·临床研究·

营养状况和认知功能在 *APOE ε4* 与阿尔茨海默病精神行为症状相关性的中介效应

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【摘 要】 **目的** 探讨营养状况和认知功能在载脂蛋白E等位基因4(*APOE ε4*)与阿尔茨海默病(AD)精神行为症状(NPS)及其亚型相关性的中介效应。**方法** 连续性收集2021年6月至2023年1月首都医科大学附属北京天坛医院阿尔茨海默病生物标志物与生活方式研究(CIBL)队列中293例AD疾病谱[包括遗忘型轻度认知障碍(aMCI)和AD痴呆期]患者,根据是否携带 *APOE ε4* 将患者分为携带组(107例)和非携带组(186例)。对各NPS亚型患者分别进一步分析入组年龄、性别、体质量指数(BMI)、简易精神状态评价量表(MMSE)、蒙特利尔认知评估量表(MoCA)和微型营养评估量表(MNA)评分等差异。采用SPSS 26.0统计软件进行数据处理。根据数据类型,分别采用 t 检验、Mann-Whitney U 检验或 χ^2 检验进行组间比较。将假设检验中有统计学意义的因素定为后面中介效应分析的混杂因素,采用简单中介效应模型分析营养状况和认知功能在 *APOE ε4* 与NPS及其亚型中的潜在中介作用。**结果** 与对照组相比,携带组患者出现幻觉、淡漠和异常运动行为的比例更高,差异有统计学意义($P<0.05$)。对NPS亚型患者分别进行分析,与非幻觉组相比,幻觉组年龄更大,受教育年限更少,携带 *APOE ε4* 比例更高,MMSE、MoCA和MNA评分均更低;与非淡漠组相比,淡漠组男性比例更高,携带 *APOE ε4* 比例更高,MMSE、MoCA和MNA评分均更低;与非异常运动行为组相比,异常运动行为组年龄更大,高脂血症比例更低,携带 *APOE ε4* 比例更低,MMSE、MoCA及MNA评分更低,差异有统计学意义($P<0.05$)。校正混杂因素后,MNA评分介导了29.80%(95%*CI* 0.062~0.522)*APOE ε4* 与淡漠的相关性,19.95%(95%*CI* 0.011~0.419)*APOE ε4* 与异常运动行为的相关性。MMSE评分介导 *APOE ε4* 与幻觉、淡漠和异常运动行为的相关性分别是24.21%(95%*CI* 0.078~0.573),39.01%(95%*IC* 0.155~0.914)和23.37%(95%*CI* 0.068~0.576)。**结论** 对于aMCI和AD患者而言,营养状况和认知功能部分介导了 *APOE ε4* 和淡漠或异常运动行为的相关性,而认知功能还部分介导了 *APOE ε4* 和幻觉的相关性。

【关键词】 阿尔茨海默病;精神行为异常症状;载脂蛋白E等位基因4;营养状况;认知功能

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Mediation effects of nutrition and cognition on association between apolipoprotein E allele 4 and neuropsychiatric symptoms in Alzheimer's disease

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【**Abstract**】 **Objective** To explore the mediation effects of nutrition and cognition in Apolipoprotein E Allele 4 (*APOE ε4*) with neuropsychiatric symptoms (NPSs) in Alzheimer's Disease (AD). **Methods** A spectrum of 293 AD patients from amnestic mild cognitive impairment (aMCI) to AD dementia stage was consecutively collected from the Alzheimer's Disease Biomarkers and Lifestyle Study (CIBL) cohort of Beijing Tiantan Hospital Affiliated to Capital Medical University from June 2021 to January 2023. The patients were divided into the carrier group (with *APOE ε4*, $n=107$) and the non-carrier group (without *APOE ε4*, $n=186$). Patients in significant NPS sub-groups were further analyzed in age, gender, body mass index (BMI), mini-mental state examination (MMSE), Montreal cognitive assessment (MoCA), and micro-nutritional assessment (MNA). SPSS 26.0 was used for data processing. According to the data type, t test, Mann-Whitney U test or χ^2 test was used for comparison between groups, and statistically significant factors in the hypothesis test were determined as confounding factors in the subsequent mediating effect analysis. A simple mediation effect model was used to analyze the potential mediating effects of nutritional status and cognitive function on *APOE ε4* and NPS and its subtypes.

