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Hypertension may lead to cognitive dysfunction in older adults via methylmalonic acid: evidence from NHANES 2011–2014 population

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Abstract

Background An enriched understanding is necessary concerning the association between hypertension and cognitive impairment in older adults, particularly regarding the potential underlying mechanisms at a biological level. This study aimed to explore the mediating role of methylmalonic acid (MMA) in the hypertension-cognition link in the older population.

Methods A total of 2762 adults (age > =60 years) from the National Health and Nutrition Examination Survey (NHANES) 2011–2014 participated. Cognitive function was assessed using a combination of the Animal Fluency Test (AFT), the Digit Symbol Substitution Test (DSST), and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Learning Test. Self-reported hypertension diagnosis, antihypertensive medications use, and blood pressure examinations were used to identify hypertension. Serum MMA (sMMA) levels were collected. Weighted multiple linear regressions and mediation analysis were applied. A subgroup analysis by sex and age was performed.

Results After adjusting for potential confounding factors, we observed a significant mediating effect of the sMMA level in the hypertension-cognition link, accounting for 11.14% (95% CI 4.09%-14.00%, $p < 0.001$) of the relationship in older adults. The proportion mediated by the sMMA level in the relationship between hypertension and cognitive function was higher in males (15.23%, 95%CI 1.32%-27.00%, $p < 0.001$) than in females (6.61%, 95%CI 2.12%-10.00%, $p < 0.001$). This mediating effect of sMMA was observed only in individuals aged 68 years and older (11.31%, 95%CI 3.80%-16.00%, $p < 0.001$), with no significant mediation detected in those younger than 68 years.

Conclusion Hypertension may lead to cognitive dysfunction in older adults through MMA. Apart from its role as a biomarker reflecting vitamin B12, MMA may act as an independent neurotoxin capable of inducing brain injury and cognitive impairment. Addressing MMA accumulation, such as through Vitamin B12 supplementation, may have a potential to mitigate hypertension-induced cognitive decline in older adults. Special attention could be paid to hypertensive males with an advanced age (> =68) to address MMA-related cognitive decline.

Keywords Hypertension, Cognitive impairment, Methylmalonic acid, Older adults, Mediation analysis

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Background

Hypertension, usually defined as persistent systolic blood pressure (SBP) at least 140 mm Hg or diastolic blood pressure (DBP) at least 90 mm Hg [1], poses a significant global health challenge, affecting over 1.3 billion individuals worldwide [2]. It is most prevalent among older adults [3, 4], with nearly two-thirds of this population experiencing high blood pressure (BP) [5], and with the aging population, the number of older adults with hypertension is expected to increase substantially [6–8]. Hypertension is not only a major risk factor for cardiovascular diseases but is also increasingly linked to cognitive decline, a critical public health concern as the population ages [9–14].

Cognitive decline encompasses a range of mental abilities, such as memory, attention, and executive function, which tend to deteriorate with age [15, 16]. Research has shown that age-associated degeneration in cognitive function is strongly linked to the risk of developing dementia [17], resulting in diminished functional independence among the older adults reduced quality of life, and heightened economic and societal burdens [18]. According to a study by Röhr et al. (2020), which analyzed 16 cohorts from 15 countries, the prevalence of subjective cognitive decline—defined as a self-experienced decline in cognitive ability compared to a previously normal status and often considered an early sign preceding more noticeable conditions such as mild cognitive impairment (MCI) and dementia —was approximately 25% in adults aged 60 and older [19]. The overall prevalence of MCI in community-dwelling adults aged 50 and older was estimated to be 15.56% [20]. Currently, more than 55 million people worldwide have dementia, with nearly 10 million new cases each year [21]. Thus, it is imperative to understand the changes in cognitive function in older population and explore all the possibilities to delay the onset of or slow down cognitive decline.

There is growing evidence that hypertension is one of the modifiable risk factors for cerebral vessel dysfunction, which contributes to cognitive decline and dementia [22–26]. Based on a low-income population aged over 60 years in northern China, Bao et al. (2021) had found that the prevalence of cognitive impairment in hypertensive patients was significantly higher than that in non-hypertensive individuals [27]. Similarly, Jia et al. (2020) found that individuals with high blood pressure had an 86% higher risk of developing dementia and a 62% higher risk of MCI compared to those with normal blood pressure [28]. According to Walker et al. (2019), individuals with consistently high blood pressure in both middle and old age faced a 49% higher risk of developing dementia compared to those with normal blood pressure [29].

However, inconsistencies remain, with some studies finding no significant association between late-life hypertension and cognitive decline [30–33]. For example, with a longitudinal study, Posner et al. (2002) reported that hypertension after age 65 years was not associated with mental diseases and did not adversely affect memory, language, or general cognitive function [34]. Although meta-analyses of BP lowering trials indicated a notable decrease in the risk of dementia among individuals receiving antihypertensive treatments, the relative and absolute risk reductions were modest [14]. Furthermore, the mechanisms linking hypertension to cognitive dysfunction remain unclear, though most studies focus on structural changes in the brain and microvascular damage [14, 35, 36]. Questions remain about the development and progression of hypertension-induced cognitive impairment and the targeted treatment. Hence, there is a need for a more comprehensive understanding of the link between hypertension and cognitive impairment, especially the potential underlying mechanisms.

Methylmalonic acid (MMA), a by-product of propionate metabolism in human body, is considered a surrogate biomarker of mitochondrial dysfunction and oxidative stress, and can predict all-cause and cardiovascular mortality in the general population [37, 38]. Impaired mitochondrial function can hinder the production of adenosine triphosphate (ATP) and disrupt energy balance, potentially affecting MMA metabolism and leading to the accumulation of MMA in tissues [39]. Most studies, although not all, have found that elevated MMA levels are associated with cognitive impairment in older adults [40, 41]. According to Doets et al. (2013), individuals with higher MMA concentrations experienced an accelerated decline in overall cognition, with a doubling of MMA concentration being linked to a roughly 60% increase in the rate of cognitive decline [42]. Meanwhile, although the cause-and-effect relation between high BP and mitochondrial dysfunction or oxidative stress remains elusive, some studies have observed elevated MMA levels in patients suffering with hypertension [37, 43–45]. Further, a high MMA level is often viewed as a marker of Vitamin B12 deficiency [46, 47], which suggests that supplementing vitamin B12 may have a potential to reduce the risk of MMA accumulation and that it could be possible to use vitamin B12 to prevent hypertension-induced cognitive decline for older adults. Thus, a study on the role of MMA between hypertension and cognitive decline is promising, having a potential to provide new therapeutic options.

Given that no particular study has explored the association between hypertension, MMA, cognitive decline in the older population, this study aims to elucidate the association between hypertension and cognitive function

in this population by assessing the potential mediating role of MMA. It may add new knowledge on the pathway in the hypertension-cognition link and provide valuable insights into the development of appropriate measures for managing hypertension in older adults, especially preventing or delaying hypertension-induced cognitive decline.

