0.001);Q3组(*OR*=2.68,95%*CI*:1.69~4.24,*P*<0.001),且呈现出明确的剂量-反应关系(表6)。

表3 FSI与胆结石之间的关联

Table 3 Association between FSI and gallstone disease

Variable	Model 1		Model 2		Model 3	
	OR(95%*CI*)	*P*	*OR*(95%*CI*)	*P*	OR(95%*CI*)	*P*
FSI	1.29(1.24~1.35)	<0.001	1.32(1.22~1.43)	<0.001	1.31(1.20~1.44)	<0.001
Q1	Reference		Reference		Reference	
Q2	1.79(1.09~2.97)	0.023	1.58(0.95~2.64)	0.080	1.57(0.96~2.58)	0.075
Q3	2.72(1.73~4.26)	<0.001	2.47(1.54~3.98)	<0.001	2.51(1.55~4.06)	<0.001
Q4	4.00(2.57~6.23)	<0.001	3.82(2.40~6.07)	<0.001	3.67(2.21~6.09)	<0.001
P for trend	1.56(1.38~1.77)	<0.001	1.56(1.36~1.79)	<0.001	1.54(1.32~1.81)	<0.001

Model 1: Unadjusted; Model 2: Adjusting for age, gender, race, education level, PIR and marital status; Model 3: Additionally adjusting for GGT, ALP, HDL-C, hypertension, diabetes, smoking status and drinking status. FSI: Framingham steatosis index; *OR*: Odd ratio; *CI*: Confidence interval; PIR: Poverty-to-income ratio; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase; HDL-C: High-density lipoprotein cholesterol

表4 双分段线性回归模型结果

Table 4 Results of two-segment linear regression model

Item	*OR*(95%*CI*)	*P*
Model 1: Simple linear model	1.14(1.01~1.29)	0.031
Model 2: Two-segment linear regression		
Threshold: −0.27		
FSI <−0.27	1.48(1.15~1.89)	0.002
FSI ≥−0.27	1.04(0.96~1.13)	0.306
Log-likelihood ratio test		0.021

OR: Odd Ratio; *CI*: Confidence interval; FSI: Framingham Steatosis Index

2.5 外部数据集的验证

在独立的中国住院患者队列中(*n*=750),FSI与胆结石风险之间的正向关联得到重复验证。在未调整协变量的模型1中,FSI与胆结石之间存在显著正向关联(*OR*=1.32,95%*CI*:1.19~1.47,*P*<0.001)。在调整年龄、性别及婚姻状况的模型2中,该关联仍然存在(*OR*=1.23,95%*CI*:1.11~1.39,*P*<0.001)。在进一步调整GGT、ALP、HDL-C、高血压、糖尿病、吸烟及饮酒等混杂因素的模型3中,FSI与胆结石风险之间的正向关联依旧稳健(*OR*=1.14,95%*CI*:1.03~1.30,*P*=0.031)。

将FSI以四分位数分组后,以Q1组为参考,在完全调整模型中,Q3组(*OR*=2.82,95%*CI*:1.60~5.06,*P*<0.001)与Q4组(*OR*=2.41,95%*CI*:1.30~4.56,*P*=0.006)的胆结石风险均显著高于Q1组(表9)。

此外,限制性立方样条分析显示FSI与胆结石风险之间存在显著的非线性关系(*P* for nonlinear=0.022,见图3)。

3 讨论

本研究基于全国代表性样本,系统评估FSI与GSD风险的关联,提示两者之间呈显著正向关联。进一步RCS分析提示,FSI与胆结石风险之间存在非线性关系,风险变化拐点约为FSI=−0.27,敏感性分析验证了FSI与GSD风险之间正向关联的稳健性。这些发现不仅为理解胆结石病的代谢病理机制提供了新的流行病学线索,也提示了FSI在公共卫生筛查中具有潜在应用价值。

3.1 FSI可作为综合代谢指标的背景

目前尚无直接探讨FSI与胆结石风险关系的研究,但近年来多项研究关注了脂肪相关代谢指数及内脏脂肪指标与胆结石的联系。例如,ZHANG等[7]发现,BRI、腹型肥胖容积指数和体质量调整腰围指数等综合性肥胖参数均与胆结石风险呈正相关;XIE等[19]提出的ZJU指数作为脂肪肝代谢异常的综合指标,也与胆结石风险显著相关;GAO等[20]基于NHANES数据分析发现,相对脂肪质量增加可稳定升高胆结石风

