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Exploring the association between hemoglobin glycation index and cognitive function in older adults with hypertension: a cross-sectional study

Hong Ding[1†], Tingyue Kang[2†], Wenbo Gao[2†], Qi Wang[2], Shu Liu[1], Xiaowei Zhang[1*] and Jing Yu[1*]

Abstract

Background The Hemoglobin Glycation Index (HGI) quantifies the difference between the actual and expected values of glycosylated hemoglobin (HbA1c), a marker that has been closely linked to various adverse health outcomes. Nonetheless, a significant gap exists in the current literature concerning the association between HGI and cognitive function. This study aims at testing such association in older adults with hypertension, a topic that has not yet been extensively investigated.

Methods A linear regression model between glycated hemoglobin A1c (HbA1c) levels and fasting plasma glucose (FPG) was constructed for the calculation of the HGI. The cross-sectional study focused on evaluating the cognitive function of hypertensive individuals (≥ 60 years old), based on the data from the 2011–2014 National Health and Nutrition Examination Survey (NHANES), by using a series of standardized tests, including the Word List Learning (CERAD-WL) and Delayed Recall (CERAD-DR) tests from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), the Animal Fluency Test (AFT), and the Digit Symbol Substitution Test (DSST). Weighted logistic and linear regression models served for evaluating the effect of HGI on hypertensive patients' cognitive function. Restricted cubic spline (RCS) curves assisted in detecting the underlying nonlinear associations between HGI and cognitive outcomes. Furthermore, subgroup analyses and interaction tests were performed to gain deeper insights into these associations.

Results The study included 1023 participants ≥ 60 years old from 2011 to 2014 NHANES. Higher HGI was accompanied by lower DSST score ($P = 0.009$). In the fully adjusted model, participants in the highest quartile (Q4) of HGI possessed a lower DSST score (β = -4.50, 95% CI -8.10– -0.88) versus the lowest quartile (Q1), and were more likely to exhibit low cognitive function as evaluated by the DSST (OR = 2.21, 95% CI 0.98–5.03). According to the results from

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RCS analysis, HGI presented a linear relevance to cognitive function scores in older adults with hypertension. There is no interaction between HGI and the stratifying variables (sex, age, BMI, alcohol consumption, and smoking status).

Conclusion High HGI was an important risk factor leading to reduced cognitive performance in hypertensive patients, ensuring HGI to be used for effectively predicting patients' cognitive decline.

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 data sets). No clinical trial was conducted by the authors, and therefore, a clinical trial number was not available.

Keywords Hypertension, Hemoglobin glycation index (HGI), Cognitive function, NHANES, Cross-sectional study

Introduction

Hypertension is a prevalent condition and also a leading risk factor for cardiovascular disease and stroke, especially among the elderly [1]. According to the China Patient-Centered Evaluative Assessment of Cardiac Events (PEACE) Million Persons Project (2014–2017), approximately 50% of the participants aged 35–75 years could be affected by hypertension, with the prevalence increasing progressively with age [2]. Hypertension is a well-established risk factor for cognitive decline and dementia, as it contributes to vascular damage, reduced cerebral blood flow, and neuronal injury. In hypertensive patients, the relationship between glycation burden and cognitive function may be exacerbated due to the combined effects of vascular and metabolic stressors [3].

Cognitive impairment is a significant global contributor to death and disability [4]. The World Health Organization's 2021 Global Status Report on dementia estimated that there were approximately 55.2 million of dementia cases in 2019, with the number expected to rise to 78 million and 139 million by 2030 and 2050, respectively [5]. Obviously, midlife hypertension significantly adds the possibility of developing cognitive decline in late life, independent of genetic predisposition to cognitive impairment [6]. Therefore, understanding the mechanisms linking hypertension to cognitive impairment remains a critical area of research. Although some studies suggest the possible effect of effective blood pressure (BP) management on lowering the risk of cognitive decline, they fail to yield conclusive results [7, 8]. Additionally, previous studies have not well elucidated whether specific classes of antihypertensive drugs can offer superior cognitive benefits [8]. There is an urgent need for new discoveries and innovative therapeutic targets to safeguard hypertensive patients' cognitive function. Identifying individuals at risk in early stage also could benefit the retardation or prevention of the progression to dementia.

Glycosylated hemoglobin (HbA1c) is widely used in diagnosing and managing diabetes mellitus, providing an estimate of the mean blood glucose levels of an individual over the past three months [9]. At present, it is the most commonly used surrogate marker for evaluating the effectiveness of glucose-lowering interventions [10]. However, evidence indicates that HbA1c levels may consistently differ from fasting plasma glucose (FPG) levels, being either higher or lower in certain populations [11], affected by various factors such as erythrocyte lifespan difference [12], cell membrane glucose transmembrane gradients [13], enzyme abnormalities [14], and genetic factors [15]. As a result, HbA1c measurement may not fully capture an individual's blood glucose metabolic status.

The hemoglobin glycation index (HGI) is to quantify the variable relationship between HbA1c and plasma glucose levels [16]. The HGI is a measure that reflects interindividual variation in HbA1c levels after accounting for blood glucose levels [17]. This is particularly relevant for cognitive function, as emerging evidence suggests that chronic hyperglycemia and glycation end products (AGEs) contribute to neurodegeneration and cognitive decline [11]. Numerous studies have shown that HGI is a predictor of diabetes-related complications, such as mortality [18, 19], cardiovascular disease [20], and microvascular complications [21]. In particular, a high HGI has been strongly associated with major adverse cardiovascular events in the populations studied [22]. Previous studies have indicated that HGI can serve as a relatively intuitive indicator of glycemic variability in patients [23]. However, there is limited research on glycemic variability in patients with cognitive impairment. This study aims to enhance understanding of the pathogenesis of cognitive function in older adults with hypertension and provide important scientific evidence for future prevention and treatment strategies.

Materials and methods

Study population

The National Health and Nutrition Examination Survey (NHANES), a population-based study, is conducted by the National Center for Health Statistics (NCHS) using a complex, multistage design. This survey, which releases data in two-year cycles, monitors the nutritional and health status pertaining to noninstitutionalized civilians in the United States. Detailed descriptions

of the NHANES design and operations have been previously published [24]. Our study analyzed data from the NHANES cycles spanning 2011 to 2014, conducting cognitive testing on participants ≥ 60 years old, which has been described previously [25]. Initially, data from 19,931 participants were collected, but 16,299 were excluded due to being younger than 60 years, 698 due to incomplete cognitive impairment data, 1,528 due to incomplete HGI data, and 383 because they were not diagnosed with hypertension. Ultimately, the study included data from 1,023 participants ≥ 60 years old. The selection process for the study sample is illustrated in Fig. 1.