Methods

Study design and participants

We conducted a cross-sectional study, utilizing the National Health and Nutrition Examination Survey (NHANES) database 2011–2014. NHANES is a national cross-sectional survey program conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) in two-year cycles, with a goal of providing insights into various health conditions, risk factors, and nutritional patterns of families and populations in the United States (https://www.cdc.gov/nchs/nhanes/index.htm). The NHANES 2011–2012 and 2013–2014 cycles, which are the only two cycles providing data on both serum MMA (sMMA) levels and cognitive function assessments with multiple tests, present a unique opportunity for conducting the proposed study. The survey's data collection procedures were approved by the research ethics review board of the National Center for Health Statistics. Written informed consent was obtained from all participants in the NHANES [48]. For protecting the identities of the individuals involved, the NHANES database anonymizes participants' data and employs unique identifiers called "Respondent sequence number" (SEQN).

Our researchers found relevant datasets, i.e., Demographics Data, Dietary Data, Examination Data, Laboratory Data, and Questionnaire Data, for the years 2011–2012 and 2013–2014 at the section of "Questionnaires, Datasets, and Related Documentation" in NHANES homepage. We downloaded all the datasets and combined them by SEQN for each cycle. We harmonized all the data for making variable names and coding consistent between the two cycles.

Figure 1 outlines the process of identifying the study population. The inclusion criteria for participant selection were: 1) adults aged 60 years or older, and 2) individuals with complete data on hypertension status, sMMA levels, and cognitive function assessments. Participants were excluded if they were under 60 years of age or had missing or incomplete data on hypertension, sMMA, or cognitive tests. As this study involved individuals aged 60 and above, a total of 19931 participants were identified. After excluding participants with missing information on hypertension, sMMA, and any test of cognitive function, 2762 participants were included in the analysis.

NHANES created weights applied to the data to account for oversampling, nonresponse, and noncoverage, thereby forming representative samples of the U.S. civilian noninstitutionalized resident population. In this study involving Mobile Examination Center (MEC) data, the 2-year sample weight (wtmec2yr) accounted for 2 cycles (1/2*wtmec2yr) was used for all analyses, which allowed for the generation of nationally representative estimates with a weighted population estimated to be around 101 million. More information about the weights

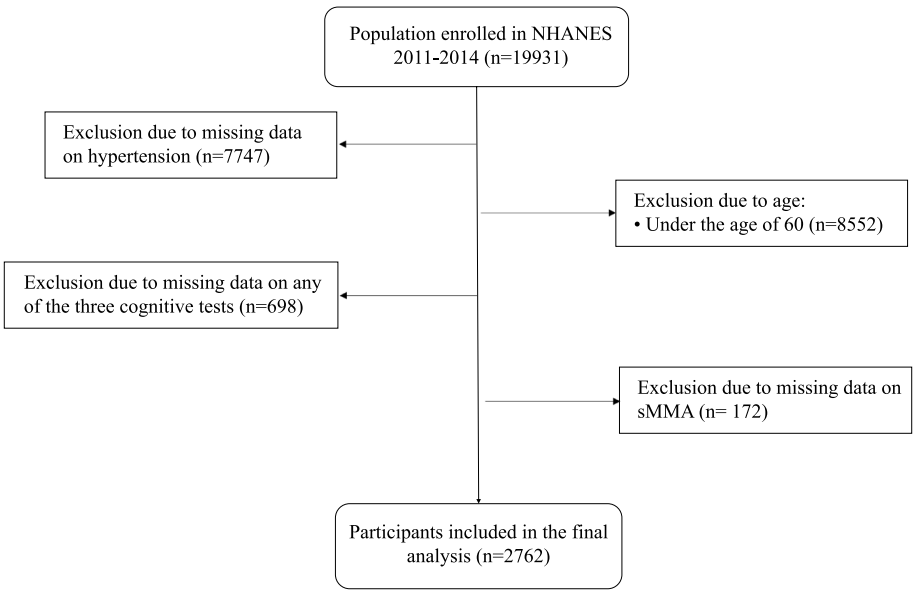

Fig. 1 Flowchart of the study population. Figure 1 presents the flow chart of identifying the study population

and their associated process could be found on the NHANES website via the following link: https://wwwn.cdc.gov/nchs/nhanes/tutorials/weighting.aspx.

Hypertension

In this study, hypertension (no/yes) was defined as systolic blood pressure > =140 mmHg, diastolic blood pressure > =90 mmHg [49], taking antihypertensive medications, or self-reported diagnosis of hypertension by the participants. These criteria have been widely used in NHANES-based studies to identify hypertension [50]. Participants who reported not having hypertension but taking antihypertensive medications were considered non-hypertensive, as the medications might be prescribed for reasons other than a high blood pressure.

In the NHANES program, BP is measured by trained clinicians at the MEC using a mercury sphygmomanometer and an appropriately sized blood pressure cuff. Blood pressure is measured after 5 min of sitting still, and three blood pressure readings is taken at 30-s intervals. If one of the three blood pressure measurements is invalid, a fourth reading will be taken. The participants had 1 to 4 blood pressure readings in the study. Some participants had only one reading, which was considered the final record. In cases where participants had more than one reading, the first reading was excluded in blood pressure calculation, which is a common practice in research and clinical practices to mitigate the potential impact of transient factors such as stress or physical activities that may influence the initial reading [51, 52]. In this study, the blood pressure was determined by averaging the readings after excluding the first reading.

Cognitive function

Participants' cognitive function was assessed using a combination of tests, including the Animal Fluency Test (AFT), the Digit Symbol Substitution Test (DSST), and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Learning Test [53]. We employed Z-transformation to standardize the AFT, CERAD wordlist learning test, and DSST scores individually and combined these standardized scores (AFT_Z, CERAD_Z, and DSST_Z) into a composite score called " Total_Score_Z," which served as a representation of the participants' overall cognitive function in this study [54].

The AFT is a verbal fluency test that assesses semantic memory and executive function by requiring participants to name as many animals as possible within 1 min, resulting in a final score representing the total number of correct answers. The CERAD wordlist learning test, commonly utilized in clinical and research settings to assess cognitive function in relation to Alzheimer's disease and other forms of dementia, assess verbal episodic memory and include three consecutive learning trials (CERAD Trial 1 Recall, CERAD Trial 2 Recall, and CERAD Trial 3 Recall) followed by a delayed recall (CERAD Delayed Recall), with the total score (CERAD wordlist learning test total) representing the sum of the four trials. As participants match symbols to 133 adjacent number boxes within 2 min, the DSST, a cognitive performance test from the Wechsler Adult Intelligence Scale-III, measures processing speed, sustained attention, and working memory, with higher scores reflecting better cognitive function.

