

·基础研究·

内脏脂肪代谢评分与心血管代谢共病及认知分域的关联性

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摘要:【目的】探讨内脏脂肪代谢评分(METS-VF)与老年人群心血管代谢共病(CMM)及认知功能的关联,揭示METS-VF作为评估工具在老年人群中的作用,并为CMM和认知功能的早期筛查及干预策略提供依据和新视角。【方法】本研究基于湖北老年记忆队列(HMACS)的横断面数据,纳入60岁及以上老年人,计算METS-VF指数并进行四分位分组(Q1-Q4)。通过问卷调查评估CMM(糖尿病、心脏病、中风中至少两种共存),并采用标准化认知测试评估总体认知、记忆、语言、执行功能和注意力。采用Logistic和Linear回归分析METS-VF与CMM患病风险及认知功能之间的关联性,采用限制性立方样条检验剂量-反应关系,亚组分析评估METS-VF在不同群体中的差异性,并采用多分类无序Logistic回归评估METS-VF与CMM患病模式的表现。【结果】共纳入3790名≥60岁的老年参与者。校正混杂因素后,与最低四分位组Q1组相比,Q4组METS-VF与更高的CMM患病风险相关[OR=3.00,95%CI(2.18,4.16)],且与更低的总体认知[b=-0.12,95%CI(-0.21,-0.04)]、注意[b=-0.14,95%CI(-0.24,-0.05)]和执行功能[b=-0.10,95%CI(-0.20,-0.00)]得分相关。剂量-反应分析未显示出METS-VF指数与CMM或认知功能的非线性关系(P for nonlinear>0.05)。亚组分析显示,高METS-VF指数的男性群体中的总体认知得分更低,而女性群体中执行功能得分更低(P for interaction均<0.05)。多分类无序Logistic回归分析显示,METS-VF指数与糖尿病合并冠心病[OR=2.62,95%CI(1.66,4.15)]或中风[OR=2.66,95%CI(1.73,4.09)]的患病风险增加相关,尤其在糖尿病同时伴随中风和冠心病的组别中,METS-VF与患病风险的关联最强。【结论】METS-VF升高与老年人群更高的CMM患病率及更低的总体认知、注意和执行功能得分相关,糖尿病可能是多病共存模式的关键驱动因素,METS-VF指数可作为筛查心血管代谢风险和评估认知功能的双用途工具。

关键词:内脏脂肪代谢指数;心血管代谢共病;认知分域;老年人群;肥胖

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The Association between Metabolic Score for Visceral Fat, Cardiometabolic Comorbidities and Cognitive Domain

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Abstract: 【Objective】 To explore the association between metabolic score for visceral fat (METS-VF) and cardiometabolic multimorbidity (CMM) as well as cognitive function in the elderly population, revealing the role of METS-

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VF as an assessment tool in this population, and providing evidence and new perspectives for the early screening and intervention strategies of CMM and cognitive function. **【Methods】** This study is based on cross-sectional data from the Hubei memory and aging cohort study (HMACS), which includes elderly individuals aged 60 and above. The METS-VF index was calculated and divided into quartiles (Q1-Q4). CMM was assessed through a questionnaire, defining CMM as the coexistence of at least two of the following conditions: diabetes, heart disease, and stroke. Standardized cognitive tests were used to evaluate overall cognition, memory, language, executive function, and attention. Logistic and Linear regression analysis was performed to explore the association between METS-VF and the risk of CMM as well as cognitive function. A restricted cubic spline was used to test the dose-response relationship, and subgroup analysis was conducted to assess the variation of METS-VF in different populations. Additionally, multinomial unordered logistic regression was used to evaluate the performance of METS-VF in predicting CMM morbidity patterns. **【Results】** A total of 3 790 elderly participants aged 60 and above were included. After adjusting for confounding factors, compared with the lowest quartile (Q1), the Q4 group of METS-VF was associated with a higher risk of CMM [OR=3.00, 95%CI (2.18, 4.16)], and with lower scores in overall cognition [$b=-0.12$, 95%CI (-0.21, -0.04)], attention [$b=-0.14$, 95%CI (-0.24, -0.05)], and executive function [$b=-0.10$, 95%CI (-0.20, -0.00)]. Dose-response analysis did not show a nonlinear relationship between METS-VF and either CMM or cognitive function (P for nonlinear > 0.05). Subgroup analysis revealed that the male group with higher METS-VF had lower overall cognitive scores, while the female group showed lower executive function scores (P for interaction < 0.05 for both). Multinomial unordered logistic regression analysis indicated that the METS-VF index was associated with an increased risk of diabetes with coronary heart disease [OR=2.62, 95%CI (1.66, 4.15)] or concomitant stroke [OR=2.66, 95%CI (1.73, 4.09)], especially in the group with both diabetes and stroke and coronary heart disease, where the association between METS-VF and the risk was strongest. **【Conclusions】** An increased METS-VF is associated with a higher risk of CMM and lower scores in overall cognition, attention, and executive function in the elderly population. Diabetes may be a key driving factor in the multimorbidity model. The METS-VF index can serve as a dual-purpose tool for screening cardiovascular metabolic risks and assessing cognitive function.

Key words: metabolic score for visceral fat; cardiometabolic multimorbidity; cognitive domains; elderly population; obesity

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人口老龄化加剧伴随着一系列的健康问题,如心血管代谢共病(cardiometabolic multimorbidity, CMM)和认知功能下降。研究表明,CMM(定义为两种及以上心血管代谢疾病同时存在,包括糖尿病、中风、心脏病。)与全因死亡率升高和预期寿命缩短密切相关,且危险度随并存疾病数量及特定高危组合(尤其卒中合并糖尿病/冠心病)而递增^[1-3]。同时,认知能力下降会显著影响个体的生活质量和日常功能,这通常是痴呆症的早期表现^[4],仅在中国,2020年即有约1 507万痴呆患者^[5]。因此,识别可改变的危险因素以预防CMM和认知功能下降对于临床和公共卫生策略至关重要。肥胖作为一个重要的健康风险,不仅显著增加心血管代谢疾病的发生率^[6],还与认知功能受损密切相关^[7]。已有的研究表明,脂肪组织的过度积累会诱发内皮功能障碍、血流动力学改变和心肌细胞损伤,从而促进动

