四川大学学报（医学版） 2025，56（4）：956－963
J Sichuan Univ（Med Sci）

在线全文

中国老年人肥胖表型与认知障碍的关联研究及遗传分层分析*

陈 馨[1]，严海瑜[1]，赵晴雯[1]，杨 楠[1]，许 彬[2△]，廖加强[1,3]，姜 侠[1,4]，李佳圆[1]

1. 四川大学华西公共卫生学院/四川大学华西第四医院 流行病与卫生统计学系（成都 610041）；2. 成都医学院公共卫生学院流行病与卫生统计学系（成都 610500）；3. 哈尔滨医科大学公共卫生学院 流行病学教研室（哈尔滨 150081）；4. 四川大学华西公共卫生学院/四川大学华西第四医院 营养与食品卫生系（成都 610041）

【摘要】 目的 分析中国老年人不同肥胖表型及其组分与认知障碍风险的关联，评估不同认知相关遗传背景下肥胖与认知障碍的关联。**方法** 基于华西老年人群健康队列的一项横断面研究。采用logistic回归估计中国老年人肥胖表型及组分与认知障碍的关联，并进行*APOE*基因及遗传风险评分分层分析。**结果** 纳入7316名受试者，其中认知障碍者1820名。体重增加与认知障碍风险降低相关〔优势比（odds ratio，OR）=0.96，95%置信区间（confidence interval，CI）：0.95～0.97〕。腰臀比正常的超重状态是认知的保护因素（OR=0.74，95%CI：0.61～0.90），但腰臀比升高与超重同时存在时认知功能障碍风险未增加。肌肉减少症与认知障碍风险升高相关，在超重（OR=2.03，95%CI：1.71～2.41）和未超重的老年人中均发现这种关联（OR=1.86，95%CI：1.58～2.20），并且这种关联在所有遗传风险分层中均显著。**结论** 增加体质量是老年人预防认知损伤的关键保护因素。肌肉减少型肥胖与认知障碍的风险升高相关，且独立于遗传易感性。

【关键词】 肥胖 瘦体重 认知障碍 多基因风险评分

Association of Obesity Phenotypes With Cognitive Impairment and Genetic Stratification Analysis in Older Chinese Adults

CHEN Xin[1], *YAN Haiyu*[1], *ZHAO Qingwen*[1], *YANG Nan*[1], *XU Bin*[2△], *LIAO Jiaqiang*[1,3], *JIANG Xia*[1,4], *LI Jiayuan*[1].

1. *Department of Epidemiology and Biostatistics, West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu 610041, China*; 2. *Department of Epidemiology and Biostatistics, School of Public Health, Chengdu Medical College, Chengdu 610500, China*; 3. *Department of Epidemiology, School of Public Health, Harbin Medical University, Harbin 150081, China*; 4. *Department of Nutrition and Food Hygiene, School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu 610041, China*

△ Corresponding author, E-mail: 1290043261@qq.com

[Abstract] Objective To evaluate the association of different obesity phenotypes and their components with the risk of cognitive impairment in older Chinese adults, and to assess the association between obesity and cognitive impairment in different cognition-related genetic backgrounds. **Methods** A cross-sectional study based on the West China Health and Aging Cohort was conducted. Logistic regression was applied to estimate the association of obesity phenotypes and components with cognitive impairment in older Chinese adults stratified by *APOE* gene and polygenic risk scores. **Results** A total of 7 316 participants were enrolled, of whom 1 820 had cognitive impairment. Weight gains were associated with a reduced risk of cognitive impairment (odds ratio [OR] = 0.96, 95% CI, 0.95-0.97). Being overweight with a normal waist-to-hip ratio was a protective factor for cognition (OR = 0.74, 95% CI, 0.61-0.90), whereas the coexistence of elevated waist-to-hip ratio and overweight did not increase the risk of cognitive impairment. Sarcopenia was associated with an elevated risk of cognitive impairment. This association was found in both overweight (OR = 2.03, 95% CI, 1.71-2.41) and non-overweight older adults (OR = 1.86, 95% CI, 1.58-2.20), and was significant across all polygenic risk score strata. **Conclusion** Increasing body mass may serve as a key protective factor against cognitive decline in older adults. Having sarcopenia and obesity is associated with an elevated risk of cognitive impairment, independent of genetic susceptibility.