Definition of hypertension

Three to four blood pressure measurements were taken following standard procedures. For analysis, the mean of all measurements, excluding the first, was used when multiple readings were available. Hypertension refers to the disease situation with receiving measurement indicative of hypertension (DBP ≥ 90 mmHg or SBP ≥ 140 mmHg), the use of prescribed antihypertensive

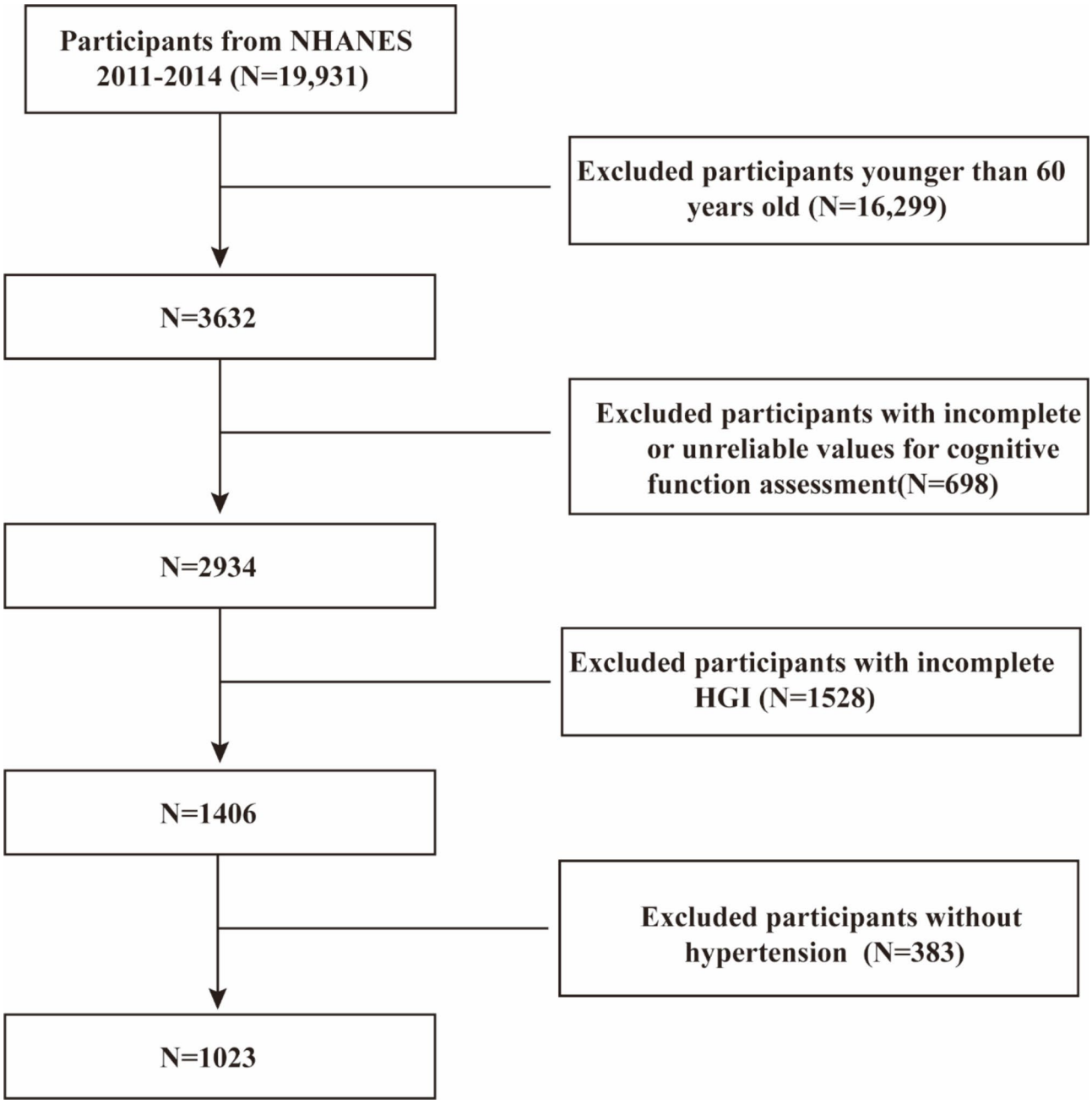

Fig. 1 Flowchart of the sample selection from the NHANES 2011–2014 assessment of cognitive functioning

medications, or a prior diagnosis by a physician [26]. Classification of hypertension defined according to the 2023 ESH Guidelines for the management of arterial hypertension [27]: Grade 1 hypertension, systolic blood pressure 140–159 mmHg and/or diastolic blood pressure 90–99 mmHg; Grade 2 hypertension, systolic blood pressure 160–179 mmHg and/or diastolic blood pressure 100–109 mmHg; Grade 3 hypertension, systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg.

HGI calculation

HbA1c and FPG values were combined to calculate HGI, thereby estimating the inter-individual difference in the HbA1c level. We determined the predicted HbA1c through a regression equation based on baseline FPG and HbA1c measurements: Predicted HbA1c = 3.412 + 0.416 × FPG (mmol/L), as shown in Fig. 2. HGI = measured HbA1c – predicted HbA1c [17]. The study population fell into 4 HGI quartiles: Q1 (-3.29 to -0.35), Q2 (-0.35 to -0.05), Q3 (-0.05 to 0.25), and Q4 (0.25 to 3.69).