脉粥样硬化性、心律失常、心力衰竭等心血管疾病的发生^[6,8]。同时,肥胖与多项认知领域(如情景记忆和工作记忆)呈负相关,肥胖个体在词语的延迟回忆和识别、视觉记忆任务及工作记忆任务中的表现较差^[7,9-10];神经影像学研究表明,肥胖个体的前额叶皮层区域血流量较低,且与情景记忆相关的皮层区域(如海马、角回和背外侧前额叶皮层)的功能活动显著减少,肥胖个体在执行工作记忆任务时,右侧顶叶皮层的激活程度也较低^[11]。此外,肥胖还是高血压、糖尿病、血脂异常等已知心血管危险因素的主要诱因^[10,12-13]。迄今为止,关于肥胖与CMM、认知功能之间关系的研究,多数聚焦于体质指数(body mass index, BMI)和腰围(waist circumference, WC)等传统肥胖评估指标。然而其存在局限性,BMI无法区分肌肉与脂肪,也难以反映脂肪分布^[14-15]。WC在一定程度上弥补了BMI的

不足,但仍受到身高和体型等因素的影响^[15-16],无法区分内脏脂肪组织(visceral adipose tissue, VAT)和皮下脂肪组织,从而可能低估中心性肥胖的风险。研究表明,VAT与言语记忆、注意力、海马体积、脑室体积以及左侧前额叶皮质厚度之间存在负相关,且VAT升高与健康老年人认知功能和脑形态的恶化相关^[17]。此外,VAT与代谢健康和心血管疾病风险增加密切相关,尤其在老年女性中,表现尤为突出^[18]。目前,磁共振成像(magnetic resonance imaging, MRI)技术被认为是VAT测量的金标准^[19],但由于成本高昂、设备体积大、操作复杂且检查耗时等因素,在资源有限的研究环境中难以广泛开展^[20]。Bello-Chavolla等人于2019年提出的内脏脂肪代谢评分(metabolic score for visceral fat, METS-VF)^[21]被验证了在评估VAT方面优于其他指标,可作为VAT的替代指标^[21]。越来越多的证据表明,METS-VF与多种健康结果相关,包括抑郁、认知功能、肌肉减少症^[22-24]等。然而,METS-VF与中国老年人群中的CMM及认知功能之间的关系尚未得到充分研究。心血管代谢疾病与认知障碍在老年人中高度共病^[25-26],存在共同致病路径,VAT的过度蓄积正是路径之一。作为一种高度活跃的内分泌器官,功能失调的VAT通过驱动系统性慢性炎症、诱发胰岛素抵抗及导致血管内皮功能障碍等核心机制,不仅直接损害心血管系统与代谢稳态^[27-30],还引发神经炎症、脑灌注不足与神经元能量代谢障碍^[31-33],从而对认知功能造成直接与间接的损伤。因此,心血管代谢共病与认知障碍很可能是同一病理生理过程在不同器官系统的表现。然而,传统研究多将他们作为独立的健康终点进行考察。而识别共同的关联因素将能超越单一疾病视角,整合性地揭示VAT与人类健康的多重关联,对综合管理心血管风险与认知障碍的精准公共卫

生策略具有重要价值。基于此,本研究利用湖北老年记忆队列(the Hubei memory and aging cohort study, HMACS)60岁以上的人群,探讨METS-VF与CMM及认知功能之间的关系,旨在为该领域提供新的视角,并为中国人群基于METS-VF的早期筛查和干预策略的制定提供依据。

1 材料与方法

1.1 研究对象

湖北老龄记忆队列研究(HMACS, www.chictr.org.cn;注册号:ChiCTR1800019164)是一项关于阿尔茨海默病(Alzheimer's disease, AD)早期检测的持续性前瞻性研究,收集湖北省60岁及以上人群的认知功能、生活方式和健康状况数据。详细的研究设计、招募程序和数据收集方法已在之前的出版物中描述^[34],在HMACS的初始招募阶段,排除了患有严重精神或神经疾病的个体,以及服用可能影响认知功能的药物或物质的个体。本研究已获得武汉科技大学医学院医学伦理委员会的批准(201945)。所有参与者均签署了书面知情同意书。

纳入标准为:①年龄 ≥ 60 岁,并在基线时提供完整的自变量计算相关数据;②在基线时完成了CMM及认知分域评估。最终有3 790人纳入本研究,见图1。

1.2 研究变量

1.2.1 自变量的评估 为了计算METS-VF,需要整合多种指标,如:胰岛素抵抗代谢评分(metabolic score for insulin resistance index, METS-IR)^[35]、腰围身高比(waist-to-height ratio, WHTR)^[36]、BMI^[37]、性别、年龄、空腹血糖(fasting blood glucose, FBG),血清甘油三酯(triglycerides, TG)和高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C),

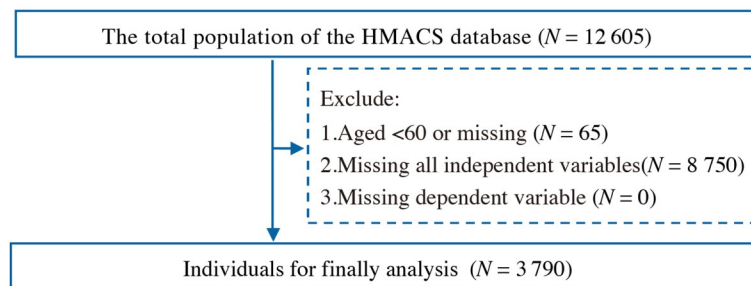


图1 研究流程图

Fig. 1 Flowchart of the study

所有血液数据均在空腹状态下测量。此外,性别作为二分类变量(女性=0,男性=1)进行分类。为控制异常值影响,METS-VF指数采用两端截尾处理(即1%和99%分位数的Winsorization),最终保留分布中98%的数据。

$$\text{METS - VF} = 4.466 + 0.011 \times [\ln(\text{METS - IR})^3] \\ + 3.239 \times [\ln(\text{WHTR})^3] + 0.319 \\ \times \text{Sex} + 0.594 \times \ln(\text{Age})$$

$$\text{METS-IR} = \ln \left\{ \left[2 \times \text{FBG} (\text{mg/dL}) + \text{TG} (\text{mg/dL}) \right] \times \text{BMI} \right\} \\ \div \ln \left[\text{HDL-C} (\text{mg/dL}) \right] \\ \text{BMI} = \frac{\text{Mass} (\text{kg})}{\text{Height} (\text{m})^2} \\ \text{WHTR} = \frac{\text{Waist circumference} (\text{cm})}{\text{Height} (\text{cm})}$$

