BMC Psychology

RESEARCH

Open Access

Increased level of serum asymmetric dimethylarginine in individuals with more severe cognitive impairment, as evaluated using Montreal Cognitive Assessment instead of Mini-Mental State Examination

Lei Liu[1†], Jia-Xin Guan[1†], Zhi-Qiang Song[1†], Qiang Gao[1], Su-Jun Cheng[1], Zhao-Qi Yan[2*] and Ying Fan[1*]

Abstract

Background This study aimed to explore the link between cognitive impairment and levels of asymmetric dimethylarginine (ADMA).

Methods The study included 172 patients from the Department of Geriatrics and Neurology at the Second Affiliated Hospital of Harbin Medical University. The enrollment period spanned from October 2013 to July 2014. To assess their cognitive function, we used the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). Additionally, automatic biochemical analyzers were employed to measure various biochemical blood indexes, while enzyme-linked immunosorbent assay was used to determine the serum ADMA concentrations.

Results The participants were categorized into four groups based on the MMSE scale, which reflects cognition (higher scores indicating better cognitive function), and five groups based on the MoCA scale, which also measures cognition (higher scores indicating better cognitive function). Various factors were analyzed for their statistical significance in relation to different cognitive impairment groups determined by each scale. Regarding the MoCA scale, the following factors were found to be statistically significant: Age ($P=0.0001$), systolic blood pressure ($P=0.0261$), ALT ($P=0.0104$), AST ($P=0.0106$), endogenous creatinine clearance ($P=0.0006$), and serum ADMA concentration ($P=0.0383$). For the MMSE scale, the following factors showed statistical significance: Age ($P=0.0008$), ALT ($P=0.0002$), AST ($P=0.0088$), CRP ($P=0.0407$), and endogenous creatinine clearance ($P=0.0027$). Interestingly, as the scores on the MoCA scale decreased, the serum ADMA concentration increased ($P=0.0383$), but this trend was not observed in the groups classified based on the MMSE scale ($P>0.05$).

[†]Lei Liu, Jia-Xin Guan and Zhi-Qiang Song contributed equally to this study.

*Correspondence:
Zhao-Qi Yan
yanchaoqi2002@163.com
Ying Fan
fanyingyan@163.com

Full list of author information is available at the end of the article

Conclusion The level of sensitivity measured by the MoCA scale indicated the presence of initial cognitive dysfunction. The extent of cognitive impairment showed a direct correlation with ADMA levels, indirectly implying a connection between impaired endothelial function and cognitive dysfunction.

Keywords ADMA, Cognitive impairment, Endothelial function, MMSE, MoCA

Background

Earlier research has demonstrated that alterations in the activity of brain microvascular endothelial cells are indirectly linked to reduced blood flow in the brain's small blood vessels, which contributes to the primary development of leukoaraiosis. Vascular endothelial dysfunction [1, 2] plays a role in this process, as it heightens the permeability of the blood-brain barrier and contributes to cognitive decline. Nitric oxide (NO), a significant vasoactive mediator produced by vascular endothelial cells [3] and synthesized through the catalysis of L-arginine (L-Arg) by the nitric oxide synthase (NOS) family, plays a critical role in modulating cerebral blood flow and inhibiting the proliferation of vascular smooth muscle cells. Asymmetric dimethylarginine (ADMA), an endogenous NOS inhibitor produced by endothelial cells, competes with L-Arg to bind to the active site of NOS, reducing the production of vasoactive NO. This results in endothelial dysfunction and vasoconstriction, and our prior studies have shown that ADMA is positively associated with leukoaraiosis [4–6]. Consequently, vascular endothelial dysfunction leads to increased blood-brain barrier permeability, further promoting cognitive impairment. A strong correlation has been observed between mild cognitive impairment, diagnosed using the Montreal Cognitive Assessment (MoCA) scale [7], and leukoaraiosis [6]. Possible causes of cognitive impairment include the proliferation of smooth muscle cells in the vascular wall and disruptions in cerebral blood flow regulation.

