Association Between Urinary Flow Rate and Cognition in the Elderly: A Cross-Sectional Study

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Research Article

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Abstract

Background

Age-related lower urinary tract symptoms (LUTS) is a common disease in the elderly. The reduction of urinary flow rate (UFR) as an assessment of LUTS is associated with cognitive impairment. The association between UFR and cognitive performance has not been studied to date.

Methods

We used data from the 2011 to 2014 U.S. National Health and Nutrition Examination Survey (NHANES). Finally, 2,724 participants aged 65-80 with available data on UFR and cognitive assessments were included. The cognitive function assessment used the digit symbol substitution test (DSST), Animal Fluency Test (AFT) and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) immediate recall test. Multivariate logistic regressions were used to assess the association between UFR (exposure) and cognitive performance (outcome). Additionally, to ensure the reliability of data analysis, we converted UFR into categorical variables through tertile and then calculated the P for trend.

Results

Among 2,724 participants, the mean (SD) age was 69.26 (6.65) years, and 54.56% were women. After adjusting for covariates, UFR showed a positive correlation with DSST score (β = 2.00, [95%CI:1.20-2.80], P<0.0001), AFT score (β = 0.57,[95%CI:0.28-0.87], P=0.0001), CERAD immediate score(β = 0.24, [95%CI:0.01-0.47], P=0.0435). In addition, we found a similar linear trend when UFR was regarded as a categorical variable (tertile) (P for trend <0.0001(both in AFT and DSST); P for trend =0.0403 in CERAD immediate test).

Conclusions

The decrease of UFR is related to cognitive decline in the elderly, which may suggest that UFR may be a clinical marker of predicting cognitive decline.

Key Points

- This study aims to study the correlation between lower urinary tract dysfunction and the decline of cognitive function in the elderly. The decrease of urinary flow rate may become a risk factor for predicting cognitive impairment in the elderly.
- To investigate the association between UFR and cognitive performance, which can provide a clinical marker for predicting cognitive decline in elderly.

Introduction

The global population aging has largely led to the increase of morbidity and disability[1]. Age-related cognitive decline begins in middle age and continues with time[2]. Elderly cognitive impairment has a great impact on the daily life of patients and their families, increases the mortality of the elderly, and brings a huge burden to the society[3–5]. In view of the occult incidence of cognitive decline and the slow progress to dementia, and the fact that there is no effective treatment for this disorder at present, it is very important to screen high-risk groups and find early cognitive decline markers for primary prevention[6].

Urinary flow rate (UFR) represents the amount of urine excreted from the urethra per unit time in a natural state, which is mainly influenced by detrusor contraction strength and bladder outlet resistance[7]. As a common noninvasive examination, the determination of UFR has the advantages of rapidity, low cost and high repeatability, which is widely used in the preliminary screening of lower urinary tract symptoms (LUTS). As far as we knew, the low UFR was considered to be a bladder dysuria, which is manifested as the underactive bladder (UAB) caused by detrusor underactivity[8]. According to the definition of the International Continence Society, the detrusor underactivity refers to bladder weakness or prolonged bladder emptying time due to decreased contractility[9]. Many previous studies have shown that poor urination is caused by both myogenic and neurogenic mechanisms[10–13]. Therefore, as a disease characterized by neurologic impairment, cognitive impairment plays an important role in urination.

At present, some studies have proved that the cognitive decline of the elderly is related to the dysfunction of urination. Jellinger[14] found that LUTS, which consist of storage (frequency, urgency, nocturia) and voiding symptoms (delayed urination, poor or prolonged urine flow), were common in patients with Parkinson's disease (PD) (prevalence 27% - 85%). Picillo et al [15] also mentioned that dysuria is an early marker of progression of PD, and suggested that urinary dysfunction can be used to predict the development of the disease, which may represent a valuable variable in neuroprotective clinical trials. However, so far, there is no relevant predictor to indicate the occurrence of cognitive impairment.

In this study, we aimed to examined the association between UFR and cognitive performance based on the U.S. National Health and Nutrition Examination Survey (NHANES) database, which objective to provide predictive indicators for the occurrence of cognitive impairment in the elderly in order to prevent and control earlier.

