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在线全文

·青年编委论坛·

不同类型的肥胖在体力活动水平与代谢功能障碍相关脂肪肝关联中的修饰作用*

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【摘要】 目的 探讨体力活动水平与代谢功能障碍相关脂肪肝（metabolic dysfunction-associated fatty liver disease, MAFLD）的关联以及不同类型肥胖在其中的效应修饰作用。**方法** 对中国西南区域自然人群队列成都子队列2018–2019年招募的19 925名参与者进行横断面研究。采用广义倾向评分（generalized propensity score, GPS）逆概率加权法（inverse probability weighting, IPW）研究体力活动与MAFLD患病率之间的关联。以轻度体力活动组作为参考组，计算中度、剧烈体力活动的比值比（odds ratio, OR）及其95%置信区间（confidence interval, CI）。利用限制性三次立方样条函数拟合体力活动与MAFLD患病风险的暴露-反应关系。评估肥胖类型在不同性别人群中对体力活动与MAFLD关联的潜在效应修饰作用。**结果** MAFLD的患病率为17.30%。从事剧烈、中度的体力活动分别比从事轻度体力活动的人患MAFLD风险低，OR（95%CI）分别为0.76（0.67, 0.86）、0.85（0.76, 0.94）。暴露-反应关系显示体力活动与MAFLD风险呈非线性关系（$P_{非线性}$=0.005），当体力活动达到约20 METs-h/d时，对MAFLD患病风险的保护作用开始显现；然而，当体力活动增至超过70 METs-h/d后，其对MAFLD患病风险无显著作用。在女性人群中，肥胖类型对体力活动与MAFLD的关联具有效应修饰作用（P<0.05）。对于中心型肥胖女性，体力活动对MAFLD 的保护作用呈阈值效应，体力活动量约为25 METs-h/d时，患病风险最低，但超过约37.5 METs-h/d时，体力活动与MAFLD患病风险的关联无统计学意义；而对于周围型肥胖女性，高体力活动对降低MAFLD患病风险的作用有限。**结论** 适度的体力活动可显著降低MAFLD患病风险，肥胖类型可修饰二者之间的关联。推荐参与者体力活动达到约20～70 METs-h/d。建议中心型肥胖女性的体力活动量不超过37.5 METs-h/d，周围型肥胖女性则不超过30 METs-h/d。

【关键词】 肥胖症 腹部脂肪 体力活动 非酒精性脂肪性肝病 倾向性评分

Different Types of Obesity Play a Modifying Role in the Association Between Physical Activity and Metabolic Dysfunction-Associated Fatty Liver Disease

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[Abstract] Objective To explore the association between physical activity levels and metabolic dysfunction-associated fatty liver disease (MAFLD) and the modifying effects of different types of obesity. **Methods** A cross-sectional study was conducted on 19 925 participants recruited from the Chengdu sub-cohort of the Southwest China Natural Population Cohort. The participants were recruited between 2018 and 2019. The association between physical activity and MAFLD prevalence was examined using the inverse probability weighting (IPW) method based on the generalized propensity score (GPS). The odds ratios (OR) and the 95% confidence interval (CI) for moderate and vigorous physical activity were calculated using the mild physical activity group as a reference. A restricted cubic spline function was used to model the exposure-response relationship between physical activity and MAFLD risk. The potential modifying effects of obesity types on the association between physical activity and MAFLD were evaluated in male and female populations. **Results** The prevalence of MAFLD was 17.30%. Compared to those engaging in mild physical activity, individuals participating in vigorous and moderate physical activities had a lower risk of MAFLD, with OR (95% CI) being 0.76 (0.67, 0.86) and 0.85 (0.76, 0.94), respectively. The exposure-response relationship showed a nonlinear association between physical activity and MAFLD risks ($P_{\text{nonlinearity}}$ = 0.005). The protective effect of physical activity against MAFLD was observed when physical activity reached approximately 20 METs-h/d. However, when physical activity exceeded 70 METs-h/d, no significant effect on MAFLD risk was observed. Among the female population, obesity type significantly modified the association between physical activity and MAFLD (P < 0.05). In females with central obesity, the protective effect of physical activity on MAFLD showed a threshold effect, with the lowest disease risk observed at approximately 25