Theoretical cognitive deficits encompass various challenges in memory, visuospatial abilities, executive function, and numeracy, alongside conditions such as aphasia, apraxia, agnosia, mild cognitive impairment, and dementia. These issues lead to a significant deterioration in the individual's overall quality of life. Currently, the assessment of cognitive impairment is commonly performed using the Mini-Mental State Examination (MMSE) and MoCA scales [7, 8]. Each scale serves a distinct and important purpose. The MMSE primarily focuses on memory and language function, temporal orientation, attention, item naming, word expression, immediate and delayed recall, and sentence repetition. It shows low sensitivity but high specificity. On the other hand, the MoCA places emphasis on executive function, number span, animal naming, language fluency, delayed recall, and abstract memory, exhibiting high retest reliability, internal consistency, high sensitivity, and low specificity.

Nonetheless, the early stages of cognitive impairment remain inconspicuous, making it challenging to detect. However, in recent times, there has been significant interest in studying the potential risk factors that contribute to cognitive impairment [9, 10]. MoCA is a better measure of cognitive function due to lack of ceiling effect and with good detection of cognitive heterogeneity. MCI prevalence is higher using MoCA compared to MMSE. Both tools identify concordantly modifiable factors for MCI, which provide important evidence for establishing intervention measures [11]. This heightened focus on risk factors aims to facilitate early intervention and prevention strategies. The objective of this study was to assess ADMA concentrations and compare potential risk factors associated with cognitive impairment, thereby enhancing the prospects of preventing, diagnosing, and treating cognitive decline.

Materials and methods

Participants

Patients meeting the criteria for eligibility were enrolled from the Department of Geriatrics and Neurology at the Second Affiliated Hospital of Harbin Medical University during the period spanning October 2013 to July 2014. The inclusion criteria encompassed conscious individuals with unimpaired hearing and vision, lacking any paralysis and exhibiting independent behavior. The exclusion criteria encompassed the following conditions: individuals who were currently using hormones, angiotensin-converting enzyme inhibitors, hypoglycemic agents, statins, or other medications for a duration exceeding 2 weeks, as these could potentially impact serum ADMA concentrations prior to recruitment; patients with acute coronary syndrome, acute cerebral infarction, cerebral hemorrhage, epilepsy, normal intracranial pressure hydrocephalus, intracranial tumor, or traumatic brain injury; those with hypothyroidism, severe heart, lung, liver, or severe kidney disorders which are defined as endogenous creatinine clearance rate is less than 15 m/min/1.73m^2); individuals with central nervous system infection, carbon monoxide poisoning, immune system diseases, or radiation encephalopathy.

The ethics committee of Second Affiliated Hospital of Harbin Medical University granted approval for the study (No.: KY2016-177). All participants willingly agreed to take part in the research and provided written informed consent.

Cognitive function evaluation

In a serene and cozy setting, free from any external disturbances, all patients underwent the MMSE and MoCA (Beijing version). The previously reported threshold of 26 was used for assessment. Based on their MMSE and MoCA scores, participants were classified into distinct cognitive categories.

MMSE

The scale primarily examines memory and language abilities while neglecting evaluations of executive function, visual spatial skills, and abstract reasoning. It places particular emphasis on immediate memory. The scale shows low sensitivity but high specificity. The grading system ranges from 0 to 30 points, with higher scores indicating better cognitive performance. An additional point is added if the education level is ≤ 12 years [12, 13]. Participants' scores are used to categorize them into four groups: those scoring 27–30 are considered normal, 25–26 fall into level 1, 22–24 into level 2, and 0–21 into level 3.

MoCA

The focus of the scale centers around memory retention, with particular attention to assessing cognitive abilities and attention span over time. The scale demonstrates high sensitivity and test-retest reliability, as well as internal consistency. It uses a grading system with a maximum score of 30 points, where higher scores indicate better cognitive function. An additional point is added if the education level is ≤ 12 years. To account for variations in dementia severity across different countries and regions, participants were categorized into five groups based on their scores: scores ≥ 26 were classified as the normal group, scores of 22 to 25 as level 1, scores of 19 to 21 as level 2, scores of 14 to 18 as level 3, and scores of 0 to13 as level 4.