表5 FSI与胆结石病交互与亚组分析

Table 5 Interaction and subgroup analyses of FSI and gallstone disease

Variable	*OR*(95%*CI*)	*P* for interoction
Age/years		0.374
<65	1.33(1.21~1.48)	
≥65	1.32(1.08~1.61)	
Gender		
Female	1.34(1.20~1.49)	0.544
Male	1.29(1.08~1.53)	
Race		0.447
Mexican American	1.19(0.97~1.45)	
Non-Hispanic black	1.29(1.11~1.49)	
Non-Hispanic white	1.33(1.18~1.49)	
Other race	1.30(1.08~1.56)	
Education level		0.098
Less than high school	1.30(1.03~1.64)	
High school	1.16(0.96~1.40)	
College or above	1.44(1.29~1.61)	
PIR		0.319
<1.3	1.14(0.95~1.37)	
1.3~3.5	1.29(1.12~1.48)	
>3.5	1.53(1.31~1.79)	
Martial status		0.386
Married/Cohabitating	1.31(1.17~1.46)	
Divorced/Widowed/Separated	1.24(1.02~1.51)	
Never married	1.41(1.05~1.88)	
BMI		0.733
≤24.9	1.13(0.69~1.85)	
25.0~29.9	1.25(0.84~1.86)	
≥30.0	1.26(1.06~1.50)	
Smoking status		0.285
Current smoker	1.30(1.07~1.58)	
Former smoker	1.38(1.20~1.59)	
Never smoked	1.31(1.13~1.53)	
Drinking status		0.755
No	1.36(1.13~1.63)	
Yes	1.30(1.17~1.45)	

FSI: Framingham steatosis index; *OR*: Odd ratio; *CI*: Confidence interval; PIR: Poverty-to-income ratio; BMI: Body mass index

表6 FSI与胆结石之间的关联

Table 6 Association between FSI and gallstone disease

Variable	n	Model 1		Model 2		Model 3	
		OR(95%*CI*)	*P*	*OR*(95%*CI*)	*P*	*OR*(95%*CI*)	*P*
FSI	5 705	1.29(1.24~1.35)	<0.001	1.32(1.22~1.43)	<0.001	1.31(1.20~1.44)	<0.001
Excluding FSI values below the 2nd percentile	5 647	1.31(1.23~1.40)	<0.001	1.32(1.24~1.40)	<0.001	1.30(1.18~1.44)	<0.001
Excluding FSI values above the 99th percentile	5 647	1.30(1.22~1.40)	<0.001	1.30(1.22~1.39)	<0.001	1.29(1.16~1.43)	<0.001
Q1	1 902	Reference		Reference		Reference	
Q2	1 901	2.02(1.43~2.85)	<0.001	1.85(1.27~2.68)	<0.001	1.76(1.09~2.83)	<0.001
Q3	1 902	3.26(2.47~4.31)	<0.001	3.05(2.26~4.12)	<0.001	2.68(1.69~4.24)	<0.001

Model 1: Unadjusted; Model 2: Adjusting for age, gender, race, education level, PIR and marital status; Model 3: Additionally adjusting for GGT, ALP, HDL-C, hypertension, diabetes, smoking status and drinking status. FSI: Framingham steatosis index; *OR*: Odd ratio; *CI*: Confidence interval; PIR: Poverty-to-income ratio, GGT: Gamma-glutamyl transferase, ALP: Alkaline phosphatase; HDL-C: High-density lipoprotein cholesterol

表7 剔除低于第2百分位数后FSI与胆结石之间的关联

Table 7 Association between FSI and gallstone disease after excluding values below the 2nd percentile

Variable	Model 1		Model 2		Model 3	
	OR(95%*CI*)	*P*	*OR*(95%*CI*)	*P*	*OR*(95%*CI*)	*P*
FSI	1.31(1.23~1.40)	<0.001	1.32(1.24~1.40)	<0.001	1.30(1.18~1.44)	<0.001
Q1	Reference		Reference		Reference	
Q2	1.76(1.04~2.96)	0.036	1.58(0.93~2.70)	0.085	1.56(0.75~3.24)	0.148
Q3	2.85(1.74~4.67)	<0.001	2.64(1.59~4.37)	0.001	2.63(1.29~5.36)	0.023
Q4	3.94(2.50~6.20)	<0.001	3.81(2.42~6.00)	<0.001	3.55(1.86~6.80)	0.008
P for trend	1.56(1.38~1.77)	<0.001	1.56(1.38~1.77)	<0.001	1.53(1.31~1.78)	<0.001

Model 1: Unadjusted; Model 2: Adjusting for age, gender, race, education level, PIR and marital status; Model 3: Additionally adjusting for GGT, ALP, HDL-C, hypertension, diabetes, smoking status and drinking status. FSI: Framingham steatosis index; *OR*: Odd ratio; *CI*: Confidence interval; PIR: Poverty-to-income ratio; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase; HDL-C: High-density lipoprotein cholesterol