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Results Compared with non-carrier group, the carrier group had higher rates of hallucinations, apathy, and abnormal motor behaviors, the differences were statistically significant ($P<0.05$). The NPS subtype patients were analyzed separately. Compared with non-hallucination group, patients in hallucination group were older, had lower education years, carried a higher proportion of *APOE* ε4, and lower MMSE, MoCA and MNA scores. Compared with non-apathy group, patients in apathy group had a higher proportion of males, carried a higher proportion of *APOE* ε4, and had lower MMSE, MoCA and MNA scores. Compared with non-aberrant motor activity group, patients in aberrant motor activity group were older, had a lower proportion with hyperlipidaemia, carried a lower proportion of *APOE* ε4, and had lower MMSE, MoCA and MNA scores, with statistically significant differences ($P<0.05$). After adjusting for confounding factors, MNA scores mediated 29.80% (95%*CI* 0.062-0.522) of the correlation between *APOE* ε4 and apathy and 19.95% (95%*CI* 0.011-0.419) of the correlation between *APOE* ε4 and aberrant motor behaviors. The correction mediated by MMSE scores on *APOE* ε4 and hallucinations, apathy, aberrant motor behaviors were 24.21% (95%*CI* 0.078-0.573), 39.01% (95%*CI* 0.155-0.914), and 23.37% (95%*CI* 0.068-0.576). **Conclusion** For patients with aMCI and AD, nutritional status and cognitive function partially mediate the correlation between *APOE* ε4 and apathy and aberrant motor behaviors, and cognition also partially mediate the correlation between *APOE* ε4 and hallucination.

【Key words】 Alzheimer's disease; neuropsychiatric symptoms; *APOE* ε4; nutrition; cognition

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载脂蛋白 E 等位基因 4(Apolipoprotein E allele 4, *APOE* ε4)是散发性阿尔茨海默病(Alzheimer's disease, AD)最常见的遗传风险因素,与认知功能下降、加速轻度认知障碍(mild cognitive impairment, MCI)向 AD 转化密切相关[1,2]。然而,精神行为症状(neuropsychiatric symptom, NPS)作为 AD 疾病谱常见且重要的临床症状群,其与 *APOE* ε4 的关联目前仍不清楚[3]。这可能与纳入人群差异、缺乏进一步统计学手段来解释阴性结果,以及小样本研究出现假阳性结果等有关。研究显示,APOE 蛋白不仅参与调节 Aβ 沉积、Tau 磷酸化水平与聚集、神经炎症等 AD 病理过程,其作为主要的胆固醇载体,也参与脂质运输与代谢和糖代谢等营养代谢过程[4]。因此,鉴于目前关于 *APOE* ε4 与 NPS 相关性研究的局限与差距,以及营养状况和认知功能与二者之间的潜在联系,本研究分析首都医科大学附属北京天坛医院阿尔茨海默病生物标志物与生活方式研究(Chinese Imaging, Biomarkers and Lifestyle Study of Alzheimer's Disease, CIBL)队列中遗忘型 MCI(aMCI)和 AD 痴呆期患者的临床资料,探索营养状况和认知功能在 *APOE* ε4 和 NPS 及其亚型相关性的潜在中介作用,为进一步揭示 *APOE* ε4 和 NPS 及其亚型的关系提供理论依据。

