论著·临床研究

空腹血糖升高与认知功能恶化的代谢关联研究

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［摘要］**目的**·分析探讨空腹血糖（fasting blood glucose，FBG）升高人群中导致认知功能恶化的影响因素和导致认知功能恶化风险变化的代谢线索。**方法**·从阿尔茨海默病神经影像学计划数据库中下载阿尔茨海默病队列数据，并筛选出具有FBG数据和随访数据的样本，获得其临床资料［包括年龄、性别、身体质量指数、教育程度、载脂蛋白E4（apolipoprotein E4，*APOE4*）基因型、人种］和代谢指标数据（包括氨基酸、脂肪酸、蛋白质等）。根据受试者的FBG水平和认知障碍阶段诊断，将其分为正常FBG并无/有认知功能恶化组、FBG升高并无/有认知功能恶化组。采用单因素分析、Cox比例风险回归模型、正交偏最小二乘判别分析、Spearman相关性分析对数据进行分析。**结果**·共纳入1 317例具有FBG数据且具有较为完整的临床资料与代谢物数据的受试者，其中FBG正常（>3.9 mmol/L且<6.1 mmol/L）共1 153例，FBG升高（≥6.1 mmol/L）共164例。FBG正常的受试者中，275例有认知功能恶化；FBG升高的受试者中，53例有认知功能恶化。基线人口统计学特征分析结果显示，正常FBG组和高FBG组在性别、人种上差异有统计学意义，无认知功能恶化组和有认知功能恶化组在年龄、性别、*APOE4*基因携带率上差异有统计学意义（均P<0.05）。Cox回归分析表明，认知功能恶化的主要促进因素依次为*APOE4*基因阳性、FBG升高和年龄增长（HR=2.22，HR=1.38，HR=1.02；均P<0.05）。不同FBG水平下无认知功能恶化和有恶化组的基线代谢指标，以及认知功能恶化前与认知功能恶化后的代谢指标的差异分析结果显示：在认知功能恶化人群中，高密度脂蛋白（high-density lipoproteins，HDL）携带的磷脂在总脂质中的比值显著升高；低密度脂蛋白（low-density lipoprotein，LDL）颗粒浓度及其携带的脂质含量在认知功能恶化后显著升高。相关性分析结果显示，在认知功能恶化人群中，缬氨酸、亮氨酸不仅与FBG水平显著相关，还与血浆磷酸化tau蛋白（phosphorylated tau，pTau）水平显著相关；HDL携带的胆固醇含量、磷脂与总脂质的比值与脑脊液pTau水平显著相关。**结论**·相较于FBG正常的人群，FBG升高人群认知功能恶化风险显著增加；且不同FBG水平下，无认知功能恶化人群和有认知功能恶化的人群以及认知恶化前与认知恶化后显著差异的代谢指标有所不同。总体而言，LDL及其携带的脂质、HDL携带的磷脂在认知功能恶化过程中呈上升趋势，且支链氨基酸中的缬氨酸与亮氨酸与pTau水平有显著相关性，提示这几个代谢指标在认知功能恶化过程中或许起重要作用。

［关键词］血糖升高；认知障碍；代谢组学；危险因素；脂蛋白
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Study of metabolic association between elevated fasting blood glucose and cognitive deterioration

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[Abstract] Objective·To analyze and explore the influencing factors that lead to cognitive deterioration in individuals with elevated fasting blood glucose (FBG) and the metabolic clues associated with changes in the risk of cognitive deterioration. **Methods**·Data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database were downloaded, and the samples with FBG and follow-up data were selected from the database. Clinical information, including age, gender, body mass index, education

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years, apolipoprotein E4 (*APOE4*) genotype and race, and corresponding metabolic indicator data, including amino acids, fatty acids, proteins and others were obtained. Based on the FBG levels and diagnosis of cognitive impairment stages in Alzheimer's disease, the subjects were categorized into four groups: normal FBG without/with cognitive deterioration, and elevated FBG without/with cognitive deterioration. The univariate analysis method, the Cox proportional hazards model, orthogonal projections to latent structures discriminant analysis (OPLSDA), and Spearman correlation analysis were employed for data analysis. **Results**·A total of 1 317 subjects were included, among which 1 153 had normal FBG level (>3.9 mmol/L and <6.1 mmol/L) and 164 had elevated FBG level (≥6.1 mmol/L). In the normal FBG group, 275 subjects showed cognitive deterioration, while in the elevated FBG group, 53 subjects showed cognitive deterioration. Univariate analysis revealed significant differences in gender and race between the normal FBG and elevated FBG group, and significant differences in age, gender, and *APOE4* genotype between the groups with and without cognitive deterioration (all $P<0.05$). Cox regression analysis indicated that primary influencing factors for cognitive deterioration were *APOE4* positivity, elevated FBG, and increasing age in order ($HR=2.22$, $HR=1.38$, $HR=1.02$; all $P<0.05$). In the analysis of baseline metabolic indicators in the groups without and with cognitive deterioration, as well as metabolic indicators before and after cognitive deterioration at different FBG levels, the results of the analysis of variance revealed that in the cognitively deteriorated population, the ratio of phospholipids carried by high-density lipoproteins (HDL) to total lipids was significantly higher; low-density lipoprotein (LDL) particle concentration and the lipids carried by LDL were significantly higher after cognitive deterioration. Correlation analysis showed that valine and leucine were significantly correlated not only with FBG level but also with phosphorylated tau (pTau) level in the plasma in the cognitively deteriorated population. Cholesterol and the ratio of phospholipids to total lipids carried by HDL were significantly correlated with pTau levels in cerebrospinal fluid (CSF). **Conclusion**·Compared to the individuals with normal FBG level, those with high FBG level have a significantly higher risk of cognitive deterioration. Additionally, different metabolic indicators show significant differences between the groups without and with cognitive deterioration, as well as metabolic indicators before and after cognitive deterioration at different FBG levels. Overall, LDL and its lipid content, and HDL-carried phospholipids show an increasing trend during cognitive deterioration, and the branched-chain amino acids valine and leucine are significantly correlated with pTau levels in CSF and plasma, suggesting that these metabolic markers may play an important role in cognitive deterioration.