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METs-h/d. However, physical activity exceeding 37.5 METs-h/d showed no statistically significant association with MAFLD risk. In contrast, for females with peripheral obesity, high levels of physical activity had limited effects on reducing MAFLD risks. **Conclusion** Moderate physical activity can significantly reduce the risk of MAFLD, and the obesity types can modify this association. It is recommended that individuals engage in approximately 20-70 METs-h/d of physical activity. For females with central obesity, physical activity should not exceed 37.5 METs-h/d, while for females with peripheral obesity, it should not exceed 30 METs-h/d.

[Key words] Obesity Abdominal fat Physical activity Nonalcoholic fatty liver disease Propensity score

代谢功能障碍相关脂肪肝(metabolic dysfunction-associated fatty liver disease, MAFLD)是一种以肝脂肪变性为特征的代谢相关综合征,是全球范围内最常见的慢性肝病之一[1]。2008–2018年,中国MAFLD的患病率从18%增加到29%[2],预计到2030年,MAFLD将影响中国3.1458亿人[3]。MAFLD可导致纤维化、肝硬化、肝癌等多种肝内疾病,甚至引起心血管疾病、2型糖尿病和慢性肾病等肝外疾病,从而导致严重的疾病负担[4]。

目前MAFLD尚无特异性的药物治疗。体力活动被广泛认为是预防和管理MAFLD的重要干预手段[5]。研究表明,适当的体力活动能改善胰岛素敏感性和脂肪代谢,降低MAFLD的风险[6]。然而,人体不同的脂肪分布对体力活动的敏感性可能不同。腹型肥胖者,因其内脏脂肪堆积,与代谢功能障碍联系更紧密,可能对体力活动的代谢改善效果更为敏感[7]。相反,周围型肥胖者的反应可能较弱。

此外,肥胖,尤其是腹部肥胖,被认为是MAFLD的主要驱动因素之一[8]。传统上,肥胖通过体质量指数(body mass index, BMI)来定义,这种方法虽简便,但仅反映整体体质量,难以准确评估脂肪分布,尤其是内脏脂肪的积累[9]。最新的研究及欧洲肥胖协会(EASO)的肥胖定义表明,即使个体的BMI在正常范围内,腹部脂肪堆积仍可增加心血管疾病和代谢综合征等风险[10]。此外,腰臀比(waist to hip ratio, WHR)相比BMI更能反映内脏脂肪分布且对代谢风险的预测力更强[11]。因此,本研究采用WHR来定义肥胖类型,能更准确地评估腹部脂肪对代谢功能的影响。鉴于肥胖类型可能影响体力活动对MAFLD的保护效果且目前缺乏此类研究,本研究将基于大型队列的横断面数据,分析体力活动与MAFLD的关联,并进一步识别肥胖类型的效应修饰作用,为MAFLD的个性化预防措施及政策制定提供科学依据。

1 资料与方法

1.1 研究设计与资料收集

本研究基于中国西南自然人群队列成都子队列的基线数据,于2018–2019年通过多阶段抽样方法招募了19925名年龄30~79岁的参与者。经过培训的工作人员通过面对面的电子问卷收集了参与者的相关信息,包括社会人口学特征、生活方式和健康相关病史。此外,临床医生还对参与者进行了体格检查和放射检查,并对参与者的生物样本(即血液、尿液和唾液)进行了实验室检测。更多有关中国西南自然人群队列成都子队列基线调查的详细信息可见既往研究[12]。

目前研究包括西南自然人群队列成都子队列的参与者,排除①自我报告患有肝炎/肝硬化或超声检测到肝硬化的参与者(n=1332),②没有明确诊断为MAFLD的参与者(n=8),③缺少暴露变量、关键协变量、效应修饰变量的参与者(n=327),最终共纳入19925人。本研究经四川大学伦理委员会审查并批准(审批号:K2016038),所有调查对象参与调查前均签署了知情同意书。