General data collection

Information concerning the age, education, gender, history of coronary heart disease, diabetes, and other relevant factors of the patients was gathered and documented. Additionally, the height (in meters), weight (in kilograms), and body mass index (BMI) were assessed for all patients. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a validated cuff sphygmomanometer, and two readings were taken at 5-minute intervals, with the average of these two readings recorded.

Blood index collection

The fasting plasma glucose (FPG) levels were assessed using the oxidase method. Low-density lipoprotein cholesterol (LDL) was directly measured. Total cholesterol (TC) was analyzed using enzyme colorimetry, while triglyceride (TG) levels were determined through colorimetry. CRP was measured by nephelometry, and alanine aminotransferase (ALT) as well as aspartate aminotransferase (AST) were assessed using colorimetry. BUN was evaluated with an enzymatic test, and Cr was measured through colorimetry on a Hitachi 7600 automatic biochemical analyzer. The white blood cells (WBC) were quantified using the flow plus electrical impedance method and detected on the XE5000 automatic flow cytometer.

Serum ADMA assay

All individuals provided a blood sample of 5 ml, which was collected into a coagulation tube. The tubes were then subjected to centrifugation at 3000 r/min for 20 min within 2 h. After centrifugation, the resulting supernatant serum was carefully extracted using a sterile pipette and transferred to sterile EP tubes. Subsequently, the samples were stored at -80 ℃ for preservation.

The concentration of ADMA in each group of participants was assessed using enzyme-linked immunosorbent assay (ELISA) at -80 ℃ using a refrigerated setup. The ELISA measurements for ADMA concentrations were performed with the help of a kit from Rapidbio Inc., USA, following the manufacturer's instructions, and the quantification was carried out based on the optical density at 450 nm.

Statistical analysis

SAS 9.4 statistical software was employed to perform the statistical analyses. The counting data were tested for normality by Shapiro Wilk test. Depending on the normal distribution of the data, descriptive statistics were reported as mean ± standard deviation or median (P25, P75). To compare groups, either analysis of variance or Kruskal-Wallis H test was used, and pair comparisons were conducted using the LSD-T test. Univariate and multivariate linear regression were applied to identify the influencing factors of ADMA, with significant variables from the univariate analysis being included in the multivariate regression. To explore the relationship between ADMA and MMSE and MoCA, Spearman's rank correlation was employed.

Results

We enrolled 172 patients based on the inclusion and exclusion criteria. A summary of the characteristics of all enrolled subjects can be found in Table 1. The correlation between cognitive function scores and ADMA concentration can be summarized as follows: When ADMA concentration is lower, endothelial function is less impaired, and cognitive function is better. This is evident in Fig. 1, where a higher adjusted MMSE score is associated with

Table 1 Demographics and baseline characteristics

Variable	$\overline{X} \pm S$ or M(IQR) or *n*(%)
Age	65(59–75)
Sex(male/female)	99(57.56) / 73(42.44)
Education level (y)(≥12)	144(83.72) 28(16.28)
Hypertension	114(66.28)
Coronary heart disease	66(38.37)
Diabetes mellitus	34(19.77)
Smoking	80(46.51)
Drinking	70(40.7)
Stroke or cerebral infarction	87(50.58)
Hypohepatia	12(6.98)
Renal dysfunction	15(8.72)
Thyroid dysfunction	12(6.98)
Family history of dementia	19(11.05)
Other family history	83(48.26)
Hight(cm)	165(160–170)
Weight(kg)	66.63 ± 11.51
SBP(mmHg)	140(130–150)
DBP(mmHg)	85(80–91)
Glu(mmol/L)	5.6(5.03–6.95)
TG(mmol/L)	1.37(1.02–2.06)
T-CH(mmol/L)	4.5(4.01–5.27)
LDL-C(mmol/L)	2.9(2.33–3.41)
HDL-C(mmol/L)	1.14(0.96–1.38)
BUN(mmol/L)	5.74(4.74–6.93)
Cr(umol/L)	80.85(66.5–92.5)
ALT(U/L)	17(12–24)
AST(U/L)	16(13-21.5)
WBC (10^9/L)	7.1(5.9–8.3)
CRP(mg/L)	1.79(0.98–4.62)
ADMA concentration(umol/L)	53.85(42.28–61.87)
GFR(ml/min)	64.51(37.65–94.23)
Ccr(ml/min)	72.07 ± 23.89
MMSE score	24(21–26)
MoCA score	17.11 ± 5.57
Adjustive MMSE (Based on education)	25(22–27)
Adjustive MoCA (Based on education)	19(13.5–21.5)