表8 剔除高于第99百分位数后FSI与胆结石之间的关联

Table 8 Association between FSI and gallstone disease after excluding values above the 99th percentile

Variable	Model 1		Model 2		Model 3	
	OR(95%*CI*)	*P*	*OR*(95%*CI*)	*P*	*OR*(95%*CI*)	*P*
FSI	1.30(1.22~1.40)	<0.001	1.30(1.22~1.39)	<0.001	1.29(1.16~1.43)	<0.001
Q1	Reference		Reference		Reference	
Q2	2.09(1.19~3.68)	0.013	1.86(1.04~3.30)	0.037	1.82(0.82~4.05)	0.097
Q3	3.04(1.80~5.14)	<0.001	2.75(1.57~4.82)	0.002	2.77(1.21~6.32)	0.030
Q4	4.20(2.64~6.66)	<0.001	3.94(2.47~6.29)	<0.001	3.75(1.82~7.71)	0.010
P for trend	1.56(1.37~1.76)	<0.001	1.54(1.36~1.75)	<0.001	1.52(1.27~1.83)	0.002

Model 1: Unadjusted; Model 2: Adjusting for age, gender, race, education level, PIR and marital status; Model 3: Additionally adjusting for GGT, ALP, HDL-C, hypertension, diabetes, smoking status and drinking status. FSI: Framingham steatosis index; *OR*: Odd ratio; *CI*: Confidence interval; PIR: Poverty-to-income ratio, GGT: Gamma-glutamyl transferase, ALP: Alkaline phosphatase, HDL-C: High-density lipoprotein cholesterol

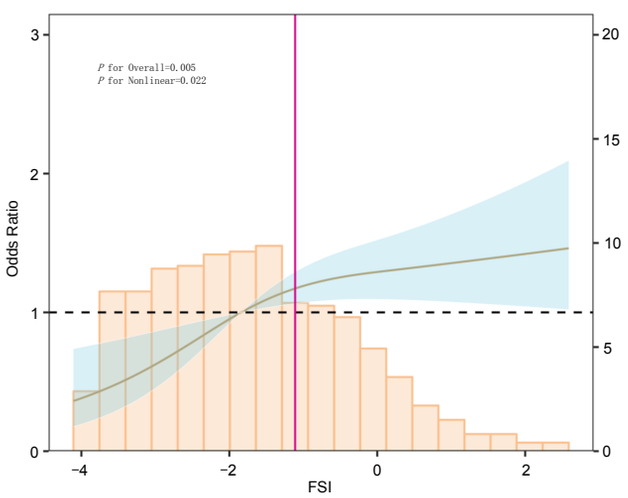
险,并呈线性剂量-反应趋势。这些证据共同支持脂肪蓄积水平是胆结石发生的重要影响因素。与上述指数相比,FSI综合了脂肪分布及体型结构的特征,能够更全面反映内脏脂肪堆积与代谢状态,这可能使其在揭示胆结石的病理生理机制方面具有独特价值。

表9 FSI与胆结石之间的关联

Table 9 Association between FSI and gallstone disease

Variable	Model 1		Model 2		Model 3	
	OR(95%*CI*)	*P*	*OR*(95%*CI*)	*P*	*OR*(95%*CI*)	*P*
FSI	1.32(1.19~1.47)	<0.001	1.23(1.11~1.39)	<0.001	1.14(1.03~1.30)	0.031
Q1	Reference		Reference		Reference	
Q2	2.45(1.45~4.21)	<0.001	1.76(1.02~3.09)	0.045	1.70(0.97~3.04)	0.066
Q3	4.56(2.77~7.73)	<0.001	3.11(1.84~5.39)	<0.001	2.82(1.60~5.06)	<0.001
Q4	4.52(2.75~7.66)	<0.001	3.16(1.86~5.50)	<0.001	2.41(1.30~4.56)	0.006
P for trend	1.61(1.39~1.87)	<0.001	1.46(1.25~1.72)	<0.001	1.34(1.11~1.62)	0.003

Model 1: Unadjusted; Model 2: Adjusting for age, gender, race, education level, PIR and marital status; Model 3: Additionally adjusting for GGT, ALP, HDL-C, hypertension, diabetes, smoking status and drinking status. FSI: Framingham steatosis index; *OR*: Odd ratio; *CI*: Confidence interval; PIR: Poverty-to-income ratio; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase; HDL-C: High-density lipoprotein cholesterol



FSI: Framingham Steatosis Index

图3 FSI与胆结石病风险之间的剂量-反应关系

Figure 3 Dose-response relationship between FSI and the risk of gallstone disease