1.2 变量定义

1.2.1 结局定义

根据国际专家共识声明提出的MAFLD定义,如果参与者患有肝脂肪变性并满足以下3个标准中的至少1项,则被确定为MAFLD病例:超重或肥胖、2型糖尿病或体质量正常并有代谢失调的证据[13]。肝脏脂肪变性由专家通过腹部超声波检查诊断。2型糖尿病通过自我报告的医生诊断或空腹血糖测量确定。超重或肥胖的定义是BMI≥24 kg/m^2。在体质量偏瘦/正常的参与者中,出现以下两种或两种以上情况即可诊断为代谢失调:①男性/女性腰围≥90/80 cm;②血压≥130/85 mmHg(1 mmHg=0.133 kPa)或正在接受降压治疗;③甘油三酯≥1.70 mmol/L或正在接受降脂治疗;④男性/女性高密度脂蛋白胆固醇<1.0/1.3 mmol/L;⑤糖尿病前期(空腹血糖水平>5.6 mmol/L或糖化血红蛋白>5.7%);⑥胰岛素抵抗稳态模型评估评分≥2.5;⑦血浆高敏C反应蛋白>2 mg/L。由于目前西南自然人群队列成都子队列缺乏胰岛素和高敏C反应蛋白的血浆水平,本研究在实际评估中使用了前5项条件。

1.2.2 暴露定义

体力活动量通过国际体力活动问卷(IPAQ)测量[14]。

问卷调查收集参与者在过去一年中与职业、家务、交通和闲暇时间锻炼相关的活动类型和持续时间等信息。根据文献[15], 活动量按每天代谢当量任务进行量化, 即将每天参与每项活动的小时数乘以该活动的代谢当量(metabolic equivalent, MET)分数。将上述4种相关活动的代谢当量小时数相加得出每天的总体力活动量。体力活动水平根据总体力活动量的三分位数进行分类(轻度: < 12.6 METs-h/d; 中度: 12.6 ~ 24.5 METs-h/d; 剧烈: > 24.5 METs-h/d)。

1.2.3 效应修饰变量定义

肥胖类型分为中心型(腹型)和周围型肥胖, 反映了人体脂肪分布的情况。根据亚洲人群肥胖类型的定义[16], 中心型肥胖标准为: 男性WHR≥0.9, 女性WHR≥0.8。周围型肥胖(非中心型肥胖)标准为: 男性WHR< 0.9, 女性WHR< 0.8。

1.2.4 协变量定义

根据以往有关体力活动和MAFLD的文献[17-18], 本研究模型控制了以下协变量: 年龄(连续型变量)、性别(男性或女性)、婚姻(是/否)、地区(农村/城镇)、家庭收入(< 59 999元/≥60 000元)、教育水平〔低(小学及以下)、中(初中/高中)、高(大专及以上)〕、吸烟(是/否)、饮酒(是/否)、久坐时长(连续型变量)和膳食模式(连续型变量)。通过停止高血压的饮食方法(dietary approaches to stop hypertension, DASH)评分来评估膳食模式的好坏。DASH评分总分范围7(最差) ~ 35分(最好)。摄入较高比例的全谷物、新鲜水果、新鲜蔬菜、豆制品、乳类及制品给予高评分; 而摄入较高比例的红肉及制品和钠盐给予低评分。高DASH评分意味膳食更加均衡健康, 有利于对高血压的预防和控制, 反之低分则表示不利于[19]。

1.3 统计学方法

本研究根据是否患MAFLD将研究对象分为两组, 分别描述研究对象的基线特征并作组间差异性分析。计量资料采用$\bar{x} \pm s$进行统计描述, t检验作差异性分析; 计数资料采用频数(构成比)进行统计描述, χ^2检验作差异性分析。