Materials And Methods

Data Collection and participants selection

The NHANES study is a nationally representative study of population in the United States, which is also a cross-sectional survey based on a national sample of non-institutionalized population in the USA. It is conducted by the U.S. National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). The survey consist of three main parts. Initial screening of qualified participants

through the questionnaire. Then, extensive interviews are conducted, including age, gender, race, medical history and health status. What is more, physical examination and clinical evaluation are performed in specially designed mobile examination centers (MECs). In the process of data acquisition, all interviewers have received the training plan and reached the required standards. NHANES started in 1999 and is an ongoing annual survey with data published every 2 years and made publicly available online. This study gained Institutional Review Board (IRB; project identification code protocol #2011-17) approval by the NCHS in line with the revised Helsinki Declaration[16]. Informed consent was provided by all study participants before the data collection and examination procedures. More NHANES data and information are available at https://www.cdc.gov/nchs/nhanes/index.htm.

Participants from the NHANES were included in this population-based cross-sectional research. There were 19,932 participants in the NHANES from two 2-year survey cycles: 2011-2012 and 2013-2014. We screen participants according to the exclusion criteria listed below: (1) subjects without cognitive performance score (n =16,997); (2) subjects without UFR data (n =166); (3) subjects with missing data for covariate (n=45). Eventually, 2,724 eligible individuals of the NHANES survey were included in our study **(Figure 1)**.

The whole informed consents from each eligible participant were obtained after explaining the whole process of the research. All experimental methods were performed in accordance with the relevant guidelines and regulations of the CDC.

Measurement of Urinary Flow Rate

The UFR was measured by uroflowmetry (mL/min). The calculation formula of UFR is $UFR=V/t$, where V is the volume of the present urine sample and t is the time duration between the former urination and the present urine collection[17]. The participants had to record their last urination time before coming to the MECs. Then, at the centers, they would record the voiding time and volume of the urine sample and calculate the UFR for three times. The specimens were collected in different containers to guaranteeing enough data for various analyses. The composite UFR (mL/min) was measured by dividing the total urine volume collected by the total time covered by all collected voids[18].

Measurement of Cognitive Function

The following 3 cognitive function measurements designed to assess a wide range of neurocognitive function across a variety of demo graphic backgrounds were studied: the Digit Symbol Substitution Test (DSST), the Animal Fluency Test (AFT) and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) immediate recall test. The three assessment methods of cognitive function score are detailed in the **Supplementary File**.

Covariates

Multivariate model contains variables that may confound the association between UFR and cognitive function. For covariates, continuous variables included age (year). Categorical variables included: sex (male; female), poverty income ratio (PIR)(<1; ≥1), body mass index (BMI) (<25; ≥25<30; ≥30), alcohol intake per week (0; 1; 2), marital status (married or living with partner; living alone) ,smoking status (never; former; current) and comorbidity index (0, 1, 2, 3 ,4 ,5). BMI values were calculated by dividing participants' weight (in kilograms) by their height (in square meters)[19]. Diabetes mellitus, congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease (chronic bronchitis and/or emphysema) and hypertension, cancer consisted of comorbid conditions. The number of subjects reported conditions were then combined to generate an ordinal comorbidity index[20].

Statistical analysis

The statistical analysis was performed according to the CDC analytical reporting guidelines for complex NHANES data analysis (https://wwwn.cdc.gov/nchs/nhanes/tutorials/default.aspx). A sample weight was assigned to each person participating in NHANES. Therefore, we accounted for masked variance and used the proposed recommended weighting methodology. Continuous variables were expressed as mean ±standard deviation. Categorical variables were expressed in frequency or as a percentage. Weighted linear regression model (for continuous variables) or weighted chi-square test (for categorical variables) were used to calculate the differences among different UFR groups (tertiles). To investigate whether UFR is correlated with cognitive function in selected participants, our statistical analysis consisted of two main steps.

First, weighted multivariate logistic regression model were employed. We estimated three models: crude model, no covariates were adjusted; model I,only adjusted for gender, age and BMI data; in the final model (model II), model I + other covariates presented in Table 1 (i.e. PIR; marital status; comorbidity index; alcohol intake per week and smoking status).

Moreover, the subgroup analyses were then performed using weighted stratified logistic regression models to further determine the correlation between UFR and cognitive function. To ensure the robustness of data analysis, we did the sensitivity analysis.

All analyses were performed using the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empower stats.com, X&Y Solutions, Inc., Boston, MA). All P values less than 0.05 (two-sided) were considered statistically significant.