[Key words] Obesity Lean body mass Cognitive impairment Polygenic risk score

* 四川省自然科学基金重点项目（No. 2024NSFSC0050）和智慧医养与老年健康管理四川省哲学社会科学重点实验室开放基金（No. ZHYYZKYB2416）资助

△ 通信作者，E-mail：1290043261@qq.com

出版日期：2025-07-20

随着人口老龄化加剧, 认知障碍的患病率逐年攀升[1]。中国至少有5 384万老年人存在认知障碍, 药物在延缓和治疗痴呆上作用有限, 给社会和家庭带来巨大的负担[2-3]。因此对高危人群进行早期认知筛查和干预是预防和控制痴呆的有效手段[2, 4]。其中, 肥胖对神经系统的作用备受关注, 大量流行病学研究提示体质量指数(body mass index, BMI)定义的肥胖与神经退行性疾病风险增加有关[5]。然而, 肥胖对认知功能的影响结论尚不统一。研究提示晚年肥胖与痴呆风险降低有关[6], 而较高的中年BMI与较高的痴呆风险相关[7]。这种不一致可能与老年期生命历程的独特性及肥胖衡量标准不同有关[8]。BMI是评估肥胖最常用的工具, 但无法区分肌肉和脂肪组织。目前, 基于体成分分析和血清学检测定义的肥胖程度和肥胖亚型已在健康研究中广泛应用。本研究应用华西老年人群健康队列(West China Health and Aging Cohort, WCHAC), 根据BMI(代表整体肥胖)和特定指标(包括生命历程肥胖、中心性肥胖、肌肉减少型肥胖和代谢性肥胖)的组合定义肥胖表型, 探究肥胖表型及其组分与认知障碍风险的关联, 并依据*APOE*基因及认知功能障碍相关的多基因风险评分(polygenic risk score, PRS)进行分层分析, 探究不同认知遗传背景下肥胖表型及组分与认知障碍的关联, 从而确定干预认知损伤的潜在目标, 为优化老年人肥胖管理提供参考。

1　资料与方法

1.1　数据来源

WCHAC 是一项前瞻性队列研究, 重点关注中国西南地区老年人群[9-10], 在成都郫都区红光社区卫生服务中心服务区域从2022年5月–2023年12月, 招募年龄60岁或以上、能够正常交流的参与者, 完成临床检查并进行神经心理学评估调查。目前入组60岁及以上老年自然人群共10 651例, 其中7933例参与了问卷调查。WCHAC已通过四川大学华西第四医院伦理委员会审查(HXSY-EC-2022034), 所有受试者在参与前均给予口头和书面知情同意。

本研究纳入标准: ①基线年龄≥60岁; ②有完整体成分测量及入户问卷数据。排除标准: ①未完成认知功能评估; ②基线时患有神经或精神系统疾病; ③体格检查等体检资料缺失者。最终排除617名, 纳入7 316名受试者, 见图1。

1.2　调查内容

1.2.1　认知障碍测量方法

认知功能以简易精神状态检查(mini-mental state examination, MMSE)评估, 该问卷共30分, 得分越高表示认知功能越好[11]。满足以下条件者被定义为认知障碍: ①未受过正规教育且MMSE< 17分, 仅受过初等教育且MMSE得分< 20分, 受过中等和高等教育且MMSE得分< 24分[12]; ②日常生活活动无明显受损。

1.2.2　*APOE*基因分型及PRS

本研究共有7 215例有*APOE*基因分型资料。根据rs7412和rs429358进行*APOE*基因型分型。*APOE* ε2/3为中低遗传风险, *APOE* ε4为高遗传风险[13]。使用国际阿尔茨海默病基因组计划的阿尔茨海默病 (Alzheimer's disease, AD) 全基因组关联研究的汇总统计数据[14], 利用PLINK的聚类和阈值法计算PRS_{AD}。采用线性回归评估不同阈值下PRS_{AD}与MMSE得分的关联以确定最佳PRS_{AD}[15]。最终