此外, 本研究采用广义倾向性评分均衡关键协变量后, 对体力活动与MAFLD进行逆概率加权的logistic回归模型以研究二者之间的关联。以轻度体力活动组作为参考组, 计算了中度、剧烈体力活动相对于轻度体力活动的比值比(odds ratio, OR)及其95%置信区间(confidence interval, CI)。本研究拟合了4个模型来估计关联, 模型0未调整任何协变量, 模型1调整了人口统计学特征相关的协变量(年龄、性别、地区), 模型2在模型1的基础上额外调整了社会经济地位相关的协变量(家庭收入、教育水平), 模型3在模型2的基础上进一步调整了潜在的生活方式风险因素相关的协变量(饮酒、吸烟、久坐时长、膳食模式)。本研究还利用限制性三次立方样条函数拟合体力活动与MAFLD患病风险的暴露-反应关系。

鉴于男女在代谢功能上存在显著差异, 为探究其个性化的体力活动干预方法, 本研究进一步在不同性别层中, 分别评估肥胖类型对体力活动与MAFLD关联的潜在效应修饰作用。通过在模型中加入肥胖类型与体力活动的交互项, 使用似然比检验对有/无交互项的模型进行比较, 得到P值判断不同组别间效应差异是否有统计学意义。本研究的统计分析均通过R 4.3.1软件完成并采用双侧检验, 检验水准α= 0.05。

2 结果

2.1 基线特征

本研究共纳入19 925名研究对象。参与者的平均年龄为(51.31±12.35)岁, 其中56.31%为女性, MAFLD的总患病率为17.30%。MAFLD患者较非MAFLD患者年龄大, 男性较多, 城镇人口居多, 吸烟和饮酒比例更高, DASH评分更低, 久坐时间更长, 轻度体力活动占比更大, 以上差异均有统计学意义(P< 0.000 1)。详细信息见表1。

2.2 体力活动与MAFLD的关联

体力活动水平增加与 MAFLD 患病率降低存在统计学关联, 且随着体力活动强度越大, MAFLD的患病风险越低(P< 0.001)。模型3结果显示, 从事剧烈、中度的体力活动分别比从事轻度体力活动的人患MAFLD风险降低24%和15%, 详见表2。此外, 如图1 所示, 参与者的体力活动水平与MAFLD存在显著的非线性关联($P_{非线性}$< 0.01), 并呈现出递减的剂量-反应趋势。当体力活动达到约20 METs-h/d时, 体力活动对MAFLD患病风险的保护作用开始显现。当体力活动增加至超过70 METs-h/d时, 其对MAFLD患病风险的影响不显著。

2.3 肥胖类型对体力活动与MAFLD关联的修饰效应

亚组分析的结果如图2所示, 在女性人群中, 肥胖类型对体力活动与MAFLD的关联具有效应修饰作用(P< 0.05)。具体而言, 在中心型肥胖的女性人群中, 体力活动与MAFLD风险呈现显著的U形关联($P_{非线性}$< 0.01), 风险最低的阈值点约为25 METs-h/d, 并且当体力活动量超过约37.5 METs-h/d时, 体力活动与MAFLD患病风险的关联无统计学意义。对于周围型肥胖女性, 体力活动量与MAFLD患病风险呈递减的线性关联($P_{非线性}$> 0.05)。随着体力活动的增加, MAFLD的风险逐步下降。但高体力

