Risk factors for cognitive decline in non-demented elders with amyloid-beta positivity

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Abstract

Background As a currently incurable but preventable disease, the prevention and early diagnosis of Alzheimer's disease (AD) has long been a research hotspot. Amyloid deposition has been shown to be a major pathological feature of AD. Notably, not all the people with amyloid-beta (Aβ) pathology will have significant cognitive declines and eventually develop AD. Therefore, the aim of this study was to explore the risk factors for cognitive decline in Aβ-positive participants.

Methods We included 650 non-demented participants who were Aβ-positive at baseline from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Mixed effects and COX regression models were applied to assess 37 potential risk factors. Mixed effects models were employed to assess the temporal associations between potential risk factors and four cognitive assessment scales. COX regression models were used to assess the impact of potential risk factors on cognitive diagnosis conversion. Univariate and multivariate analyses were applied to the above models. Additionally, we used the Cochran-Armitage trend test to examine whether the incidence of cognitive decline increased with the number concurrent of risk factors.

Results Six factors (low diastolic pressure, low body mass index, retired status, a history of drug abuse, Parkinsonism, and depression) were the identified risk factors and four factors (a history of urinary disease, musculoskeletal diseases, no major surgical history, and no prior dermatologic-connective tissue diseases) were found to be suggestive risk factors. The incidence of cognitive decline in the Aβ-positive participants gradually increased as the number of concurrent risk factors increased (*p* for trend = 0.0005).

Conclusions Our study may facilitate the understanding of the potential pathological processes in AD and provide novel targets for the prevention of cognitive decline among participants with Aβ positivity.

Keywords Alzheimer's disease, Amyloid-beta positivity, Cognitive decline, Risk factors

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Introduction

With population growth and population aging, the number of people with dementia worldwide is estimated to reach 150 million in 2050, which is about triple the number in 2019 [1]. Alzheimer's disease (AD), as the main cause of dementia [2], imposes a heavy burden on the health care system [3], patients and the society [4]. Amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) are considered to be the core neuropathological characteristics of AD [5–7]. The former contains fibrillar aggregates of Aβ peptides, and the latter contains aggregates of hyperphosphorylated tau proteins. In the past, we solely relied on late clinical symptoms or postmortem examination to make an AD diagnosis. Since Aβ depositions precede the clinical onset of AD for more than 10 years, Aβ pathology can currently serve as part of the evidence for AD diagnosis [8]. With the development of biomarkers and imaging techniques, Aβ pathology can be early detected both by cerebrospinal fluid (CSF) biomarkers and positron emission tomography (PET) scanning [9]. Furthermore, the National Institute on Aging and Alzheimer's Association (NIA-AA) redefined AD by proposing the ATN framework based on Aβ deposition, pathologic tau, and neurodegeneration [10], which makes it possible to recognize AD by biomarkers before the clinical stage. However, not all the people with Aβ pathology will have significant cognitive declines and eventually develop AD [11]. For instance, a longitudinal study with an average follow-up duration of 11 years revealed that individuals exhibiting low levels of Aβ and tau proteins did not exhibit any cognitive decline even after several years of follow-up [12], suggesting that Aβ pathology might only be an initiating factor for AD.

Many observational and randomized controlled trials have investigated the risk factors of cognitive decline and AD in detail, such as advanced age, genetic, socioeconomic, and environmental factors, as well as psychiatric symptoms of anxiety, depression, or apathy [13, 14]. Moreover, previous meta-analyses and reviews have shown that approximately one-third of AD cases may be attributable to modifiable risk factors, such as diabetes, hypertension, physical activity, diet, and social activity [15, 16]. However, although the risk factors for cognitive decline and those for AD have been extensively studied, few previous studies have focused on the risk factors for cognitive decline in the Aβ-positive (A+) non-demented population. As Aβ pathology has been detected in an increasing number of people, identifying risk factors for cognitive decline in A+ non-demented participants is of vital importance to AD prevention. Whether the well-established AD risk factors still confer a risk of cognitive decline among A+non-demented participants is unclear. Therefore, the purpose of our study was to identify the risk factors for cognitive decline in the A+ non-demented

population. Additionally, some identified AD risk factors showed a synergistic effect with Aβ [17, 18]. Specifically, risk factors, such as *apolipoprotein E ε4 (APOE-ε4)* allele, α-synuclein, and age may lead to faster cognitive decline in people with Aβ pathology. The risk factors for cognitive decline in a non-demented population with Aβ pathology deserve further exploration.

Methods

Study participants

The participants in our study were included in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study. The ADNI study is a large multicenter study that collected extensive data on clinical, imaging, genetic, and biochemical biomarkers of preclinical AD and AD. The ADNI study has been approved by the Institutional Review Boards of all participating institutional centers and the written informed consent form has been signed by all participants according to the Declaration of Helsinki.

In the ADNI database, there were 899 A+ participants at baseline. Among them, we included 650 A+ non-demented participants at baseline who provided basic clinical characteristics and imaging data at baseline, as well as cognitive measurements at follow-up (see Fig. 1 for details). The exclusion criteria included significant neurologic diseases, psychiatric disorders with psychotic features, current use of specific psychoactive medications, and so forth. Detailed inclusion and exclusion criteria for the ADNI database can be found at adni.loni.usc.edu. The ADNI divided participants into cognitively normal (CN), mild cognitive impairment (MCI), and AD participants according to strict criteria [19]. In our study, participants with a transition from CN to MCI/AD or from MCI to AD during the follow-up were considered as cognitive diagnosis conversions. According to whether the participants experienced a cognitive diagnostic conversion during follow-up, we categorized them into the cognitive decline group and the no cognitive decline group. According to the *APOE-ε4* status, participants were categorized into *APOE-ε4* carriers and non-carriers. Participants were classified as *APOE-ε4* carriers if they had at least one *APOE-ε4* allele.

CSF and amyloid imaging measures

CSF concentrations of Aβ$_{42}$ and p-tau were measured at the University of Pennsylvania using Innogenetics immunoassay kits on the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX), and the measuring method has been described in detail in a previous study [20]. We applied the cut-off values for determining biomarker positivity which were published in previous articles. A positive CSF Aβ$_{42}$ was defined as having a CSF Aβ$_{42}$ level less than 977 picograms per milliliter (pg/mL), and CSF p-tau
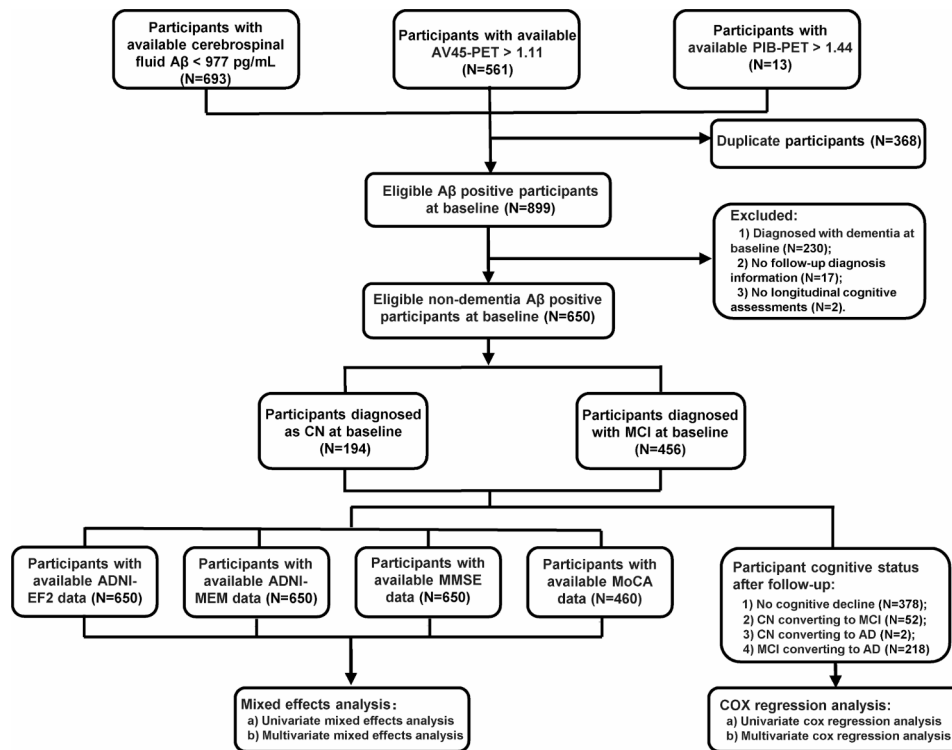
Fig. 1 Screening process and workflow of the study. The flowchart describes the details of screening participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database for analysis. Abbreviations: pg/ml, picograms per milliliter; PET, positron emission tomography; Aβ, amyloid-β; ADNI-EF2, the ADNI Composite Executive Function 2 score; ADNI-MEM, the ADNI Composite Memory Score; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CN, cognitively normal; MCI, mild cognitive impairment; AD, Alzheimer's disease