Cognitive function assessment

Participants ≥ 60 years old were administered a cognitive battery comprising four tests in the Mobile Examination Center (MEC): the Animal Fluency Test (AFT) [28], the Digit Symbol Substitution Test (DSST) [29], the Word List Learning (CERAD-WL) and Delayed Recall (CERAD-DR) tests from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [30]. The CERAD test included 3 consecutive learning trials and 1 delayed recall task. In the AFT, testers required participants to name as many animals as they could in one minute to complete the verbal fluency assessment, with the score determined by the total number of animals named. Testers set a cut-off score of less than fourteen for the identification of potential cognitive impairment, as previously established in peer-reviewed research [31]. The DSST, part of the Wechsler Adult Intelligence Scale, was designed to measure cognitive functions (sustained attention, working memory, and information processing speed). Participants were given a set of symbols paired with a corresponding key and asked to accurately draw

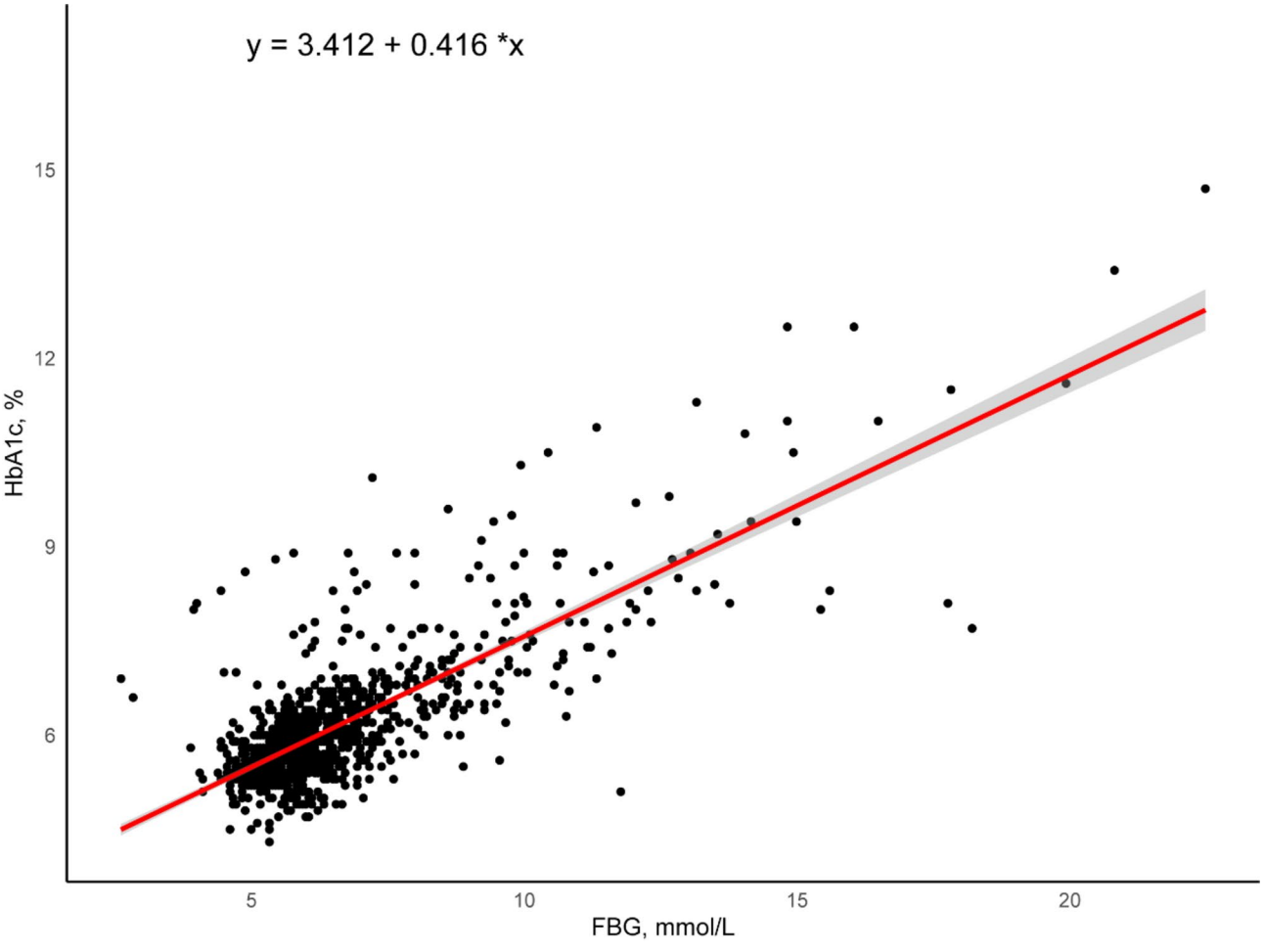

Fig. 2 The correlation between HbA1c and FBG

as many symbols as possible within 120 s, with a threshold score of less than 40, as suggested by a prior NCHS report accounting for the "Flynn effect." The CERAD battery was widely used for diagnosing dementia associated with Alzheimer's disease, evaluating abilities of new learning, recognition memory, and delayed recall. The CERAD-WL test involved 3 consecutive learning trials, requiring participants to recite a list of distinct words and recall as many as possible. The maximum score was 30, with the trials featuring different word orders. After a 8–10 min interval, CERAD-DR test was conducted, requiring participants to recall the 10 words from the previous test. Threshold scores of less than 17 for the CERAD Word Learning and less than 5 for the CERAD Delayed Recall were selected based on existing scientific literature [31].

Selection of covariates

We included covariates associated with HGI [32] or cognitive function [25] identified in previous studies, while addressing concerns of collinearity. These covariates included sex (male/female), age (years), race/ethnicity (Mexican American/Other Hispanic/Non-Hispanic White/Non-Hispanic Black/Other race), education level (below high school/high school/above high school), alcohol consumption, BMI (body mass index), poverty–income ratio (RIP), diastolic blood pressure (DBP), systolic blood pressure (SBP), antihypertensive medication use, BP classification, smoking status, heart failure and diabetes. Trained medical professionals administered the questionnaires and collected all data through standardized interviews, physical examinations, and laboratory tests.

Statistical analysis

The complex survey design adopted specific sample weights, in accordance with NHANES analytic standards. Experimenters are arranged to collect all data specific to each cycle in a single interview. For the weighted participants, baseline characteristics were presented as means ± standard deviations for continuous variables and numbers (%) for categorical variables. HGI was analyzed both as a continuous variable and in quartiles. Weighted linear regression analyses engaged in calculating the β coefficients and 95% CI for the confirmation of the possible associations between HGI and scores on the three cognitive tests. Logistic regression analyses served for calculating the odds ratios (OR) and CIs for the exploration of the possible associations between HGI and low cognitive function. The Model 1 did not adjust for any covariates. Model 2 involved age adjustment, while Model 3 involved adjustments for sex, age, race/ethnicity, education level, alcohol consumption, poverty-to-income ratio (PIR), BMI, DBP, SBP, antihypertensive medication use, BP classification, and smoking status. Subgroup analyses involved gender, age, BMI, smoking status, and alcohol consumption. Data analysis relied on the R software (version 4.2.2). $P < 0.05$ reported statistical significance.