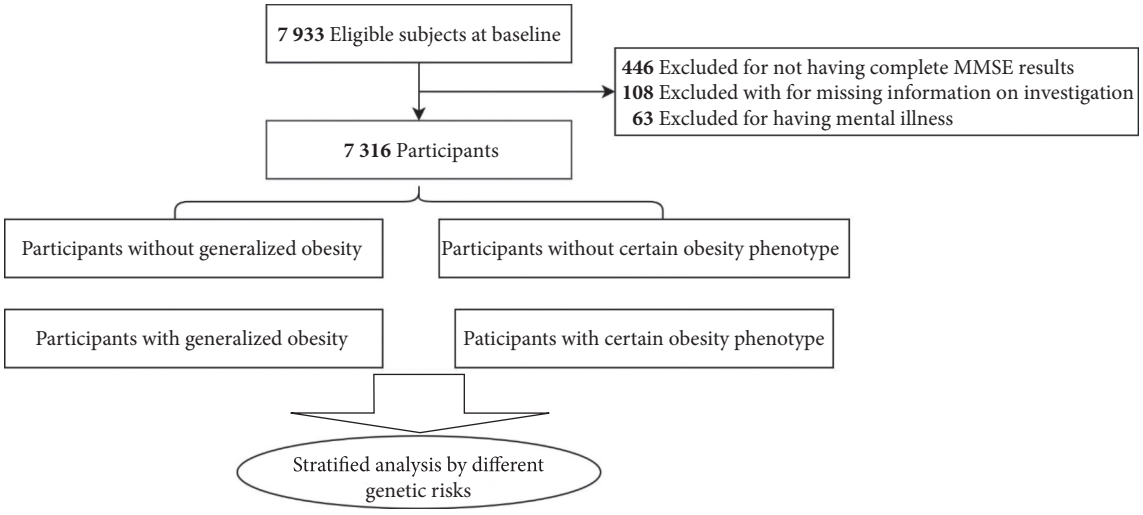

图 1　流程图及研究设计

Fig 1　Flowchart and study design

P值为0.05时的PRS_{AD}预测值最高，F统计量为14。

1.2.3 肥胖表型确立

本研究的肥胖表型由单一的肥胖组分组合定义。通过不同方式测定肥胖组分，①生物阻抗人体成分分析仪(InBody770)测得：体重、BMI、骨骼肌质量、瘦体重、身体脂肪百分比及内脏脂肪面积；②身体测量：腰臀比(waist-to-hip ratio, WHR)、小腿围、握力、收缩压(systolic blood pressure, SBP)、舒张压(diastolic blood pressure, DBP)；③问卷询问：25岁时BMI；④临床检测指标(体检当天采集老年人的空腹静脉血样5 mL)：总胆固醇(total cholesterol, TC)、低密度脂蛋白胆固醇(low density lipoprotein cholesterol, LDL-C)、高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)、甘油三酯(triglyceride, TG)、载脂蛋白A1、载脂蛋白B及葡萄糖。

肥胖表型定义如下：①全身性肥胖：由目前BMI划分，BMI< 18.5 kg/m^{2}为体重过轻，BMI 18.5 ~ 23.9 kg/m^{2}为正常，BMI 24.0 ~ 27.9 kg/m^{2}为超重，BMI≥28.0 kg/m^{2}为肥胖；②终身肥胖：结合25岁BMI与目前BMI，分为正常、仅现在超重、仅在25岁时超重、两次均超重；③中心性肥胖：BMI联合WHR(WHR男性≥0.9，女性≥0.85为WHR偏高)，分为正常、仅超重、仅WHR偏高、中心性肥胖(超重且WHR偏高)；④肌少性肥胖：BMI联合握力(男性< 28 kg，女性< 18 kg为肌少症)[16]：正常、仅超重、仅肌少症(握力不足)、肌少性肥胖(超重且握力不足)；⑤代谢性肥胖：BMI联合临床检测指标：正常、仅超重、仅代谢不健康、代谢性肥胖(代谢不健康且肥胖)。其中成人代谢健康定义为[17]：TC≤1.7 mmol/L，HDL-C男性> 1.0 mmol/L或女性> 1.3 mmol/L，SBP≤130 mmHg(1 mmHg= 0.133 kPa)，DBP≤85 mmHg，无降压治疗，空腹血糖≤5.6 mmol/L，无降糖药治疗。

1.2.4 协变量定义

日常生活活动量表(activities of daily living, ADL)[18]：≥24分为日常生活明显受损。老年抑郁量表(GDS-15)[19]：≥5分为抑郁状态。广泛性焦虑量表(GAD-7)[20]：≥5分为焦虑状态。满足以下任一条件定义为高血压：自我报告既往高血压史；正在服用降压药物；未满足前两者情况下3个不同时间测量的平均收缩压≥140 mmHg和/或平均舒张压≥90 mmHg[21]。根据以下十种食物计算健康膳食指数：①全谷物(0：男性≤90 g/d或女性≤75 g/d；1：男性> 90 g/d或女性> 75 g/d)；②新鲜蔬菜、新鲜水果、豆制品、鱼类和蛋类(0：很少或从不；1：偶尔；2：有时；3：几乎每天)；③糖、肉、腌菜(0：几乎每天；1：每周至少一次、每月至少一次或有时；2：很少或从不)；④酒精(0：男性≥25 g/d或女性≥15 g/d；1：男性< 25 g/d或女性< 15 g/d)。

1.3 统计学方法

参与者一般特征连续变量以$\bar{x} \pm s$表示，组间比较采用t检验或方差分析；分类变量以计数和百分比表示，组间比较采用卡方检验。采用多因素logistic回归分析肥胖组分、肥胖表型组合与认知障碍的关联，结果以优势比(odds ratio, OR)及95%置信区间(confidence interval, CI)表示，包括三个模型，模型1调整与认知和肥胖相关的人口学特征(年龄、性别、教育程度和职业)，除BMI外的肥胖组分及表型均控制BMI，模型2在模型1的基础上调整与认知和肥胖相关的身体及心理状态(高血压、糖尿病、焦虑和抑郁评分)，模型3在模型2的基础上调整了与认知和肥胖相关的生活习惯(吸烟和饮酒)[22-24]。根据遗传风险分层进一步分析肥胖表型的影响，以森林图展示。在敏感性分析中，①考虑不同*APOE*基因分层下的效应；②在模型3的基础上控制膳食与运动。双侧P< 0.05为差异有统计学意义。所有的分析在R 4.0.2中执行。