positivity was defined as having a CSF p-tau level greater than 21.8 pg/mL [21].

PET imaging data in the ADNI database were acquired by PET scanners at different sites across the country, and the detailed process has been described in previous studies [22, 23]. In this study, the SUV ratio (SUVR) was used as a main indicator of PET performance. SUVR PIB-PET values or SUVR AV45-PET values were calculated as the average of several representative regions of interest (ROIs), using the cerebellum as a reference region. We used two established thresholds to define A+: PIB-PET (SUVR > 1.44) and AV45-PET (SUVR > 1.11) [21, 24]. For tau PET, we selected ROIs in the inferior temporal, amygdala, bilateral entorhinal, fusiform, and middle temporal regions for evaluation. The meta-ROI SUVR threshold of tau PET (AV1451-PET) was 1.37 [25].

Participants were classified as A+ based on either a positive CSF Aβ$_{42}$ value or positive amyloid PET (using either PIB-PET or AV45-PET). Participants were classified as tau positivity (T+) based on either a positive CSF p-tau value or a positive AV1451 tau PET imaging.

Cognitive assessments

We applied the ADNI Composite Memory Score (ADNI-MEM) and the ADNI Composite Executive Function 2 score (ADNI-EF2) as tools to evaluate the memory

function and executive function of participants, respectively. We used the Mini-Mental State Examination (MMSE) scale and Montreal Cognitive Assessment (MoCA) scores to assess the overall cognitive performance. Higher scores represent better cognitive functioning, and all of these measures have excellent robustness and external validity [26]. ADNI-EF2 includes the Trail-Making Test parts A and B, WAIS-R Digit Symbol Substitution, Category Fluency tasks, five Clock Drawing tasks, and Digit Span Backwards [27]. ADNI-MEM is derived from several tasks, including word list learning and recognition from ADAS-Cog, the Rey Auditory Verbal Learning Task, the 3-word recall item from the MMSE, and recall from Logical Memory I of the Wechsler Memory Scale-Revised [28].

Baseline information of participants

The ADNI database collected the baseline information of the participants, consisting of age (continuous), gender (female or male), educational years (continuous), *APOE-ε4 carrier* (yes or no), as well as other data which were potential risk factors to be explore in our study, including body weight (continuous), body height (continuous), body mass index (BMI, < 25 kg/m^2 or ≥ 25 kg/m^2), systolic pressure (continuous), diastolic pressure (continuous), pulse pressure (continuous), race (Asian, white,

black, more than one), handedness (left or right), parental dementia (yes or no), lifestyle factors (alcohol use, cigarette use, drug abuse, marital status, and retirement status), and histories of clinical diseases which included stroke, hypertension, psychiatric diseases, neurologic diseases (other than AD), otolaryngology diseases, cardiovascular diseases, respiratory diseases, hepatic diseases, dermatologic connective tissue diseases, musculoskeletal diseases, endocrine-metabolic diseases, gastrointestinal diseases, hematopoietic-lymphatic diseases, urinary disease, drug allergies, malignancy diseases, major surgical procedures, Parkinsonism, subjective cognitive decline (SCD), significant visual impairment, and significant auditory impairment. All the above lifestyle factors and histories of clinical diseases were dichotomous variables (yes or no). For these dichotomous variables, "no" was coded as 0, and "yes" was coded as 1.

Additionally, the Geriatric Depression Scale (GDS) and Hachinski Ischemic Scale (HIS) [29] were utilized to assess depressive symptoms and the risk of vascular dementia, respectively. According to previous literature, we divided participants into depressed and non-depressed based on a GDS cutoff value of 0 [30].

Statistical analysis

In this study, continuous variables were described using the mean and standard deviation, while categorical variables were described using numbers and prevalence. To analyze the intergroup differences, the Mann-Whitney U test and the chi-square test were performed for continuous variables and categorical variables, respectively. The Shapiro-Wilk test showed that ADNI-MEM, ADNI-EF2, MMSE, and MoCA scores were skewed, and then these scores were transformed into a normal distribution using the car package of R software.

We used five models to identify risk factors. Mixed effects models were employed to assess the temporal associations between potential risk factors and ADNI-EF2 (Model 1), ADNI-MEM (Model 2), MMSE (Model 3), and MoCA (Model 4) scores. COX regression models (Model 5) were carried out to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of these risk factors for cognitive diagnosis conversion. These five models were conducted in two steps in a similar way: first, a univariate analysis was performed, followed by a multivariate analysis. Initially, univariate models were used to screen for risk factors potentially contributing to cognitive decline in the A+population (*$p < 0.1$). Subsequently, multivariate models, including multivariate mixed-effects models and multivariate Cox regression models, were employed to further analyze the significant risk factors identified in the univariate analysis (*$p < 0.05$) [31]. Age, gender, years of education, *APOE-ε4* status, and baseline cognitive status are included as basic covariates. Factors validated by only one multivariate analysis model are considered suggestive risk factors, while those validated by two or more multivariate analysis models are considered identified risk factors.

In addition, gender and age are common unmodifiable risk factors for AD, so we applied COX regression analysis to conduct subgroup analyses by age. (younger elderly group: < 70 years; older elderly group: ≥ 70 years) [32], gender (male; female), and T status (T+; tau negative, T-). To assess whether the incidence of cognitive decline in the A+ population increases with the number of concurrent risk factors, we conducted the Cochran-Armitage trend test. The Cochran-Armitage trend test was applied to all significant factors in the multifactorial analysis. Multicollinearity was assessed using the variance inflation factor (VIF).

To ensure the robustness of the results, sensitivity analyses and post hoc analyses were conducted as follows: (1) The analyses were repeated for participants with complete data only, since some hadn't completed risk factor data. (2) The analyses were repeated after adjusting for tau status to determine if tau status influenced the results. (3) Sensitivity analyses were conducted by excluding the 21 participants with cognitive reversion (MCI to CN) to examine whether their inclusion affected the results. (4) The false discovery rate (q value) results from the univariate analysis were provided to mitigate potential bias from the single-variable selection method.

A *p*-value < 0.05 was considered significant. All analyses were carried out using R version 3.5.1 and SPSS 26.0.