Results

Baseline characteristics of participants

The weighted distribution of selective participants sociodemographic characteristics and other related covariates for the selected 2,724 NHANES participants from 2011 to 2014, according to UFR tertiles, is shown in **Table 1**. The average age of the participants was 69.26±6.65, and 54.56% were women. Among

different tertile groups (T1-T3), there was no obvious difference in the following distributions: smoking status, BMI, comorbidity index and alcohol intake per week. We found that both UFR declined and cognitive performance scores (DSST, AFT and CERAD immediate recall test) decreased with age (p 0.0001).

Multivariate Logistic Regression Analysis

Associations between UFR as a continuous variable and cognitive performance (DSST, AFT and CERAD immediate recall test) is demonstrated in **Table 2**. Our multivariate logistic regression analysis showed UFR was positively correlated with DSST, AFT and CERAD immediate recall test in the crude model (AFT:β=1.07, 95%CI: [0.76–1.39], *P*<0.0001; DSST: β=3.83, 95%CI: [2.91–4.74], *P*<0.0001; CERAD immediate:β=0.59, 95%CI: [0.34–0.83], *P*<0.0001) (see **Table 2**). In the adjusted model I (adjusted by gender, age and BMI)(AFT:β=0.64, 95%CI: [0.33–0.94], *P*<0.0001; DSST: β=2.34, 95%CI: [1.49–3.20], *P*<0.0001; CERAD immediate:β=0.28, 95%CI: [0.05–0.52], *P*=0.0180) and model II (adjusted by gender; age; smoking status; alcohol intake per week; marital status; BMI; ratio of family income to poverty; comorbidity index) (AFT:β=0.57, 95%CI: [0.28–0.87], *P*<0.0001; DSST: β=2.00, 95%CI: [1.20–2.80], *P*<0.0001; CERAD immediate:β=0.24, 95%CI: [0.01–0.47], *P*=0.0435), the results remained stable.

In addition, to further test the correlation between UFR and cognitive function, participants were divided into three groups according to UFR (0.01-0.51, 0.51-0.92 and 0.92-3.45). Regarding UFR as a categorical variable (tertile), we found the similar trend (AFT: *P* for trend <0.0001; DSST: *P* for trend <0.0001; CERAD immediate: *P* for trend =0.0403) (see **Table 2**).

Subgroup Analyses

Table 3 shows the results of our subgroup analysis. We found that after adjusting for potential confounding factors, the interaction test had no significant effect on age (grouped by 65 years old), gender, smoking status, marital status, comorbidity index, and alcohol intake per week (*P* > 0.05), except for BMI and PIR. However, due to the large difference in the number of patients between groups, and the lack of clinical significance. We think that there is still a positive relationship between UFR and cognitive ability.

Discussion

In the elderly population of the United States, we found that the UFR decline was positively correlated with the decrease of cognitive function after adjusting for a variety of potential confounders in men and women.

Previous studies have noted the high incidence of LUST in age-related cognitive impairment[21–23]. Consistent with our findings, some previous studies have found that LUST caused by cognitive impairment in the elderly are common in Alzheimer's disease (AD), PD and Lewy body syndrome[24–26]. In addition, multiple system atrophy (MSA) is another cognitive disorder in the elderly with typical LUST,

which is urinary retention[27, 28]. Sakakibara et al used pressure-flow analysis in PD during urination, and the results showed that detrusor activity was weak during urination (40% of men; 66% of women)[29].

The nervous system controls many essential aspects of the normal urination cycle (storage and urination). Especially important are cognition (e.g, decision-making, anticipation, perception of environmental / social context and conscious perception of sensation), sensory nerve activity and autonomic nerve functions (e.g, regulation of detrusor and sphincter) and motor function (e.g, mobility, balance and dexterity). Neurologic functions work together to ensure that urine storage and voiding reflect timings and environment appropriately, which are completely controlled voluntarily[30]. The neurogenic dysuria in the elderly may come from two ways: one is the disturbance of sensory consciousness, the other is the degeneration of nervous system, which leads to the loss of the function of the muscles. By default, the lower urinary tract remains in "store" mode during bladder filling. When the bladder is full, there is a "switch" to "urinate" mode. Default mode network is the key functional basis of PD cognitive impairment, for PD patients, there is the dysfunction of the corticobasal ganglia associative areas nigrostriatal and mesocortical dopamine (DA) depletion with impairment of the frontostriatal circuitry, which is important for executive problems[31]. On the other hand, detrusor underactivity is an important cause of dysuria in MSA. It may be caused by degeneration of primary motor cortex (PMC) and locus coeruleus, pontobronchial raphe and cerebellar vermis, all of which regions are considered to be important areas of brain autonomic control[32].