表 1 参与者基线特征

Table 1 Baseline characteristics of the participants

Characteristic	Non-MAFLD group (n=16 478)	MAFLD group (n=3 447)	Total (n=19 925)	P
Age/yr., $\bar{x}\pm s$	51.10±12.45	52.28±11.82	51.31±12.35	<0.000 1
Sex/case (%)				<0.000 1
Male	6 717 (40.76)	1989 (57.70)	8 706 (43.69)	
Female	9 761 (59.24)	1 458 (42.30)	11 219 (56.31)	
Region/case (%)				<0.000 1
Urban	9 063 (55.00)	2 101 (60.95)	11 164 (56.03)	
Rural	7 415 (45.00)	1 346 (39.05)	8 761 (43.97)	
Family income/case (%)				0.903
< 59 999 yuan	9 587 (58.18)	2001 (58.05)	11 588 (58.16)	
⩾60 000 yuan	6 891 (41.82)	1 446 (41.95)	8 337 (41.84)	
Educational attainment/case (%) *				0.997
Low	5 225 (31.71)	1 095 (31.77)	6 320 (31.72)	
Medium	8 183 (49.66)	1 711 (49.64)	9 894 (49.66)	
High	3 070 (18.63)	641 (18.60)	3 711 (18.62)	
Smoking/case (%)				<0.000 1
No	12 666 (76.87)	2 304 (66.84)	14 970 (75.13)	
Yes	3 812 (23.13)	1 143 (33.16)	4 955 (24.87)	
Drinking/case (%)				<0.000 1
No	13 640 (82.78)	2 591 (75.17)	16 231 (81.46)	
Yes	2 838 (17.22)	856 (24.83)	3 694 (18.54)	
DASH score ($\bar{x}\pm s$)	22.38±4.52	21.72±4.56	22.27±4.53	<0.000 1
Sedentary time/h, $\bar{x}\pm s$	7.43±5.01	7.96±5.31	7.52±5.07	<0.000 1
Physical activity/case (%)				<0.000 1
Light	5 307 (32.21)	1 337 (38.79)	6 644 (33.35)	
Moderate	5 508 (33.43)	1 135 (32.93)	6 643 (33.34)	
Vigorous	5 663 (34.37)	975 (28.29)	6 638 (33.31)	

DASH: dietary approaches to stop hypertension. * Educational attainment is categorized as low (primary school and below), medium (middle/high school), and high (junior college and above).

表 2 不同体力活动水平与MAFLD的关联

Table 2 Association between different levels of physical activity and MAFLD

Physical activity	Model 0	Model 1	Model 2	Model 3
Light	Reference	Reference	Reference	Reference
Moderate (OR [95% CI])	0.82 (0.75, 0.89)	0.86 (0.78, 0.95)	0.87 (0.79, 0.96)	0.85 (0.76, 0.94)
Vigorous (OR [95% CI])	0.68 (0.62, 0.75)	0.71 (0.64, 0.79)	0.70 (0.64, 0.78)	0.76 (0.67, 0.86)
P for trend	<0.001	<0.001	<0.001	<0.001

Model 0 was not adjusted for any covariates. Model 1 was further adjusted for age, sex, and region. Model 2 was further adjusted for household income and educational attainment. Model 3 was further adjusted for driking, smoking, sedentary hours, and dietary patterns.

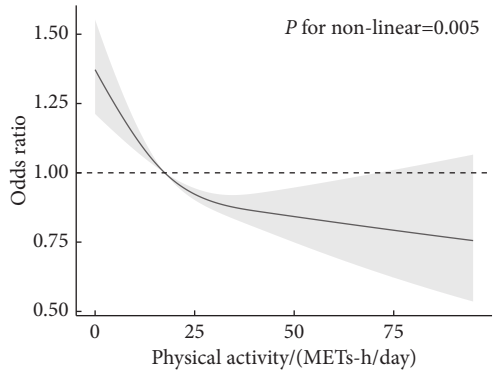

图 1 所有参与者的体力活动水平与MAFLD的非线性关联

Fig 1 Nonlinear correlation between physical activity and MAFLD in all participants

活动的保护作用较为有限,且在高强度体力活动(超过30 METs-h/d)时未观察到显著的优势。此外,在男性人群中,肥胖类型对体力活动与MAFLD的关联无效应修饰作用(P> 0.05)。

3 讨论

本研究基于中国西南自然人群队列成都子队列的横断面数据评估了体力活动水平与MAFLD患病之间的关联,识别了在不同人群中肥胖类型的效应修饰作用。本研究发现,体力活动增加会导致MAFLD风险降低。并且对女性人群,肥胖类型对体力活动水平与MAFLD的关联具有效应修饰作用。