Results

Participant characteristics

A total of 650 A+ participants without dementia were included at baseline. Among them, 272 experienced cognitive diagnostic conversion, while 378 did not. Table 1 presents the baseline information of the participants and the differences in characteristics between the two groups. The study population had an average age of 73.51±6.78 years, with approximately 45% being female. The average years of education were 16.19±2.75, and the mean duration of follow-up was 4.37±2.99 years. Significant differences were observed between the cognitive decline group and the no cognitive decline group in terms of *APOE-ε4* carrier status, marital status, history of stroke, gastrointestinal diseases, Parkinsonism, SCD, and GDS.

Potential risk factors for a cognitive decline in A+ participants

Firstly, 37 potential risk factors were analyzed using a univariate mixed-effects model (Model 1–4). Model 1 showed that diastolic pressure, race, marital status, a history of hypertension, dermatologic-connective tissue diseases, musculoskeletal diseases, depressive disorder,

Table 1 Basic characteristics of included participants

Variable	No cognitive decline	cognitive decline	Total	*p*
N	378	272	650	/
Age, year, mean [SD]	73.21 [6.67]	73.93 [6.91]	73.51 [6.78]	0.104[‡]
Gender, female/male	81/194	114/158	297/353	0.101[†]
Education, year, mean [SD]	16.27 [2.75]	16.08 [2.79]	16.19 [2.75]	0.384[‡]
APOE ε4 carrier, yes (%)	202 (53.44)	178 (65.44)	380 (58.46)	**0.004[†]**
CSF Aβ_{42}, pg/mL, mean [SD]	765.90 [247.85]	659.55 [207.98]	716.35 [236.17]	**< 0.001[‡]**
CSF p-tau, pg/mL, mean [SD]	25.85 [13.70]	34.08 [15.03]	29.63 [14.90]	**< 0.001[‡]**
Cognitive composite measures				
Memory function, mean [SD]	0.49 [0.94]	-0.49 [0.72]	0.08 [0.98]	**< 0.001[‡]**
Executive function, mean [SD]	0.07 [0.85]	-0.59 [0.90]	-0.21 [0.93]	**< 0.001[‡]**
MMSE, mean [SD]	27.34 [2.79]	24.37 [3.47]	26.10 [3.42]	**< 0.001[‡]**
MoCA, mean [SD]	23.62 [3.68]	20.12 [4.17]	22.33 [4.22]	**< 0.001[‡]**
Vital signs				
Body weight, kg, mean [SD]	77.25 [15.81]	75.75 [14.54]	76.63 [15.31]	0.495[‡]
Body height, cm, mean [SD]	169.42 [16.90]	168.89 [10.31]	169.20 [14.53]	0.587[‡]
BMI, kg/m^2, mean [SD]	27.51 [9.72]	26.43 [4.77]	27.05 [7.99]	0.128[‡]
Systolic pressure, mmHg, mean [SD]	135.88 [16.35]	136.45 [18.27]	136.12 [17.17]	0.944[‡]
Diastolic pressure, mmHg, mean [SD]	75.80 [9.46]	75.22 [9.32]	75.56 [9.40]	0.595[‡]
Pulse pressure, mmHg, mean [SD]	60.09 [14.74]	61.23 [16.21]	60.56 [15.38]	0.616[‡]
Race				0.071[†]
Asian, yes (%)	2 (0.53)	4 (1.47)	6 (0.92)	
White, yes (%)	345 (92.00)	258 (94.85)	603 (93.19)	
Black, yes (%)	17 (4.50)	8 (2.94)	25 (3.86)	
More than one, yes (%)	11 (2.52)	2 (0.73)	13 (2.01)	
Participant handedness, right (%)	341 (90.45)	246 (92.13)	587 (91.14)	0.522[†]
Parental dementia, yes (%)	236 (62.59)	155 (58.05)	495 (76.86)	0.228[†]
Lifestyle				
Alcohol abuse, yes (%)	9 (2.38)	12 (4.41)	21 (3.26)	0.140[†]
Cigarette abuse, yes (%)	136 (36.07)	106 (38.97)	242 (37.58)	0.363[†]
Drug abuse, yes (%)	2 (0.53)	3 (1.10)	5 (0.78)	0.400[†]
Marital Status, yes (%)				**0.033[†]**
Married	270 (71.81)	220 (80.88)	490 (75.73)	
divorced	38 (10.11)	19 (6.99)	57 (8.80)	
Widowed	46 (13.03)	17 (6.25)	73 (11.27)	
Never married	22 (5.85)	6 (2.21)	28 (4.32)	
Retired, yes (%)	300 (80.43)	224 (86.49)	524 (83.04)	0.054[†]
Clinical diseases				
Stroke, yes (%)	2 (0.52)	7 (2.57)	9 (1.40)	**0.026[†]**
Hypertension, yes (%)	185 (49.07)	125 (45.96)	310 (48.14)	0.551[†]
Psychiatric diseases, yes (%)	126 (33.42)	95 (34.93)	221 (34.37)	0.586[†]
Neurologic diseases (other than AD), yes (%)	103 (27.32)	79 (29.04)	182 (28.26)	0.543[†]
Otolaryngology diseases, yes (%)	239 (63.40)	179 (65.81)	418 (64.91)	0.362[†]
Cardiovascular diseases, yes (%)	248 (65.78)	172 (63.24)	420 (65.22)	0.686[†]
Respiratory diseases, yes (%)	76 (20.16)	54 (19.85)	130 (20.19)	0.997[†]
Hepatic diseases, yes (%)	16 (4.24)	8 (2.94)	24 (3.73)	0.407[†]
Dermatologic-Connective Tissue diseases, yes (%)	129 (34.22)	88 (32.35)	217 (33.69)	0.721[†]
Musculoskeletal diseases, yes (%)	260 (68.97)	185 (68.01)	445 (69.10)	0.970[†]
Endocrine-Metabolic diseases, yes (%)	165 (44.50)	104 (38.24)	269 (41.77)	0.212[†]
Gastrointestinal diseases, yes (%)	189 (50.01)	113 (41.54)	302 (46.89)	**0.047[†]**
Hematopoietic-Lymphatic diseases, yes (%)	39 (10.34)	23 (8.45)	62 (9.63)	0.457[†]
Urinary disease, yes (%)	159 (42.17)	117 (43.01)	276 (42.86)	0.699[†]
Allergies or Drug Sensitivities, yes (%)	158 (41.90)	106 (38.97)	264 (40.37)	0.556[†]
Malignancy diseases, yes (%)	91 (24.13)	65 (23.90)	156 (24.22)	0.967[†]

Table 1 (continued)

Variable	No cognitive decline	cognitive decline	Total	*p*
Major Surgical Procedures, yes (%)	283 (75.10)	193 (70.90)	476 (73.91)	0.396[†]
Parkinsonism, yes (%)	0 (0.00)	3 (1.10)	3 (0.64)	**<0.001[†]**
Subjective cognitive decline, yes (%)	236 (62.59)	216 (79.41)	452 (69.54)	**<0.001[†]**
Significant Visual Impairment, yes (%)	23 (0.53)	11 (4.12)	33 (5.12)	0.179[†]
Significant Auditory Impairment, yes (%)	33 (0.88)	26 (9.74)	59 (9.16)	0.677[†]
Clinical Scale				
Geriatric Depression Scale, mean [SD]	1.34 [1.39]	1.58 [1.39]	1.44 [1.39]	**0.030[‡]**
Hachinski ischemic Scores, mean [SD]	0.60 [0.65]	0.63 [0.78]	0.61 [0.71]	0.675[‡]

N=number of participants

Bold indicated that the results were statistically significant

Abbreviations: SD, standardized deviation; *APOE ε4, apolipoprotein E ε4*; Aβ amyloid-β, p-tau phosphorylated tau, BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); CSF, cerebrospinal fluid; AD, Alzheimer's disease; pg/mL, picograms per milliliter; MMSE, the Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; kg, kilogram; cm, centimeter; mmHg, millimeters of mercury;