This study has multiple advantages. This is the first study to explore the relationship between UFR and cognitive impairment in the elderly, so as to provide a feasible marker for clinical prediction of cognitive impairment in the elderly. Second, the multi-ethnic, nationally representative data from NHANES enable our findings to be extrapolated to a broader population.

However, this study still has several imitations. First of all, NHANES is a cross-sectional study that examines cognitive scores and UFR at a specific point in time, rather than continuously collecting data over a long period of time. As a single measurement may produce biased results, causality can not be established. Secondly, although we use three cognitive assessment methods, we still can not cover the overall cognitive ability. Accompanying tests, such as mini mental state examination (MMSE), help to assess cognitive function more comprehensively. Thirdly, we used the method in the NHANES database to calculate the average urine flow rate, which can not represent the detrusor contraction and diastolic pressure values and the maximum urinary flow rate. The combination of the average UFR and the peak UFR certainly provides more comprehensive urodynamic studies, but the peak UFR requires more complex calculation with uroflowmetry. However, the average UFR data can be used as a reference index of urinary reflex and the overall bladder muscle function. In addition, previous comparative studies have used the average UFR[16], which provide us with methods that can be used for reference. In the future, more clinical studies are needed to determine the relationship between UFR and cognitive decline, which may provide a new method for predicting cognitive impairment in the elderly.

Conclusion

Using the NHANES database, this study found a positive correlation between UFR and cognitive ability in the elderly after adjusting for potential confounding factors, which may suggest that UFR can be used as a marker to predict cognitive impairment in the elderly. In order to better understand the pathophysiology of this correlation, further high-quality studies are needed.

Abbreviations

LUTS: lower urinary tract symptoms; UFR: urinary flow rate; NHANES: National Health and Nutrition Examination Survey; DSST: digit symbol substitution test; AFT: Animal Fluency Test; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; SD: standard deviation; UAB: underactive bladder; PD: Parkinson's disease; NCHS: National Center for Health Statistics; CDC: Centers for Disease Control and Prevention; MECs: mobile examination centers; BMI: body mass index; PIR: poverty income index; AD: Alzheimer's disease; DA: dopamine; MSA: multisystem atrophy; PMC: primary motor cortex; MMSE: mini mental state examination.

Declarations

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Authors' contributions

Yifan Li: Writing- Original draft preparation, Conceptualization, Investigation **Linghui Deng and Shi Qiu:** Methodology, Software **Kun Jin:** Data curation **Xingyu Xiong** and **Sheng Wang:** Software, Investigation. **Birong Dong:** Writing- Reviewing and Editing, Data curation **Lu Yang:** Writing- Reviewing and Editing, Supervision. All the authors read and approved the final manuscript.

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Availability of data and meterials

The original NHANES dataset to support this study is available from the National Center for Health Statistics, https://www.cdc.gov/nchs/nhanes/index.htm.

Ethics approval and consent to participate

This study included data from NHANES 2011-14, which obtained ethics approval from the National Center for Health Statistics (Protocol #2011-17). All methods were performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki), and all participants provided their informed consent.

Consent for publication

Not applicable.

Competing interests

The authors have declared no conflicts of interest with respect to the authorship or publication of this article.

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Tables

Table 1 Baseline Characteristics of Participants

Ccognitive Performance	Overall	Tertile 1	Tertile 2	Tertile 3	P value
	(n=2,724)	(n=2,724)	(n=2,724)	(n=2,724)	
UFR		0.01-0.51	0.51-0.92	0.92-3.45	
Age (years) [mean (SD)]	69.26 ± 6.65	70.73 ± 6.81	69.18 ± 6.59	68.05 ± 6.31	<0.0001
Gender [%]					<0.0001
Male	45.44	38.96	49.62	47.23	
Female	54.56	61.04	50.38	52.77	
Marital status [%]					0.0006
Married or living with partner	65.34	60.54	69.19	65.96	
Living alone	34.66	39.46	30.81	34.04	
BMI [%]					0.0708
< 25	26.19	26.26	26.44	25.91	
>= 25, < 30	37.18	33.71	37.80	39.64	
>= 30	36.62	40.03	35.76	34.44	
PIR [%]					0.0085
Below poverty (< 1)	8.31	10.71	6.96	7.46	
Above poverty (>1)	91.69	89.29	93.04	92.54	
Smoking status [%]					0.5115
Never	49.92	48.40	51.86	49.44	
Former	40.26	41.23	39.46	40.14	
Current	9.83	10.37	8.67	10.42	
Alcohol intake per week [%]					0.0226
0	22.6	23.72	21.62	22.52	
1	52.7	55.32	50.49	52.45	
2	24.7	20.96	27.89	25.03	
Comorbidity index [%]					0.1609
0	29.86	27.71	29.42	32.15	
1	42.93	42.70	43.30	42.79	