[Key words] hyperglycemia; cognitive impairment; metabolomics; risk factor; lipoprotein

随着糖尿病发病率在世界范围内逐年上升，糖尿病及其并发症的诊疗及预防愈显重要。长期的高血糖状态会导致糖尿病患者罹患其他疾病的风险增加[1]。近年来，糖尿病患者的认知障碍风险也愈发受到重视。《糖尿病患者认知障碍专家共识》[2]指出，2型糖尿病患者发生痴呆的风险约为非糖尿病患者的2.8倍。糖代谢紊乱是糖尿病的重要代谢特征。因此，本研究以糖代谢的重要指标空腹血糖（fasting blood glucose，FBG）为落脚点，探讨FBG升高与认知功能恶化风险的相关性。

葡萄糖是脑细胞最主要的能量来源，其中神经元对能量需求最高，其次则是星形胶质细胞[3]。研究[4-5]发现，阿尔茨海默病患者脑内的葡萄糖利用率降低，这导致此类患者脑部细胞能量供应不足且脑内有较高的葡萄糖水平；脑内的高葡萄糖状态又导致葡萄糖转运体1和葡萄糖转运体3的表达下调，从而可引起外周向中枢的葡萄糖运送受阻。另有研究[6-7]发现，糖尿病患者体内的β淀粉样蛋白水平升高，且tau蛋白磷酸化进程加速，因此糖代谢紊乱与认知功能恶化紧密相关。一项关于糖尿病模型脂肪组织移植的研究[8]表明，将糖尿病模型鼠的脂肪组织移植到正常模型鼠上可导致正常模型鼠认知障碍发生风险显著增加。故而，认知功能恶化与其他物质代谢亦紧密相关[9]。

本研究通过分析FBG水平升高与认知功能恶化风险的相关性，探讨不同FBG水平下有/无认知功能恶化人群的基线代谢指标的变化，以及认知功能恶化人群恶化前后的代谢指标的变化，探寻FBG升高导致认知功能恶化风险升高的代谢线索。

1　对象和方法

1.1　研究队列和代谢谱数据获取

从阿尔茨海默病神经影像学计划（Alzheimer's Disease Neuroimaging Initiative，ADNI）数据库（http://adni.loni.usc.edu/）中下载痴呆队列数据，从中挑选出有FBG数据的受试者，获得相应的代谢指标数据与人口统计学数据。FBG水平及血清代谢指标数据由芬兰南丁格尔健康公司（Nightingale Health）测定[10]。其中，缺失率<1%的代谢指标数据共有249个，包括脂质代谢指标217个、蛋白质代谢指标14个、氨基酸代谢指标11个、其他代谢指标7个。人口统计学数据包括年龄、性别、身体质量指数（body mass index，BMI）、教育程度、载脂蛋白

E4（apolipoprotein E4，*APOE4*）基因型、人种等。筛除关键临床信息和代谢指标缺失的样本，并筛选出具有6~84个月随访数据的受试者后，最终获得1 317例受试者数据。

1.2 研究分组

根据受试者的FBG水平，将其分为正常FBG组（>3.9 mmol/L且6.1 mmol/L）和高FBG组（≥6.1 mmol/L）[1]。因低血糖（FBG≤3.9 mmol/L）样本数低于20例，在上述数据获取时已予以剔除。

根据ADNI数据库中受试者的痴呆诊断数据，将其分为认知正常（normal cognitive function，CN）人群、轻度认知障碍（mild cognitive impairment，MCI）人群和痴呆人群。本队列中认知正常受试者为不具有抑郁、轻度认知障碍和痴呆症状的人群。若患者自述或者医师临床观察发现其具有认知功能减退症状，同时临床痴呆评定量表（Clinical Dementia Rating Scale，CDRSB）评分≥0.5分，其中记忆部分的评分≥0.5分，且认知功能减退程度尚未达到痴呆诊断标准，判断为MCI状态[11-12]。痴呆诊断根据美国国家神经病学和卫生学研究所（National Institute of Neurological and Communicative Disorders and Stroke，NINCDS）和阿尔茨兹海默病及相关疾病协会（Alzheimer's Disease and Related Disorders Association，ADRDA）共同指定的诊断原则判断[11-12]。根据受试者在基线时和随访时的认知障碍阶段诊断是否发生变化，来判断受试者是否存在认知功能恶化。若受试者基线时诊断为认知正常、随访时转变为MCI/痴呆阶段，或基线时诊断为MCI阶段、随访时转变为痴呆阶段，则判定受试者具有认知功能恶化。