[*]Intergroup comparisons were tested by t-test

[†]Intergroup comparisons were tested by chi-square test

[‡]Intergroup comparisons were tested by the Mann-Whitney *U* test

and Hachinski ischemic scores had a significant impact on ADNI-EF2. Model 2 indicated that body weight, BMI, race, marital status, retirement status, the history of dermatologic-connective tissue diseases, hematopoietic-lymphatic diseases, Parkinsonism, and depressive disorder had a significant impact on ADNI-MEM. Model 3 showed that body weight, BMI, race, marital status, retirement status, the history of parental dementia, psychiatric diseases, Parkinsonism, urinary disease, depressive disorder, and major surgical procedures had a significant impact on MMSE. Model 4 showed that BMI, diastolic pressure, race, marital status, retirement status, depressive disorder, history of drug abuse, cardiovascular diseases, allergies or drug sensitivities, and major surgical history had a significant impact on MoCA. Combining the results from Models 1–4, a total of 20 risk factors were screened by the univariate mixed-effects model. For specific details, see Fig. 2 and Supplementary Tables S1-S2. Then, we analyzed these 37 potential risk factors using a univariate COX regression model (Model 5). As shown in Fig. 2 and Supplementary Table S3, there were 11 significant risk factors, consisting of body weight, BMI, race, marital status, retirement status, the histories of alcohol abuse, stroke, hepatic diseases, gastrointestinal diseases, depressive disorder, and Parkinsonism.

In the second step, we separately incorporated the 20 factors identified from the univariate mixed-effects models and the 11 risk factors identified from the univariate COX regression models into multivariate models for further analysis. Multivariable mixed effects model analysis revealed that the faster decline in ADNI-EF2 scores was associated with low diastolic blood pressure (β=0.0146; 95% CI: 0 to 0.03; *p*=0.0440), no history of dermatologic-connective tissue diseases (β=0.0188; 95% CI: 0 to 0.03; *p*=0.0085), and depression (β = -0.0306; 95% CI: -0.04 to -0.02; *p*<0.0001). The faster decline rate of ADNI-MEM

scores was linked to low BMI (β=0.0188; 95% CI: 0 to 0.04; *p*=0.0367), a history of drug abuse (β = -0.0214; 95% CI: -0.04 to 0; *p*=0.0136), musculoskeletal diseases (β = -0.0187; 95% CI: -0.04 to 0; *p*=0.0368), Parkinsonism (β = -0.0227; 95% CI: -0.04 to 0; *p*=0.0129), and depression (β = -0.0210; 95% CI: -0.04 to 0; *p*=0.0116). The faster decline rate of MMSE scores was related to retired status (β =-0.0297; 95% CI: -0.05 to -0.01; *p*=0.0048), a history of urinary disease (β = -0.0240; 95% CI: -0.04 to 0; *p*=0.0242;), Parkinsonism (β = -0.0319; 95% CI: -0.06 to -0.01; *p*=0.0115) and depression (β = -0.0301; 95% CI: -0.05 to -0.01; *p*=0.0029). The accelerated decline of MoCA scores was associated with low BMI (β=0.0191; 95% CI: 0 to 0.04 *p*=0.0306), low diastolic blood pressure (β=0.0200; 95% CI: 0 to 0.04; *p*=0.0214), the history of drug abuse (β = -0.0237; 95% CI: -0.04 to -0.01; *p*=0.0113), retired status (β = -0.0269; 95% CI: -0.04 to -0.01; *p*=0.0025), without major surgical procedures (β=0.0183; 95% CI: 0 to 0.04; *p*=0.0350) and depressive state (β = -0.0285; 95% CI: -0.04 to -0.01; *p*=0.0005). In the multivariate COX regression model, a history of Parkinsonism (HR: 6.55, 95% CI: 1.80 to 23.91, *p*=0.0044) and depressive state (HR: 2.38; 95% CI: 1.58 to 3.60; *p*<0.0001) remained statistically significant risk factors. More details can be seen in Fig. 3; Tables 2, 3 and 4.

Based on the analysis results of the mixed effects model, low BMI, low diastolic blood pressure, retired status, a history of drug abuse, musculoskeletal diseases, urinary disease, Parkinsonism, and depression significantly positively associated with longitudinal cognitive decline. Conversely, a history of dermatologic-connective tissue diseases and major surgical procedures showed a significant negative association. Additionally, the Cox regression model analysis indicated that Parkinsonism and depression increased the risk of cognitive diagnosis conversion. In summary, we concluded from the above
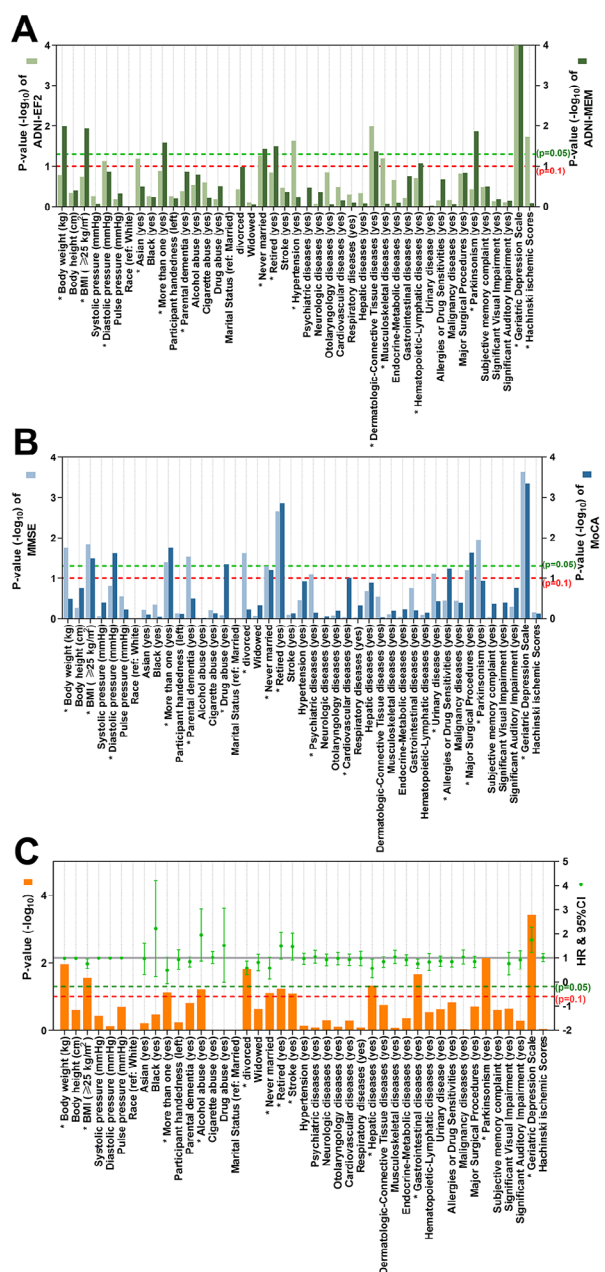
Fig. 2 Risk factors for a cognitive decline in A+ participants in univariate analyses. An initial screening was conducted using univariate models for the risk factors that might contribute to a cognitive decline in the A+ population. Univariate mixed-effect models were used to evaluate the temporal associations of the risk factors with ADNI-EF2, and ADNI-MEM scores (**A**). Univariate mixed-effect models were used to evaluate the temporal associations of the risk factors with overall cognitive performance (MMSE and MoCA) (**B.**) Univariate COX regression models were carried out to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of these risk factors for cognitive diagnosis conversion (**C**). Age, gender, years of education, *APOE-ε4* status, and baseline cognitive status are included as basic covariates. "*" indicated that the results were statistically significant (*$p < 0.1$*). Abbreviations: Aβ, amyloid-β; BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); ADNI-EF2, the ADNI Composite Executive Function 2 score; ADNI-MEM, the ADNI Composite Memory Score; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment

results of 5 models that among the 37 potential risk factors, six factors were identified risk factors (low diastolic pressure, low BMI, retired status, a history of drug abuse, depression, and Parkinsonism), and four were suggestive risk factors (a history of urinary disease, musculoskeletal diseases, no major surgical procedures, and no prior dermatologic-connective tissue diseases).