3.2 机制阐释:从内脏脂肪堆积到多通路代谢紊乱

FSI与胆结石病风险的关联可能由多重机制共同驱动,其中肥胖,尤其是腹部内脏脂肪的堆积,被认为是重要的危险因素。多项研究证实,不同维度的肥胖指标均与胆结石风险显著相关[21],即使在代谢健康的肥胖人群中,这一风险仍然存在[22]。此外,通过计算机断层扫描测得的内脏脂肪含量升高,即使在体质量正常者中,也与胆结石风险增加密切相关[23]。内脏脂肪是肥胖相关代谢异常的核心,其堆积可能通过多条途径促进胆结石的发生:首先,破坏肝脏正常脂质代谢,导致胆汁胆固醇浓度升高,超过胆汁酸和磷脂的溶解极限时形成胆固醇结晶[24-25];其次,分泌炎症因子(如肿瘤坏死因子-α、白介素-6等),加重代谢紊乱并损害胆囊收缩功能,造成胆汁排出不畅,从而促进结石形成[26]。内脏脂肪堆积引发的IR可同时促进肝脏胆固醇合成并抑制胆盐和磷脂分泌,打破胆汁成分平衡,从而提高胆固醇结晶的饱和度[27-29]。相关研究显示,IR标志物——甘油三酯-葡萄糖指数与胆结石风险显著相关,且在肥胖人群及女性中更为明显[30]。

此外,与内脏脂肪密切相关的激素(如雌激素和瘦素等)也可能在FSI与胆结石风险的关联中发挥作用。研究表明,雌激素水平升高可促进胆固醇向胆汁分泌并降低胆汁酸比例,导致胆汁中胆固醇过饱和,从而增加胆结石的发生风险[31]。动物实验进一步发现,瘦素水平升高与胆结石的发生显著相关,可能通过影响脂质代谢和胆汁成分促进胆固醇结晶形成[32]。肠道微生物群失调亦可能通过调节胆汁酸代谢、影响宿主能量平衡及脂质稳态等方式,间接促进胆结石形成[33-35]。

3.3 临床应用潜力:阈值拐点或可作为风险分层与筛查工具

本研究识别出FSI与胆结石病风险关联存在拐点(FSI=-0.27),并揭示了其效应强度在此拐点两侧存在差异,即当FSI<-0.27时,关联强劲(*OR*=1.48),风险快速上升;而当FSI≥-0.27后,效应值有所减弱(*OR*=1.04)。这一发现提示,FSI阈值或可作为一个简易的风险分层工具,比如用于识别风险急剧增加的高危人群(FSI<-0.27),需加强预警及进一步检查;对于FSI≥-0.27的风险增幅放缓的中低危人群,建议采取针对生活方式的干预措施。然而,这需要进行高质量前瞻性、多中心的研究,才能考虑将其作为未来的精准预防工具。

3.4 控制潜在混杂是获得稳健关联估计的关键

本研究中部分协变量(教育程度、GGT、HDL-C)在基线比较中差异无统计学意义,然而这些变量的纳入是基于先验知识和既往文献。有研究指出高学历已被证实与较低的胆结石风险相关[36],且作为人口学基础变量,教育程度常在类似研究中被校正;GGT是胆管损伤及氧化应激的敏感标志物,可在胆结石刺激下升高,其水平升高是胆结石的独立危险因素[37];HDL-C则通过促进胆汁酸合成、增强胆固醇溶解能力以及逆向转运胆固醇,可以降低胆汁中的胆固醇饱和度[38-39]。HDL-C还被认为是胆结石的独立保护因素,低水平HDL-C显著增加胆结石风险[37]。因此,本研究纳入这些变量旨在控制潜在混杂,以获得FSI与GSD关联的稳健效应估计。

3.5 本研究的局限性

本研究仍存在若干局限。首先,作为横断面研究,其设计特性限制了对FSI与胆结石风险之间因果关系的推断。其次,胆结石的诊断信息来自自我报告,可能存在回忆偏倚或误分类。此外,本研究对缺失数据采用完整案例分析法,未来研究可考虑使用多重填补等方法来处理缺失值。再次,尽管已在多因素模型中调整了多种潜在混杂因素,仍难以完全排除残余混杂的可能。最后,本研究样本主要来源于美国人群,虽然建立了外部验证队列,但其单中心、回顾性的设计同样无法证实因果关系。

3.6 公共卫生实践启示

综上所述,本研究为FSI作为胆结石代谢风险标志物提供了证据。通过前瞻性研究验证后,FSI有潜力被开发为一个用于社区胆结石病或代谢性疾病风险协同评估与初步分层的工具。这进一步凸显了将胆结石预防整合至以生活方式干预为核心的代谢综合征管理体系中的必要性,为未来实现针对性的早期防控、优化卫生资源分配提供了参考。

利益冲突 本文所有作者声明不存在利益冲突

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