Results

Characteristics of study population

Our study included 1023 hypertensive patients in total, with a mean age of 69.9 ± 6.8 years, with 538 female patients (55%) and 485 male patients (45%). Sex, BMI categories, race, alcohol consumption, diabetes status, and DSST scores were obviously different in statistical level in the HGI quartiles (Table 1).

Association between the HGI and cognition function

Upon the adjustment for confounding factors, a strong correlation was observed between HGI (as a continuous variable) and DSST test scores [β = -2.50 (95% CI: -4.60, -0.36)]. However, no significant correlations were identified between HGI and the CERAD or AFT test scores.

Similarly, when analyzing HGI by quartiles, the fourth quartile of HGI showed a strong correlation with DSST test scores [β = -4.50 (95% CI: -8.10, -0.88)], while no significant associations were found with CERAD or AFT test scores (Table 2). Results persisted in analyses excluding BP classification adjustments (Supplementary Table s2).

Potential nonlinear relationship between HGI and cognition function

According to the RCS analysis, there were no significant nonlinear relationships between HGI and the outcome indicators ($P > 0.05$). In fully adjusted weighted linear regression models, CREAD, AFT, and DSST test scores showed a roughly linear decline with increasing HGI levels (CREAD-WL: P-nonlinear = 0.79, CREAD-DR: P-nonlinear = 0.29, AFT: P-nonlinear = 0.58, DSST: P-nonlinear = 0.43) (Fig. 3). Exclusion of BP classification-adjusted variables did not materially alter the effect estimates, supporting the stability of our models (Supplementary Figure s3).

Association between the HGI and low cognition function

Upon the full adjustment for confounding factors, participants in the 4th quartile of HGI more tended to present low cognitive function as measured by the DSST test compared to those in the first quartile ($P = 0.029$). No significant associations were found between HGI quartiles and low cognitive function from the CERAD and AFT tests (Fig. 4).

Subgroup analyses

Similarly, HGI presented different degrees of correlation with cognitive function in older adults with hypertension

Table 1 Characteristics of participants stratified by quartile of hemoglobin glycation index

Characteristic	Overall, $N=1023$[1]	Q1, $N=256$[1]	Q2, $N=257$[1]	Q3, $N=254$[1]	Q4, $N=256$[1]	*p*-value[2]
Age (years)	69.9 (6.8)	69.6 (7.2)	70.1 (6.7)	70.2 (6.6)	70.0 (6.5)	0.70
Age, (%)						> 0.90
60–69 years	459 (47%)	119 (49%)	109 (47%)	115 (46%)	116 (44%)	
70–79 years	310 (30%)	70 (26%)	81 (29%)	80 (32%)	79 (32%)	
80 + years	254 (24%)	67 (24%)	67 (24%)	59 (22%)	61 (24%)	
Sex, (%)						0.02
Female	538 (55%)	109 (46%)	136 (55%)	155 (64%)	138 (56%)	
Male	485 (45%)	147 (54%)	121 (45%)	99 (36%)	118 (44%)	
BMI, (%)						0.02
Underweight (< 18.5)	9 (1.0%)	3 (0.5%)	2 (1.0%)	3 (1.5%)	1 (1.0%)	
Normal (18.5 to < 25)	232 (22%)	51 (18%)	66 (27%)	61 (23%)	54 (19%)	
Overweight (25 to < 30)	346 (35%)	93 (32%)	100 (41%)	91 (41%)	62 (23%)	
Obese (30 or greater)	424 (42%)	107 (50%)	86 (31%)	95 (35%)	136 (57%)	
Race, (%)						< 0.001
Mexican American	82 (3.2%)	24 (3.8%)	20 (2.5%)	17 (2.7%)	21 (4.1%)	
Other Hispanic	93 (3.5%)	23 (3.1%)	20 (2.5%)	22 (3.2%)	28 (6.0%)	
Non-Hispanic White	500 (78%)	133 (83%)	155 (86%)	131 (79%)	81 (60%)	
Non-Hispanic Black	249 (9.0%)	54 (6.7%)	34 (4.4%)	64 (9.1%)	97 (19%)	
Other/multiracial	99 (6.1%)	22 (3.4%)	28 (4.9%)	20 (6.3%)	29 (12%)	
Alcohol, (%)						0.01
1–5 drinks/month	481 (46%)	114 (45%)	117 (42%)	121 (46%)	129 (54%)	
5–10 drinks/month	36 (4.8%)	8 (4.4%)	9 (4.5%)	13 (8.2%)	6 (1.1%)	
10 + drinks/month	157 (21%)	55 (30%)	49 (24%)	30 (17%)	23 (10%)	
Non-drinker	332 (28%)	73 (21%)	80 (29%)	84 (29%)	95 (34%)	
Smoke, (%)						0.13
Current smoker	120 (11%)	26 (9.5%)	34 (11%)	26 (8.5%)	34 (16%)	
Former smoker	391 (42%)	104 (50%)	88 (36%)	103 (45%)	96 (36%)	
Never smoker	512 (47%)	126 (41%)	135 (52%)	125 (46%)	126 (48%)	
Education, (%)						0.06
Less Than 9th Grade	109 (6.5%)	24 (4.2%)	17 (5.4%)	25 (6.3%)	43 (12%)	
9-11th Grade	159 (12%)	45 (12%)	31 (11%)	44 (12%)	39 (12%)	
High School Grad/GED	254 (24%)	53 (20%)	66 (25%)	60 (22%)	75 (31%)	
Some College or AA degree	287 (32%)	74 (36%)	84 (33%)	61 (27%)	68 (34%)	
College Graduate or above	213 (25%)	60 (28%)	59 (25%)	64 (32%)	30 (11%)	
Unknown	1 (< 0.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	
PIR	3.04 (1.56)	3.28 (1.50)	3.14 (1.60)	2.96 (1.53)	2.68 (1.53)	0.05
SBP, mmHg	135 (20)	137 (19)	135 (21)	134 (17)	135 (20)	0.40
DBP, mmHg	67 (15)	68 (14)	67 (14)	66 (17)	66 (13)	0.40
Antihypertensive drug, (%)						0.90
Yes	835 (95%)	205 (94%)	196 (94%)	206 (95%)	228 (97%)	
No	41 (5.0%)	13 (5.4%)	15 (5.9%)	7 (5.0%)	6 (2.9%)	
Unknown	1 (< 0.1%)	1 (< 0.1%)	0 (0%)	0 (0%)	0 (0%)	
BP classification, (%)						0.60
Grade 1 hypertension	31 (2.5%)	11 (3.6%)	9 (3.3%)	5 (1.7%)	6 (1.1%)	
Grade 2 hypertension	4 (0.4%)	2 (0.2%)	1 (0.4%)	1 (0.8%)	0 (0%)	
Grade 3 hypertension	1 (< 0.1%)	0 (0%)	0 (0%)	1 (0.1%)	0 (0%)	
Normal	957 (97%)	239 (96%)	235 (96%)	240 (97%)	243 (99%)	
Heart failure, (%)						0.30
Yes	93 (9.6%)	24 (8.3%)	15 (6.3%)	25 (10%)	29 (15%)	
No	929 (90%)	232 (92%)	241 (94%)	229 (90%)	227 (85%)	
Diabetes, (%)						< 0.001
Yes	270 (23%)	64 (19%)	30 (11%)	54 (18%)	122 (56%)	
No	705 (72%)	185 (78%)	219 (86%)	180 (73%)	121 (41%)	