MMA

For measuring sMMA, blood samples were collected from participants by trained phlebotomists at the MEC, and the amount of blood drawn varied depending on the participant's age, with 75 μL of serum used for the analysis of sMMA. Serum samples were sent to the Division of Laboratory Sciences at the National Center for Environmental Health, CDC for analysis. For more information about the laboratory procedures of blood withdrawals, please consult the NHANES manual, which can be accessed on NHANES website [55]. An internal standard solution (d3-MMA) was added to 75 μl of serum, followed by MMA extraction through liquid–liquid extraction with tert-butylmethylether/H+. The extracted acid was then derivatized with butanol to form a dibutylester. Subsequently, the derivatized sample was reconstituted in acetonitrile–water, and MMA was separated chromatographically and quantified using liquid chromatography-mass spectrometry (LC–MS/MS) with multiple reaction monitoring [56].

Covariates

Variables, with available data from NHANES 2011–2014 (missing data < 60%), representing baseline characteristics of the participants, and identified as potential confounding factors that could exert an influence on the outcome based on previous studies [57, 58] or discussions conducted in the research team, were considered in this study and grouped into three categories as follows: 1) demographic characteristics including age, sex (male, female), ethnicity/race (non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic, other race), marital status (married or living with partner, widowed/divorced/separated/never married), education level (below high school, high school or equivalent, college or above); 2) other health conditions, mainly body mass index (BMI) and Vitamin B12 levels (divided into three groups: < 148 pmol/L defined as severe deficiency, 148–220 pmol/L as mild deficiency, and > =220 pmol/L as normal) [59–64]; 3) health-related lifestyle, including alcohol intake (a. short-term alcohol intake levels: within the recommended daily limits / exceeding the recommended

limits [assessed by averaging alcohol consumption per day in grams of two 24 h dietary recall interviews; according to updated national guidelines and recommendations regarding daily alcohol consumption [65–67], the recommended daily alcohol intake is up to 14 g/day for women and up to 28 g/day for men]; b. at least 12 drinks in the past 12 months (no/yes) [defined by participants' self-report of having at least 12 drinks of any type of alcoholic beverage in the past 12 months]), smoking (based on self-reported information, categorized as "never" if smoked < 100 cigarettes, "former" if not currently smoking but smoked ≥ 100 cigarettes in the past, or "current" if smoked ≥ 100 cigarettes and currently smokes every day or on some days), and physical activity (inactive/moderate/vigorous /both moderate and vigorous).

Statistical analysis

Descriptive statistics included mean with standard deviation (SD) and median with interquartile range (IQR) for continuous data, and frequencies and proportions for categorical data. The normality of the distribution of continuous variables in the dataset was assessed by the Kolmogorov–Smirnov as well as its histogram. As sMMA, a continuous variable, did not satisfy the assumption of normality, log-transformation was performed for its positively skewed distribution (Log_sMMA).

Prior to conducting the regression, we assessed multicollinearity among variables by calculating Variance Inflation Factors (VIFs) and found no evidence of multicollinearity among the variables. Linear regression models were employed to investigate the relationship between hypertension and cognitive function, between hypertension and the sMMA level, as well as between the sMMA level and cognitive function. Both unadjusted and multivariate-adjusted modeling were performed. The standardized regression coefficients (β) and their 95% confidence intervals (CIs) were calculated.

In detecting the potential mediating role of sMMA in the association between hypertension and cognitive function, we applied the strategy of distribution–of–the–product (Fig. 2), by checking 1) the total effect of hypertension on cognitive function while adjusting for all covariates (effect of path c), 2) the direct effect of hypertension on cognitive function after all covariates and sMMA were controlled (effect of path c'), 3) the indirect effect of hypertension on cognitive function through sMMA after all covariates were controlled (effect of path a * effect of path b), 4) the proportion mediated by sMMA (i.e., indirect effect/total effect).

Previous studies have demonstrated that sex and sex hormones are associated with both hypertension and cognitive function [68–70]. Additionally, research has indicated that sex influences the relationship between hypertension and cognitive function [70]. Taking into account the potential impact of sex on the results, we performed a subgroup analysis to investigate the variations in the mediating effect of sMMA on the relationship between hypertension and cognitive function in males and females.

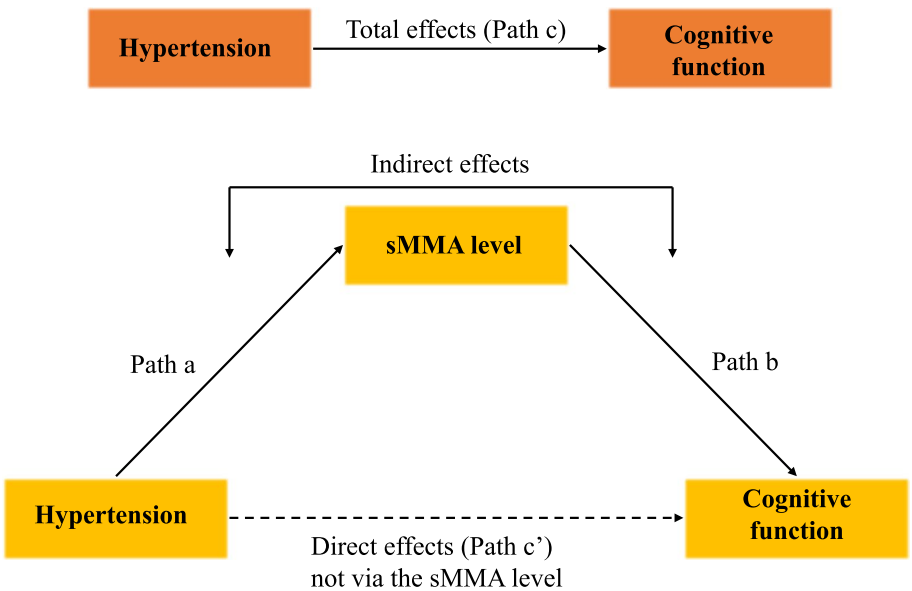

Fig. 2 Theoretical diagram of the mediation analysis. Figure 2 shows the theoretical model of the mediation analysis for the association between hypertension and cognitive function with the serum methylmalonic acid (sMMA) level as a potential mediator

A two-tailed p-value less than 0.05 was considered statistically significant. All statistical analyses were conducted using R version 4.3.1. The R mediation package was employed to conduct mediation analysis, with non-parametric bootstrapping in 1,000 resamplings [71]. Our analysis incorporated the complex sampling design and considered sampling weight (wtmec2yr/2) to enhance representativeness and accuracy in estimation. The R survey package was used to address the complex sampling design in practice [72].

Results

Participant characteristics

The characteristics, hypertension status, cognitive function scores, and the sMMA level of 2762 older adults (aged 60 years and above) are detailed in Table 1. The median age of the participants was 68 years (IQR: 12). The study population was evenly split between men and women. A significant majority of participants held a college degree or higher (75.00%). More than half were married or in a relationship (57.93%). Nearly half of the population identified as Mexican American (48.90%). Most participants were with abnormal BMI (74.50%). Approximately 70% of participants reported a low level of physical activity, nearly 90% indicated that their short-term alcohol consumption was within recommended limits, about 70% reported consuming more than 12 alcoholic drinks in the past 12 months and nearly 50% stated that they had never smoked. Around 70% of the participants had hypertension.