1.3 研究方法

采用Cox比例风险回归模型分析导致认知功能恶化的独立危险因素，模型校正了*APOE4*基因型、年龄、性别、BMI和教育年限。

差异代谢物的筛选根据数据分布选择*t*检验/*U*检验，同时进行正交偏最小二乘判别分析（orthogonal projections to latent structures discriminant analysis，OPLSDA）。综合以上结果，在249个代谢指标中筛选出单维检验（*t*检验/*U*检验）$P<0.05$并且多维检验变量重要程度（variable importance in the projection，VIP）>1的差异显著代谢指标，从而获得在不同FBG水平下，认知功能恶化组和无恶化组、认知功能恶化前和恶化后具有显著差异的血清代谢指标。根据差异分析结果，将显著差异的代谢指标与FBG、其他认知功能恶化指标［①认知量表评分。量表包括简易精神状态量表（the Mini-Mental State Examination，MMSE）、阿尔茨海默病评估量表11（the Alzheimer's Disease Assessment Scale 11，ADAS11）、ADAS13、CDRSB。②脑脊液（cerebrospinal fluid，CSF）/血浆中β淀粉样蛋白42（amyloid β protein 42，Aβ42）。③CSF/血浆中磷酸化tau蛋白（phosphorylated tau，pTau）］做Spearman相关性分析，获得同时与FBG、其他认知功能恶化指标有显著相关性的代谢指标。

1.4 统计学分析

采用SPSS 26.0、Excel 2021、R 4.3.1软件进行数据统计分析。使用Shapiro-Wilk检验检查数据分布，当数据不符合正态分布时使用非参数检验方法或对数据进行对数转换。人口统计学数据中，定量资料均用$\bar{x}\pm s$表示，组间比较采用*t*检验/*U*检验。定性资料以例数（百分率）表示，组间比较采用χ^2检验。$P<0.05$表示差异具有统计学意义。

2 结果

2.1 FBG水平升高伴认知功能恶化人群的基线资料

基线状态下，1 317例受试者中FBG正常共1 153例（87.5%），FBG升高共164例（12.5%）；FBG正常和FBG升高人群的性别、人种分布差异有统计学意义（均$P<0.05$）。结果见表1。全人群中认知功能恶化组（$n=328$）与无认知功能恶化组（$n=989$）相比，年龄、性别、*APOE4*基因携带率差异有统计学意义（均$P<0.05$）。FBG正常的受试者中，275例（23.9%）有认知功能恶化，878例（76.1%）无认知功能恶化。FBG升高的受试者中，53例（32.3%）有认知功能恶化，111例（67.7%）无认知功能恶化。结果见表2~4。

2.2 认知功能恶化影响因素的Cox比例风险回归分析

存在认知功能恶化人群的纵向队列Cox比例风险回归分析结果如图1所示。在基线数据队列中，导致

表1　正常FBG组和高FBG组的基线特征比较

Tab 1　Comparison of baseline characteristics between the normal FBG group and high FBG group

Characteristic	Total (*n*=1 317)	Normal FBG (*n*=1 153)	High FBG (*n*=164)	χ^2/U value	*P* value
Glucose/(mmol·L^{-1})	5.36±0.90	5.11±0.47	7.10±1.23	0.00	0.000
Age/year	73.86±7.04	73.78±7.11	74.43±6.44	89 440.50	0.263
BMI/(kg·m^{-2})	26.80±4.61	26.80±4.53	26.78±5.12	73 600.50	0.475
Gender/*n*(%)				7.64	0.006
Male	727 (55.20)	620 (53.77)	107 (65.24)		
Female	590 (44.80)	533 (46.23)	57 (34.76)		
Education/year	15.94±2.79	15.94±2.81	15.95±2.66	93 899.50	0.886
Race/*n*(%)				23.57	0.001
White	1 224 (92.94)	1 081 (93.76)	143 (87.20)		
Black	52 (3.95)	41 (3.56)	11 (6.71)		
Asian	22 (1.67)	18 (1.56)	4 (2.44)		
Other	19 (1.44)	13 (1.13)	6 (3.66)		
APOE4/*n*(%)				0.05	0.828
Negative	693 (52.62)	608 (52.73)	85 (51.83)		
Positive	624 (47.38)	545 (47.27)	79 (48.17)		

表2　无认知功能恶化组和认知功能恶化组的基线特征比较(全人群)

Tab 2　Comparison of baseline characteristics between individuals without and with cognitive deterioration (all data)

Characteristic	Without cognitive deterioration (*n*=989)	With cognitive deterioration (*n*=328)	χ^2/U value	*P* value
Glucose/(mmol·L^{-1})	5.34±0.86	5.41±1.02	158 106.00	0.493
Age/year	73.62±7.08	74.59±6.84	147 380.00	0.013
BMI/(kg·m^{-2})	26.79±4.65	26.82±4.47	126 838.50	0.700
Gender/*n*(%)			5.28	0.022
Male	528 (53.90)	199 (60.67)		
Female	461 (46.61)	129 (39.33)		
Education/year	15.93±2.83	15.98±2.65	161 357.50	0.887
Race/*n*(%)			4.66	0.588
White	913 (92.32)	311 (94.82)		
Black	41 (4.15)	11 (3.35)		
Asian	17 (1.72)	5 (1.52)		
Other	18 (1.82)	1 (0.30)		
APOE4/*n*(%)			29.54	0.000
Negative	563 (56.93)	130 (39.63)		
Positive	426 (43.07)	198 (60.37)		