Table 1 (continued)

Characteristic	Overall, *N* = 1023[1]	Q1, *N* = 256[1]	Q2, *N* = 257[1]	Q3, *N* = 254[1]	Q4, *N* = 256[1]	*p*-value[2]
CERAD - WL	19.4 (4.6)	19.3 (4.7)	19.8 (4.7)	19.5 (4.4)	18.9 (4.4)	0.40
CERAD - DR	6.18 (2.28)	6.19 (2.23)	6.24 (2.21)	6.32 (2.41)	5.87 (2.26)	0.40
AFT	17.5 (5.7)	17.6 (5.5)	18.2 (5.7)	17.8 (6.0)	16.0 (5.1)	0.06
DSST	50 (17)	51 (16)	52 (18)	50 (17)	43 (15)	0.009

[1]Mean (SD); n (unweighted) (%)

[2]Wilcoxon rank-sum test for complex survey samples; chi-squared test with Rao & Scott's second-order correction

Abbreviation: HGI, hemoglobin glycation index; BMI, body mass index; RIP, poverty–income ratio; DBP, diastolic blood pressure; SBP, systolic blood pressure; CERAD-WL/DR, the Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest for assessing learning and memory; AFT, the Animal Fluency Test for verbal fluency; and DSST, the Digit Symbol Substitution Test; Q, quartile

Table 2 Associations between HGI with CERAD– WL, CERAD -DR, AFT, and DSST

Characteristic	Model 1	Model 2	Model 3
	β (95% CI)	**β (95% CI)**	**β (95% CI)**
CERAD– WL			
HGI (continuous)	-0.29 (-0.90, 0.32)	-0.38 (-0.91, 0.15)	-0.32 (-0.74, 0.10)
HGI (categories)			
Q1	Reference	Reference	Reference
Q2	0.47 (-0.66, 1.60)	0.58 (-0.53, 1.70)	0.40 (-0.76, 1.60)
Q3	0.25 (-0.84, 1.30)	0.38 (-0.61, 1.40)	-0.13 (-1.50, 1.30)
Q4	-0.41 (-1.40, 0.60)	-0.31 (-1.30, 0.67)	-0.02 (-0.75, 0.70)
CERAD -DR			
HGI (continuous)	-0.14 (-0.41, 0.12)	-0.19 (-0.44, 0.06)	-0.11 (-0.33, 0.10)
HGI (categories)			
Q1	Reference	Reference	Reference
Q2	0.05 (-0.52, 0.62)	0.11 (-0.45, 0.67)	0.25 (-0.34, 0.83)
Q3	0.14 (-0.30, 0.57)	0.20 (-0.18, 0.59)	0.01 (-0.55, 0.58)
Q4	-0.31 (-0.80, 0.17)	-0.27 (-0.72, 0.19)	-0.02 (-0.50, 0.46)
AFT			
HGI (continuous)	-0.55 (-1.80, 0.71)	-0.65 (-1.70, 0.44)	-0.19 (-1.10, 0.74)
HGI (categories)			
Q1	Reference	Reference	Reference
Q2	0.63 (-0.52, 1.80)	0.75 (-0.31, 1.80)	**1.6 (0.14, 3.10)**
Q3	0.25 (-1.40, 1.90)	0.40 (-1.10, 1.90)	0.74(-1.20, 2.60)
Q4	-1.6 (-3.60, 0.46)	-1.5 (-3.30, 0.37)	-0.40(-2.30, 1.50)
DSST			
HGI (continuous)	**-3.80 (-7.20, -0.28)**	**-4.20 (-6.90, -1.60)**	**-2.50 (-4.60, -0.36)**
HGI (categories)			
Q1	Reference	Reference	Reference
Q2	0.42 (-2.70, 3.60)	0.94 (-2.00, 3.90)	1.10 (-2.50, 4.80)
Q3	-1.20 (-4.70, 2.40)	-0.52 (-13.00, -3.90)	0.00 (-3.30, 3.30)
Q4	**-8.90 (-14.00, -3.40)**	**-8.50 (-13.00, -3.90)**	**-4.50 (-8.10, -0.88)**

Model 1 was adjusted for none

Model 2 was adjusted for age

Model 3 was adjusted for sex, age, race, education level, PIR, BMI, smoking status, alcohol consumption, SBP, DBP, antihypertensive drug use and BP classification

Abbreviation: HGI, hemoglobin glycation index; CERAD-WL/DR, the Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest for assessing learning and memory; AFT, the Animal Fluency Test for verbal fluency and DSST, the Digit Symbol Substitution Test; Q, quartile