## Subgroup analyses and trend test

Subgroup analyses stratified by gender, age, and T status were conducted to examine the differential effects of these variables on the outcomes. In the subgroup analysis by age, a history of Parkinsonism and depression were only significant in the older elderly subgroup. In the subgroup analysis by gender, having a history of Parkinsonism significantly increased the risk of cognitive diagnostic conversion in men, and no significant differences were found in depression status among gender subgroups. In the subgroup analysis by T status, depression was more pronounced in the T- subgroup, while body weight, race, and a history of Parkinsonism were only significant in the T- subgroup. Details are presented in Tables S4-S6. The Cochran-Armitage trend analysis showed that the risk of cognitive decline in A+ subjects increased with the number of concurrent risk factors (*p* for trend=0.0005). Details are presented in Fig. 4. We found no multicollinearity in each multivariate model.

Sensitivity analyses and post hoc analyses

In the post hoc analysis, after repeating the analysis only for participants with complete data, the results were largely consistent with our main findings. Details are presented in Tables S7-S12. We found that tau status had no significant influence on our results. When we excluded 21 participants with cognitive reversal for the analysis, the sensitivity analysis showed that our results remained robust. Details are presented in Tables S13-S14. The false discovery rate results of the univariate analysis revealed that the primary variables identified in the study remained significant.

Discussion

This large-scale study explores 37 potential risk factors for cognitive decline in A+ non-demented individuals. The study showed ten risk factors, of which six were identified risk factors (low diastolic pressure, low BMI, retired status, a history of drug abuse, Parkinsonism, and depression) and four were suggestive risk factors (a history of urinary disease, musculoskeletal diseases, no major surgical history, and no prior dermatologic-connective tissue diseases). The 10 factors mentioned above were associated with longitudinal cognitive decline, with a history of Parkinsonism and depression linked to both cognitive decline and cognitive diagnosis conversion.
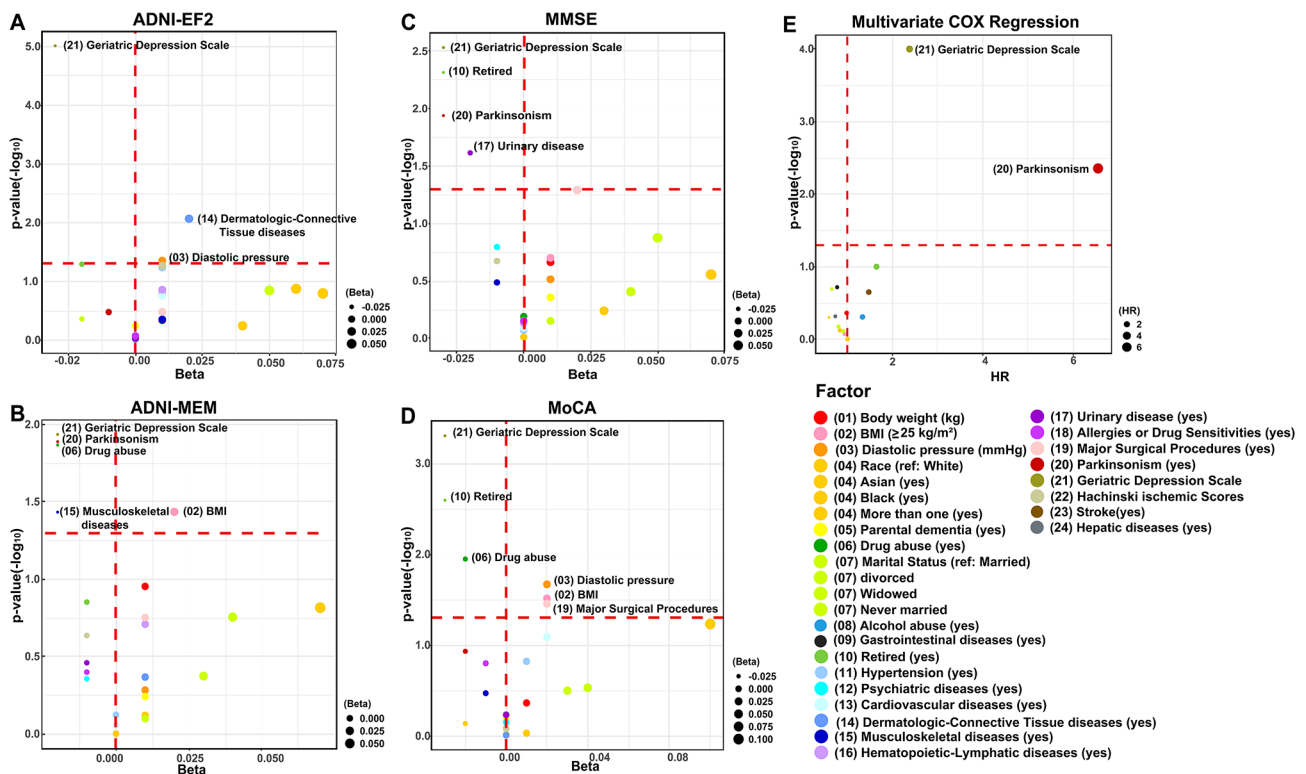
Fig. 3 Risk factors for a cognitive decline in A+ participants in multivariate analyses. Multivariate models were used to further analyze the significant risk factors (**p < 0.1**) found in univariate models. Similarly, multivariate mixed effect models were used to evaluate the temporal associations of the risk factors with ADNI-EF2 (**A**), ADNI-MEM (**B**), MMSE (**C**), and MoCA (**D**) scores. Multivariate COX regression models were carried out to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of these risk factors for cognitive diagnosis conversion (**E**). Notably, age, gender, years of education, *APOE-ε4* status, and baseline cognitive status were adjusted in the multivariate models. Abbreviations: HR, hazard ratio; BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); ADNI-EF2, the ADNI Composite Executive Function 2 score; ADNI-MEM, the ADNI Composite Memory Score; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; Beta, regression coefficient; HR, hazard ratio

Our results will facilitate the formulation of better strategies for the early prevention of AD, thereby contributing to reducing the prevalence of dementia.

The amyloid cascade hypothesis for AD has been well-known in the academic community, in which Aβ peptide deposition is the central event in the pathogenesis of AD [33]. A large number of previous studies have examined the risk factors for AD and dementia [24, 34], whereas only a few studies explored the risk factors for cognitive decline in the A+ but non-demented population. A previous study involving 248 A+ participants showed that advanced age and *APOE-ε4* were associated with greater Aβ burden and they were important risk factors for cognitive impairment and decline [35]. A longitudinal observational study demonstrated that *APOE-ε4* carriers had faster rates of memory decline than non-carriers in preclinical AD (A+ participants), and advanced age might exacerbate this adverse effect of *APOE-ε4* [36]. The above previous studies primarily focused on unmodifiable risk factors such as age and *APOE-ε4*. However, our observations have identified many modifiable risk factors.