1 对象与方法

1.1 研究对象

本研究为队列研究的横断面研究,研究对象为 2021 年 6 月至 2023 年 1 月 CIBL 队列中的 293 例 aMCI 和 AD 痴呆期患者。纳入标准:(1)年龄 50~90 岁;(2)AD 痴呆期符合 2011 或 2018 美国国立老化研究所与阿尔茨海默病协会的诊断标准[5,6];(3)aMCI 符合 1999 Peterson 诊断标准[7]。排除标准:(1)有其他中枢神经退行性疾病的核心特征,如路易体痴呆或额颞叶痴呆;(2)同时患有可能导致认知障碍的中枢神经系统疾病,如脑血管病、肿瘤、脑炎和癫痫;(3)有精神障碍病史,诊断符合《精神疾病诊断与统计手册-5》[8];(4)因脑外伤而出现认知障碍;(5)过去 2 年存在吸毒或有毒环境接触史;(6)有系统性疾病,如梅毒或人类免疫缺陷病毒感染;(7)研究资料不全。本研究通过首都医科大学附属北京天坛医院医学伦理委员会批准(KY2021-028-01),并在中国临床试验注册中心注册(登记号:ChiCTR2100049131),患者或其亲属均签署知情同意书。

1.2 方法

1.2.1 资料收集 (1)一般资料:收集所有入组患者社会人口学数据,包括性别、年龄、体质量指数(body mass index, BMI)、受教育年限、婚姻状况;有无高血压、糖尿病、高脂血症、卒中、冠心病病史;有无吸烟、饮酒史。(2)量表评估:采用神经精神科问卷(neuropsychiatric inventory, NPI)[9]评估患者最近 1 个月是否出现 12 种 NPS(幻觉、妄想、欣快、抑郁、焦虑、淡漠、易激惹、脱抑制、激越与攻击行为、异常运动行为、睡眠障碍、进食或食欲障碍)及其频率(每个子项 1~4 分)与严重程度(每个子项 1~3 分),各子项的总严重程度=频率×严重程度(0~12 分),总项目严重程度评分为 12 项之和,范围为 0~144 分,分数越高表示 NPS 越严重。所有患者的认知功能

评估均采用简易精神状态评价量表(mini-mental state examination,MMSE)和蒙特利尔认知评估量表(Montreal cognitive assessment,MoCA)。营养状况采用微型营养评估量表(mini-nutritional assessment,MNA)[10],包括人体测量、整体评估、饮食问卷和主观评估。MNA总分为0~30分,得分越高,营养状况越好。

1.2.2 *APOE* ε4测定 取患者清晨空腹静脉血,采用WeGene实验室(中国深圳)的Illumina WeGene V3阵列评估遗传数据。*APOE*的基因型为两个单核苷酸多态性位点(rs7412和rs429358)[11]。

1.3 统计学处理

采用SPSS 26.0统计软件进行数据分析。符合正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示,组间比较采用t检验;不符合正态分布的计量资料使用中位数(四分位数间距)[$M(Q_1,Q_3)$]表示,组间比较采用Mann-Whitney U检验。计数资料以例数(百分率)表示,组间比较采用χ^2检验。将假设检验中有统计学意义的因素定为后面中介效应分析的混杂因素。本研究采用简单中介分析模型进行评估。将*APOE* ε4(X)作为中介模型的自变量,NPS及其亚型(Y)作为因变量,营养状况或认知功能(M)作为中介变量。首先,选择多因素二元logistic回归分析*APOE* ε4(X)与NPS及其亚型(Y)的相关性;其次,采用多因素线性回归分析*APOE* ε4(X)与营养状况或认知功能(M)的相关性;最后,在控制*APOE* ε4(X)后,采用多因素二元logistic回归分析营养状况或认知功能(M)与NPS及其亚型(Y)的关联。在同时符合上述3个步骤后,进行中介分析,并计算总效应(total effect,TE)、自然直接效应(natural direct effect,NDE)以及自然间接效应(natural indirect effect,NIE)的置信区间。TE=NDE+NIE,中介百分比(percentage mediated,*PM*)=NIE/TE×100%。如果95%*CI*不为零,则认为中介效应显著。双侧$P<0.05$为差异有统计学意义。

2 结 果

2.1 *APOE* ε4携带组与非携带组患者NPS及其亚型情况比较

共纳入符合条件的aMCI和AD疾病谱患者293例,其中*APOE* ε4携带者为107例(携带组),*APOE* ε4非携带者186例(非携带组)。与非携带组相比,携带组NPI总分更高,存在幻觉、淡漠和异常运动行为的比例更高,差异有统计学意义($P<0.05$;表1)。