2 结果

2.1 一般特征

本研究纳入7 316名参与者，其中认知障碍者1 820名。认知障碍者多为年老、女性、受教育程度较低、体力劳动者(P< 0.001)，其中有8.5%人处焦虑状态(P= 0.04)，14.1%的人处于抑郁状态(P< 0.001)。认知障碍者大多不吸烟(79.3%)、不饮酒(88.1%)，此外，*APOE ε4*基因型在认知障碍者中占比18.8%更为普遍(P= 0.006)。见表1。

2.2 肥胖组分与认知障碍

多因素logistic回归分析发现多个肥胖的测量组分与认知障碍风险相关(表2)。体重更高(OR= 0.95, 95%CI: 0.95 ~ 0.97)、小腿围更大(OR= 0.94, 95%CI: 0.92 ~ 0.96)、握力更强(OR= 0.95, 95%CI: 0.94 ~ 0.96)、骨骼肌更多(OR= 0.97, 95%CI: 0.96 ~ 0.98,)、瘦体重更高(OR= 0.96, 95%CI: 0.94 ~ 0.97)的老年人发生认知障碍风险更低。

2.3 肥胖表型组合与认知障碍

如表3，全身性肥胖与认知障碍之间无显著关联。仅老年时期超重(OR= 0.86, 95%CI: 0.76 ~ 0.98)、WHR正常的超重(OR= 0.74, 95%CI: 0.61 ~ 0.90)与认知障碍风险降低相关。无论是否肥胖，肌少症始终与认知障碍风险升高相关(仅肌少症OR= 2.03, 95%CI: 1.71 ~ 2.41；肌少性肥胖OR= 1.86, 95%CI: 1.58 ~ 2.20)。超重的老年人似乎更能耐受代谢异常带来的认知受损(仅超重OR= 1.02, 95%CI: 0.76~1.36，仅代谢不健康OR= 1.25, 95%CI:

表 1　研究参与者的特征

Table 1　Characteristics of the participants

Characteristic	Normal cognition (n = 5 496)	Cognitive impairment (n = 1 820)	P
Age/yr., $\bar{x} \pm s$	68.71 ± 5.61	69.61 ± 6.55	< 0.001
Female/case (%)	2 870 (52.2)	1 152 (63.3)	< 0.001
Education/case (%)			< 0.001
Below primary school	1 609 (29.3)	688 (37.8)	
Primary school	1 284 (23.4)	334 (18.4)	
Secondary school and above	2 603 (47.4)	798 (43.8)	
Manual laborer/case (%)	3 477 (63.3)	1 385 (76.1)	< 0.001
Diabetes/case (%)	854 (15.5)	301 (16.5)	0.329
Hypertension/case (%)	2 037 (37.1)	680 (37.4)	0.841
Anxiety/case (%)	386 (7.0)	155 (8.5)	0.040
Depression/case (%)	477 (8.7)	256 (14.1)	< 0.001
Smoking/case (%)			< 0.001
Never	3 995 (72.7)	1 443 (79.3)	
Previous smoking	652 (11.9)	151 (8.3)	
Current smoking	849 (15.4)	226 (12.4)	
Drinking/case (%)	812 (14.8)	216 (11.9)	0.002
Body mass/kg, $\bar{x} \pm s$	60.78 ± 9.86	58.30 ± 9.68	< 0.001
BMI/(kg/m^2), $\bar{x} \pm s$	24.53 ± 3.25	24.46 ± 3.38	0.453
BMI at age 25/(kg/m^2), $\bar{x} \pm s$	21.76 ± 3.38	22.16 ± 3.80	< 0.001
WHR ($\bar{x} \pm s$)	0.89 ± 0.06	0.89 ± 0.07	0.303
Calf circumference ($\bar{x} \pm s$)	33.64 ± 3.04	32.99 ± 3.03	< 0.001
Grip strength/kg, $\bar{x} \pm s$	23.38 ± 8.58	19.62 ± 8.19	< 0.001
Skeletal muscle mass/kg, $\bar{x} \pm s$	22.02 ± 5.42	20.69 ± 4.09	< 0.001
Lean body mass/kg, $\bar{x} \pm s$	40.93 ± 7.29	38.70 ± 6.80	< 0.001
Percentage of body fat/%, $\bar{x} \pm s$	32.39 ± 7.44	33.21 ± 7.66	< 0.001
Visceral fat area/cm^2, $\bar{x} \pm s$	99.31 ± 35.87	100.40 ± 38.14	0.266
TG/(mmol/L), $\bar{x} \pm s$	0.35 ± 0.51	0.34 ± 0.53	0.431
TC/(mmol/L), $\bar{x} \pm s$	1.65 ± 0.21	1.65 ± 0.21	0.425
HDL-C/(mmol/L), $\bar{x} \pm s$	1.64 ± 0.43	1.66 ± 0.44	0.056
LDL-C/(mmol/L), $\bar{x} \pm s$	2.91 ± 0.82	2.89 ± 0.81	0.405
ApoA1/(g/L), $\bar{x} \pm s$	1.68 ± 0.25	1.69 ± 0.26	0.022
ApoB/(g/L), $\bar{x} \pm s$	0.93 ± 0.23	0.93 ± 0.23	0.948
Glucose/(mmol/L), $\bar{x} \pm s$	5.90 ± 1.63	6.02 ± 1.90	0.006
SBP/mmHg, $\bar{x} \pm s$	140.39 ± 18.13	141.64 ± 17.84	0.011
DBP/mmHg, $\bar{x} \pm s$	84.69 ± 10.90	84.74 ± 10.98	0.874
APOE/case (%)			0.006
ε2/3	4 537 (82.6)	1 453 (79.8)	
ε4	882 (16.0)	343 (18.8)	
Missing	77 (1.4)	24 (1.3)	
Healthy eating index ($\bar{x} \pm s$)	10.02 ± 1.88	9.71 ± 1.99	< 0.001
Physical activity/case (%)			0.245
< 2 h/d	2 606 (47.4)	899 (49.4)	
2-4 h/d	2 033 (37.0)	661 (36.3)	
>4 h/d	857 (15.6)	260 (14.3)	