In the study, some basic vital signs were risk factors for cognitive decline in the A+ participants, such as low diastolic blood pressure and low BMI. Previous studies, consistent with our research, indicated that lower diastolic blood pressure was associated with cognitive decline [37]. Mathew et al. also pointed out that higher diastolic blood pressure was associated with better cognitive performance in the absence of elevated systolic blood pressure levels [38]. The possible reason for these results is that higher diastolic blood pressure can prevent cerebral hypoperfusion, thereby achieving better cognitive function. At the same time, the study suggested that in A+ participants, low BMI was associated with a faster decline in ADNI-MEM and MoCA scores. The relationship between BMI and AD risk is complex and appears to vary across different life stages. While midlife obesity is a known risk factor, recent research suggested a potential protective effect of higher BMI in late life [16, 39]. A longitudinal study indicated that overweight/obese individuals with favorable metabolic profiles have a lower risk of AD, with the effect likely driven by Aβ [40]. Jules et al. found a positive correlation between BMI and Aβ$_{42}$ levels in CSF in subjects with cognitive impairment [41]. One possible explanation for the association between BMI and the risk of AD is that a decline in BMI

Table 2 Multivariate mixed-effects model analyses of the temporal associations between executive function/memory function and risk factors

Factors	Executive function				Memory function			
	β	SE	95% CI	p	β	SE	95% CI	p
Body weight (kg)	0.01	0.01	[-0.01, 0.02]	0.4553	0.01	0.01	[0.00, 0.03]	0.1114
BMI (≥ 25 kg/m^2)	0.01	0.01	[0.00, 0.02]	0.1637	0.02	0.01	[0.00, 0.04]	**0.0367**
Diastolic pressure (mmHg)	0.01	0.01	[0.00, 0.03]	**0.0440**	0.01	0.01	[-0.01, 0.02]	0.5205
Race (ref: White)								
Asian (yes)	0.06	0.04	[-0.02, 0.13]	0.1330	0.01	0.05	[-0.07, 0.10]	0.7585
Black (yes)	0.04	0.07	[-0.09, 0.17]	0.5672	<-0.01	0.10	[-0.19, 0.19]	0.9968
More than one (yes)	0.07	0.05	[-0.03, 0.17]	0.1594	0.07	0.05	[-0.03, 0.17]	0.1528
Parental dementia (yes)	<0.01	0.01	[-0.01, 0.02]	0.5658	0.01	0.01	[-0.01, 0.02]	0.5731
Drug abuse (yes)	<0.01	0.01	[-0.02, 0.02]	0.9423	-0.02	0.01	[-0.04, 0.00]	**0.0136**
Marital Status (ref: Married)								
Divorced	<-0.01	0.03	[-0.05, 0.05]	0.9483	0.04	0.03	[-0.02, 0.10]	0.1758
Widowed	-0.02	0.02	[-0.06, 0.03]	0.4332	0.01	0.03	[-0.05, 0.06]	0.7974
Never married	0.05	0.04	[-0.02, 0.12]	0.1417	0.03	0.04	[-0.05, 0.11]	0.4229
Retired (yes)	-0.02	0.01	[-0.03, 0.00]	0.0506	-0.01	0.01	[-0.03, 0.00]	0.1406
Hypertension (yes)	0.01	0.01	[0.00, 0.03]	0.0576	<-0.01	0.01	[-0.02, 0.01]	0.7536
Psychiatric diseases (yes)	<-0.01	0.01	[-0.01, 0.01]	0.9450	-0.01	0.01	[-0.02, 0.01]	0.4401
Cardiovascular diseases (yes)	0.01	0.01	[0.00, 0.02]	0.1744	<0.01	0.01	[-0.02, 0.02]	0.8774
Dermatologic-Connective Tissue diseases (yes)	0.02	0.01	[0.00, 0.03]	**0.0085**	0.01	0.01	[-0.01, 0.02]	0.4292
Musculoskeletal diseases (yes)	0.01	0.01	[-0.01, 0.02]	0.4430	-0.02	0.01	[-0.04, 0.00]	**0.0368**
Hematopoietic-Lymphatic diseases (yes)	0.01	0.01	[0.00, 0.02]	0.1382	0.01	0.01	[-0.01, 0.03]	0.1955
Urinary disease (yes)	<-0.01	0.01	[-0.01, 0.01]	0.9301	-0.01	0.01	[-0.03, 0.01]	0.3469
Allergies or Drug Sensitivities (yes)	<-0.01	0.01	[-0.02, 0.01]	0.8407	-0.01	0.01	[-0.02, 0.01]	0.3987
Major Surgical Procedures (yes)	0.01	0.01	[-0.01, 0.02]	0.3284	0.01	0.01	[-0.01, 0.03]	0.1771
Parkinsonism (yes)	-0.01	0.01	[-0.03, 0.01]	0.3313	-0.02	0.01	[-0.04, 0.00]	**0.0129**
Geriatric Depression Scale	-0.03	0.01	[-0.04, -0.02]	**< 0.0001**	-0.02	0.01	[-0.04, 0.00]	**0.0116**
Hachinski ischemic Scores	0.01	0.01	[0.00, 0.03]	0.0539	-0.01	0.01	[-0.03, 0.01]	0.2312

Bold indicated that the results were statistically significant (*p<0.05)

The age, gender, years of education, *apolipoprotein Eε4* status, and baseline cognitive status were included as basic covariates

Abbreviations: β, regression coefficient; 95%CI, 95% Confidence Interval; SE, Standard Error; BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); kg, kilogram; cm, centimeter; kg/m^2, kilograms per square meter; mmHg, millimeters of mercury

may reflect systemic worsening frailty, which is associated with brain Aβ deposition [42]. On the other hand, chronic systemic inflammation, caused by low BMI, may aggravate Aβ pathology [43]. Additionally, certain adipokines, such as leptin, may play a key role. Studies have shown that higher levels of leptin in obese populations are associated with better cognitive function [44]. Meanwhile, the impact of BMI on dementia appears to be threshold-dependent. A review found that in late life, the risk of AD decreases when BMI exceeds 27 kg/m². However, this protective effect for vascular dementia (VaD) is absent when BMI surpasses 39 kg/m² [45]. Therefore, future research should further investigate the optimal BMI range for late-life cognitive health.

As for lifestyle risk factors, both retired status and a history of drug abuse were found to be identified risk factors. For retired status, retired participants may engage in fewer social activities, and studies have shown that extensive social interaction was associated with better cognitive function [46]. For drug abuse, there is little literature on drug abuse and cognitive decline. Previous literature has found an association between long-term cannabis application and cognitive dysfunction [47] and smaller hippocampal volumes [48]. However, a study from 2018 found that opioid use was not associated with an increased risk of AD [49]. The specific mechanism is not clear. Drug abuse can be harmful to physical and mental health, including mood disorders, neurocognitive disorders, and cardiovascular and respiratory systems [50, 51], which may make abusers more susceptible to pathological amyloid deposition. Furthermore, dysfunction of the opioid system may be involved in the production of Aβ and hyperphosphorylation of tau [49].