2.2 幻觉、淡漠、异常运动行为患者临床资料比较

根据表1的研究结果,进一步对出现幻觉、淡漠和异常运动行为的NPS亚型患者的临床特征进行比较。与非幻觉组($n=257$)相比,幻觉组($n=36$)年龄更大,受教育年限更少,携带*APOE*ε4的比例更高,MMSE、MoCA和MNA评分更低,差异有统计学意义($P<0.05$;表2)。与非淡漠组($n=180$)相比,淡漠组($n=113$)男性比例更高,携带*APOE*ε4比例更高,MMSE、MoCA和MNA评分均更低,差异有统计学意义($P<0.05$;表3)。与非异常运动行为组($n=264$)相比,异常运动行为组($n=29$)年龄更大,高脂血症比例更低,携带*APOE*ε4比例更低,MMSE、MoCA和MNA评分更低,差异有统计学意义($P<0.05$;表4)。

表1 携带组与非携带组患者NPS及其亚型情况比较

Table 1 Comparison of general and specific NPS characteristics of patients between carrier group and non-carrier group

Item	Carrier group($n=107$)	Non-carrier group($n=186$)	χ^2/U	P value
General NPS[n(%)]	83(77.57)	134(72.04)	1.080	0.299
Total NPI[points, $M(Q_1, Q_3)$]	6.00(2.00,18.00)	4.00(0.00,12.00)	−2.526	0.012
Delusion[n(%)]	24(22.43)	32(17.20)	1.200	0.277
Hallucination[n(%)]	21(19.63)	15(8.07)	8.430	0.004
Agitation/aggression[n(%)]	31(28.97)	43(23.12)	1.233	0.267
Depression[n(%)]	47(43.93)	62(33.33)	3.262	0.071
Anxiety[n(%)]	45(42.06)	70(37.63)	0.557	0.455
Euphoria[n(%)]	6(5.61)	16(8.60)	0.877	0.349
Apathy[n(%)]	51(47.66)	62(33.33)	5.887	0.015
Disinhibition[n(%)]	18(16.82)	24(12.90)	0.850	0.357
Irritability[n(%)]	34(31.78)	56(30.11)	0.089	0.766
Aberrant motor activity[n(%)]	17(15.89)	12(6.45)	6.782	0.009
Sleep and night-time behavior[n(%)]	30(28.04)	53(28.49)	0.007	0.933
Appetite or eating disturbances[n(%)]	18(16.82)	20(10.75)	2.217	0.136

NPS: neuropsychiatric symptom; NPI: neuropsychiatric inventory.

表 2 幻觉组与非幻觉组临床资料比较

Table 2 Comparison of clinical data between hallucination group and non-hallucination group

Item	Hallucination group(n=36)	Non-hallucination group(n=257)	$t/\chi^2/Z$	P value
Age[years, M (Q_1, Q_3)]	71.00(64.25,78.00)	66.00(59.25,71.00)	−3.301	0.001
Gender[female, n(%)]	23(63.89)	155(60.31)	0.170	0.681
BMI[kg/m^2, $\bar{x}\pm s$]	23.81±3.42	23.74±3.33	−0.113	0.911
Duration of education[years, M(Q_1, Q_3)]	9.00(5.00,12.00)	12.00(9.00,13.00)	−2.710	0.007
Marital status[married, n(%)]	30(83.33)	234(91.05)	2.109	0.146
APOE ε4 carrier[n(%)]	21(58.33)	86(33.46)	8.425	0.004
Hypertension[n(%)]	20(55.56)	117(45.53)	1.276	0.259
Diabetes mellitus[n(%)]	8(22.22)	50(19.46)	0.152	0.696
Stroke[n(%)]	9(25.00)	46(17.90)	1.044	0.307
Coronary heart disease[n(%)]	10(27.78)	47(18.29)	1.815	0.178
Dyslipidemia[n(%)]	16(44.44)	116(45.14)	0.010	0.922
Smoking[n(%)]	5(13.90)	55(21.40)	1.094	0.296
Alcohol drinking[n(%)]	9(25.00)	78(30.35)	0.433	0.511
MMSE[points, M(Q_1, Q_3)]	16.00(9.00,21.00)	25.00(19.00,28.00)	−5.798	<0.001
MoCA[points, M(Q_1, Q_3)]	10.00(3.00,15.75)	20.00(13.00,23.00)	−5.417	<0.001
MNA[points, M (Q_1, Q_3)]	23.00(20.50,25.50)	26.00(23.00,28.00)	−3.749	<0.001