1.2.2 因变量的评估 本研究纳入三种心血管代谢疾病(cardiomatabolic disease, CMD),符合各疾病任意条件即判定为患此疾病:①糖尿病(自述医生诊断;服用降糖药;空腹血糖 ≥ 126 mg/dl);②心脏病(自述医生诊断;服用相关药物);③中风(自述医生诊断;服用相关药物)。CMM事件定义为同时存在至少两种CMD,其余情况则视为非CMM事件(对照组)。CMM诊断标准与既往文献中使用的标准一致^[38]。对于次要结局(单个心血管代谢疾病),病例组定义为满足该CMD诊断标准且合并其他CMD的个体;对照组则为未患该特定CMD且同时不存在其他CMD的健康个体。据个体罹患的CMD组合情况,将CMM患病模式分为以下8种类型:①无任何CMD(对照组);②仅患糖尿病;③仅患心脏病;④仅患中风;⑤糖尿病伴随心脏病;⑥糖尿病伴随中风;⑦心脏病伴随中风;⑧糖尿病伴随心脏病和中风(3种CMD共患)。认知分域包括记忆、语言、执行功能、注意力和总体认知。HMACS在基线时进行了全面的认知测试,提供了详细和客观的特定领域的认知评估^[34],包括:①华山版听觉词语学习测验(auditory verbal learning test, AVLT)评估记忆功能,②波士顿命名(boston naming test, BNT)和语言流畅性测试(verbal fluency test, VFT)评估语言功能,③形状连线测验(shape trails test, STT-A)评估执行功能,④数字广度测验(digit span test, DST)评估注意力。每个认知领域的分数在确认正态分布后被标准化为Z分数(均值=0,标准差=1)。若同

一认知功能涉及多个评估方法,则计算其平均值。总体认知分数是二到四个认知功能领域分数的平均值,分数越高表示整体认知表现越好。

1.2.3 协变量的评估 在HMACS队列中,协变量包括年龄、性别、教育水平、稳定收入、居住地、居住状况、婚姻状况、吸烟状况、饮酒状况、体育锻炼、抑郁。教育水平被统一划分为3个类别:小学及以下、初中、高中及以上;年龄则分为70岁以下、70~74岁、75~80和80岁以上以上4个年龄组。收入分为“有稳定收入”和“无稳定收入”;居住地为“城市”和“农村”;居住状况分为“独居”和“非独居”;婚姻状况分为“当前已婚”和“未婚”;吸烟状况分为“当前吸烟”和“不吸烟”;饮酒状况分为“当前饮酒”和“不饮酒”;体力活动分为“有体育锻炼”和“无体育锻炼”;抑郁分为“有抑郁”和“无抑郁”。

1.3 统计学方法

所有统计分析均使用R软件(版本4.5.0; <https://www.r-project.org>)完成。所有统计检验均为双侧检验, $P < 0.05$ 被认为具有统计学显著性。研究参与者根据公式计算得到METS-VF指数,并按四分位数(Q1~Q4)分组。对于存在缺失的协变量,采用mice包进行多重插补。对于符合正态分布的计量资料以均值 \pm 标准差($\bar{x} \pm s$)表示,非正态分布的计量资料用中位数(四分位数间距) $M(P_{25} \sim P_{75})$ 表示。计数资料以频数和百分比(%)表示;组间差异的评估采用t检验或Mann-Whitney U检验(连续变量)和卡方检验(分组变量)。使用Logistic回归模型评估METS-VF指数的四分位组与CMM患病风险及单个心血管代谢疾病的关联性;使用Linear回归模型评估METS-VF指数的四分位组与认知分域的关联,并通过趋势性检验将各METS-VF指数的四分位组的中位值作为连续变量纳入模型,以评估线性趋势,均以Q1组为参考,并调整混杂因素:调整性别、年龄、受教育水平、居住地、居住状况、婚姻状况、稳定收入、吸烟、饮酒、体育锻炼和抑郁。为进一步探讨剂量反应关系,使用Rms包进行限制性立方样条分析,结点设定在第5%、35%、65%和95%分位数处。针对性别、年龄、居住地、教育水平等人群特征进行亚组分析,以探讨METS-VF指数的四分位组在不同人群中的差异性。使用多分类无序Logistic回归模型评估METS-VF指数与CMM患病模式(多分类变量)之间的关联,通过似然比检验(likelihood ratio test, LRT)评估

模型的整体有效性(比较仅含截距的零模型与包含 METS-VF 及所有协变量的完整模型),采用 Benjamini-Hochberg 方法对 P 值进行校正,以控制假发现率(false discovery rate, FDR)。

2 结果

2.1 基本特征描述

根据纳入和排除标准(图1),来自 HMACS 的

3 790 名参与者被纳入基线分析(表1),并根据 METS-VF 指数的四分位数分层展示基线特征。参与者的平均年龄为 71 岁,其中 57.5% 为女性。与 Q1 分位数的参与者相比, METS-VF 指数较高的参与者年龄更大、受教育年限较低、体育锻炼较少,并且更易患糖尿病、心脏病和中风。此外, Q4 分位数组的参与者的总体认知、记忆、语言、注意和执行功能得分均低于 Q1 分位数的参与者。