In the study, a history of musculoskeletal diseases and urinary disease were both found to be risk factors. The connection between musculoskeletal diseases and cognitive decline in the A+ participants might be attributed to several underlying mechanisms. Chronic inflammation

Table 3 Multivariate mixed-effects model analyses of the temporal associations between MMSE/MoCA and risk factors

Factors	MMSE				MoCA			
	β	SE	95% CI	p	β	SE	95% CI	p
Body weight (kg)	0.01	0.01	[-0.01, 0.03]	0.2170	0.01	0.01	[-0.01, 0.02]	0.4318
BMI (≥ 25 kg/m^2)	0.01	0.01	[-0.01, 0.04]	0.1986	0.02	0.01	[0.00, 0.04]	**0.0306**
Diastolic pressure (mmHg)	0.01	0.01	[-0.01, 0.03]	0.3055	0.02	0.01	[0.00, 0.04]	**0.0214**
Race (ref: White)								
Asian (yes)	0.03	0.06	[-0.08, 0.14]	0.5754	-0.02	0.05	[-0.11, 0.08]	0.7280
Black (yes)	<-0.01	0.13	[-0.25, 0.24]	0.9735	0.01	0.09	[-0.16, 0.18]	0.9302
More than one (yes)	0.07	0.06	[-0.05, 0.18]	0.2778	0.10	0.05	[0.00, 0.21]	0.0585
Parental dementia (yes)	0.01	0.01	[-0.01, 0.03]	0.4393	<0.01	0.01	[-0.01, 0.02]	0.6298
Drug abuse (yes)	<-0.01	0.01	[-0.03, 0.02]	0.6438	-0.02	0.01	[-0.04, -0.01]	**0.0113**
Marital Status (ref: Married)								
Divorced	0.05	0.03	[-0.01, 0.12]	0.1329	<0.01	0.03	[-0.06, 0.06]	0.9595
Widowed	0.01	0.03	[-0.05, 0.08]	0.7045	0.03	0.03	[-0.03, 0.08]	0.3165
Never married	0.04	0.05	[-0.05, 0.13]	0.3920	0.04	0.04	[-0.04, 0.12]	0.2939
Retired (yes)	-0.03	0.01	[-0.05, -0.01]	**0.0048**	-0.03	0.01	[-0.04, -0.01]	**0.0025**
Hypertension (yes)	<0.01	0.01	[-0.02, 0.02]	0.8495	0.01	0.01	[0.00, 0.03]	0.1505
Psychiatric diseases (yes)	-0.01	0.01	[-0.04, 0.01]	0.1599	<0.01	0.01	[-0.01, 0.02]	0.7046
Cardiovascular diseases (yes)	<0.01	0.01	[-0.02, 0.02]	0.8146	0.02	0.01	[0.00, 0.03]	0.0815
Dermatologic-Connective Tissue diseases (yes)	<0.01	0.01	[-0.02, 0.02]	0.6984	<-0.01	0.01	[-0.02, 0.02]	0.9776
Musculoskeletal diseases (yes)	-0.01	0.01	[-0.03, 0.01]	0.3257	-0.01	0.01	[-0.03, 0.01]	0.3376
Hematopoietic-Lymphatic diseases (yes)	<-0.01	0.01	[-0.02, 0.02]	0.7390	<0.01	0.01	[-0.01, 0.02]	0.8210
Urinary disease (yes)	-0.02	0.01	[-0.04, 0.00]	**0.0242**	<-0.01	0.01	[-0.02, 0.01]	0.5832
Allergies or Drug Sensitivities (yes)	<-0.01	0.01	[-0.03, 0.02]	0.7050	-0.01	0.01	[-0.03, 0.00]	0.1582
Major Surgical Procedures (yes)	0.02	0.01	[0.00, 0.04]	0.0510	0.02	0.01	[0.00, 0.04]	**0.0350**
Parkinsonism (yes)	-0.03	0.01	[-0.06, -0.01]	**0.0115**	-0.02	0.01	[-0.05, 0.01]	0.1168
Geriatric Depression Scale	-0.03	0.01	[-0.05, -0.01]	**0.0029**	-0.03	0.01	[-0.04, -0.01]	**0.0005**
Hachinski ischemic Scores	-0.01	0.01	[-0.03, 0.01]	0.2119	<0.01	0.01	[-0.02, 0.02]	0.8309

Bold indicated that the results were statistically significant (*p<0.05)

The age, gender, years of education, *apolipoprotein Eε4* status, and baseline cognitive status were included as basic covariates

Abbreviations: MMSE, the Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; β, regression coefficient; 95%CI, 95% Confidence Interval; SE, Standard Error; BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); kg, kilogram; cm, centimeter; kg/m^2, kilograms per square meter; mmHg, millimeters of mercury

is a common feature of both musculoskeletal disorders, such as osteoarthritis [52] and myositis, and neurodegenerative diseases. Elevated levels of pro-inflammatory cytokines may inhibit the phagocytosis of Aβ in the brain. Concurrently, the abnormal accumulation of amyloid oligomers can trigger excessive release of pro-inflammatory factors, further exacerbating neuronal damage and cognitive decline [53]. Another aspect to consider is the role of physical activity. Musculoskeletal diseases often lead to reduced mobility and physical inactivity, which are known risk factors for cognitive decline. Exercise training can upregulate the expression of the hippocampal Dicer gene, which may help reduce Aβ accumulation and slow the progression of AD [54]. For urinary disease, previous studies have shown that brain-derived Aβ and tau proteins could be transported to the periphery for clearance, and the kidneys are key organs in this process. Declining kidney function can lead to the accumulation of these neurotoxic substances, further impacting brain health and cognitive function [55, 56].

Our study found that Parkinsonism was associated with a cognitive decline in A+ participants, especially in older men (≥70 years). One possible explanation is that serotoninergic system degeneration in Parkinson's disease (PD) promotes the development of cerebral amyloidosis [57]. Parkinsonism could occur in many diseases, including PD and Lewy body dementia. These diseases are associated with α-synuclein. Another possible explanation for this is that there is a correlation between Aβ load and accumulation of abnormal α-synuclein [58]. Abnormally aggregated α-synuclein may be a synergistic factor between amyloid aggregation [59]. However, some studies suggested the prevalence of amyloid deposition is lower in PD patients with MCI compared to non-PD MCI participants [60]. In our study, there were fewer participants with Parkinsonian symptoms, so this conclusion should be approached with caution. Depression was also a risk factor for cognitive decline in A+ participants. Consistent with our finding, depression has been reported to have associations with Aβ levels

Table 4 Multivariate Cox regression analysis of risk factors for cognitive diagnostic conversion

Factors	HR	β	95%CI	*p*
Body weight (kg)	0.99	-0.01	[0.98, 1.01]	0.4328
BMI (≥ 25 kg/m^2)	0.95	-0.05	[0.60, 1.51]	0.8382
Race (ref: White)				
Asian (yes)	0.84	-0.17	[0.30, 2.40]	0.7516
Black (yes)	1.01	0.01	[0.24, 4.29]	0.9909
More than one (yes)	0.60	-0.50	[0.14, 2.60]	0.4981
Alcohol abuse (yes)	1.34	0.29	[0.59, 3.05]	0.4911
Marital Status (ref: Married)				
Divorced	0.91	-0.09	[0.49, 1.70]	0.7683
Widowed	0.66	-0.42	[0.34, 1.26]	0.2030
Never married	0.81	-0.21	[0.31, 2.13]	0.6662
Retired (yes)	1.65	0.50	[0.91, 3.01]	0.0996
Stroke (yes)	1.48	0.39	[0.79, 2.78]	0.2232
Hepatic diseases (yes)	0.74	-0.31	[0.31, 1.73]	0.4819
Gastrointestinal diseases (yes)	0.78	-0.24	[0.54, 1.13]	0.1912
Parkinsonism (yes)	6.55	1.88	[1.80, 23.91]	**0.0044**
Geriatric Depression Scale	2.381	0.87	[1.58, 3.60]	**< 0.0001**

Bold indicated that the results were statistically significant (*p < 0.05)

The age, gender, years of education, *apolipoprotein Eε4* status, and baseline cognitive status were included as basic covariates