认知功能恶化的显著风险因素包括FBG水平升高、携带*APOE4*基因、年龄增长。其中携带*APOE4*基因对认知功能恶化起到的促进作用最大，风险比（hazard ratio，*HR*）为2.22，*P*<0.001。其次是FBG水平升高，*HR*为1.38，*P*=0.046。年龄增长的*HR*为1.02，*P*=0.033。

2.3　认知功能恶化相关的代谢指标

结合*t*检验/*U*检验（*P*<0.05）与OPLSDA分析结果（VIP>1），筛选出在不同FBG水平时，认知功能有恶化组和无恶化组之间以及认知功能恶化前和恶化后差异具有统计学意义的血清代谢指标。

分析认知功能恶化和无认知功能恶化人群的基线数据差异代谢指标，发现全人群的差异代谢指标5个，高FBG组9个，正常FBG组4个；其中，3个人群共有的差异代谢指标2个，高FBG组独特的差异代谢指标6个，正常FBG组独特的差异代谢指标1个（图2A）。超小极低密度脂蛋白（very low-density lipoprotein，VLDL）中的磷脂与总脂质的比值、中等高密度脂蛋白（high-density lipoprotein，HDL）中的磷脂与总脂质的比值，在全人群、正常FBG组、高FBG组均显著升高。不同于正常FBG组，高FBG组的缬氨酸、组氨酸水平，中间密度脂蛋白（intermediate-density lipoprotein，IDL）中的磷脂与总脂质的比值，以及超大VLDL中磷脂含量、游离胆固

表3 无认知功能恶化组和认知功能恶化组的基线特征比较(正常FBG组)

Tab 3 Comparison of baseline characteristics between individuals without and with cognitive deterioration (normal FBG group)

Characteristic	Without cognitive deterioration (*n*=878)	With cognitive deterioration (*n*=275)	χ^2/U value	*P* value
Glucose/(mmol·L^{-1})	5.11±0.47	5.09±0.46	117 183.00	0.462
Age/year	73.57±7.15	74.45±6.96	110 131.50	0.028
BMI/(kg·m^{-2})	26.80±4.60	26.80±4.32	93 583.00	0.627
Gender/*n*(%)			3.31	0.069
Male	459 (52.28)	161 (58.55)		
Female	419 (47.72)	114 (41.45)		
Education/year	15.96±2.84	15.90 ± 2.70	118 879.00	0.698
Race/*n*(%)			5.33	0.377
White	817 (93.05)	264 (96.00)		
Black	34 (3.87)	7 (2.55)		
Asian	14 (1.59)	4 (1.45)		
Other	13 (1.48)	0 (0)		
APOE4/*n*(%)			26.25	0.000
Negative	500 (56.95)	108 (39.27)		
Positive	378 (43.05)	167 (60.73)		

表4 无认知功能恶化组和认知功能恶化组的基线特征比较(高FBG组)

Tab 4 Comparison of baseline characteristics between individuals without and with cognitive deterioration (high FBG group)

Characteristic	Without cognitive impairment (*n*=111)	With cognitive impairment (*n*=53)	χ^2/U value	*P* value
Glucose/(mmol·L^{-1})	7.11±1.13	7.09±1.42	2 569.00	0.190
Age/year	74.00±6.54	75.33±6.19	2 635.50	0.282
BMI/(kg·m^{-2})	26.72±5.07	26.90±5.27	2 383.50	0.956
Gender/*n*(%)			1.44	0.230
Male	69 (62.16)	38 (71.70)		
Female	42 (37.84)	15 (28.30)		
Education/year	15.73±2.77	16.42±2.37	2 565.50	0.177
Race/*n*(%)			1.25	0.869
White	96 (86.49)	47 (88.68)		
Black	7 (6.31)	4 (7.55)		
Asian	3 (2.70)	1 (1.89)		
Other	5 (4.50)	1 (1.89)		
APOE4/*n*(%)			3.34	0.068
Negative	63 (56.76)	22 (41.51)		
Positive	48 (43.24)	31 (58.49)		

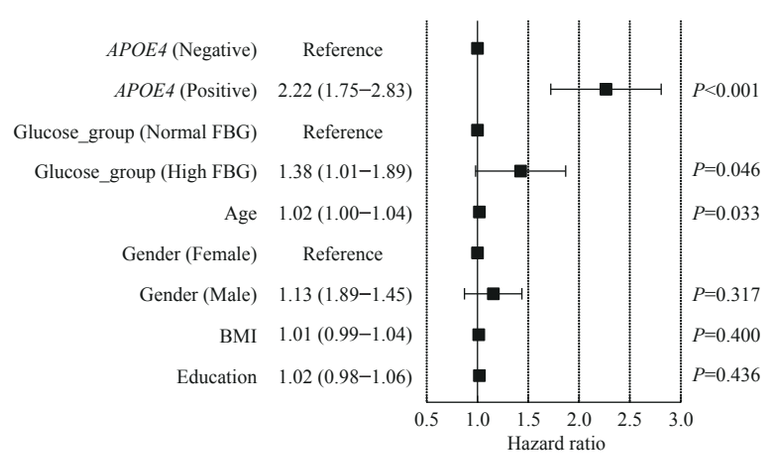
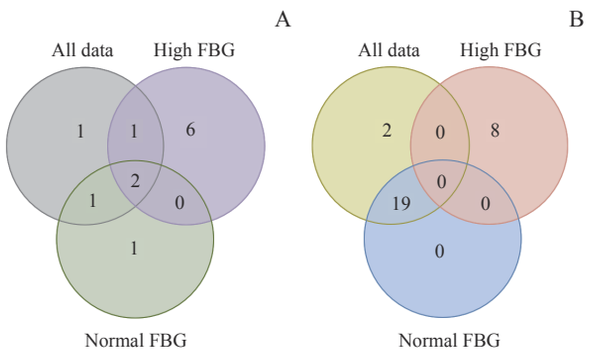