表1 研究人群的基线特征

Table 1 Baseline characteristics of participants

$[\bar{x} \pm s, M(P_{25}, P_{75}), n(\%)]$

Characteristics	Total($n=3\ 790$)	Q ₁ ($n=954$)	Q ₂ ($n=953$)	Q ₃ ($n=936$)	Q ₄ ($n=1\ 047$)	P
Sex						<0.001
Female	1 612(42.5)	274(28.7)	332(34.8)	391(41.8)	615(64.9)	
Male	2 178(57.5)	680(71.3)	621(65.2)	545(58.2)	332(35.1)	
Residence						<0.001
Rural	1 105(29.2)	206(21.6)	234(24.6)	278(29.7)	387(40.9)	
Urban	2 685(70.8)	748(78.4)	719(75.4)	658(70.3)	560(59.1)	
Age/years	71(67-76)	69(66-73)	70(67-75)	71(68-76)	73(69-78)	<0.001
Age level						<0.001
60-69	1 293(36.8)	445(49.9)	335(39.2)	289(33.0)	224(25.0)	
70-74	1 094(31.1)	241(27.0)	279(32.7)	287(32.8)	287(32.0)	
75-80	729(20.7)	144(16.2)	163(19.1)	198(22.6)	224(25.0)	
≥81	402(11.4)	61(6.8)	77(9.0)	102(11.6)	162(18.1)	
Education level						<0.001
≤6	1 291(34.3)	227(23.9)	260(27.5)	346(37.2)	458(48.5)	
6-9	929(24.6)	239(25.2)	250(26.4)	230(24.7)	210(22.2)	
>9	1 549(41.1)	482(50.8)	437(46.1)	354(38.1)	276(29.2)	
Marital status						<0.001
Single	979(26.2)	187(19.9)	237(25.0)	237(25.6)	318(34.2)	
Married	2 759(73.8)	751(80.1)	710(75.0)	687(74.4)	611(65.8)	
Living status						<0.001
Living alone	515(14.6)	101(11.6)	133(14.9)	106(12.2)	175(19.7)	
Not living alone	3 005(85.4)	767(88.4)	762(85.1)	763(87.8)	713(80.3)	
Smoking						<0.001
No	2 737(73.3)	680(72.5)	651(68.7)	685(74.9)	721(77.3)	
Yes	997(26.7)	258(27.5)	297(31.3)	230(25.1)	212(22.7)	
Drinking						0.043
No	2 751(74.3)	708(75.6)	665(70.7)	682(75.4)	696(75.2)	
Yes	954(25.7)	228(24.4)	275(29.3)	222(24.6)	229(24.8)	

续表

Characteristics	Total(n=3 790)	Q ₁ (n=954)	Q ₂ (n=953)	Q ₃ (n=936)	Q ₄ (n=1 047)	P
Stable income						<0.001
No	452(12.6)	88(9.7)	89(9.8)	120(13.6)	155(17.5)	
Yes	3 137(87.4)	823(90.3)	822(90.2)	762(86.4)	730(82.5)	
PA						<0.001
No	783(21.0)	165(17.6)	171(18.2)	192(21.0)	255(27.3)	
Yes	2 943(79.0)	770(82.4)	771(81.8)	724(79.0)	678(72.7)	
Depression						0.005
No	3 384(95.2)	860(95.1)	872(96.2)	830(96.3)	822(93.1)	
Yes	171(4.8)	44(4.9)	34(3.8)	32(3.7)	61(6.9)	
Diabetes						<0.001
No	2 715(71.6)	735(77.0)	708(74.3)	639(68.3)	633(66.8)	
Yes	1 075(28.4)	219(23.0)	245(25.7)	297(31.7)	314(33.2)	
Heart disease						<0.001
No	3 090(83.0)	832(88.5)	788(83.7)	761(82.9)	709(76.6)	
Yes	635(17.0)	108(11.5)	153(16.3)	157(17.1)	217(23.4)	
Stroke						<0.001
No	3 051(82.0)	815(86.7)	776(82.6)	754(82.2)	706(76.3)	
Yes	671(18.0)	125(13.3)	164(17.4)	163(17.8)	219(23.7)	
FBG/(mmol/L)	5.21(4.74, 6.02)	5.13(4.71, 5.96)	5.23(4.76, 5.97)	5.25(4.74, 6.06)	5.26(4.78, 6.18)	0.035
TG/(mmol/L)	1.27(0.91, 1.78)	1.21(0.89, 1.66)	1.28(0.93, 1.76)	1.30(0.92, 1.82)	1.31(0.94, 1.89)	0.046
HDL-C/(mmol/L)	1.34(1.16, 1.59)	1.41(1.20, 1.68)	1.36(1.18, 1.59)	1.34(1.17, 1.59)	1.26(1.08, 1.48)	<0.001
BMI/(kg/m ²)	23.7(21.5, 25.9)	20.9(19.3, 22.3)	23.1(21.6, 24.6)	24.5(22.9, 26.19)	26.6(24.7, 28.8)	<0.001
WHTR	0.54(0.50, 0.58)	0.47(0.45, 0.49)	0.52(0.51, 0.54)	0.56(0.54, 0.58)	0.61(0.58, 0.64)	<0.001
Global	0.18(-0.64, 0.80)	0.41(-0.30, 1.00)	0.26(-0.48, 0.83)	0.17(-0.71, 0.74)	-0.14(-0.86, 0.58)	<0.001
Memory	0.03(-0.63, 0.70)	0.21(-0.45, 0.94)	0.10(-0.51, 0.71)	-0.03(-0.76, 0.68)	-0.16(-0.73, 0.54)	<0.001
Language	0.02(-0.56, 0.59)	0.02(-0.56, 0.78)	0.02(-0.56, 0.59)	0.02(-0.56, 0.59)	-0.17(-0.75, 0.40)	<0.001
Attention	0.21(-0.61, 0.82)	0.42(-0.40, 0.82)	0.21(-0.61, 0.82)	0.01(-0.61, 0.82)	-0.20(-1.02, 0.62)	<0.001
Executive	0.20(-0.52, 0.76)	0.29(-0.36, 0.82)	0.27(-0.39, 0.77)	0.22(-0.53, 0.76)	-0.06(-0.74, 0.61)	<0.001
CMM						<0.001
No	3 295(86.9)	886(92.9)	837(87.8)	816(87.2)	756(79.8)	
Yes	495(13.1)	68(7.1)	116(12.2)	120(12.8)	191(20.2)	
METS-VF	6.85(6.48, 7.15)	6.17(5.90, 6.35)	6.69(6.59, 6.77)	6.99(6.92, 7.07)	7.33(7.24, 7.47)	<0.001

PA: physical activity.