Abbreviations SBP, systolic blood pressure; DBP, diastolic blood pressure; Glu, glucose; TG, triglyceride; T-CH, total cholesterol; LDL-C, low-density-lipoprotein; HDL-C, high-density-lipoprotein; BUN, urea nitrogen; Cr, creatinine; ALT, alanine transaminase; AST, aspartate aminotransferase; WBC, white blood cell count; CRP, c reactive protein; GFR, glomerular filtration rate; Ccr, endogenous creatinine clearance rate

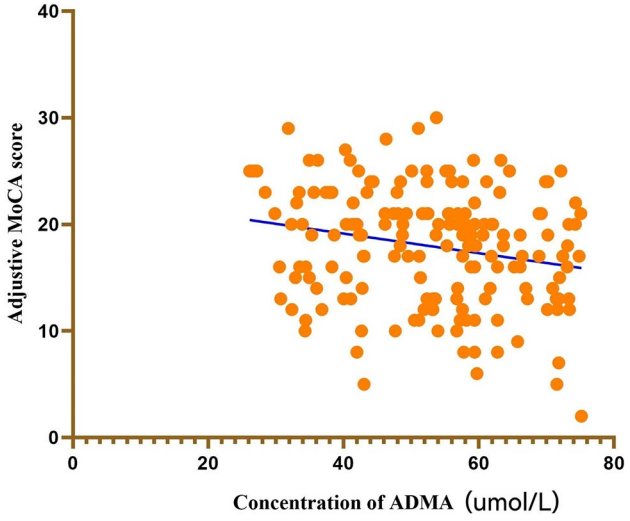

Fig. 1 Scatter plot of the relationship between MMSE score and ADMA concentration

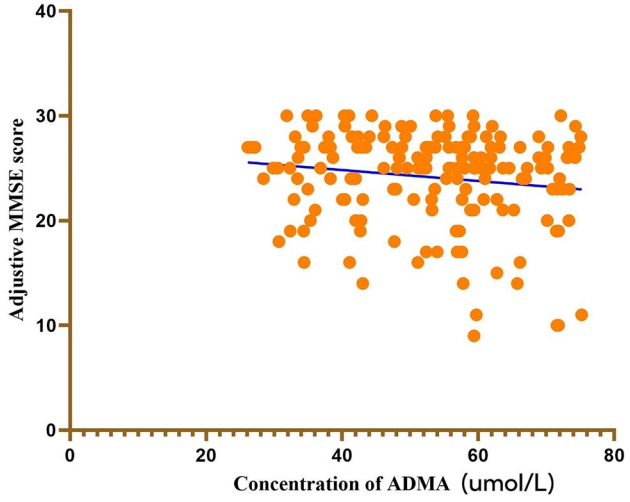

Fig. 2 Scatter plot of the relationship between MoCA score and ADMA concentration

Table 2 Relationship between ADMA concentration and cognitive function score

Variable	Parameter estimation	standard error	OR value	*P*
MMSE score	-0.4130	0.2137	-1.9321	0.0550
MoCA score	-0.4780	0.1725	-2.7753	0.0061*
Adjustive MMSE	-0.4351	0.2185	-1.9911	0.0481*
Adjustive MoCA	-0.512	0.1765	-2.8908	0.0043*

Note (regression analysis) * means $P<0.05$, and the effect of the variable on ADMA is statistically significant

lower ADMA concentration. Similarly, in Fig. 2, a higher MoCA score indicates better cognitive function, which is also linked to lower ADMA concentration. Regression analysis in Table 2 further supports these findings, revealing a negative correlation between ADMA concentration and the adjusted MMSE and MoCA scores.