BMI: body mass index; WHR: waist-to-hip ratio; ApoA1: apolipoprotein A1; ApoB: apolipoprotein B; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

表 2 肥胖组分与认知障碍的关系（*n*=7 316）

Table 2 The association between obesity index and cognitive impairment (*n* = 7 316)

Obesity index	Model 1			Model 2			Model 3		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Body mass	0.96	0.95-0.97	< 0.001	0.96	0.95-0.97	< 0.001	0.96	0.95-0.97	< 0.001
BMI	0.99	0.97-1.01	0.245	0.99	0.97-1.01	0.232	0.99	0.97-1.01	0.242
BMI at age 25	1.03	1.02-1.05	< 0.001	1.03	1.01-1.05	< 0.001	1.03	1.01-1.04	< 0.001
WHR	1.12	1.02-1.22	0.015	1.12	1.02-1.23	0.016	1.12	1.02-1.23	0.015
Calf circumference	0.94	0.92-0.96	< 0.001	0.94	0.92-0.96	< 0.001	0.94	0.92-0.96	< 0.001
Grip strength	0.95	0.94-0.96	< 0.001	0.95	0.94-0.96	< 0.001	0.95	0.94-0.96	< 0.001
Skeletal muscle mass	0.97	0.96-0.98	< 0.001	0.97	0.96-0.98	< 0.001	0.97	0.96-0.98	< 0.001
Lean mass	0.96	0.94-0.97	< 0.001	0.96	0.94-0.97	< 0.001	0.96	0.94-0.97	< 0.001
Percentage of body fat	1.01	0.99-1.02	0.263	1.01	0.99-1.02	0.265	1.01	0.99-1.02	0.247
Visceral fat area	1.00	1.00-1.00	0.897	1.00	1.00-1.00	0.974	1.00	1.00-1.00	0.950
TC	0.91	0.70-1.19	0.495	0.93	0.72-1.22	0.617	0.94	0.72-1.22	0.631
LDL-C	0.97	0.90-1.03	0.299	0.97	0.91-1.04	0.347	0.97	0.91-1.04	0.354
HDL-C	0.96	0.84-1.10	0.586	0.97	0.85-1.11	0.641	0.97	0.85-1.11	0.665
TG	0.93	0.84-1.04	0.221	0.94	0.84-1.04	0.238	0.94	0.84-1.04	0.235
ApoA1	0.92	0.74-1.16	0.494	0.94	0.75-1.18	0.582	0.94	0.75-1.18	0.601
ApoB	0.96	0.76-1.21	0.720	0.97	0.77-1.23	0.805	0.97	0.77-1.23	0.809
Glucose	1.05	1.02-1.08	0.001	1.06	1.02-1.10	0.002	1.06	1.02-1.10	0.002
Systolic blood pressure	1.00	1.00-1.01	0.010	1.00	1.00-1.01	0.005	1.00	1.00-1.01	0.005
Diastolic blood pressure	1.00	1.00-1.01	0.124	1.00	1.00-1.01	0.084	1.00	1.00-1.01	0.075

OR: odds ratio; the other abbreviations are explained in the note to Table 1. Model 1 is adjust for age, sex, education, BMI, and occupation. Model 2 is adjusted for the findings for hypertension, diabetes, anxiety, and depression on the basis of Model 1. Model 3 is adjust for smoking and drinking on the basis of Model 2.