2.2 内脏脂肪代谢评分与心血管代谢共病及认知分域的关联

采用多因素 Logistic 回归评估 METS-VF 与 CMM 及单个心血管代谢疾病的横断面关联,采用多因素 Linear 回归评估 METS-VF 与认知分域的横断面关联,均调整混杂因素。METS-VF 根据四分位数进行分组,第一分位数(Q1)作为对照组。结果显示,METS-VF 与更高的 CMM 患病风险、更低的认知功能得分相关(表 2)。具体而言,调整混杂因素后的结果显示(Model 2),Q2-Q4 组 METS-VF 发生 CMM 的风险为 Q1 组的 1.66~3.00 倍;Q2 组

[OR=1.66, 95%CI (1.20, 2.31)]、Q3 组 [OR=1.75, 95%CI (1.27, 2.44)]、Q4 组 [OR=3.00, 95%CI (2.18, 4.16)]。同时,Q4 组 METS-VF 与更低的总体认知 [b=-0.12, 95%CI (-0.21, -0.04)]、注意 [b=-0.14, 95%CI (-0.24, -0.05)]、执行 [b=-0.10, 95%CI (-0.20, -0.00)] 功能得分相关。趋势检验提示 CMM 风险随 METS-VF 指数升高而增加;总体认知、注意和执行功能得分随 METS-VF 指数升高而降低,表明 METS-VF 指数与 CMM 风险及认知分域之间存在趋势性关系 (P for trend < 0.05)。

表 2 METS-VF 与 CMM 及认知分域的关联性

Table 2 The association between METS-VF, CMM, and cognitive domain functions

Variables	Q ₁	Q ₂	P	Q ₃	P	Q ₄	P	P for trend
	Ref	OR (95%CI)		OR (95%CI)		OR (95%CI)		
CMM	1 (Ref)	1.66 (1.20, 2.31)	0.002	1.75 (1.27, 2.44)	<0.001	3.00 (2.18, 4.16)	<0.001	<0.001
Diabetes	1 (Ref)	1.03 (0.80, 1.34)	0.809	1.56 (1.21, 2.02)	<0.001	1.50 (1.14, 1.97)	0.004	0.001
HD	1 (Ref)	1.26 (0.86, 1.85)	0.231	1.34 (0.91, 1.99)	0.142	1.56 (1.05, 2.33)	0.029	0.031
Stroke	1 (Ref)	1.26 (0.88, 1.79)	0.206	1.30 (0.90, 1.87)	0.163	1.26 (0.86, 1.86)	0.240	0.144

Variables	Q ₁	Q ₂	P	Q ₃	P	Q ₄	P	P for trend
	Ref	b (95%CI)		b (95%CI)		b (95%CI)		
Global	0 (Ref)	-0.12 (-0.19, -0.04)	0.003	-0.10 (-0.18, -0.02)	0.013	-0.12 (-0.21, -0.04)	0.004	0.003
Memory	0 (Ref)	-0.08 (-0.18, 0.02)	0.098	-0.12 (-0.22, -0.02)	0.014	-0.07 (-0.17, 0.04)	0.194	0.080
Language	0 (Ref)	-0.06 (-0.15, 0.03)	0.195	-0.05 (-0.14, 0.04)	0.279	-0.06 (-0.16, 0.03)	0.195	0.219
Attention	0 (Ref)	-0.10 (-0.19, -0.01)	0.027	-0.07 (-0.16, 0.02)	0.125	-0.14 (-0.24, -0.05)	0.002	0.003
Executive	0 (Ref)	-0.05 (-0.14, 0.04)	0.258	-0.08 (-0.17, 0.02)	0.119	-0.10 (-0.20, -0.00)	0.047	0.018

Model adjusted for sex, age, education, residence, living situation, marital status, stable income, smoking, drinking, physical activity, and depression; OR: odds ratios; b: effect size; CI: confidence interval; Ref: reference; HD: heart disease.

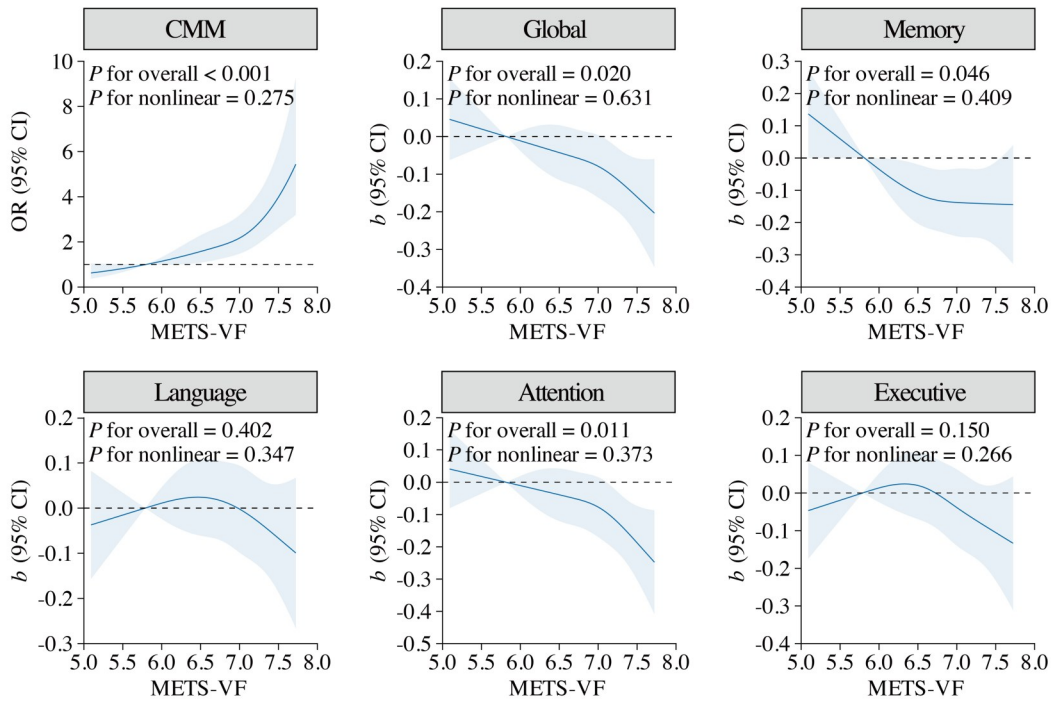
2.3 内脏脂肪代谢评分与心血管代谢共病及认知分域的剂量 - 反应关系

在 Logistic 和 Linear 回归的基础上,分别使用限制性立方样条模型探讨 METS-VF 与 CMM 及认知分域之间的剂量 - 反应关系。在调整混杂因素后,结果显示:METS-VFI 与 CMM 及认知分域均未呈现剂量反应关系(图 2),非线性效应不具有统计学意义 (P for nonlinear > 0.05)。

2.4 内脏脂肪代谢评分与心血管代谢共病及认知分域的亚组分析

通过 Logistic 和 Linear 回归模型,在模型中加

入了交互作用项,以分别探讨 METS-VF 与 CMM 及认知分域的关联性在分层变量之间是否保持稳定。结果显示,METS-VF 与认知分域的关联在性别亚组中存在交互效应(表 3, P for interaction < 0.05)。具体而言,在男性人群中,高 METS-VF 与更低的总体认知得分相关;而在女性群体中,高 METS-VF 则与更低的执行功能得分的相关。此外,尽管其他亚组未显示出明显的交互作用,但 METS-VF 与 CMM 之间的关联仍然呈正相关,且与各认知分域之间呈负相关。



Model adjusted for sex, age, education, residence, living situation, marital status, stable income, smoking, drinking, physical activity, and depression; OR: odds ratios; *b*: effect size; CI: confidence interval; Ref: reference; *P* for overall is the overall association test, and *P* for nonlinear is the nonlinear test.