图1 Cox比例风险回归分析森林图

Fig 1 Cox proportional hazards analysis forest plot

醇与总脂质比值，均显著升高；IDL中的胆固醇酯含量、小HDL中的游离胆固醇与总脂质的比值显著降低。结果见表5。

分析认知功能恶化发生前后的差异代谢指标，发现全人群的差异代谢物指标共21个，高FBG组8个，正常FBG组19个；其中，高FBG组独特的差异代谢指标8个（图2B）。不同于正常FBG组，高FBG组的中等LDL颗粒浓度，中等LDL中的总脂质、胆固醇酯、磷脂含量，以及小LDL中的总脂质、胆固醇酯、磷脂含量均显著升高，IDL中磷脂与总脂质的比值显著下降。值得注意的是，在正常FBG组中，小LDL中的胆固醇酯含量虽然没有显著升高，但其中胆固醇酯与总脂质的比值显著升高。结果见表6。



Note: A. The Venn diagram of differential metabolites between the individuals with cognitive deterioration and without cognitive deterioration at baseline. B. The Venn diagram of differential metabolites between baseline and follow-up in the individuals with cognitive deterioration.

图2　差异代谢物维恩图

Fig 2　Venn diagram of differential metabolites

表5　无认知功能恶化人群和有认知功能恶化人群的基线数据差异代谢指标（全人群）

Tab 5　Differential metabolic indicators between the individuals without and with cognitive deterioration at baseline (all data)

Indicator	*P* value	Trend	VIP value
All data			
Sphingomyelins	0.041	↓	1.66
Phospholipids to total lipids ratio in medium HDL	0.011	↑	1.93
Cholesterol to total lipids ratio in medium HDL	0.037	↓	1.31
Phospholipids to total lipids ratio in IDL	0.034	↑	2.71
Phospholipids to total lipids ratio in very small VLDL	0.009	↑	2.39
Normal FBG group			
Cholesteryl esters to total lipids ratio in large HDL	0.026	↓	1.13
Phospholipids to total lipids ratio in medium HDL	0.020	↑	2.23
Cholesterol to total lipids ratio in medium HDL	0.045	↓	1.78
Phospholipids to total lipids ratio in very small VLDL	0.049	↑	2.51
High FBG group			
Valine	0.023	↑	1.02
Histidine	0.014	↑	1.38
Phospholipids to total lipids ratio in medium HDL	0.042	↑	1.08
Free cholesterol to total lipids ratio in small HDL	0.017	↓	1.21
Cholesteryl esters to total lipids ratio in IDL	0.044	↓	1.53
Phospholipids to total lipids ratio in IDL	0.010	↑	2.16
Phospholipids to total lipids ratio in very large VLDL	0.049	↑	1.91
Free cholesterol to total lipids ratio in very large VLDL	0.016	↑	1.92
Phospholipids to total lipids ratio in very small VLDL	0.033	↑	1.75

Note: Trend refers to the trend of changes in indicators in the individuals with cognitive deterioration compared with those without cognitive deterioration. "↑" means an uptrend, "↓" means a declining trend. Differences were considered significant at $P<0.05$ and VIP>1.

表6　认知功能恶化人群在认知恶化发生前后的显著差异代谢指标

Tab 6　Differential metabolic indicators between the individuals with cognitive deterioration before and after cognitive deterioration

Indicator	*P* value	Trend	VIP value
All data			
Leucine	0.001	↑	1.03
Phenylalanine	<0.001	↑	1.63
Albumin	0.008	↑	1.24
Total lipids in very large HDL	0.046	↓	2.06
Free cholesterol in very large HDL	0.027	↓	2.48