2,3,4,5	27.21	29.59	27.28	25.06	
Animal Fluency Test Score Language [mean (SD)]	18.15 ± 5.68	16.95 ± 5.18	18.40 ± 5.64	18.99 ± 5.95	<0.0001
DSST Scores [mean (SD)]	**52.25 ± 16.69**	**48.54 ± 17.23**	**53.10 ± 15.85**	**54.70 ± 16.45**	**<0.0001**
CERAD immediate [mean (SD)]	19.79 ± 4.45	19.32 ± 4.67	19.76 ± 4.35	20.22 ± 4.30	<0.0001

BMI: body mass index.

PIR: poverty income ratio .

DII: dietary inflammatory index

Comorbidity index: diabetes mellitus, congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease (chronic bronchitis and/or emphysema) and hypertension, cancer consisted of comorbid conditions.

Note: Mean ± SD for continuous variables: P value was calculated by weighted linear regression model.

Number (%) for Categorical variables: P value was calculated by weighted chi-square test.

Table 2 Association between Urinary flow rate and Cognitive performance

Exposure	Urinary flow rate					
	β (95% CI[2]), P value					
	Model 1	p Value	Model 2	p Value	Model 3	p Value
	n=2,724		n=2,724		n=2,724	
Animal Fluency test score language	1.07 (0.76, 1.39)	<0.0001	0.64 (0.33, 0.94)	<0.0001	0.57 (0.28, 0.87)	0.0001
Animal Fluency test score language (tertiles)						
T1	0		0		0	
T2	1.50 (0.97, 2.03)	<0.0001	1.08 (0.57, 1.59)	<0.0001	0.84 (0.35, 1.34)	0.0009
T3	2.07 (1.56, 2.59)	<0.0001	1.38 (0.88, 1.88)	<0.0001	1.26 (0.77, 1.75)	<0.0001
P for trend	1.85 (1.35, 2.35)	<0.0001	1.20 (0.72, 1.68)	<0.0001	1.13 (0.66, 1.61)	<0.0001
DSST	3.83 (2.91, 4.74)	<0.0001	2.34 (1.49, 3.20)	<0.0001	2.00 (1.20, 2.80)	<0.0001
DSST (tertiles)						
DSST	3.83 (2.91, 4.74)	<0.0001	2.34 (1.49, 3.20)	<0.0001	2.00 (1.20, 2.80)	<0.0001
T1	0		0		0	
T2	4.66 (3.10, 6,22)	<0.0001	3.54 (2.10, 4.98)	<0.0001	2.63 (1.28, 3.99)	<0.0001
T3	6.15 (4.64, 7.67)	<0.0001	3.86 (2.45, 5.28)	<0.0001	3.38 (2.06, 4.71)	<0.0001
P for trend	5.42 (3.95, 6.89)	<0.0001	3.21 (1.85, 4.57)	<0.0001	2.94 (1.66, 4.22)	<0.0001
CERAD immediate	0.59 (0.34, 0.83)	<0.0001	0.28 (0.05, 0.52)	0.0180	0.24 (0.01, 0.47)	0.0435
CERAD immediate (tertiles)						

T1	0		0		0	
T2	0.38 (-0.04, 0.80)	0.0772	0.18 (-0.22, 0.57)	0.3838	0.05 (-0.34, 0.44)	0.7828
T3	0.90 (0.49, 1.31)	<0.0001	0.44 (0.05, 0.83)	0.0271	0.37 (-0.01, 0.75)	0.0589
P for trend	0.87 (0.48, 1.27)	<0.0001	0.43 (0.05, 0.80)	0.0253	0.39 (0.02, 0.75)	0.0403