图2 基于调整后的回归模型绘制限制性立方样条(RCS)曲线

Fig. 2 Restricted cubic spline (RCS) curves derived from multivariable-adjusted regression models

表3 METS-VF与CMM及认知分域的关联的亚组分析

Table 3 The subgroup analysis of the association between METS-VF and CMM, as well as cognitive domains

Variables	Group	Count <i>n</i>	Percent <i>%</i>	Q ₁ Ref	Q ₂ OR (95%CI)	Q ₃ OR (95%CI)	Q ₄ OR (95%CI)	<i>P</i> for inter-action
CMM								
Sex	Female	1 485	42.3	1(Ref)	1.56(0.85, 2.87)	1.71(0.94, 3.09)	3.64(2.14, 6.20)	0.408
	Male	2 025	57.7	1(Ref)	1.71(1.16, 2.51)	1.67(1.12, 2.49)	2.28(1.47, 3.53)	
Residence	Rural	1 053	30	1(Ref)	1.72(0.96, 3.09)	1.60(0.90, 2.86)	2.93(1.71, 5.02)	0.861
	Urban	2 457	70	1(Ref)	1.61(1.08, 2.39)	1.70(1.13, 2.54)	2.74(1.82, 4.13)	
Age	<75	2 484	70.8	1(Ref)	1.67(1.14, 2.46)	1.85(1.25, 2.73)	3.25(2.21, 4.78)	0.363
	≥75	1 026	29.2	1(Ref)	1.60(0.86, 2.97)	1.53(0.83, 2.82)	2.43(1.36, 4.37)	
Education	<0	649	18.5	1(Ref)	1.21(0.56, 2.64)	0.82(0.38, 1.77)	1.85(0.93, 3.7)	0.215
	≥0	2 861	81.5	1(Ref)	1.76(1.22, 2.52)	1.96(1.36, 2.82)	3.09(2.15, 4.46)	
Variables	Group	Count <i>n</i>	Percent <i>%</i>	Q ₁ Ref	Q ₂ <i>b</i> (95%CI)	Q ₃ <i>b</i> (95%CI)	Q ₄ <i>b</i> (95%CI)	<i>P</i> for inter-action
Global								
Sex	Female	1 055	42.1	0(Ref)	-0.18(-0.32, -0.04)	0.01(-0.13, 0.14)	-0.13(-0.26, -0.01)	0.009
	Male	1 450	57.9	0(Ref)	-0.08(-0.18, 0.01)	-0.17(-0.27, -0.07)	-0.10(-0.21, 0.02)	
Residence	Rural	849	33.9	0(Ref)	-0.12(-0.26, 0.02)	-0.12(-0.25, 0.02)	-0.09(-0.23, 0.04)	0.878
	Urban	1 656	66.1	0(Ref)	-0.11(-0.20, -0.02)	-0.08(-0.18, 0.02)	-0.12(-0.23, -0.02)	