Association between hypertension and cognitive function

Table 2 demonstrates that hypertension was significantly associated with cognitive function (β [95% CI]: −0.982[−1.283, −0.680], $p < 0.001$). After sequentially introducing demographic characteristics, other health conditions, health-related lifestyle factors, and Log_MMA into the model, there was still a significant association between hypertension and cognitive function (β [95% CI]: −0.640[−0.935, −0.346], $p < 0.001$). Specifically, the individuals with hypertension had lower cognitive abilities than the ones without hypertension. From the crude model to Model 4, by gradually adding controlled variables, the R-square increased significantly, with F change values being statistically significant, except for the transition from model 1 to model 2 with the addition of BMI and Vitamin B12. This indicated that most additional variables had a notable effect on the dependent variable, namely the cognitive function score, and the model's explanatory power increased significantly with the addition of controlled variables.

Table 1 Basic characteristics of the study sample (NHANES 2011-2014)

Characteristics	Overall (*N*=2762)
Age, N (%)	
<68	1266(45.80)
>=68	1496(54.20)
Sex, N (%)	
Male	1355(49.10)
Female	1407(50.90)
Ethnicity/Race, N (%)	
Non-Hispanic White	244(8.80)
Non-Hispanic Black	625(22.60)
Mexican American	1351(48.90)
Other Hispanic	278(10.10)
Other Race	264(9.60)
Education Level, N (%)	(*n*=2760)
Below high school	310(11.23)
High school or equivalent	379(13.73)
College or above	2071(75.04)
Marital status, N (%)	(*n*=2760)
Married/Living with partner	1599(57.93)
Widowed/Divorced/Separated/ Never married	1161(42.07)
BMI, kg/m^2, N (%)	(*n*=2722)
18.5-24.9	694(25.50)
<18.5	39(1.43)
25-29.9	966(35.49)
>=30	1023(37.58)
Vitamin B12, pmol/L, N (%)	(*n*=2757)
<148	74(2.68)
148-220	257(9.32)
>=220	2426(88.00)
Physical Activity, N (%)	
Inactive	1919(69.48)
Moderate	543(19.66)
Vigorous	80(2.90)
Both moderate and vigorous	220(7.96)
Short-term Alcohol Intake, gm, N (%)	(*n*=2393)
<= 28 (Male) / <=14 (Female)	2140(89.43)
>28 (Male) / >14 (Female)	253(10.57)
Alcohol Drinks >=12 in the Past 12 Months, N (%)	(*n*=2715)
No	850(31.31)
Yes	1865(68.69)
Smoking, N (%)	(*n*=2760)
Never	1362(49.30)
Former	1040(37.70)
Current	358(13.00)
Hypertension, N (%)	
No	821(29.03)
Yes	1941(70.97)
sMMA, nmol/L, median (IQR)	210.96(101.50)
Log_sMMA, mean (SD)	5.18(0.52)
Total_Score, mean (SD)	87.47(24.71)
Total_Score_Z, mean (SD)	0.44(2.41)

Categorical variables are number of subjects(percentage),continuous variables are mean±standard deviation. *BMI* Body mass index, *sMMA* Serum methylmalonic acid, *Log_sMMA* The log transformed sMMA; Total_Score: sum of CERAD wordlist learning test, AFT and DSST scores; Total_Score_Z: the sum of standardized scores of CERAD wordlist learning test, AFT and DSST

Association between hypertension and the sMMA level

Following adjustments for age, sex, ethnicity/race, education level, marital status, BMI, Vitamin B12, physical activity, short-term alcohol intake, alcohol drinks > =12 in the past 12 months, and smoking, it was observed that there was a significant association between hypertension and the sMMA level (β [95% CI]:0.123[0.078, 0.169], $p < 0.001$). Specifically, the individuals with hypertension had a higher sMMA level than the ones without hypertension. Table 3 shows the results of regressions regarding the association between the hypertension and the sMMA level.

The association between the sMMA level and cognitive function

There was a significant relationship between the sMMA level and cognitive function score ($p < 0.001$). Following adjustments for age, sex, ethnicity/race, education level, marital status, BMI, Vitamin B12, physical activity, short-term alcohol intake, alcohol drinks > =12 in the past 12 months, and smoking, it was observed that Total_Score_Z decreased by around 0.567 SDs (approximately 1.366 points in the original scale) for each SD increase in the Log_sMMA (approximately 0.52 points in the natural scale). Table 4 shows the results of regressions regarding the association between the sMMA level and cognitive function.

The mediating role of sMMA in the association between hypertension and cognitive function

We further explored the potential mediating effect of sMMA on the relationship between hypertension and cognitive function reflected by Total_Score_Z. Table 5 and Fig. 3 show that after adjusting for controlled variables, the sMMA significantly mediated the link between hypertension and cognitive function (proportion mediated: 11.14%; Indirect effect: −0.0668[−0.0830, −0.0300], $p < 0.001$). In the subgroup analysis based on sex (male and female), after adjusting for all other covariates, the proportion mediated by the sMMA level in the relationship between hypertension and cognitive function was higher in males (15.23%, 95%CI 1.32%−27.00%, $p < 0.001$) than in females (6.61%, 95%CI 2.12%−10.00%, $p < 0.001$). Furthermore, this mediating effect was observed in individuals aged 68 years and older (11.32%, 95% CI: 3.80%—16.00%, $p < 0.001$), with no significant mediation detected in those younger than 68 years.

Discussion

Our results revealed a significant association between hypertension and lower cognitive function, with sMMA mediating a significant portion of this relationship. The mediating effect of sMMA was more pronounced in males and individuals aged 68 years and older. This study highlights the potential importance of addressing both hypertension and MMA levels to mitigate cognitive decline in older adults.

The association between hypertension and cognitive function found in the study was consistent with numerous large-scale cross-sectional or longitudinal studies across different regions and age groups [29, 73–75]. For example, Wei et al. (2018), using longitudinal data from the China Health and Retirement Longitudinal Study (CHARLS), found that uncontrolled hypertension had a negative impact on cognitive function, particularly in the aspects of episodic memory and executive function [75]. However, inconsistent results have been reported in other studies, with some indicating no significant impact of hypertension on cognitive decline in older adults [76–78]. This variation could be partially attributed to differences in the characteristics of the studied populations, the approaches to defining hypertension, as well as the methods used to assess cognitive function or other confounding factors. Our results emphasize the importance of addressing hypertension in older individuals to prevent adverse cognitive decline and offering hypertensive older adults with proactive screening and tailored interventions.