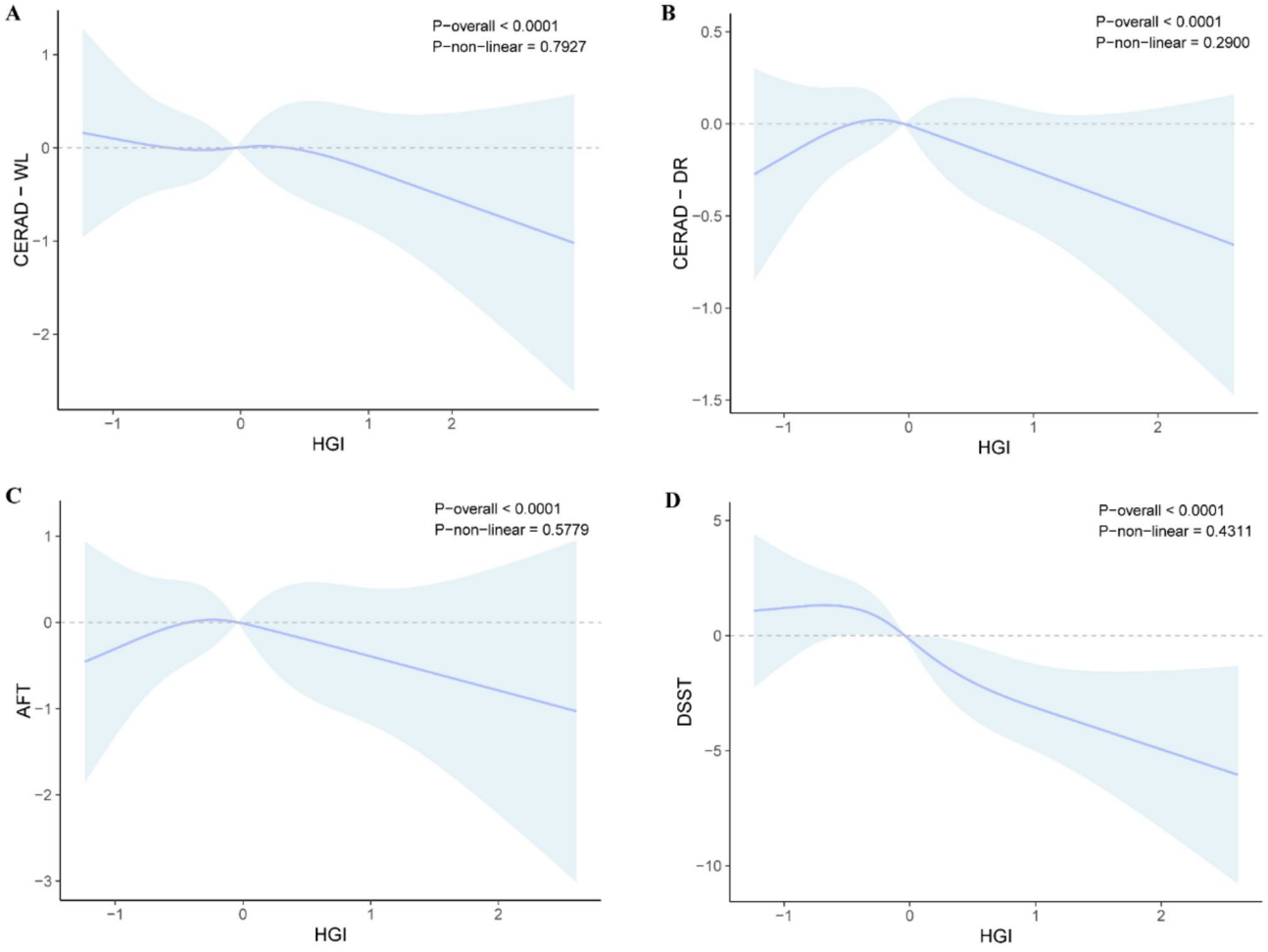

Fig. 3 Results of restrictive cubic spline analysis. (**A**) CERAD-WL; (**B**) CERAD-DR; (**C**) AFT; (**D**) DSST. Adjusted for sex, age, race, education level, PIR, BMI, smoking status, alcohol consumption, SBP, DBP, antihypertensive drug use and BP classification. The solid line and blue area represent the estimated values and their corresponding 95% CIs, respectively (HGI, hemoglobin glycation index; CERAD-WL/DR, the Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest for assessing learning and memory; AFT, the Animal Fluency Test for verbal fluency and DSST, the Digit Symbol Substitution Test)

in different subgroups, as illustrated in Fig. 5. According to the interaction tests, sex, age, BMI, alcohol use, or smoking status failed to exert a remarkable impact on the association (P for interaction > 0.05).

Discussion

Our study is the first one that conducts a large-scale investigation on the HGI-cognitive impairment relationship in a hypertensive population. According to the cross-sectional analysis, increased HGI resulted in a higher risk of cognitive impairment, even after the adjustment for covariates such as sex, age, race, education level, PIR, BMI, smoking status, alcohol consumption, SBP, DBP, antihypertensive medication use, and BP classification. A linear relationship between the two parameters was ascertained in the smooth curve fitting analysis. there is no interaction between HGI and the stratifying variables (sex, age, BMI, alcohol consumption, and smoking status). Hence, HGI indicates the risk of cognitive impairment in hypertensive individuals, thereby benefiting the relevant assessment.

Cognitive impairment together with the subsequent onset of dementia primarily account for the morbidity and mortality in the elderly population [11]. The prevalence among individuals aged 60 and older is 10.12% in China [33]. There is growing evidence that hypertension is closely related to older adults' cognitive impairment [34]. The backdrop that hypertension prevails worldwide due to the aged tendency of population and cognitive decline detrimentally influences people's life quality highlights the necessity to well ascertain the hypertension-cognitive impairment relationship. This knowledge is essential for improving hypertension management and reducing the risk of cognitive decline.

HbA1c is produced through the nonenzymatic reaction between intracellular HbA1c and glucose [35]. Discrepancies between actual and predicted HbA1c levels exist,