BMI: body mass index; *APOE* ε4: apolipoprotein E allele 4; MMSE: mini-mental state examination; MoCA: Montreal cognitive assessment; MNA: mini-nutritional assessment.

表 3 淡漠组与非淡漠组临床资料比较

Table 3 Comparison of clinical data between apathy group and non-apathy group

Item	Apathy group(n=113)	Non-apathy group(n=180)	$t/\chi^2/Z$	P value
Age[years, M (Q_1, Q_3)]	67.00(60.00,76.00)	66.00(61.00,70.00)	−1.504	0.133
Gender[female, n(%)]	59(52.21)	119(66.11)	5.624	0.018
BMI[kg/m^2, $\bar{x}\pm s$]	23.36±3.49	23.99±3.22	1.562	0.120
Duration of education[years, M(Q_1, Q_3)]	12.00(9.00,13.00)	11.00(9.00,14.00)	−0.105	0.916
Marital status[married, n(%)]	101(89.38)	163(90.56)	0.107	0.743
APOE ε4 carrier[n(%)]	51(45.13)	56(31.11)	5.887	0.015
Hypertension[n(%)]	51(45.13)	86(47.78)	0.195	0.659
Diabetes mellitus[n(%)]	21(18.58)	37(20.56)	0.170	0.680
Stroke[n(%)]	22(19.47)	33(18.33)	0.059	0.809
Coronary heart disease[n(%)]	25(22.12)	32(17.78)	0.837	0.360
Dyslipidemia[n(%)]	48(42.48)	84(46.67)	0.554	0.457
Smoking[n(%)]	25(22.12)	35(19.44)	0.306	0.580
Alcohol drinking[n(%)]	34(30.09)	53(29.44)	0.014	0.907
MMSE[points, M(Q_1, Q_3)]	18.00(10.00,24.00)	26.00(23.00,28.00)	−8.574	<0.001
MoCA[points, M(Q_1, Q_3)]	13.00(5.00,18.00)	21.00(16.00,24.00)	−8.403	<0.001
MNA[points, M(Q_1, Q_3)]	24.00(21.00,26.00)	27.00(24.00,28.50)	−6.580	<0.001

BMI: body mass index; *APOE* ε4: apolipoprotein E allele 4; MMSE: mini-mental state examination; MoCA: Montreal cognitive assessment; MNA: mini-nutritional assessment.

表 4 异常运动行为组与非异常运动行为组临床资料比较

Table 4 Comparison of clinical data between aberrant motor activity group and non-aberrant motor activity group