95%CI: 95% Confidence interval

Model 1: no covariates were adjusted

Model 2: adjusted for gender; age; BMI

Model 3: adjusted for gender; age; smoking status; alcohol intake per week; marital status; BMI; ratio of family income to poverty; comorbidity index

UFR tertiles ranges: Tertile 1 =0.01 to 0.51; Tertile 2 =0.51 to 0.92; Tertile 3 =0.92 to 3.45

Table 3: Stratified logistic regression analysis to identify variables that modify the correlation between Urinary low rate and Cognitive performance

Subgroup					
	DSST				
	n	Crude	P Value	Model II	P Value
Gender [%]					
Male	1322	4.14 (2.64, 5.64)	<0.0001	2.42 (1.04, 3.79)	0.0006
Female	1402	4.08 (2.70, 5.47)	<0.0001	2.96 (1.70, 4.22)	<0.0001
P interaction		0.955		0.5678	
Age [%]					
<65	833	2.64 (0.95, 4.32)	0.0022	2.15 (0.57, 3.73)	0.0076
≥65	1891	3.92 (2.67, 5.18)	<0.0001	3.61 (2.44, 4.79)	<0.0001
P interaction		0.2299		0.1439	
PIR [%]					
Below poverty (< 1)	415	3.18 (0.60, 5.77)	0.0160	1.36 (-1.03, 3.76)	0.2646
Above poverty (≥1)	2309	3.91 (2.82, 5.00)	<0.0001	2.95 (1.94, 3.96)	<0.0001
P interaction		0.6126		0.2294	
Comorbidity index [%]					
0	784	5.17 (3.34, 7.01) 9	<0.0001	3.42 (1.76, 5.09)	<0.0001
1	1242	3.44 (1.91, 4.97)	<0.0001	2.29 (0.91, 3.68)	0.0012
2,3,4,5	698	3.11 (1.02, 5.20)	0.0036	2.56 (0.67, 4.45)	0.0079
P interaction		0.2526		0.5790	

Smoking status [%]					
Never	1346	4.79 (3.32, 6.26)	<0.0001	3.22 (1.88, 4.56)	<0.0001
Former	1087	3.13 (1.54, 4.72)	0.0001	1.99 (0.56, 3.43)	0.0066
Current	291	3.97 (0.73, 7.20)	0.0165	3.23 (0.30, 6.16)	0.0310
P interaction		0.3209		0.4387	
BMI [%]					
< 25	734	5.25 (3.23, 7.27)	<0.0001	4.24 (2.42, 6.07)	<0.0001
>= 25, < 30	987	4.98 (3.27, 6.68)	<0.0001	3.13 (1.59, 4.68)	<0.0001
>= 30	1003	2.31 (0.65, 3.97)	0.0065	1.27 (-0.23, 2.78)	0.0963
P interaction		0.0350		0.0376	
Alcohol intake per week [%]					
0	747	3.58 (1.51, 5.64)	0.0007	1.92 (0.08, 3.76)	0.0410
1	1446	4.20 (2.85, 5.55)	<0.0001	2.51 (1.31, 3.72)	<0.0001
2	531	3.04 (0.80, 5.28)	0.0467	2.03 (0.03, 4.02)	0.0467
P interaction		0.8355		0.8355	
Subgroup	**Animal Fluency test score language**				
	n	**Crude**	**P Value**	**Model II**	**P Value**
Gender [%]					
Male	1322	1.04 (0.55, 1.52)	<0.0001	0.65 (0.18, 1.11)	0.0020
Female	1402	0.70	0.3198	0.46	0.5557

		(0.26, 1.15)		(0.03, 0.89)	
P interaction		0.3198		0.5557	
Age [%]					
<65	833	0.54 (-0.00, 1.08)	0.0517	0.38 (-0.15, 0.92)	0.1598
≥65	1891	0.84 (0.44, 1.25)	<0.0001	0.79 (0.39, 1.19)	0.0001
P interaction		0.3821		0.2298	
PIR [%]					
Below poverty (< 1)	415	0.01 (-0.83, 0.85)	0.9881	-0.34 (-1.15, 0.47)	0.4102
Above poverty (≥1)	2309	0.97 (0.61, 1.32)	<0.0001	0.70 (0.36, 1.04)	<0.0001
P interaction		0.0389		0.02	
Comorbidity index [%]					
0	784	1.19 (0.60, 1.77)	<0.0001	0.83 (0.26, 1.39)	0.0040
1	1242	0.52 (0.03, 1.01)	0.0360	0.23 (-0.24, 0.70)	0.3364
2,3,4,5	698	0.95 (0.28, 1.62)	0.0052	0.76 (0.12, 1.40)	0.0204
P interaction		0.2144		0.2074	
Smoking status [%]					
Never	1346	0.77 (0.30, 1.24)	0.0014	0.40 (-0.05, 0.85)	0.0850
Former	1087	0.92 (0.41, 1.43)	0.0004	0.66 (0.17, 1.15)	0.0084
Current	291	1.07 (0.03, 2.10)	0.0433	0.78 (-0.22, 1.77)	0.1273
P interaction		0.8321		0.6650	