Variables	Group	Count <i>n</i>	Percent <i>%</i>	Q ₁ Ref	Q ₂ <i>b</i> (95%CI)	Q ₃ <i>b</i> (95%CI)	Q ₄ <i>b</i> (95%CI)	<i>P</i> for inter- action
Age	<75	1 750	69.9	0(Ref)	-0.12(-0.21, -0.03)	-0.12(-0.21, -0.02)	-0.15(-0.25, -0.05)	1.000
	≥75	755	30.1	0(Ref)	-0.12(-0.29, 0.04)	-0.10(-0.27, 0.06)	-0.12(-0.28, 0.04)	
Education	<0	486	19.4	0(Ref)	-0.14(-0.33, 0.05)	-0.10(-0.28, 0.08)	-0.03(-0.21, 0.14)	0.319
	≥0	2 019	80.6	0(Ref)	-0.09(-0.18, 0.00)	-0.11(-0.21, -0.02)	-0.16(-0.26, -0.06)	
Memory								
Sex	Female	995	42	0(Ref)	-0.17(-0.35, 0.00)	-0.04(-0.21, 0.13)	-0.05(-0.21, 0.10)	0.101
	Male	1 373	58	0(Ref)	-0.04(-0.15, 0.08)	-0.17(-0.29, -0.05)	-0.08(-0.23, 0.07)	
Residence	Rural	719	30.4	0(Ref)	0.04(-0.14, 0.22)	-0.07(-0.25, 0.10)	0.04(-0.14, 0.21)	0.346
	Urban	1 649	69.6	0(Ref)	-0.12(-0.23, 0.00)	-0.12(-0.24, 0.00)	-0.1(-0.24, 0.03)	
Age	<75	1 672	70.6	0(Ref)	-0.11(-0.22, 0.00)	-0.18(-0.30, -0.07)	-0.11(-0.23, 0.01)	0.525
	≥75	696	29.4	0(Ref)	-0.01(-0.23, 0.21)	-0.02(-0.23, 0.19)	-0.01(-0.22, 0.19)	
Education	<0	392	16.6	0(Ref)	0.09(-0.18, 0.36)	-0.01(-0.26, 0.24)	0.07(-0.17, 0.32)	0.578
	≥0	1 976	83.4	0(Ref)	-0.09(-0.20, 0.02)	-0.14(-0.25, -0.03)	-0.1(-0.22, 0.02)	
Language								
Sex	Female	1 277	42.3	0(Ref)	-0.07(-0.23, 0.09)	-0.05(-0.20, 0.10)	-0.12(-0.26, 0.03)	0.495
	Male	1 745	57.7	0(Ref)	-0.06(-0.16, 0.05)	-0.05(-0.17, 0.06)	0.01(-0.13, 0.15)	
Residence	Rural	866	28.7	0(Ref)	-0.12(-0.29, 0.04)	-0.08(-0.24, 0.07)	-0.07(-0.22, 0.09)	0.951
	Urban	2 156	71.3	0(Ref)	-0.04(-0.15, 0.06)	-0.04(-0.15, 0.07)	-0.07(-0.19, 0.06)	
Age	<75	2 169	71.8	0(Ref)	-0.05(-0.15, 0.05)	-0.06(-0.17, 0.05)	-0.08(-0.20, 0.04)	0.957
	≥75	853	28.2	0(Ref)	-0.10(-0.28, 0.08)	-0.03(-0.21, 0.14)	-0.05(-0.22, 0.13)	
Education	<0	498	16.5	0(Ref)	-0.12(-0.35, 0.12)	-0.03(-0.26, 0.19)	-0.01(-0.23, 0.21)	0.415
	≥0	2 524	83.5	0(Ref)	-0.05(-0.15, 0.05)	-0.07(-0.17, 0.03)	-0.1(-0.21, 0.01)	
Attention								
Sex	Female	1 027	42.1	0(Ref)	-0.2(-0.35, -0.04)	-0.03(-0.19, 0.12)	-0.18(-0.33, -0.04)	0.160
	Male	1 413	57.9	0(Ref)	-0.06(-0.16, 0.05)	-0.1(-0.20, 0.01)	-0.12(-0.25, 0.01)	
Residence	Rural	847	34.7	0(Ref)	-0.19(-0.35, -0.04)	-0.12(-0.27, 0.03)	-0.17(-0.31, -0.02)	0.579
	Urban	1 593	65.3	0(Ref)	-0.05(-0.16, 0.06)	-0.03(-0.14, 0.08)	-0.12(-0.24, 0.00)	
Age	<75	1 695	69.5	0(Ref)	-0.09(-0.19, 0.01)	-0.08(-0.18, 0.03)	-0.16(-0.27, -0.05)	0.978
	≥75	745	30.5	0(Ref)	-0.12(-0.30, 0.05)	-0.07(-0.24, 0.11)	-0.13(-0.30, 0.04)	
Education	<0	491	20.1	0(Ref)	-0.18(-0.38, 0.03)	-0.12(-0.31, 0.07)	-0.07(-0.26, 0.11)	0.341
	≥0	1 949	79.9	0(Ref)	-0.06(-0.16, 0.03)	-0.07(-0.17, 0.04)	-0.17(-0.28, -0.06)	
Executive								
Sex	Female	843	43	0(Ref)	-0.04(-0.21, 0.12)	0.09(-0.08, 0.25)	-0.04(-0.18, 0.11)	0.027
	Male	1 117	57	0(Ref)	-0.06(-0.17, 0.05)	-0.19(-0.31, -0.07)	-0.14(-0.29, 0.00)	
Residence	Rural	425	21.7	0(Ref)	0.03(-0.20, 0.26)	-0.14(-0.37, 0.10)	-0.13(-0.35, 0.09)	0.444
	Urban	1 535	78.3	0(Ref)	-0.06(-0.16, 0.03)	-0.06(-0.16, 0.05)	-0.09(-0.21, 0.02)	
Age	<75	1 418	72.3	0(Ref)	-0.06(-0.16, 0.04)	-0.03(-0.14, 0.07)	-0.09(-0.21, 0.02)	0.111
	≥75	542	27.7	0(Ref)	-0.1(-0.32, 0.11)	-0.27(-0.48, -0.06)	-0.26(-0.48, -0.05)	
Education	<0	152	7.8	0(Ref)	0.02(-0.35, 0.39)	-0.34(-0.72, 0.04)	0.02(-0.34, 0.37)	0.156
	≥0	1 808	92.2	0(Ref)	-0.03(-0.13, 0.06)	-0.07(-0.17, 0.03)	-0.12(-0.23, -0.01)	

Model adjusted for sex, age, education, residence, living situation, marital status, stable income, smoking, drinking, physical activity, and depression; OR: odds ratios; *b*: effect size; CI: confidence interval; Ref: reference

2.5 内脏脂肪代谢评分与心血管代谢共病模式的关联

基于多分类无序 Logistic 回归,探讨了 METS-VF 指数与 CMM 在不同患病模式下的具体关联,并调整了混杂因素。结果显示,与未患病人群相比,仅患一种疾病的人群中,METS-VF 与更高的糖尿病患病风险相关[表4,OR=1.44,95%CI(1.19,1.74)],且校正后 P 值(FDR 值) <0.05 ,而与仅患中风或冠心病的人群未出现统计学上的关联性。仅患两种疾病的人群中,METS-VF 值与3种组合的患病风险增加均相关(P 值 <0.05 ,FDR 值 <0.05),其中,METS-VF 值与糖尿病合并中风者表现出最高的患病风险[表4,OR=2.66,95%CI(1.73,4.09)]。此外,METS-VF 值与三病共患的人群在 CMM 患病模式中的关联性最强,是未患病人群的 3.70 倍[95%CI(2.03,6.72), P 值 <0.001 ,FDR 值 <0.001]。

表4 METS-VF 与 CMM 患病模式的关联性
Table 4 The association between METS-VF and CMM disease patterns

Variables	OR (95%CI)	P	FDR
No disease	1(Ref)		
Stroke only	1.14(0.88, 1.47)	0.314	1.000
HD only	1.29(0.99, 1.70)	0.063	0.445
Diabetes only	1.44(1.19, 1.74)	<0.001	0.001
Stroke + HD	1.87(1.25, 2.81)	0.003	0.017
Diabetes + HD	2.62(1.66, 4.15)	<0.001	<0.001
Diabetes + Stroke	2.66(1.73, 4.09)	<0.001	<0.001
Diabetes + HD + Stroke	3.70(2.03, 6.72)	<0.001	<0.001
P for Log-likelihood ratio		<0.001	

Model adjusted for sex, age, education, residence, living situation, marital status, stable income, smoking, drinking, physical activity, and depression; OR: odds ratios; CI: confidence interval; Ref: reference.