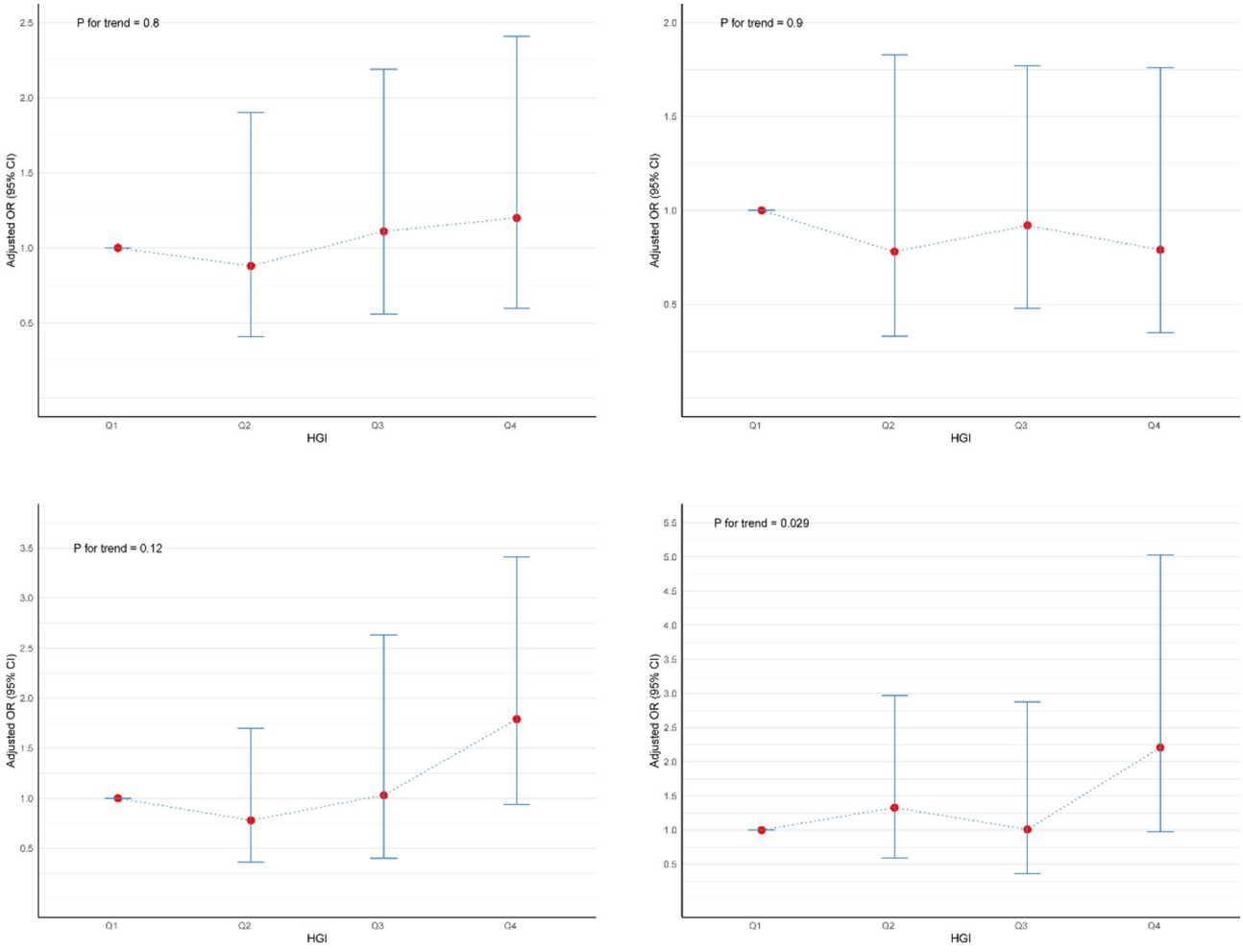

Fig. 4 Association of HGI with low cognitive function. (**A**) CERAD-WL; (**B**) CERAD-DR; (**C**) AFT; (**D**) DSST. Adjusted for sex, age, race, education level, PIR, BMI, smoking status, alcohol consumption, SBP, DBP, antihypertensive drug use and BP classification. The solid symbols and error bars represent the odds ratios and their corresponding 95% confidence intervals. (HGI, hemoglobin glycation index; CERAD-WL/DR, the Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest for assessing learning and memory; AFT, the Animal Fluency Test for verbal fluency and DSST, the Digit Symbol Substitution Test)

despite the unclear underlying mechanisms. Significant interindividual variation in the relationship between HbA1c and FPG can arise from factors influencing glucose metabolism, and the HGI quantifies this variability [17]. HGI appears to capture glycemic variability across different populations, serving as a crucial indicator for the risk of microvascular complications [36], which may contribute to their development. According to studies, HGI elevation is related to reduced telomere length [37] and increased inflammation and oxidative stress biomarkers [38]. There are some factors influencing the HGI-hypertension connection: insulin resistance [32], a pivotal mechanism affecting the hypertension; inflammation, a significant contributor to hypertension [39]; and oxidative stress, which crucially affects hypertension development [40]. By reflecting cumulative glycemic exposure, HGI, which also indicates the cardiovascular risk, may provide valuable insights into metabolic health for hypertensive patients in the long run.

While existing studies fail to specifically examine the relationship between the HGI and cognitive impairment in hypertensive populations, there is evidence linking hypertension to impaired glucose metabolism and insulin resistance [41]. Glycemic dysregulations are accompanied by worsening cognitive function in the short term among individuals at high cardiovascular risk [42]. The precise mechanisms underlying the relationship remain unclear, but several potential mechanisms have been proposed. First, insulin plays a critical role in regulating brains' learning and memory functions [43]. Insulin resistance in the brain can impair these functions meanwhile weakening insulin transport across the blood-brain barrier (BBB) [44], potentially leading to poorer cognitive outcomes [45]. Additionally, peripheral insulin resistance might decrease