表 3 肥胖表型与认知障碍的关系（*n*=7 316）

Table 3 The association between obesity phenotypes and cognitive impairment (*n* = 7 316)

Phenotypes	*n*	Model 1			Model 2			Model 3		
		OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Generalized obesity (BMI)										
Normal	3 104					Ref				
Underweight	168	1.31	0.93-1.85	0.120	1.33	0.94-1.88	0.107	1.33	0.94-1.88	0.107
Overweight	3 074	0.93	0.83-1.05	0.231	0.94	0.83-1.05	0.281	0.94	0.83-1.06	0.293
Obese	970	0.95	0.80-1.12	0.520	0.94	0.79-1.12	0.513	0.95	0.80-1.12	0.527
Life-course obesity (current BMI combined BMI at 25 yr.)										
Normal	2 834					Ref				
Overweight only now	3 015	0.86	0.76-0.97	0.016	0.86	0.76-0.98	0.022	0.86	0.76-0.98	0.020
Overweight only at 25 yr.	438	1.25	1.00-1.57	0.049	1.24	0.99-1.55	0.065	1.24	0.99-1.55	0.065
Overweight at both	1 029	1.24	1.05-1.45	0.009	1.24	1.06-1.46	0.009	1.24	1.05-1.46	0.010
Central obesity (BMI combined with WHR)										
Normal	1 771					Ref				
Overweight only	1 035	0.74	0.61-0.90	0.002	0.74	0.61-0.90	0.002	0.74	0.61-0.90	0.002
High WHR only	1 501	1.00	0.85-1.17	0.980	0.99	0.84-1.17	0.910	0.99	0.84-1.17	0.926
Central obesity	3 009	0.98	0.86-1.13	0.802	0.98	0.86-1.13	0.833	0.99	0.86-1.14	0.859
Sarcopenic obesity (BMI combined with grip strength)										
Normal	1 516					Ref				
Overweight only	2 063	1.00	0.84-1.19	0.986	1.00	0.84-1.20	0.959	1.01	0.84-1.20	0.954
Sarcopenia only	1 756	2.07	1.75-2.45	< 0.001	2.03	1.72-2.41	< 0.001	2.03	1.71-2.41	< 0.001
Sarcopenic obesity	1 981	1.89	1.60-2.23	< 0.001	1.86	1.58-2.20	< 0.001	1.86	1.58-2.20	< 0.001
Metabolic obesity (BMI combined with metabolic factors)										
Normal	680					Ref				
Overweight only	444	1.00	0.75-1.34	0.997	1.02	0.76-1.36	0.886	1.02	0.76-1.36	0.892
Metabolic unhealthy only	2 592	1.23	1.00-1.50	0.048	1.25	1.02-1.55	0.034	1.25	1.02-1.55	0.035
Metabolic obesity	3 600	1.09	0.90-1.33	0.370	1.13	0.91-1.39	0.262	1.13	0.92-1.39	0.256

The abbreviations are explained in the notes to Table 1 and Table 2. Model 1 is adjusted for age, sex, education, BMI, and occupation. Model 2 is adjusted the findings for hypertension, diabetes, anxiety, and depression on the basis of Model 1. Model 3 is adjusted for smoking and drinking on the basis of Model 2.

1.02 ~ 1.55, 代谢性肥胖OR= 1.13, 95%CI: 0.92 ~ 1.39)。

2.4　按遗传风险分层的肥胖表型与认知障碍

仅老年时期超重(PRS-Q1: OR= 0.75, 95%CI: 0.57 ~ 0.97)(PRS-Q2: OR= 0.71, 95%CI: 0.54 ~ 0.90)和WHR正常的超重(OR= 0.75, 95%CI: 0.57 ~ 0.97)对认知障碍的保护作用仅在PRS_{AD}低者中显著。相反, 对于PRS_{AD}高者, 两时期都超重的人(PRS-Q4: OR= 1.62, 95%CI: 1.16 ~ 2.27)表现出更高的认知障碍风险。在肌少症患者中, 无论肥胖状况如何, 认知障碍的风险通常随着PRS_{AD}的升高而增加, 仅肌少症时PRS-Q1至PRS-Q4的OR(95%CI)依次为1.48(1.05 ~ 2.10)、1.85(1.28 ~ 2.69)、2.47(1.72 ~ 3.55)、2.21(1.54 ~ 3.16); 肌少性肥胖PRS-Q1至PRS-Q4的OR(95%CI)依次为1.30(0.91 ~ 1.85)、1.55(1.07 ~ 2.23)、1.86(1.29 ~ 2.68)、2.51(1.78 ~ 3.54)(表4)。

表 4　根据肥胖表型和PRS分层的认知障碍风险（*n*=7316）

Table 4　Risk of cognitive impairment stratified by obesity phenotypes and PRS (*n* = 7316)