Moreover, given the potential impact of age, sex, ethnicity/race, education level, marital status, and smoking on cognitive function, it may be crucial to offer additional support to older men from non-white ethnic groups, with lower levels of education, without a partner, or who are smoking. Interestingly, alcohol intake > =12 drinks in the past 12 months was positively associated with cognitive function, while short-term alcohol intake showed no significant association with cognitive performance. This may be due to the fact that only a small proportion of the participants ($n = 253$, 9.2%) exceeded the recommended daily alcohol consumption limits, while the majority engaged in light to moderate alcohol consumption, which has been shown to have protective effects on cognitive function [79–81]. The protective effects of moderate alcohol intake on cognition are likely due to mechanisms such as improved cardiovascular health, which is closely linked to brain health [82, 83]. These findings highlight the importance of considering both the quantity and frequency of alcohol consumption, as well as capturing habitual drinking patterns alongside recent consumption behaviors, when assessing the effects of alcohol intake on cognition.

An important observation from this study is that the sMMA level was associated with hypertension. Recently, similar to our study, Wang et al. (2022) using data from NHANES 2013–2014, and Dhar et al. (2023) using data from two large clinical cohorts in Norway,

Table 2 Regressions exploring the association between hypertension and cognitive function

	Crude model			Model 1			Model2			Model 3			Model 4		
	β	95%CI	*P*	β	95%CI	*P*	β	95%CI	*P*	β	95%CI	*P*	β	95%CI	*P*
Hypertension															
No	Ref			Ref			Ref			Ref			Ref		
Yes	−0.982	−1.283, −0.680	< 0.001	−0.640	−0.931, −0.358	< 0.001	−0.666	−0.956, −0.375	< 0.001	−0.699	−0.983, −0.416	< 0.001	−0.640	−0.935, −0.346	< 0.001
Age															
< 68				Ref			Ref			Ref			Ref		
> = 68				−1.582	−1.803, −1.361	< 0.001	−1.536	−1.771, −1.300	< 0.001	−1.439	−1.666, −1.213	< 0.001	−1.376	−1.601, −1.151	< 0.001
Sex															
Male				Ref			Ref			Ref			Ref		
Female				0.590	0.387, 0.793	< 0.001	0.608	0.385, 0.831	< 0.001	0.699	0.429, 0.970	< 0.001	0.681	0.405, 0.956	< 0.001
Ethnicity/Race															
Non-Hispanic White				Ref			Ref			Ref			Ref		
Non-Hispanic Black				−1.397	−1.711, −1.082	< 0.001	−1.416	−1.736, −1.095	< 0.001	−1.289	−1.628, −0.941	< 0.001	−1.385	−1.754, −1.016	< 0.001
Mexican American				−0.766	−1.165, −0.368	< 0.001	−0.799	−1.199, −0.398	< 0.001	−0.829	−1.243, −0.416	0.001	−0.896	−1.327, −0.466	0.001
Other Hispanic				−1.538	−1.874, −1.203	< 0.001	−1.535	−1.864, −1.206	< 0.001	−1.408	−1.744, −1.071	< 0.001	−1.468	−1.842, −1.094	< 0.001
Other Race				−0.755	−1.115, −0.394	< 0.001	−0.701	−1.077, −0.325	0.001	−0.468	−0.884, −0.053	0.031	−0.558	−0.975, −0.140	0.015
Education Level															
Below high school				Ref			Ref			Ref			Ref		
High school or equivalent				1.022	0.585,1.459	< 0.001	0.998	0.559, 1.437	< 0.001	0.837	0.345, 1.329	0.004	0.796	0.311, 1.282	0.005
College or above				2.436	2.046,2.827	< 0.001	2.420	2.024, 2.816	< 0.001	2.125	1.647, 2.603	< 0.001	2.072	1.562, 2.581	< 0.001
Marital Status															
Married/Living with partner				Ref			Ref			Ref			Ref		

Table 2 (continued)

	Crude model			Model 1			Model2			Model 3			Model 4		
	β	95%CI	*P*	β	95%CI	*P*	β	95%CI	*P*	β	95%CI	*P*	β	95%CI	*P*
Widowed/ Divorced/ Separated/ Never married				−0.382	−0.689, −0.075	0.017	−0.382	−0.694, −0.069	0.020	−0.330	−0.651, −0.010	0.045	−0.280	−0.609, 0.050	0.087
BMI															
18.5–24.9							Ref			Ref			Ref		
< 18.5							−0.482	−1.337, 0.372	0.250	−0.510	−1.546, 0.526	0.299	−0.458	−1.498, 0.583	0.346
25–29.9							0.085	−0.245, 0.415	0.593	0.073	−0.277, 0.422	0.653	0.056	−0.289, 0.401	0.722
> = 30							0.205	−0.151, 0.560	0.242	0.206	−0.143, 0.555	0.217	0.194	−0.159, 0.547	0.246
Vitamin B12															
< 148							Ref			Ref			Ref		
148–220							0.563	−0.050, 1.176	0.070	0.554	−0.142, 1.251	0.107	0.343	−0.417, 1.103	0.334
> = 220							0.504	−0.040, 1.047	0.067	0.503	−0.063, 1.068	0.076	0.129	−0.429, 0.688	0.613
Physical Activity															
Inactive										Ref			Ref		
Moderate										0.275	−0.021, 0.571	0.065	0.267	−0.038, 0.572	0.079
Vigorous										0.144	−0.396, 0.684	0.566	0.211	−0.313, 0.735	0.386
Both moderate and vigorous										0.436	0.008, 0.864	0.047	0.395	−0.048, 0.839	0.075
Short-term Alcohol Intake, gm, N (%)															
< = 28 (Male) / < = 14 (Female)										Ref			Ref		
> 28 (Male) / > 14 (Female)										0.192	−0.269, 0.654	0.374	0.184	−0.286, 0.654	0.399

Table 2 (continued)

	Crude model			Model 1			Model2			Model 3			Model 4		
	β	95%CI	*P*	β	95%CI	*P*	β	95%CI	*P*	β	95%CI	*P*	β	95%CI	*P*
Alcohol Drinks > = 12 in the Past 12 Months, N (%)															
No										Ref			Ref		
Yes										0.590	0.315, 0.864	< 0.001	0.578	0.305, 0.852	< 0.001
Smoking															
Never										Ref			Ref		
Former										−0.285	−0.628, 0.057	0.093	−0.304	−0.646, 0.038	0.076
Now										−0.596	−1.015, −0.177	0.010	−0.590	−1.019, −0.160	0.013
Log_sMMA													−0.476	−0.725, −0.227	0.002
R-squared	0.0370			0.3120			0.3130			0.3290			0.3360		
Adjusted R-squared	0.0367			0.311			0.3100			0.3261			0.3329		
F-change				825.225, $p < 0.001$			5.886, $p = 0.344$			34.814, $p = 0.017$			18.703, $p = 0.002$		

Crude model: Non-adjusted

Model 1: Adjusted for age, sex, ethnicity, education level, marital status

Model 2: Adjusted for age, sex, ethnicity, education level, marital status, BMI, Vitamin B12

Model 3: Adjusted for age, sex, ethnicity, education level, marital status, BMI, Vitamin B12, physical activity, short-term alcohol intake, alcohol drinks > = 12 in the past 12 months, smoking