BMI [%]					
< 25	734	0.86 (0.21, 1.50)	0.0092	0.61 (-0.01, 1.23)	0.0532
>= 25, < 30	987	1.01 (0.47, 1.56)	0.0003	0.59 (0.06, 1.11)	0.0282
>= 30	1003	0.72 (0.19, 1.26)	0.0074	0.46 (-0.05, 0.97)	0.0792
P interaction		0.7601		0.9112	
Alcohol intake per week [%]					
0	747	0.80 (0.14, 1.47)	0.0177	0.41 (-0.23, 1.05)	0.2101
1	1446	0.88 (0.45, 1.31)	<0.0001	0.50 (0.08, 0.92)	0.0187
2	531	0.64 (-0.08, 1.36)	0.0838	0.33 (-0.36, 1.02)	0.3537
P interaction		0.8481		0.9050	
Subgroup	**CERAD immediate**				
	n	**Crude**	**P Value**	**Model II**	**P Value**
Gender [%]					
Male	1322	0.83 (0.43, 1.23)	<0.0001	0.49 (0.12, 0.86)	0.0090
Female	1402	0.49 (0.10, 0.87)	0.0139	0.25 (-0.10, 0.61)	0.1649
P interaction		0.2264		0.3793	
Age [%]					
<65	833	0.42 (-0.04, 0.88)	0.0726	0.41 (-0.04, 0.86)	0.0722
≥65	1891	0.55 (0.20, 0.89)	0.0018	0.51 (0.18, 0.85)	0.0025

P interaction		0.6648		0.7129	
PIR [%]					
Below poverty (< 1)	415	-0.03 (-0.74, 0.68)	0.9407	-0.41 (-1.08, 0.27)	0.2373
Above poverty (≥1)	2309	0.70 (0.40, 1.00)	<0.0001	0.49 (0.21, 0.78)	0.0007
P interaction		0.0646		0.0154	
Comorbidity index [%]					
0	784	0.95 (0.46, 1.45)	0.0002	0.58 (0.12, 1.05)	0.0146
1	1242	0.58 (0.17, 1.00)	0.0058	0.36 (-0.03, 0.75)	0.0726
2,3,4,5	698	0.17 (-0.39, 0.74)	0.5458	0.07 (-0.46, 0.60)	0.7954
P interaction		0.1240		0.3622	
Smoking status [%]					
Never	1346	0.47 (0.07, 0.87)	0.0201	0.18 (-0.20, 0.55)	0.3537
Former	1087	0.68 (0.25, 1.11)	0.0018	0.44 (0.03, 0.84)	0.0343
Current	291	1.05 (0.18, 1.93)	0.0183	0.91 (0.08, 1.73)	0.0317
P interaction		0.4552		0.2534	
BMI [%]					
< 25	734	0.81 (0.27, 1.36)	0.0034	0.63 (0.11, 1.14)	0.0167
>= 25, < 30	987	0.99 (0.53, 1.45)	<0.0001	0.62 (0.18, 1.05)	0.0055
>= 30	1003	0.15 (-0.30, 0.60)	0.5166	-0.07 (-0.49, 0.36)	0.7612

P interaction		0.0268		0.0424	
Alcohol intake per week [%]					
0	747	0.64 (0.07, 1.20)	0.0273	0.27 (-0.26, 0.81)	0.3140
1	1446	0.77 (0.40, 1.14)	<0.0001	0.49 (0.14, 0.84)	0.0066
2	531	0.07 (-0.54, 0.68)	0.8265	-0.13 (-0.71, 0.45)	0.6538
P interaction		0.1539		0.1938	

BMI: body mass index.

PIR: poverty income ratio .