Phenotypes	PRS-Q1 (OR [95% CI])	PRS-Q2 (OR [95% CI])	PRS-Q3 (OR [95% CI])	PRS-Q4 (OR [95% CI])
Generalized obesity (BMI)				
Normal			Ref	
Underweight	1.39 (0.67-2.87)	0.72 (0.33-1.56)	2.05 (1.01-4.14)*	1.32 (0.62-2.80)
Overweight	0.88 (0.68-1.13)	0.76 (0.58-0.99)*	0.92 (0.72-1.19)	1.11 (0.87-1.42)
Obese	0.80 (0.56-1.15)	0.73 (0.50-1.08)	1.00 (0.69-1.43)	1.17 (0.81-1.67)
Life-course obesity (current BMI combined with BMI at 25 yr.)				
Normal			Ref	
Overweight only now	0.75 (0.57-0.97)*	0.71 (0.54-0.93)*	0.83 (0.63-1.08)	1.03 (0.80-1.34)
Overweight only at 25 yr.	1.13 (0.70-1.81)	1.38 (0.85-2.26)	1.11 (0.69-1.80)	1.43 (0.90-2.27)
Overweight at both	1.22 (0.87-1.72)	1.13 (0.78-1.63)	1.19 (0.85-1.67)	1.62 (1.16-2.27)**
Central obesity (BMI combined with WHR)				
Normal			Ref	
Overweight only	0.67 (0.45-0.99)*	0.45 (0.27-0.74)**	0.81 (0.54-1.21)	0.97 (0.65-1.45)
High WHR only	0.81 (0.58-1.14)	1.29 (0.90-1.84)	0.94 (0.67-1.33)	1.18 (0.84-1.66)
Central obesity	0.80 (0.60-1.08)	1.01 (0.74-1.38)	0.90 (0.67-1.22)	1.28 (0.95-1.74)
Sarcopenic obesity (BMI combined with grip strength)				
Normal			Ref	
Overweight only	0.87 (0.61-1.24)	0.70 (0.48-1.04)	1.24 (0.86-1.80)	1.09 (0.76-1.56)
Sarcopenia only	1.48 (1.05-2.10)*	1.85 (1.28-2.69)**	2.47 (1.72-3.55)***	2.21 (1.54-3.16)***
Sarcopenic obesity	1.30 (0.91-1.85)	1.55 (1.07-2.23)*	1.86 (1.29-2.68)**	2.51 (1.78-3.54)***
Metabolic obesity (BMI combined with metabolic health)				
Normal			Ref	
Overweight only	1.00 (0.53-1.91)	0.88 (0.44-1.78)	0.88 (0.50-1.56)	1.31 (0.74-2.35)
Metabolic healthy only	1.44 (0.93-2.24)	1.41 (0.88-2.27)	0.97 (0.63-1.49)	1.21 (0.78-1.89)
Metabolic obesity	1.16 (0.75-1.80)	1.04 (0.64-1.67)	0.88 (0.57-1.36)	1.29 (0.83-2.00)

Q1: quartile 1; Q2: quartile 2; Q3: quartile 3; Q4: quartile 4; the other abbreviations are explained in the notes to Table 1 and Table 2. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

2.5　敏感性分析

经*APOE*基因分层分析(图2), *APOE* ε2/ε3效应无明显变化。特别是对于老年肌肉减少症者, 无论是否肥胖, 高PRS_{AD}组和*AOPE* ε4基因型组发生认知障碍的风险均高于低PRS_{AD}组和*APOE* ε3/ε2基因型组。单纯肌少症的老年人与*APOE*亚组的结果一致。此外, 在模型3的基础上进一步调整膳食与运动后结果与主要分析结果基本一致, 表明本研究的结果是稳健的。

3　讨论

本研究提示相较于BMI, 体重、脂肪分布和肌肉力量或是预测认知障碍风险更好的指标。超重但没有中心性肥胖的老年人患认知障碍的风险较低, 尤其在遗传风险低的个体中。而正常体重但伴有代谢异常的老年人认知受损的风险升高, 特别在遗传风险高的个体中。在所有遗传风险水平上, 肌少症和肌肉减少性肥胖都会增加认知障碍的风险。

本研究支持老年体重对认知功能的保护作用。QU等[6]的Meta分析表明, 晚年超重和肥胖分别降低21%和25%的痴呆风险。老年肥胖人群具有异质性, 包括终身肥胖者以及晚年体重增加者[25]。本研究揭示了当前体重对老年人认知的保护作用, 提示监测成年期体重变化