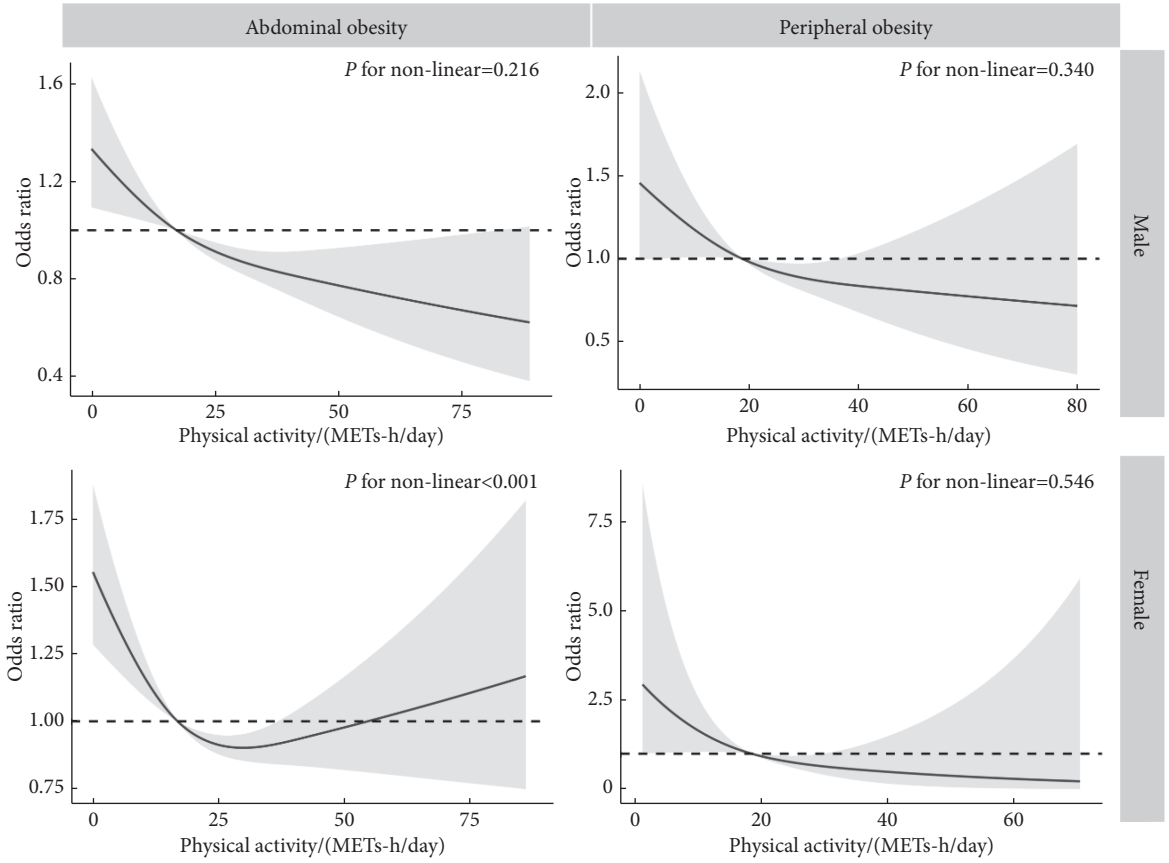

图 2 在性别分组中肥胖类型对体力活动水平与MAFLD关联的修饰效应

Fig 2 Modifying effects of obesity types on the association between physical activity and MAFLD in different sex groups

本研究结果显示体力活动水平与MAFLD呈负相关，与之前的国内外研究基本一致。KIM等[20]发现体力活动不足是MAFLD的独立危险因素，缺乏体力活动或久坐不动可能导致异位脂肪堆积；LI等[21]发现积极从事闲暇时间的体力活动可降低37%MAFLD发病风险（OR= 0.63，95%CI: 0.55 ~ 0.73）。