Model 4: Adjusted for age, sex, ethnicity, education level, marital status, BMI, Vitamin B12, physical activity, short-term alcohol intake, alcohol drinks > = 12 in the past 12 months, smoking, Log_sMMA

BMI Body mass index, *Log_sMMA* The logarithm of sMMA

Table 3 Regressions exploring the association between hypertension and sMMA

	β	95%CI	*P*-value
Crude Model	0.127	0.080,0.173	< 0.001
Model 1	0.111	0.063,0.160	< 0.001
Model 2	0.121	0.077, 0.165	< 0.001
Model 3	0.123	0.078, 0.169	< 0.001

Crude model: Non-adjusted

Model 1: Adjusted for age, sex, ethnicity, education level, marital status

Model 2: Adjusted for age, sex, ethnicity, education level, marital status, BMI, Vitamin B12

Model 3: Adjusted for age, sex, ethnicity, education level, marital status, BMI, Vitamin B12, physical activity, short-term alcohol intake, alcohol drinks > = 12 in the past 12 months, smoking

Table 4 Regressions exploring the association between sMMA and cognitive function

	β	95%CI	*P*-value
Crude Model	−0.887	−1.144, −0.631	< 0.001
Model 1	−0.557	−0.774, −0.340	< 0.001
Model 2	−0.588	−0.789, −0.388	< 0.001
Model 3	−0.567	−0.801, −0.334	< 0.001

Crude model: Non-adjusted

Model 1: Adjusted for age, sex, ethnicity, education level, marital status

Model 2: Adjusted for age, sex, ethnicity, education level, marital status, BMI, Vitamin B12,

Model 3: Adjusted for age, sex, ethnicity, education level, marital status, BMI, Vitamin B12, physical activity, short-term alcohol intake, alcohol drinks > = 12 in the past 12 months, smoking

found that a higher level of sMMA was associated with hypertension [43, 84]. According to Forte et al. (2020), hypertension accelerates vascular aging, primarily through oxidative stress and mitochondrial dysfunction [85]. These processes are reflected in elevated MMA levels, which are recognized as key mechanisms contributing to the functional and structural changes in aging blood vessels. Other researchers have suggested that the signaling involved in regulating blood pressure may contribute to vascular mitochondrial dysfunction and increase MMA [86, 87].

Previous studies noted that elevated MMA levels were associated with cognitive decline [88] and the decline in overall cognitive function was accelerated in individuals with higher MMA concentrations [42]. By controlling for B12 levels in our regressions, our study further corroborated this by observing that MMA may have an independent effect on cognition, distinct from the effect of B12. Apart from its role as a biomarker reflecting the status of other substances such as B12, MMA, a pathogenic substance, can also be considered an independent

Table 5 Direct and indirect effects of hypertension on cognitive function with sMMA as a mediator

	Adjusted Models			
	Estimate	**95%CI lower**	**95%CI upper**	***P*-value**
Indirect effect				
Total	−0.0668	−0.0830	−0.0300	< 0.001
Sex				
Male	−0.0890	−0.1103	−0.0100	< 0.001
Female	−0.0429	−0.0867	−0.0200	< 0.001
Age				
< 68	−0.0244	−0.0821	0.0200	0.280
> = 68	−0.0488	−0.0737	−0.0200	< 0.001
Direct effect				
Total	−0.5333	−0.7992	−0.4700	< 0.001
Sex				
Male	−0.4957	−0.7387	−0.1300	< 0.001
Female	−0.6061	−0.9918	−0.5500	< 0.001
Age				
< 68	−0.4013	−0.9221	−0.2300	< 0.001
> = 68	−0.3820	−0.6845	−0.3100	< 0.001
Total effect				
Total	−0.6002	−0.8377	−0.5400	< 0.001
Sex				
Male	−0.5848	−0.7801	−0.2000	< 0.001
Female	−0.6489-	−1.0437	−0.6000	< 0.001
Age				
< 68	−0.4257	−0.9696	−0.2400	< 0.001
> = 68	−0.4308	−0.7183	−0.3600	< 0.001
Proportion mediated				
Total	0.1114	0.0409	0.1400	< 0.001
Sex				
Male	0.1523	0.0132	0.2700	< 0.001
Female	0.0661	0.0212	0.1000	< 0.001
Age				
< 68	0.0574	−0.0313	0.1700	0.280
> = 68	0.1132	0.0380	0.1600	< 0.001

Adjusted Analyses: Adjusted for age, ethnicity, education level, marital status, BMI, Vitamin B12, physical activity, short-term alcohol intake, alcohol drinks > = 12 in the past 12 months, smoking. Sex was adjusted in the analyses for the total population but not in subgroup analyses of gender (female and male). Age was adjusted in the analyses for the total population (age was introduced into the models as a continuous variable) but not in subgroup analyses of age (< 68 and > = 68)

neurotoxin capable of causing brain injury and cognitive impairment [89], which deserves special attention. Some studies revealed MMA could lead to neuronal damage by inhibiting the mitochondrial respiratory chain [90, 91], the transmitochondrial malate shuttle [92], pyruvate carboxylase activity [93] and β-hydroxybutyrate [94], resulting in neuron apoptosis through mechanisms involving