Abbreviations: HR, hazard ratio; β, regression coefficient; 95%CI, 95% Confidence Interval; BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); kg, kilogram; cm, centimeter; kg/m^2, kilograms per square meter; mmHg, millimeters of mercury
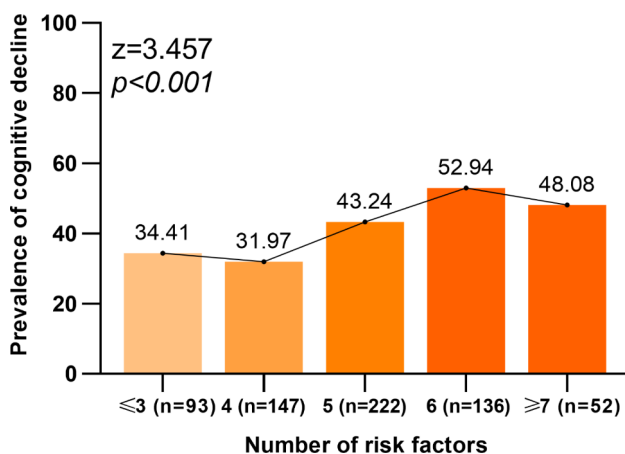
Fig. 4 Trend test. The Cochran-Armitage trend analysis showed that the risk of cognitive decline in A+ subjects increased with the number of concurrent risk factors (*p* for trend = 0.0005)

and cognition. A study showed that depression accelerated the cognitive decline in A+ MCI patients [61]. Another study of community-dwelling older adults found that participants with depressive symptoms had higher plasma Aβ$_{42}$ levels than those without depressive symptoms [62]. There are two possible explanations for these associations. First, depressive symptoms may promote the activation of chronic inflammatory pathways, and these inflammatory and pro-inflammatory cytokines are associated with the expression and processing of Aβ

precursor proteins [63]. Another possible explanation is that both AD and depression damage 5-hydroxytryptamine systems, which may increase the Aβ burden [64]. With the increase of Aβ-related pathological burden, participants will have cognitive impairment and decline [65].

We have observed that certain risk factors exhibit more significant associations within the T- subgroup. This could potentially be explained as follows: On the one hand, A+/T+ is defined as a biological diagnosis of AD, and individuals in this group typically display more typical AD pathological features compared to A+/T- individuals. These characteristics are less likely to be influenced by external factors, thereby reducing the impact of modifiable risk factors on cognitive decline. On the other hand, according to the NIA-AA Research Framework, A+/T- and A+/T+ represent a continuum of the disease process. Therefore, differences in the T status subgroup may suggest that various risk factors play different roles at different stages of the AD continuum. Another consideration is that our study focused on non-demented A+ individuals, which inherently constrained the sample composition. Compared to the T- group, the number of T+ samples was relatively smaller. The limited sample size of the T+ subgroup may be related to the lower positivity rate in this subgroup.

Surprisingly, dermatologic-connective tissue diseases and major surgical procedures were found to be protective factors for A+ participants. An observational meta-study finds rheumatoid arthritis is associated with a lower incidence of AD [66]. While another observational study found autoimmune rheumatic diseases increase dementia risk [67]. The results are difficult to interpret, but they may be related to long-term oral anti-inflammatory drugs and hormone therapy, which helped delay Aβ deposition [68]. The potential protective mechanisms of major surgical procedures for A+ patients may include the following: participants undergoing proactive treatments (such as surgical procedures) may reduce the cognitive damage caused by comorbidities or chronic pain. Moreover, successful surgical interventions can enhance mobility and physical activity, thereby improving cognitive function. However, no surgical history was considered only a suggestive risk factor. Future research with larger sample sizes is needed for further validation.

There are several important points to note in the study: (1) Different types of cognitive functions are affected by different risk factors. For example, ADNI-MEM, which represents memory function, was mainly influenced by factors such as low BMI, drug abuse, and Parkinsonism; whereas ADNI-EF2, which represents executive function, was primarily affected by low diastolic blood pressure and a lack of history of skin connective tissue disease. (2) Parkinsonism and depression, both associated with the cognitive diagnosis conversion, also increased the rate of

decline in memory-related indicators (ADNI-MEM and MMSE). This finding aligns with the main characteristics of Alzheimer's disease, which include deteriorating memory function. These results may offer new insights for developing more precise intervention strategies for different populations with cognitive dysfunction.

Some advantages existed in our study. Firstly, the large sample size and the long follow-up period increased the reliability of our study. Secondly, two models were used to assess risk factors for cognitive decline in A+ participants. The generalizability of these results is subject to certain limitations. Firstly, our study is an observational study with unavoidable bias and confounding, so more randomized controlled trials will be needed in the future. Secondly, although our study briefly described the risk factors of cognitive decline in A+ participants and provided clues for the prevention of dementia, more detailed mechanism studies are needed in the future. Third, Aβ pathology is closely related to tau pathology. The study did not assess the effect of tau pathology in detail. Subgroup analyses were conducted for tau content to observe its impact on the results. Fourth, our study only analyzed baseline risk factors; however, changes in risk factors over time are also important. Future research should incorporate a longitudinal analysis of risk factors.

In conclusion, our study identified low diastolic pressure, low BMI, retired status, a history of drug abuse, Parkinsonism, depression, urinary disease, musculoskeletal diseases, as well as no prior dermatologic-connective tissue diseases or major surgical procedures as risk factors for a cognitive decline in A+ participants. The findings of this study will be more targeted to prevent cognitive decline in A+ people and have important implications for future dementia prevention practices.

Abbreviations

AD	Alzheimer's disease
Aβ	Amyloid-beta
A+	Amyloid-beta-positive
T+	Tau positivity
ADNI	The Alzheimer's Disease Neuroimaging Initiative
PET	Positron emission tomography
CN	Cognitively normal
MCI	Mild cognitive impairment
ADNI-MEM	ADNI Composite Memory Score
ADNI-EF2	ADNI Composite Executive Function 2 Score
HRs	Hazard ratios
GDS	The Geriatric Depression Scale
HIS	Hachinski Ischemic Scale
SCD	Subjective cognitive decline
CSF	Cerebrospinal fluid
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-024-01554-0.

Supplementary Material 1

Author contributions
H.H. concepted and designed the study, analyzed the data, and drafted the manuscript. L.T. concepted and designed the study, and drafted the manuscript. A.Y.W. extracted, analyzed and interpreted the data, and drafted the manuscript. H.Y.H. analyzed the data and drafted the manuscript. L.Y.H. extracted and analyzed the data. C.Y.X. analyzed the data. Q.Y.L analyzed the data. All authors have contributed to the manuscript writing and revision. All authors reviewed the manuscript.

Data availability
The datasets supporting the conclusions of this article are available in the publicly available ADNI database. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study procedures were approved by the institutional review boards of all participating centres (http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf), and written informed consent was obtained from all participants or their authorised representatives according to the Declaration of Helsinki (consent for research). Ethics approval was obtained from the institutional review boards of each institution involved: Oregon Health and Science University; University of Southern California; University of California—San Diego; University of Michigan; Mayo Clinic, Rochester; Baylor College of Medicine; Columbia University Medical Center; Washington University, St. Louis; University of Alabama at Birmingham; Mount Sinai School of Medicine; Rush University Medical Center; Wien Center; Johns Hopkins University; New York University; Duke University Medical Center; University of Pennsylvania; University of Kentucky; University of Pittsburgh; University of Rochester Medical Center; University of California, Irvine; University of Texas Southwestern Medical School; Emory University; University of Kansas, Medical Center; University of California, Los Angeles; Mayo Clinic, Jacksonville; Indiana University; Yale University School

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