分层分析的结果发现，在女性中，肥胖类型是体力活动与MAFLD关联的潜在效应修饰因子。对于中心型肥胖女性，体力活动量与MAFLD患病风险呈U形关联。这与高血压、心血管等类似的代谢相关疾病的研究结果一致。LI等[22]发现，对于女性，体力活动与新发高血压存在U形关联。LEE等[23]表明一旦达到足够的中等强度的体力活动，进一步增加活动并不能提供额外的健康保护。ZHOU等[24]在中国进行的为期10年的前瞻性队列研究也发现身体活动与心血管风险之间存在U形关系，适度活动显著降低了风险，而低和极高的活动水平则增加了风险。对于周围型肥胖女性，体力活动与MAFLD风险呈递减的线性关系，且高体力活动的保护效应有限，当每日体力活动达到约30 METs-h后继续增加体力活动无显著的健康效益。这与以往研究结果一致，可能是由于女性的雌激素作用以及周围型肥胖均为代谢保护因素[25]，而过度体力活动引发了慢性炎症和氧化应激，从而抵消了其代谢改善的作用[26]。

肥胖类型影响体力活动水平与MAFLD的关联的机制可能与胰岛素抵抗、炎症和氧化应激有关。中心型肥胖（腹部肥胖）的特征是较高的内脏脂肪堆积，与肝脏脂肪含量和代谢异常之间存在关联[27]。腹部肥胖患者的内脏脂肪会释放促炎细胞因子（如肿瘤坏死因子α和白细胞介素6），从而加剧肝脏炎症和损伤[28]。对于腹部肥胖症患者，增强体力活动可以更有效地减少这些炎症标志物[29]，从而降低MAFLD风险。此外，高体力活动会增强胰岛素敏感性[30]，而腹部肥胖与胰岛素抵抗密切相关，故腹部肥胖者还可通过体育锻炼减少肝脏脂肪沉积并改善葡萄糖代谢。周围型肥胖（臀部和大腿周围的脂肪堆积）与皮下脂肪相关，皮下脂肪导致胰岛素抵抗和炎症的风险较低，具有代谢性疾病的保护作用[31]。因此，体力活动对周围型肥胖的保护效果有限，过量的体力活动反而会对健康产生不利[32]。

本研究仍存在一定局限性。首先，由于本研究为横断面研究，证据的强度相对较弱；其次，有关体力活动、疾

病史和膳食摄入等信息由参与者自我报告,这可能会导致回忆偏倚;最后,该研究属于观察性研究,不可避免存在一定的测量偏倚和混杂偏倚。

综上所述,本研究发现适度体力活动可显著降低MAFLD风险,肥胖类型可以修饰二者之间的关联。对于中心型肥胖女性,体力活动对MAFLD的保护作用呈现阈值效应,提示该人群的体力活动应提升或保持至约25 METs-h/d可获最低的患病风险。而对于周围型肥胖女性,高体力活动量对降低MAFLD风险的保护作用较为有限,体力活动量以不超过30 METs-h/d为宜。因此,应制定针对不同类型的肥胖的体力活动干预措施来有效降低MAFLD疾病负担。

* * *

作者贡献声明 常洋负责正式分析、研究方法、软件、可视化、初稿写作和审读与编辑写作,李佳蔚负责数据审编、软件和验证,吴功华负责论文构思、研究方法、监督指导、可视化和审读与编辑写作,张菊英负责经费获取、调查研究、研究项目管理和提供资源,郭冰负责经费获取、调查研究、研究项目管理、监督指导和审读与编辑写作,赵星负责经费获取、调查研究、研究项目管理、提供资源和监督指导。所有作者已经同意将文章提交给本刊,且对将要发表的版本进行最终定稿,并同意对工作的所有方面负责。

Author Contribution CHANG Yang is responsible for formal analysis, methodology, software, visualization, writing--original draft, and writing--review and editing. LI Jiawei is responsible for data curation, software, and validation. WU Gonghua is responsible for conceptualization, methodology, supervision, visualization, and writing--review and editing. ZHANG Juying is responsible for funding acquisition, investigation, project administration, and resources. GUO Bing is responsible for funding acquisition, investigation, project administration, supervision, and writing--review and editing. ZHAO Xing is responsible for funding acquisition, investigation, project administration, resources, and supervision. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

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