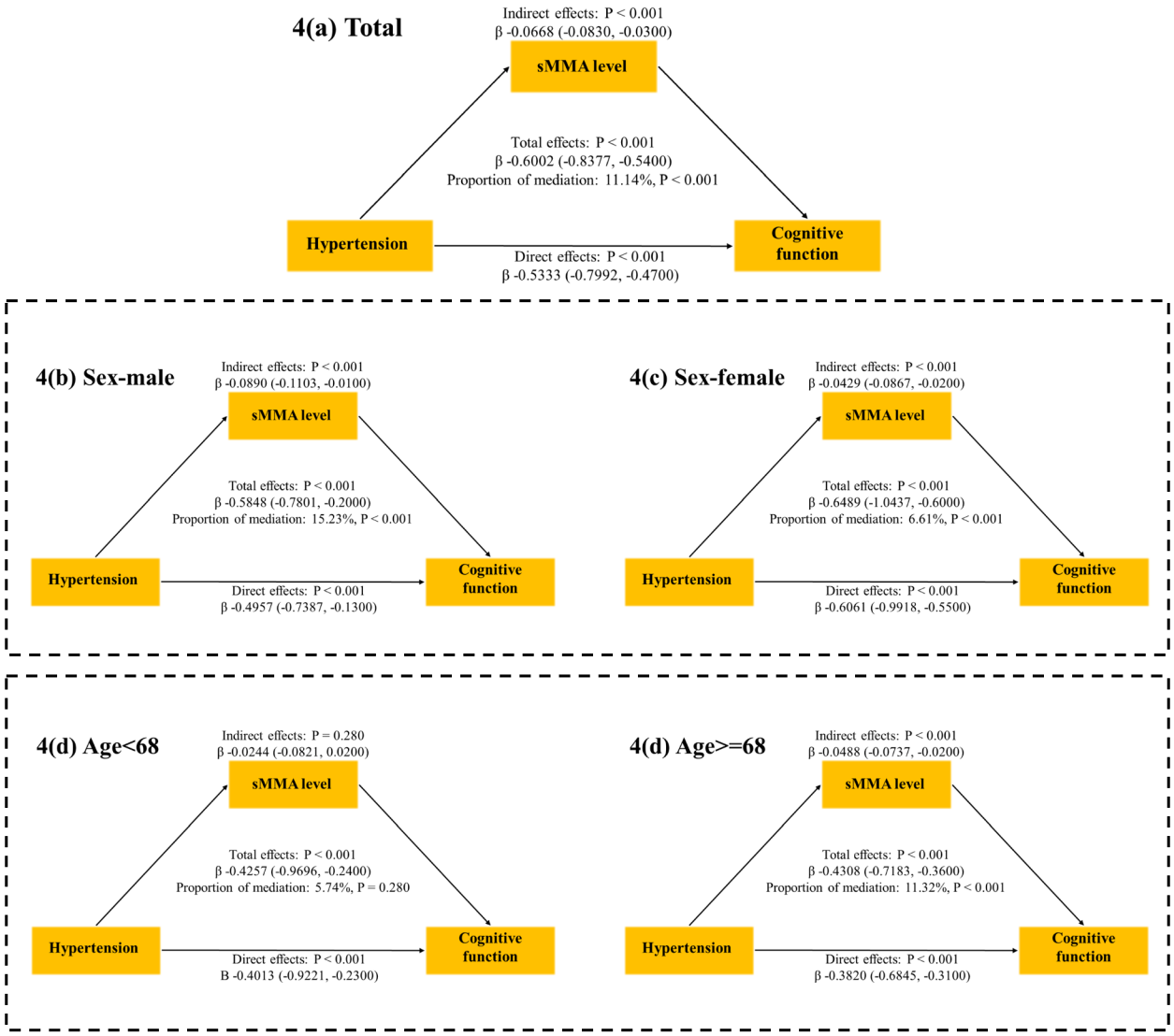

Fig. 3 Mediating role of methylmalonic acid between hypertension and cognitive function. Figure 3 shows the results of the mediation analyses for the association between hypertension and cognitive function with the serum methylmalonic acid (sMMA) level as a potential mediator, with subgroup analyses for age and sex

oxidative stress injury [44, 95], neuroinflammation [96, 97] and DNA damage [98].

The key finding in this study was that sMMA exhibited a significant mediating effect (11.14%) between hypertension and cognitive function in older adults (Fig. 3). This suggests that hypertension may impact cognitive decline through the accumulation of MMA, highlighting the potential importance of MMA in hypertension-related cognitive decline in older adults. Previous understanding on the pathway through which hypertension leads to cognitive decline was mainly related to vascular pathology [99]. Long-term exposure to hypertension contributes to microvascular damage in the brain arteries, resulting in dysfunction of the blood–brain barrier (BBB), neuroinflammation, and the accumulation of neurotoxic molecules, which initiates and promotes neurodegeneration and cognitive impairment [100, 101]. Our results provide additional perspectives and insights into the potential mechanisms involving MMA in the pathway from hypertension to cognitive decline in older adults. One possible explanation could be that high blood pressure may cause mitochondrial damage [85], promoting the accumulation of MMA, a type of neurotoxic molecules [102], and then the accumulation of MMA can disrupt normal fatty acid synthesis by interfering with metabolic pathways, potentially substituting for malonic acid (propanedioic acid)

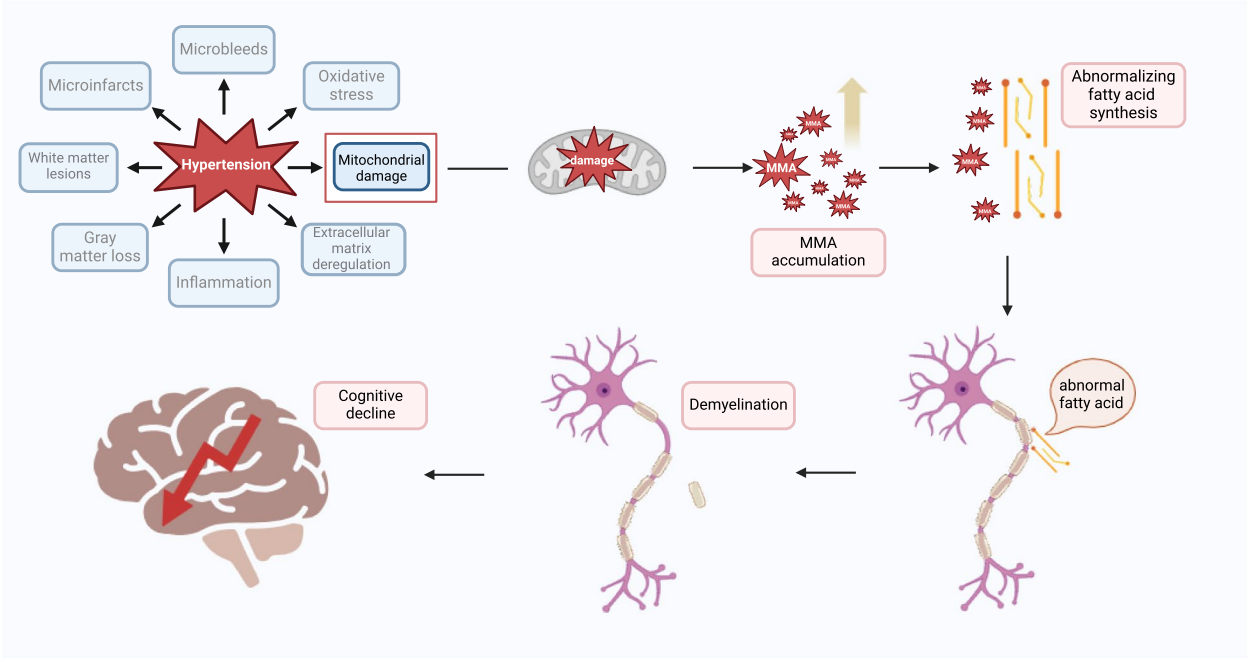

Fig. 4 A hypothesized mechanistic pathway between hypertension and cognitive decline via methylmalonic acid. Figure 4 illustrates a proposed mechanistic pathway linking hypertension to cognitive decline, highlighting the potential mediating role of MMA. (This illustration was created with BioRender.com)

in the fatty acid synthesis process [103]. This disruption can impair the production of essential fatty acids needed for cellular functions. Those abnormal or defected acids may penetrate the myelin, causing it to become fragile and resulting in demyelination [104, 105], which makes neuronal function and survival compromised, leading to axonal degeneration and progressive deterioration in neurological function [106]. Figure 4 illustrates a proposed mechanistic pathway linking hypertension to cognitive decline, highlighting the potential mediating role of MMA in older adults.