3 讨论

3.1 主要发现

本研究通过对3 790名老年人进行横断面分析发现,高 METS-VF 指数不仅与老年人 CMM 患病风

险增加相关,也与总体认知、注意、执行功能得分下降存在关联,但 METS-VF 指数与其均未存在非线性关联。值得注意的是,这种关联呈现出性别差异:男性群体主要表现为总体认知功能评分较低,而女性群体则以执行功能受损更为突出。此外,多分类无序 Logistic 回归分析显示,METS-VF 指数较高的人群中,无论是单纯糖尿病还是糖尿病合并其他疾病,均表现出更高的患病风险。这些结果具有重要的临床和公共卫生启示:首先,糖尿病在多病共存模式中扮演着核心角色,可能是推动 CMM 发展的关键病理因素;其次,METS-VF 指数作为一个有效的综合性指标,既能识别 CMM 高风险人群,又能提示认知功能减退。这提示 METS-VF 指数可以成为基层医疗机构在筛查心血管代谢风险和评估认知功能时的双用途工具,为老年人群的风险预警和早期干预提供了简单可靠的新型评估手段。

3.2 内脏脂肪与心血管疾病及认知功能的关系

长期以来,关于 VAT 与心血管疾病及认知功能之间关系的研究已有诸多积累。研究表明,VAT 是心血管代谢疾病的独立危险因素^[39]。VAT 的增加与高血压、糖尿病及代谢综合征的发生风险显著相关^[40-41],且基于 ADDITION-PRO 的横断面研究也表明 VAT 与糖耐量及胰岛素抵抗显著相关^[42]。同时,内脏脂肪增加也与认知功能下降相关^[43-44],高内脏脂肪代谢与阿尔茨海默病患者大脑葡萄糖代谢之间存在负相关关系,尤其是在顶叶和颞叶皮层^[31]。动物实验的结果显示,来自肥胖野生型小鼠的内脏脂肪移植会导致海马 IL1 β 水平升高并损害认知^[32]。

3.3 内脏脂肪指数与心血管疾病及认知功能的关系

METS-VF 是一种 VAT 的替代指标,将基础人体测量指标(身高、体质量和腰围)与实验指标(空腹血糖、血清甘油三酯和血清高密度脂蛋白胆固醇)相结合。近几年的研究发现,METS-VF 在评估心血管风险和认知功能下降方面具有重要作用。METS-VF 相比传统的内脏脂肪测量方法(如 WC 和 BMI),在预测 2 型糖尿病和高血压的性能更有效^[21];且在基于 NHANES 的横断面研究中显示更高的 METS-VF 与美国老年人更差的认知表现(尤其 CERAD 记忆得分降低)独立相关^[24]。先前的研究多基于国外人群,而我们的研究与其一致,在中国老年人群中,高 METS-VF 指数仍与更高的 CMM 患病风险、更低的认知功能得分(总域、注意和执行)有关。

我们的研究还显示, METS-VF 指数升高与男性更低的总体认知得分、女性更低的执行功能得分相关。这种性别上的差异可能与体脂分布和代谢反应上的不同有关,相较于女性,男性的内脏脂肪量更高^[45-46],且雌二醇水平减轻了 VAT 对女性认知的负面影响^[47],因此男性群体的总体认知得分可能更容易受到内脏脂肪增加的负面影响。而中国当代老年女性自年轻以来在长期承担家庭照护负担,其承受的慢性压力可能导致下丘脑-垂体-肾上腺(HPA)轴的持续激活^[48-50],导致皮质醇等糖皮质激素的长期过量分泌,进而逐渐减弱 HPA 轴的反应,导致 HPA 轴的功能紊乱和皮质醇抵抗^[51],动物实验表明,糖皮质激素会减少 tau 蛋白的降解而使其积累,从而导致海马神经元丢失,进而影响认知功能^[52]。且长期暴露于高皮质酮水平的大鼠,发现内侧前额叶皮层的树突棘形态和密度发生持久性退化性改变,提示肾上腺皮质功能紊乱可能导致前额叶皮层的结构和功能损伤。而老年女性执行功能下降可能与其长期家庭照护压力导致的慢性应激有关,且女性的压力经历对大脑结构的损害程度大于男性^[53]。慢性压力导致持续的 HPA 轴过度激活会引起皮质醇长期过量分泌,进而导致 HPA 轴功能紊乱^[48-50]。既往研究发现,糖皮质激素抑制 Tau 蛋白降解,造成海马神经元损伤^[52];动物实验表明长期处于高皮质酮水平的大鼠会导致前额叶树突棘退化^[54]。这些改变可能通过损害海马-前额叶环路功能,最终影响执行功能等高级认知能力^[55-56]。

此外,多分类无序 Logistic 回归显示,无论是单纯糖尿病还是糖尿病合并一项或两项疾病的人群中, METS-VF 指数均表现出更强的患病风险关联,且在多疾病共存时关联性最强。这一发现与先前的结果一致, NAGALA 队列的研究发现, METS - VF 在中长期(6~10年)糖尿病风险预测中优于其他

指标^[21,57]。同样,基于中国农村人群的前瞻性研究也表明, METS - VF 预测 2 型糖尿病的 AUC 在六个肥胖指标中最大。我们的研究结果凸显了 METS-VF 指数的整合评估优势,也可能成为评估多病共存相关风险的重要工具,有助于为临床实践提供更精确的疾病管理策略。

3.4 本研究的优势及局限性

本研究的优势在于,不仅评估了 METS-VF 与 CMM 患病风险的关系,还深入探讨了其与 CMM 具体模式之间的梯度关联。此外,本研究首次评估了 METS-VF 与认知领域的关系,而这一点在中国老年人群中尚未得到充分研究。然而,研究也存在一些局限性。①由于采用横断面设计,无法确定 METS-VF 与 CMM 及认知领域之间的因果关系。②CMM 的诊断依赖于自我报告的问卷,可能会引入信息偏倚。③此外,尽管在回归模型中纳入了多个潜在的混杂因素,由于研究数据固有的局限性、未测量或未识别的协变量,仍有可能存在残余的混杂效应。④本研究主要针对中国老年人群体,其特殊性可能限制研究结论在其他种族和人群中的推广性。因此,在未来的研究中,可开展前瞻性、多中心、大样本的队列研究,以更好地阐明 METS-VF 指数与 CMM 及认知功能之间的关系。

3.5 研究结论

本研究基于中国老年人群的横断面分析发现,更高的 METS-VF 不仅与更高的 CMM 患病率相关,还与更低的认知表现(总体认知、注意和执行功能)有关。研究提示, METS-VF 作为一个综合代谢指标,可提升基层医疗实践中的健康筛查效率:既能筛查 CMM 风险,又能够评估老年患者的认知表现,为老年人群的健康管理提供了新的思路和方法。未来研究应通过前瞻性设计,进一步明确 METS-VF 指数与 CMM 及认知障碍之间的因果关系。

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