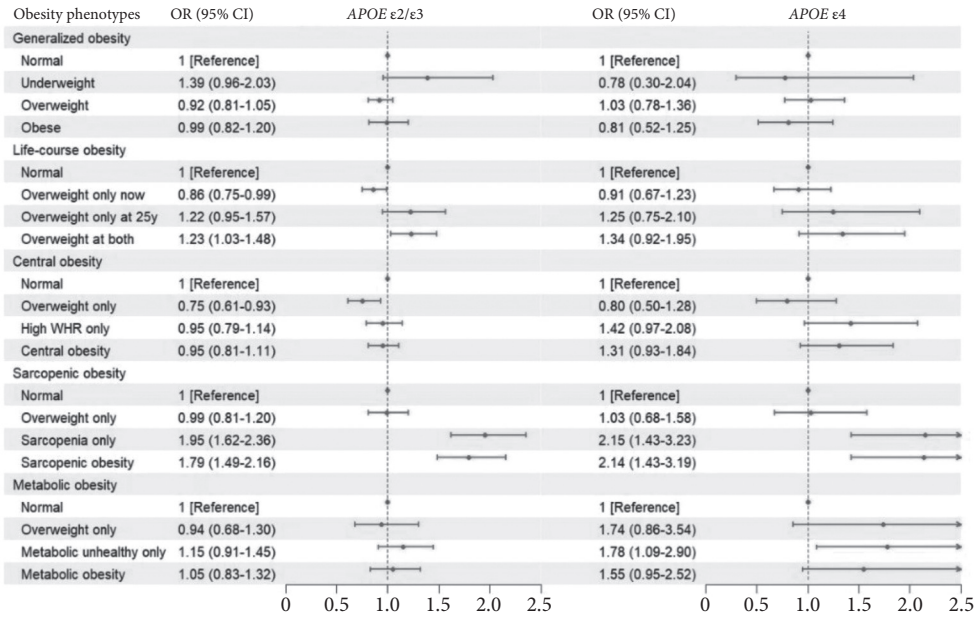

图 2 根据肥胖表型和*APOE*分层的认知障碍风险（ *n*=7 215 ）

Fig 2 Risk of cognitive impairment stratified by obesity phenotypes and *APOE* (*n* = 7 215)

有助于预防痴呆和识别高危人群。

BMI无法准确反映身体脂肪积累情况，身体维度测量和身体成分分析或是评估肥胖的简单有效手段[26]。衰老过程伴随体脂增加和肌肉量减少，导致与相同BMI的年轻人相比，老年人往往体脂率较高而瘦体重较低[27]。与白种人相比，亚洲人的BMI通常较低，但内脏脂肪含量较高，易患腹部肥胖和代谢综合征[28]。本研究发现反映中心性肥胖的腰臀升高是老年人认知障碍的危险因素，而小腿围等更大外围测量值是保护因素。

老年人的“肥胖悖论”可以从肌肉减少型肥胖的角度进一步解释，肌肉减少型肥胖与心血管疾病相关死亡、代谢紊乱、功能限制和肺部疾病的风险增加有关[29]。老年肥胖个体认知障碍风险降低取决于较高的肌肉质量和力量。此外，在一部分肥胖个体中观察到心脏代谢异常风险显著降低，因此也提出代谢健康肥胖的概念[30]。本研究发现，相较于超重的老年人，体重正常但代谢异常的老年人认知障碍风险更高，这可能是超重缓冲了一些代谢异常的有害影响。与体重正常者相比，超重但没有中心性肥胖者认知障碍的风险显著降低。这一观察结果可以解释为与超重相关的肌肉质量增加而不是中心肥胖起保护作用。在所有遗传风险水平上，肌少症和肌肉减少性肥胖均显著增加认知障碍风险。鉴于遗传因素的不可干预性，肥胖干预是降低认知障碍风险的可行方法。

本研究具有以下局限性：首先，横断面研究无法反映因果，例如某些变量（如体重、腰臀比）与认知障碍发病之间的时序关系不确定，而明确发生在认知障碍之前的暴露测量（如25岁时BMI），可能存在回忆偏倚。其次，尽管对模型中的多个协变量进行了调整，但仍不能完全消除潜在混淆的可能性（如总能量摄入）。考虑到对其他协变量进行调整的敏感性分析观察到更强的关联强度，一定程度上降低残留混淆存在的可能性。第三，本研究以中国成都常住居民为研究对象，虽涵盖不同社会经济地位的人群，但结果外推需谨慎。

本研究基于多维肥胖组分有识别益肥胖模式，为指导老年人肥胖干预措施的优化提供了科学依据。肌肉质量和力量是重要的考虑因素，未来的研究工作应该集中在检查肥胖和正常体重的老年人肌肉质量和功能下降的速度上，需重视对肌肉和脂肪成分的综合评估。此外，应努力改善高遗传风险个体的代谢健康，以及早预防认知损伤。

* * *

作者贡献声明 陈馨负责数据审编、正式分析、调查研究、初稿写作和审读与编辑写作，严海瑜和赵晴雯负责可视化和审读与编辑写作，杨楠负责正式分析，许彬负责论文构思、正式分析、调查研究、初稿写作和审读与编辑写作，廖加强、姜侠和李佳圆负责数据审编和监督指导。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 CHEN Xin is responsible for data curation, formal analysis, investigation, writing--original draft, and writing--review and editing. YAN Haiyu and ZHAO Qingwen are responsible for visualization and writing--review and editing. YANG Nan is responsible for formal analysis. XU Bin is responsible for conceptualization, formal analysis, investigation, writing--original draft, and writing--review and editing. LIAO Jiaqiang, JIANG Xia and LI Jiayuan are responsible for data curation 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.

利益冲突　本文作者李佳圆是本刊编委会编委, 姜侠是本刊编委会青年编委。该文在编辑评审过程中所有流程严格按照期刊政策进行, 且未经其本人经手处理。除此之外, 所有作者均声明不存在利益冲突。

Declaration of Conflicting Interests　LI Jiayuan is a member of the Editorial Board of the journal, JIANG Xia is a member of the Junior Editorial Board of the journal. All processes involved in the editing andreviewing of this article were carried out in strict compliance with the journal's policies and there was no inappropriate personal involvement by the authors. Other than this, all authors declare no competing interests.

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（2024 – 11 – 04收稿, 2025 – 02 – 21修回）

编辑　汤　洁