Item	Aberrant motor activity group(n=29)	Non-aberrant motor activity group(n=264)	$t/\chi^2/Z$	P value
Age[years, M (Q_1, Q_3)]	71.00(62.00,76.50)	66.00(60.00,71.75)	−1.989	0.047
Gender[female, n(%)]	17(58.62)	161(60.99)	0.061	0.805
BMI[kg/m^2, $\bar{x}\pm s$]	23.00±3.80	23.83±3.28	1.129	0.267
Duration of education[years, M(Q_1, Q_3)]	9.00(7.00,13.00)	12.00(9.00,13.00)	−1.428	0.153
Marital status[married, n(%)]	24(82.76)	240(90.91)	1.946	0.163
APOE ε4 carrier[n(%)]	12(41.38)	174(65.91)	6.782	0.009
Hypertension[n(%)]	11(37.93)	126(47.73)	1.007	0.316
Diabetes mellitus[n(%)]	7(24.14)	51(19.32)	0.382	0.536
Stroke[n(%)]	4(13.79)	51(19.32)	0.523	0.470
Coronary heart disease[n(%)]	6(20.69)	51(19.32)	0.031	0.859
Dyslipidemia[n(%)]	8(27.59)	124(46.97)	4.035	0.045
Smoking[n(%)]	6(20.69)	54(20.46)	0.001	0.976
Alcohol drinking[n(%)]	11(37.93)	76(28.79)	1.046	0.306
MMSE[points, M(Q_1, Q_3)]	16.00(6.50,22.50)	25.00(19.00,28.00)	−4.533	<0.001
MoCA[points, M (Q_1, Q_3)]	12.00(2.00,17.00)	19.00(13.00,23.00)	−4.281	<0.001
MNA[points, M (Q_1, Q_3)]	23.00(19.75,25.50)	26.00(23.00,28.00)	−3.441	0.001

BMI: body mass index; *APOE* ε4: apolipoprotein E allele 4; MMSE: mini-mental state examination; MoCA: Montreal cognitive assessment; MNA: mini-nutritional assessment.

2.3 MNA评分和MMSE评分在*APOE* ε4与3种NPS亚型间的中介作用

MNA评分在*APOE* ε4与幻觉间不存在中介作用(图1A)。MNA评分介导了29.80%(95% *CI* 0.062~0.522)*APOE* ε4与淡漠的相关性(图1B);19.95%(95% *CI* 0.011~0.419)*APOE* ε4与异常运动行为的相关性(图1C)。MMSE评分介导*APOE* ε4与幻觉、淡漠和异常运动行为的相关性分别是24.21%(95% *CI* 0.078~0.573;图1D),39.01%(95% *CI* 0.155~0.914;图1E)和23.37%(95% *CI* 0.068~0.576;图1F)。

3 讨 论

本研究结果显示,对于aMCI和AD患者而言,营养状况和认知功能部分介导了*APOE* ε4和淡漠或异常运动行为的相关性,而认知功能部分还介导了*APOE* ε4和幻觉的相关性。本研究结果首次揭示了营养状况和认知功能在*APOE* ε4与3种NPS亚型相关性的部分中介作用,为现有文献中具有争议的研究结果提供证据。携带*APOE* ε4出现幻觉、淡漠或异常运动行为的aMCI和AD患者中,约有20%~40%可归因于营养状况和认知功能。这一结果表明,靶向营养干预和认知训练可作为预防或延缓AD疾病谱NPS及其亚型的重要措施。

Norwitz等[12]总结了*APOE* ε4可以影响小胶质细胞活化、脂质代谢、胰岛素抵抗和葡萄糖代谢通路,为靶向携带*APOE* ε4的AD患者精准营养干预提供证据。一项动物研究发现,*APOE*基因敲除小鼠在再进食后不会出现生长追赶,并有更高的营养不良风险[13]。这些研究结果与本研究一致,提示*APOE* ε4与营养状况的潜在联系。一项观察性研究报道了营养状况与认知下降的AD患者更易出现言语攻击、脱抑制和淡漠[14]。一项纵向研究表明,在2.5年的随访期间,营养不良加剧了MCI和早期AD患者NPS及其亚型的严重程度,尤其是攻击行为和脱抑制[15]。此外,MMSE评分更低的AD患者,在其病程中也更易出现NPS及其亚型[16]。近期综述也强调AD疾病谱患者营养不良、认知障碍和NPS、照料者负担三者间存在恶性循环[17]。这些研究证据强调营养状况和认知功能对NPS及其亚型的影响,与本研究结论一致。