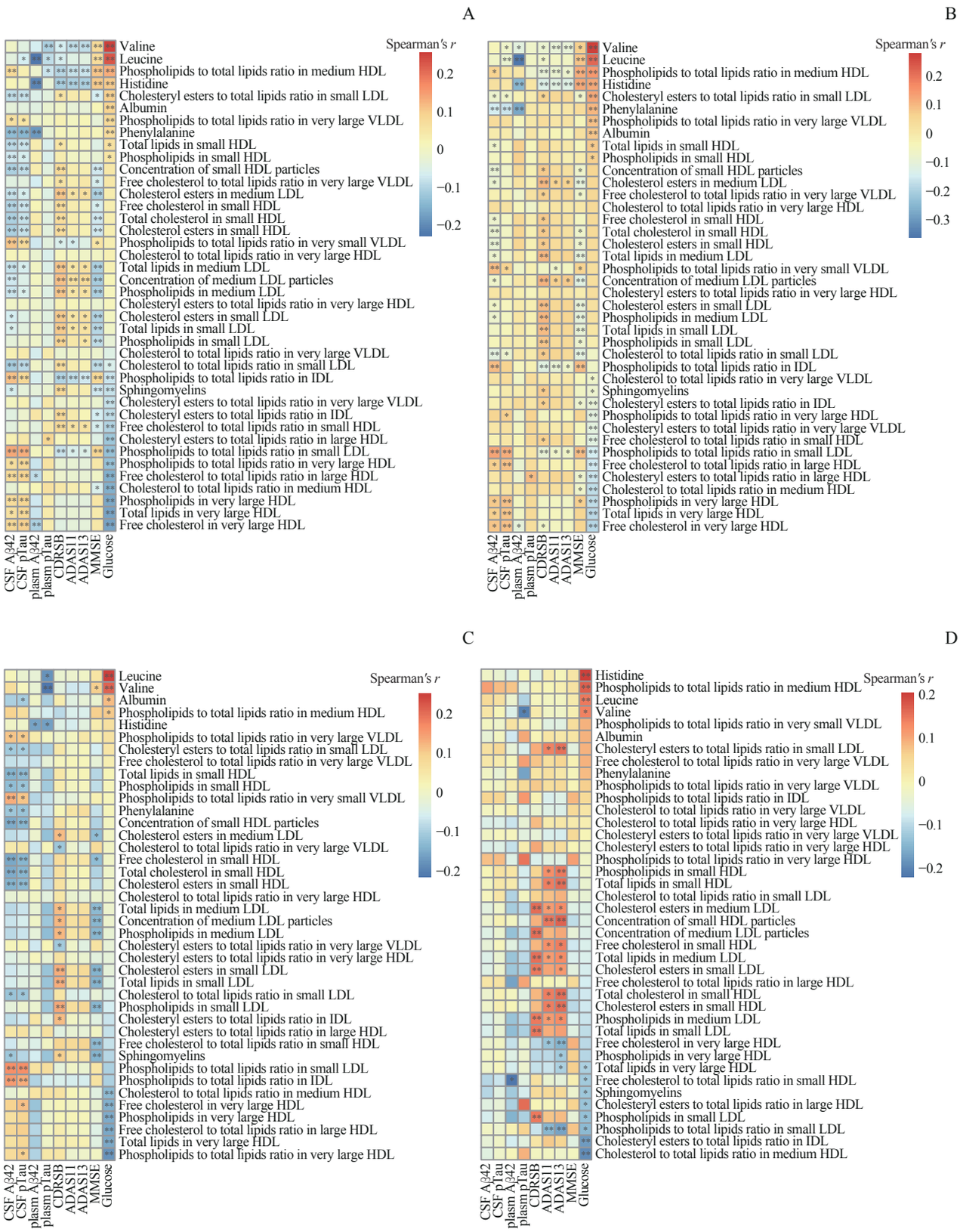
Continued Tab

Indicator	*P* value	Trend	VIP value
Phospholipids in very large HDL	0.030	↓	2.14
Cholesterol to total lipids ratio in very large HDL	0.029	↑	2.08
Cholesteryl esters to total lipids ratio in very large HDL	0.006	↑	2.40
Phospholipids to total lipids ratio in very large HDL	0.017	↓	2.37
Free cholesterol to total lipids ratio in large HDL	0.014	↓	1.73
Concentration of small HDL particles	0.002	↑	2.78
Total lipids in small HDL	0.007	↑	2.38
Total cholesterol in small HDL	0.004	↑	2.83
Free cholesterol in small HDL	0.027	↑	1.91
Cholesterol esters in small HDL	0.002	↑	3.04
Phospholipids in small HDL	0.022	↑	2.05
Cholesterol to total lipids ratio in small LDL	0.002	↑	2.28
Cholesteryl esters to total lipids ratio in small LDL	0.004	↑	1.16
Phospholipids to total lipids ratio in small LDL	0.001	↓	1.85
Cholesterol to total lipids ratio in very large VLDL	0.045	↑	1.22
Cholesteryl esters to total lipids ratio in very large VLDL	0.038	↑	1.55
Normal FBG group			
Phenylalanine	<0.001	↑	1.64
Leucine	0.005	↑	1.01
Albumin	0.030	↑	1.35
Cholesterol to total lipids ratio in very large HDL	0.043	↑	2.22
Cholesteryl esters to total lipids ratio in very large HDL	0.014	↑	2.57
Phospholipids to total lipids ratio in very large HDL	0.044	↓	2.14
Free cholesterol in very large HDL	0.048	↓	2.32
Free cholesterol to total lipids ratio in large HDL	0.022	↓	1.50
Concentration of small HDL particles	0.005	↑	2.95
Total lipids in small HDL	0.011	↑	2.60
Free cholesterol in small HDL	0.030	↑	2.19
Total cholesterol in small HDL	0.008	↑	2.97
Cholesterol esters in small HDL	0.006	↑	3.14
Phospholipids in small HDL	0.029	↑	2.29
Cholesterol to total lipids ratio in small LDL	0.003	↑	2.70
Cholesteryl esters to total lipids ratio in small LDL	0.003	↑	1.71
Phospholipids to total lipids ratio in small LDL	0.002	↓	2.26
Cholesterol to total lipids ratio in very large VLDL	0.042	↑	1.40
Cholesteryl esters to total lipids ratio in very large VLDL	0.043	↑	1.64
High FBG group			
Concentration of medium LDL particles	0.031	↑	1.93
Total lipids in medium LDL	0.030	↑	2.15
Cholesterol esters in medium LDL	0.033	↑	2.15
Phospholipids in medium LDL	0.023	↑	2.18
Phospholipids to total lipids ratio in IDL	0.037	↓	1.94
Total lipids in small LDL	0.036	↑	1.96
Cholesterol esters in small LDL	0.049	↑	1.95
Phospholipids in small LDL	0.043	↑	1.82