It has been suggested that B12-deficiency may facilitate the accumulation of MMA [107, 108], and that vitamin B12 could increase methionine for promoting the synthesis of myelin and neurotransmitters, and promote remyelination [108], meanwhile decrease the accumulation of MMA for preventing demyelination [107–112]. Evidence has shown that vitamin B12 supplementation could decrease serum MMA levels in older adults [113]. Therefore, supplementing with vitamin B12 may help in reducing hypertension-induced MMA accumulation and preventing cognitive decline for older adults with hypertension.

This study also suggests that the mediating effect of MMA may be more pronounced in males than in females. Gender differences in hypertension have been observed, likely due to variations in hormones and gene dosage on sex chromosomes [114]. Gender has also been associated with health behaviours, such as higher smoking rates in males, which increase the risk of developing chronic diseases, including hypertension [115, 116]. Sex hormones may influence cognitive function, with estradiol potentially being associated with better performance in certain cognitive domains in females [117]. It was noted by large-scale studies that there was a significant association between sex hormones and cognitive function [117]. It may be the sex hormones and lifestyles of older males that contribute to their susceptibility to hypertension-induced and MMA-related cognitive decline, and more efforts may need to be made for monitoring and addressing males' MMA among hypertensive older adults.

Additionally, the observation of age-related differences in the mediating effects of MMA suggests that MMA's role as a mediator may be more pertinent for older adults with a more advanced age. Studies have shown that the prevalence of hypertension, which is notably higher in older elderly compared to younger elderly [7, 118, 119], and cognitive decline is also notably pronounced after age 65 and accelerates significantly in the final years of life [120–122]. Gomes et al. (2020) found that sMMA accumulated with age, potentially fostering disease progression [123]. As, older elderly may have a longer duration of exposure to both hypertension and related metabolic changes, they could be more vulnerable to hypertension-induced and MMA-related cognitive decline.

Strength and limitations

The key strength of this study with a large population from NHANES 2011–2014 lies in its pioneering revelation of the potential mediation of the association between hypertension and cognitive function by the sMMA level. This contribution sheds new light on the understanding of the relationship between hypertension and cognitive decline, opening up avenues for further research and potential interventions. Furthermore, in contrast to previous studies using only one indicator [124, 125] to measure cognitive function, our study incorporated three reliable cognitive assessments (AFT, CERAD wordlist learning test, and DSST), which could provide a more robust and multifaceted evaluation of cognitive function. Meanwhile, aligning our approaches to identifying diseases and clinical conditions with that of other studies enhances the comparability of our findings with the other relevant research.

Another key strength of this study lies in the comprehensive measurement of alcohol intake, which was assessed using both short-term and long-term consumption metrics. By incorporating two methods—short-term alcohol intake based on two separate 24-h dietary recall interviews and long-term consumption defined as consuming at least 12 drinks in the past 12 months—the study captured both recent drinking behaviors and habitual patterns. This dual approach provides a more nuanced understanding of alcohol consumption and its potential impact on cognitive function and strengthens the study's findings.

However, it is important to acknowledge the limitations of our study. First, in this cross-sectional study, we were unable to establish a definitive causal relationship between hypertension, the sMMA level, and cognitive function in older adults. To address this, future research could replicate this investigation using longitudinal data to validate the associations.

Moreover, it is important to acknowledge that the cognitive function indexes (AFT, CERAD wordlist learning test, and DSST scores) utilized in this study as well as the data processing methods employed to create the composite score for assessing overall cognitive performance, may introduce potential biases in the results. While similar strategies have been utilized to assess participants' cognition in previous studies based on the NHANES dataset, the reliability and validity of this overall assessment still require further investigation, and other validated methods to assess cognitive function or decline should be considered in future studies.

Additionally, the scope of our study, the availability of data in NHANES, and limitations in sample size for successful modeling may have constrained the selection and categorization of covariates, potentially leading to the omission of certain important covariates that should be considered. For example, psychiatric disorders such as schizophrenia and depression [126, 127], which are often associated with cognitive decline, were not included in our models due to the fact that adding these variables caused model overloading and led to failures in model fitting. Thus, more potential confounders, particularly those reflecting mental health, should be included and addressed in future studies. While our study investigated the partially mediating role of sMMA in the association between hypertension and cognitive function, it is important to acknowledge that there may be other mechanisms or mediating factors at play. Further research is needed to explore these additional mechanisms in order to gain a deeper understanding of this complex relationship.

We also have to acknowledge that a large number of participants were excluded from this study due to being under the age of 60, as shown in Fig. 1. While our focus was on older adults due to the higher prevalence of both hypertension and cognitive decline in this population, future studies could explore the relationship between hypertension, MMA, and cognitive function in younger adults. Examining these factors in a younger cohort may provide insights into the early effects of hypertension and metabolic changes on vascular and cognitive health, potentially identifying earlier opportunities for intervention. In addition, as the majority of our participants probably engaged in little to moderate alcohol drinking, the overrepresentation of light to moderate drinkers may introduce bias, potentially underestimating or overlooking the negative cognitive impacts of heavier drinking. Further research could include a more diverse population with varying levels of alcohol consumption to provide more rigorous insights.

Conclusion

This study with a large population suggests that the sMMA level may mediate the link between hypertension and cognitive decline in older adults. Thus, reducing sMMA levels in older adults with hypertension could be critical for preventing cognitive decline and maintaining mental health. Monitoring B12 levels and Vitamin B12 supplementation could be considered in providing care to hypertensive older adults, particularly for males with an advanced age.

Abbreviations

AFT	Animal fluency test
ATP	Adenosine triphosphate
BBB	Blood-brain barrier
BP	Blood pressure
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CDC	Centers for disease control and prevention
CHARLS	China health and retirement longitudinal study
CI	Confidence interval
DBP	Diastolic blood pressure

DSST	Digit Symbol Substitution Test
IQR	Interquartile range
MCI	Mild cognitive impairment
MEC	Mobile examination center
MMA	Methylmalonic acid
NCHS	National center for health statistics
NHANES	National health and nutrition examination survey
SBP	Persistent systolic blood pressure
SD	Standard deviation
SEQN	Respondent sequence number
sMMA	Serum methylmalonic acid
VIFs	Variance Inflation Factors

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Clinical trial number
The authors of this study utilized data from NHANES (The National Health and Nutrition Examination Survey of the U.S., which provides open access to datasets). No clinical trial was conducted by the authors, and therefore, a clinical trial number was not available.

Authors' contributions
(CRediT author statement). Ying Xu: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization. Rucheng Chen: Methodology, Validation, Writing - Review & Editing, Paulus Torkki: Conceptualization, Methodology, Validation, Writing - Review & Editing, Weijun Zheng: Conceptualization, Methodology, Validation, Investigation, Writing - Review & Editing, Supervision. An Chen: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisition.

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Data availability
The National Health and Nutrition Examination Survey (NHANES) data are publicly available at https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate
The NHANES protocol was approved by the Institutional Review Board of the CDC's National Center for Health Statistics. Written informed consent was obtained from each participant prior to their participation in NHANES programme.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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