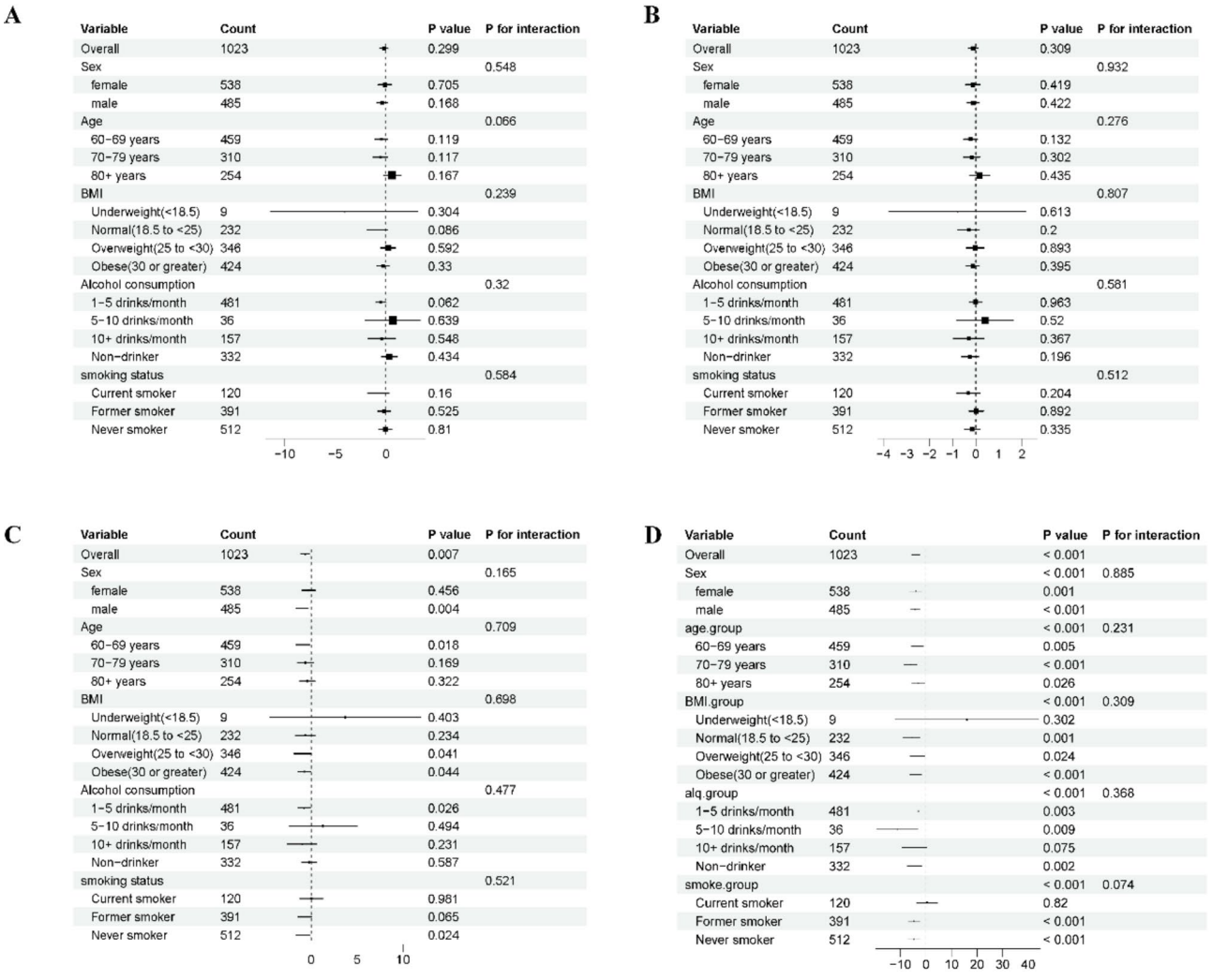

Fig. 5 Results of subgroup analysis. (**A**) CERAD-WL; (**B**) CERAD-DR; (**C**) AFT; (**D**) DSST

cerebral glucose metabolism, which could correlate with worse memory function [46]. The study indicated that insulin resistance is inversely associated with cognitive performance [47]. Inflammation is another significant factor. Individuals with prolonged elevated levels of inflammatory proteins from middle age tend to exhibit poorer cognitive function in older age [48]. Elevated inflammatory markers in the blood can elevate the risk of cognitive impairment decades later [49]. In preclinical models, peripheral inflammation activates microglia, which produce excess IL-1β and TNF-α, leading to neuroinflammation and cognitive impairment [50]. Cytokines play a central role in cognitive processes by affecting synaptic plasticity, neurogenesis, and neuromodulation [51]. These cytokines can influence cholinergic [52] and dopaminergic [53] pathways and may contribute to neurodegeneration or regeneration. Some evidence suggests the ability of peripheral cytokines to cross the BBB [54], either through less protected circumventricular regions or via vagal nerve stimulation [55]. Emerging evidence also points to oxidative stress as a key mechanism in cognitive aging [56]. Oxidative stress impairs mitochondrial function and damages various body systems, particularly the central nervous system [57]. Free radicals are capable of inducing brain chronic inflammation via releasing proinflammatory cytokines, which causes cell and synapse damage, synaptic function disruption [58], and microglial cell activation [59], ultimately resulting in neuronal damage. Furthermore, research has shown that HGI correlates with advanced AGEs [60]. Hypertension-induced oxidative stress in cerebral vessels increases the expression of receptor for AGEs (RAGE) [61], which binds to Aβ and is involved in its transport across the BBB. This interaction exacerbates the accumulation of Aβ and ROS in the brain, worsening cognitive impairment.

Our study offers several advantages over previous research. Firstly, the large sample size and application of weighted data analysis enhance the robustness of our findings. Secondly, the use of smoothed fitted curves

based on a fully adjusted model allowed us to identify potential linear relationships between variables. Lastly, our subgroup analyses account for various covariates, which helps in assessing the stability of the results. However, the study has many limitations. As the NHANES database is based on cross-sectional data, we can only examine correlations between the HGI and cognitive impairment, without establishing causality. Future research will focus on conducting prospective studies to explore causal relationships. Additionally, despite our efforts to include a broad range of covariates, there are still other potential confounding factors that can influence the analysis results. In addition, the study relied on self-reported data for recording outcomes, medical history and lifestyle factors, may introduce reporting bias. Finally, the generalizability of our findings is inherently constrained to the U.S. population due to the nature of the NHANES dataset. As such, the applicability of these conclusions to other ethnic groups or populations outside the United States warrants further investigation.

Conclusion

Taken together, our study suggests a negative correlation between the HGI and cognitive impairment in hypertensive adults ≥ 60 years old in the United States. To fully understand the mechanisms underlying this relationship, further prospective studies are necessary.

Abbreviations

HGI	Hemoglobin glycation index
HbA1c	Glycosylated hemoglobin
FPG	Fasting plasma glucose
NHANES	National Health and Nutrition Examination Survey
CERAD-WL	Consortium to Establish a Registry for Alzheimer's Disease Battery for immediate word list learning
CERAD-DR	Consortium to Establish a Registry for Alzheimer's Disease Battery for delayed recall
AFT	Animal Fluency Test
DSST	Digit Symbol Substitution Test
PEACE	Patient-Centered Evaluative Assessment of Cardiac Events
NCHS	National Center for Health Statistics
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
SD	Standard deviation
CI	Confidential interval
OR	Odds ratio
BMI	Body mass index
RCS	Restricted cubic spline
PIR	Poverty-to-income ratio
AGEs	Advanced glycation end products

Supplementary Information

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Supplementary Material 1

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Author contributions

The study design was conceived by HD, TYK, WBG, QW, SL, XWZ and JY. HD and LS organized the data, conducted the analyses, and wrote and edited the manuscript. XWZ and JY contributed to the interpretation of the results, revision, and finalization of the manuscript. All authors have reviewed and approved the final version of the manuscript.

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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

Ethical approval

The National Center for Health Statistics and Ethics Review Board approved the protocol for NHANES, and all participants provided written informed consent. The study adhered to the Declaration of Helsinki.

Consent for publication

Not applicable.

Consent to participate

Not applicable.

Competing interests

The authors declare no competing interests.

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