DII: dietary inflammatory index

Comorbidity index: diabetes mellitus, congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease (chronic bronchitis and/or emphysema) and hypertension, cancer consisted of comorbid conditions.

Note: Number (%) for Categorical variables: P value was calculated by weighted chi-square test.

Crude: no covariates were adjusted

Model II: adjusted for gender; age; smoking status; alcohol intake per week; marital status; BMI; ratio of family income to poverty; comorbidity index

Figures

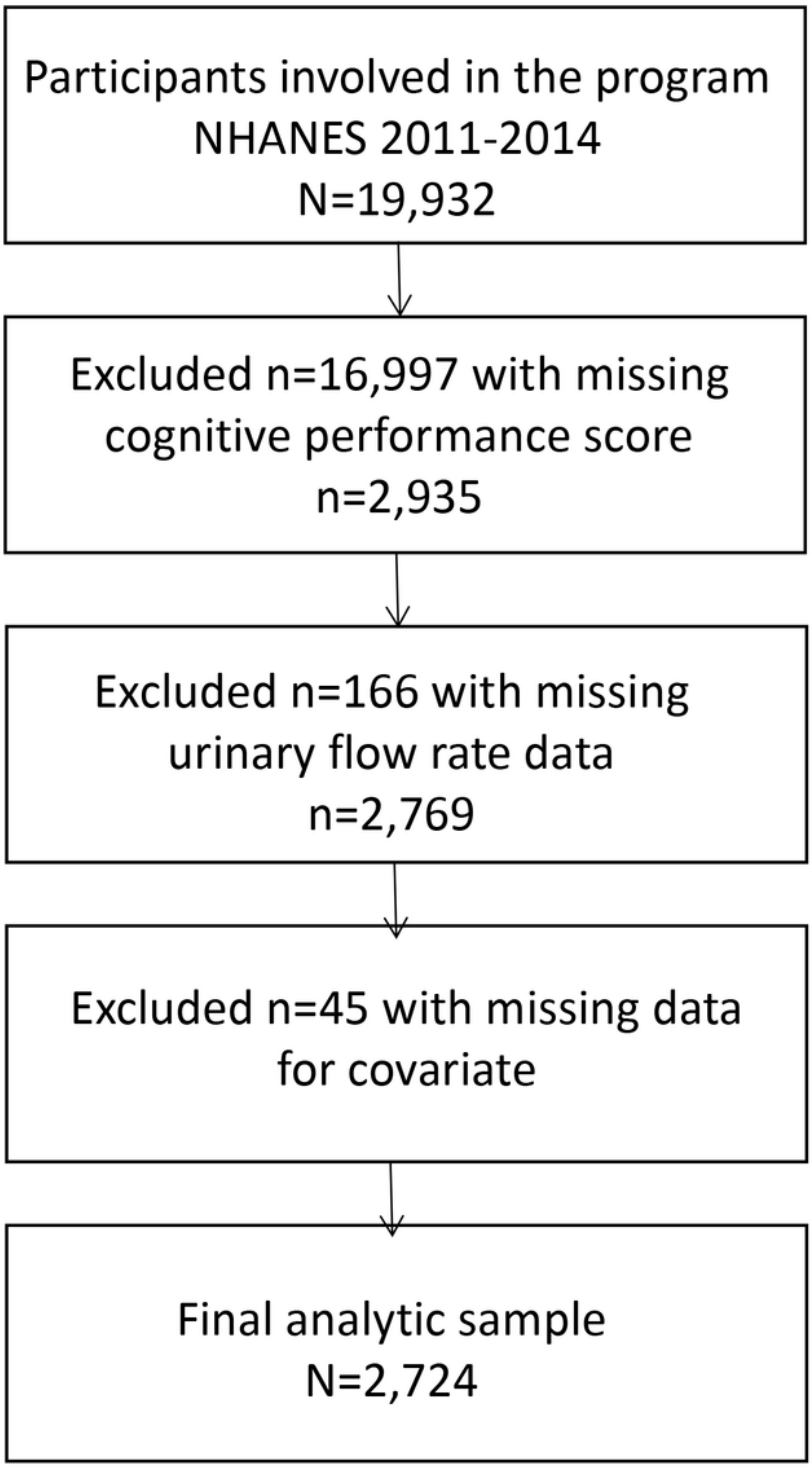

Figure 1

Flowchart of Participant Inclusion and Exclusion for Analysis

Supplementary Files

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