Note: Trend refers to the trend of changes in indicators in the individuals before and after the onset of cognitive deterioration. "↑" means an uptrend, "↓" means a declining trend. Differences were considered significant at $P<0.05$ and VIP> 1.

2.4 显著差异代谢物与其他认知功能恶化指标的相关性分析

将“2.3”部分的显著差异代谢物取并集，得到40种与认知功能恶化可能有关的代谢物。将差异代谢物与认知障碍病理标志物、认知量表评分、FBG进行Spearman相关性分析，绘制热图（图3）。如图3A所示，以缬氨酸、亮氨酸、中等HDL中的磷脂与总脂质比值、组氨酸与FBG水平的正相关性最强，



Note: Spearman analysis results illustrating the correlation between disease biomarker levels and metabolite levels across various datasets: the entire baseline dataset (A), the baseline data of the individuals without cognitive deterioration (B), the baseline data of the individuals with cognitive deterioration (C), and the data at the onset of initial cognitive deterioration (D). * means $P<0.05$, ** means $P<0.01$.

图3　代谢物与认知功能恶化指标的Spearman相关分析的热图

Fig 3　Spearman′s correlation analysis heatmap between metabolites and indicators of cognitive impairment

以超大HDL中的游离胆固醇、超大HDL中的总脂质、超大HDL中的磷脂、中等HDL中的胆固醇与总脂质的比值与FBG的负相关性最强。在认知功能恶化人群中，认知恶化发生前以及发生后亮氨酸、缬氨酸与FBG、MMSE评分以及血浆pTau水平的相关性结果显示，缬氨酸、亮氨酸与FBG升高、认知恶化均呈显著正相关（图3C、D）。在认知功能恶化人群中，超大HDL中的磷脂占总脂质的比值以及超大HDL中的游离胆固醇与FBG呈负相关；在认知恶化前其与CSF pTau水平呈显著正相关，认知恶化后其与ADAS11、ADAS13评分呈显著负相关，说明2个指标的降低与FBG升高、认知恶化显著相关（图3C、D）。

3 讨论

研究[13-14]表明，FBG升高与认知障碍密切相关。本研究验证了FBG升高与认知功能恶化的相关性，并通过对高FBG认知功能恶化人群和正常FBG认知功能恶化人群代谢指标的差异分析及相关性分析，获得了与FBG升高和认知功能恶化均显著相关的代谢指标，为明确高血糖与认知障碍的关联机制提供了代谢线索。

在我们的分析结果中，大多数具有统计学意义的代谢物为脂质代谢物。除了纳入的指标以脂质代谢物为主体的原因外，糖代谢与脂质代谢密切的关系也是原因之一[15]。脂质在大脑中有重要的功能，过多的脂质积累可能导致脑细胞和神经元的损伤，促进炎症和氧化应激。外周脂质代谢紊乱可导致体内炎症水平的升高，部分炎症因子透过血脑屏障会加速认知功能的衰退[16]。HDL、IDL、LDL和VLDL都在脂质代谢和胆固醇转运中起着重要作用。有研究[17]认为非HDL脂蛋白水平升高以及HDL水平下降可能是认知障碍发生发展的原因。然而，关于血浆脂质变化是否会影响认知功能的研究结果并不一致[18]。临床降脂药物在认知障碍患者中应用是否产生疗效也不确定[19]。本研究中分析的多为脂质代谢指标，包括但不限于脂蛋白的浓度和脂蛋白携带的各类脂质的含量。在高FBG人群认知功能恶化发生前后的代谢指标的差异分析中，发现血浆中的中等大小LDL颗粒水平及其携带的胆固醇、磷脂、总脂质含量显著升高。LDL的作用是将肝脏胆固醇运输到细胞，尽管多数情况下LDL升高被认为对健康有害，其血浆水平下降有利于降低疾病风险，但脂质也是细胞膜合成的重要原料，对维持细胞功能有重要作用。正如一些研究[20-21]所示，血液循环中的胆固醇过低亦可能导致认知损害。

本研究发现，缬氨酸与亮氨酸与FBG的相关性十分显著，其水平在认知功能恶化后显著升高且在认知恶化前后与血浆pTau呈显著负相关。现有研究[22]认为，支链氨基酸与糖尿病显著相关，但支链氨基酸与认知功能的关系却存在争议。有动物研究[23-24]发现，补充支链氨基酸可改善动物模型的认知功能；也有研究[22-25]认为，支链氨基酸会增加认知障碍风险。上述相互矛盾的结果值得进一步探究。