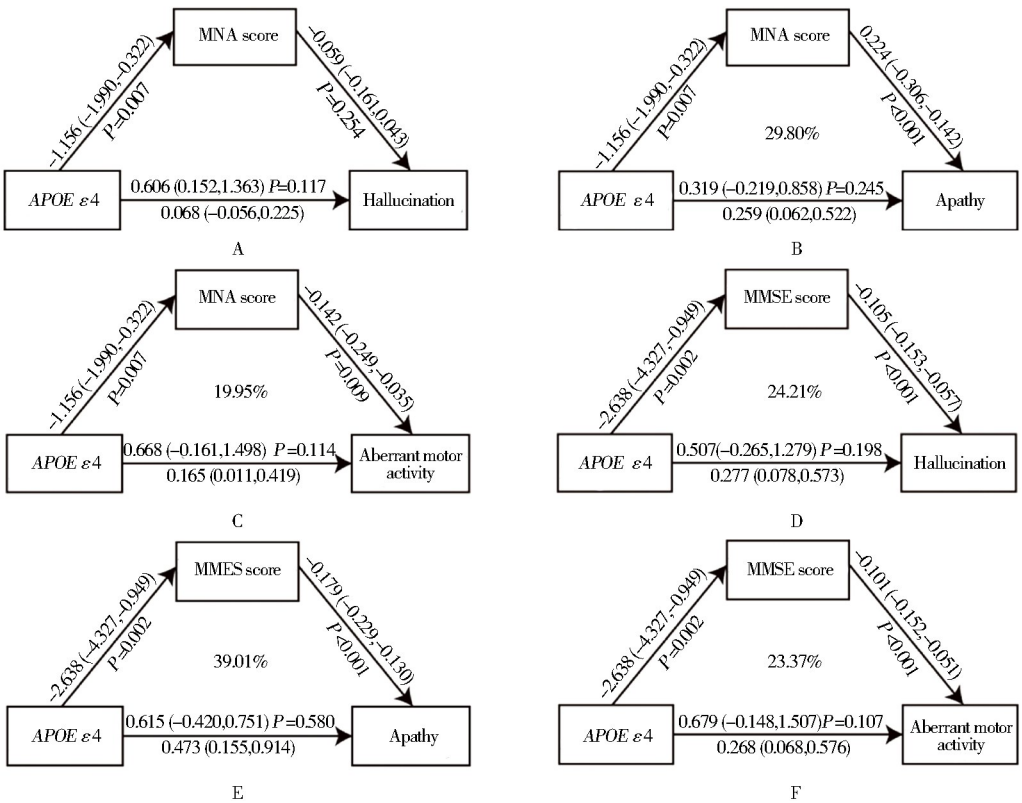


图1 MNA评分和MMSE评分在*APOE* ε4与3种NPS亚型间的中介作用

Figure 1 Mediating effect of MNA or MMSE scores on association of *APOE* ε4 with three specific NPS subtypes

A: *APOE* ε4 with hallucination; B: *APOE* ε4 with apathy; C: *APOE* ε4 with aberrant motor activity; D: *APOE* ε4 with hallucination; E: *APOE* ε4 with apathy; F: *APOE* ε4 with aberrant motor activity. MNA: mini-nutritional assessment; MMSE: mini-mental state examination; NPS: neuropsychiatric symptom; *APOE* ε4: apolipoprotein E allele 4.

本研究为观察性、单中心研究，收集信息过程中研究人员采用盲法，通过严格地纳入与排除标准减少信息偏倚，对单因素分析中有统计学意义的资料进行回归分析，以减少混杂偏倚。

综上所述，aMCI 和 AD 患者中，营养状况和认知功能对 *APOE* ε4 与 3 种 NPS 亚型（幻觉、淡漠和异常运动行为）之间的相关性具有部分中介效应。鉴于目前 NPS 及其亚型治疗策略的局限性，本研究提出新的干预思路，即靶向营养干预可有效减轻 *APOE* ε4 的不良影响并控制 NPS 及其亚型进展。未来研究可进一步探索营养状况、认知功能和 NPS 及其亚型的潜在神经环路，分析血液营养指标、脑脊液 AD 相关病理标志物，阐明 *APOE* ε4 与 NPS 及其亚型的具体关联机制。

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