尽管多数研究认为糖尿病是认知障碍发病的显著风险因素，但FBG水平升高与认知功能减退是否存在显著关联尚无定论[26]。本研究将FBG≥6.1 mmol/L作为血糖升高的标准，发现相比于正常FBG人群，FBG升高人群的认知功能恶化风险显著增加，但未发现FBG水平与认知量表评分具有显著相关性。虽然FBG与认知量表评分的关系在本研究中并不显著，但有研究者[27]发现另一种反映机体血糖水平的指标——糖化血红蛋白（hemoglobin A1c，HbA1c）；在其与认知量表评分的相关性分析中发现其与认知能力的下降显著相关。此外，近年来愈受关注的血糖时间序列复杂度（complexity of glucose time series index，CGI）与认知功能障碍的关联也十分显著。FBG水平与认知功能相关性不显著的原因可能如下。首先，FBG水平的检测结果在一定程度上受到其他因素的影响，如饮食中的碳水化合物、糖分摄入量、体育锻炼等，因此FBG水平并不能反映长期的血糖状态。其次，临床常用的认知量表，如MMSE、CDRSB，虽然在全球范围内广泛应用，常用于评估认知功能和筛查痴呆，但也存在一些争议：量表的问题可能与特定文化或教育背景相关，在跨文化人群和低教育程度的人群中可能产生偏差，且对认知功能的评估并不全面。这可能是造成FBG水平与认知量表评分相关分析结果不一致的原因。

除了外周血糖评价指标与认知量表评分之间的关联性反映了糖代谢与认知障碍的关系外，血糖与认知障碍生物标志物之间的相关亦可体现糖代谢与认知障碍的关联。有研究[6-7]表明高血糖会促进tau蛋白的磷酸化。tau蛋白存在于神经元轴突中，用以维持细

胞骨架的稳定性，在阿尔茨海默病等多种神经退行性疾病中被认为与认知减退显著相关。除tau蛋白外，高糖状态亦会加速Aβ蛋白沉积。研究[28-29]表明体内高糖状态不仅会导致产生Aβ的基因表达量增加，亦会通过抑制淀粉样前体蛋白（amyloid precursor protein，APP）降解来促进Aβ蛋白在体内的沉积。值得注意的是，也有研究[30-31]表明，血糖异常与认知障碍的关联或许并非由Aβ与tau蛋白介导；并且现有的研究中关于认知障碍病理标志物与糖代谢指标之间的关系，因不同认知障碍阶段、不同糖代谢紊乱阶段、样本的年龄差异、样本的数量较小等因素的影响，导致分析结果并不够准确。同样，在本研究队列的分析中，Aβ42蛋白、pTau蛋白与FBG的相关分析结果也不显著，因此关于这两者与FBG之间的关联有待进一步探索。此外，高血糖导致认知障碍的原因还包括胰岛素抵抗、炎症反应的增加、氧化应激、线粒体功能障碍等[22,32]。高血糖尤其是2型糖尿病受试者往往伴有胰岛素抵抗。研究[33]发现脑胰岛素抵抗或许是认知障碍的病理生理学特征之一，甚至有部分研究[34]将胰岛素抵抗相关的认知障碍称为3型糖尿病。胰岛素是体内调节血糖水平的激素。体内发生胰岛素抵抗，尤其是脑胰岛素抵抗会导致脑细胞摄取和利用葡萄糖的能力下降，从而影响神经元功能，尤其是记忆和学习方面的功能。尽管本研究中缺少胰岛素指标分析，但胰岛素抵抗与认知障碍之间的关联值得关注。

本研究具有一定的局限性。首先，回顾性研究数据的有效性有限，无法评估受试者基线时的高血糖状态是否持续，一过性的高血糖状态对体内代谢的影响通常可逆，从而对分析结果造成影响。其次，随访数据的完整性有限，尽管筛选样本时限定了随访时长范围，但部分随访数据缺失依然会对结果产生影响。最后，分析的代谢指标多为脂质代谢指标，种类不够全面。因此，血糖升高人群认知功能恶化风险升高的其他差异代谢物有待进一步更全面的分析和探索。

利益冲突声明/Conflict of Interests

所有作者声明不存在利益冲突。

All authors disclose no relevant conflict of interests.

伦理批准和知情同意/Ethics Approval and Patient Consent

ADNI数据属于公开数据库。数据库中涉及的受试者已获得伦理批准（官方网站：https://adni.loni.usc.edu/methods/documents/）。用户可下载相关数据进行研究，并发表相关文章。因为研究基于开源数据库，因此不存在伦理问题和利益冲突。

ADNI belongs to public databases. The patients involved in the database have obtained ethical approval (Official website: https://adni.loni.usc.edu/methods/documents/). Users can download relevant data for research and publish relevant articles. Because the research is based on an open source database, there are no ethical issues or conflicts of interest.

作者贡献/Authors′ Contributions

吴丽蓉负责数据库数据筛选、分析和初稿撰写；陈天璐负责论文整体构思；晁筱雯、郭雨槐、孙涛、李梦慈负责稿件修改。所有作者均阅读并同意了最终稿件的提交。

WU Lirong completed the data analysis and article writing; CHEN Tianlu was responsible for the overall conceptualization of the paper; CHAO Xiaowen, GUO Yuhuai, SUN Tao, and LI Mengci were responsible for article revision. All the authors have read the final manuscript and agreed to the submission.

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