We investigated the impact of blood pressure, glucose, and lipid levels on various cognitive functions, but no significant differences were observed ($P>0.05$). On the other hand, the effects of liver and kidney function, as well as inflammatory reaction, were also examined concerning cognitive function. Statistically significant differences were found in endogenous creatinine clearance rate ($P=0.0027$), ALT ($P=0.0002$), AST ($P=0.0088$), and CRP ($P=0.0407$). However, there was no notable difference

in serum ADMA concentration among the participants based on their MMSE scores ($P > 0.05$) (Table 3).

Various aspects of cognitive function were examined in relation to blood pressure, glucose, and lipid levels at different degrees. There were notable differences in systolic blood pressure ($P = 0.0261$). Additionally, the impact of liver and kidney function and inflammatory reactions on cognitive function at varying degrees was observed. Notably, there were significant statistical differences in endogenous creatinine clearance rate ($P = 0.0006$), ALT ($P = 0.0104$), and AST ($P = 0.0106$) among different cognitive function groups. According to the MoCA score, the

Table 3 Comparison of indicators in different MMSE score groups

Variable	1(*n* = 62)	2(*n* = 37)	3(*n* = 31)	4(*n* = 42)	χ2/F	*P*
Age [y, (P25, P75)]	62(56,69)	73(64,78)[a]	68(59,77)[a]	69.5(59,76)[a]	16.6141	0.0008*
Sex(M/F)	32/30	19/19	21/10	27/15	3.5748	0.3112
Education level ≥ 12y (n, %)	51(82.26)	34(91.89)	26(83.87)	33(78.57)	2.7276	0.4356
Hypertension (n, %)	39(62.9)	25(67.57)	20(64.52)	30(71.43)	0.8850	0.8290
History of Coronary heart disease **(n, %)**	24(38.71)	15(40.54)	12(38.71)	15(35.71)	0.2035	0.9770
History of Diabetes mellitus **(n, %)**	4(6.45)	12(32.43)[a]	6(19.35)	12(28.57)[a]	12.7295	0.0053*
History of Smoking **(n, %)**	29(46.77)	17(45.95)	16(51.61)	18(42.86)	0.5562	0.9064
History of Drinking **(n, %)**	22(35.48)	15(40.54)	16(51.61)	17(40.48)	2.2299	0.5261
History of Stroke or cerebral infarction **(n, %)**	22(35.48)	20(54.05)	20(64.52)[a]	25(59.52)[a]	9.5838	0.0225*
History of Hypohepatia **(n, %)**	6(9.68)	4(10.81)	0(0)	2(4.76)		0.2490
History of Renal dysfunction **(n, %)**	4(6.45)	5(13.51)	2(6.45)	4(9.52)		0.6454
History of Thyroid dysfunction **(n, %)**	4(6.45)	3(8.11)	2(6.45)	3(7.14)		1.0000
Family history of dementia **(n, %)**	8(12.9)	2(5.41)	3(9.68)	6(14.29)		0.6065
Other family history **(n, %)**	38(61.29)	11(29.73)[a]	18(58.06)[b]	16(38.1)[a]	12.2354	0.0066*
Hight [cm, (P25, P75)]	164(160–170)	164(159–170)	167(162–170)	165(160–170)	2.3514	0.5027
Weight(kg)	67.82 ± 11.86	63.32 ± 13.76	66.47 ± 7.77	67.88 ± 10.91	1.4176	0.2394
SBP [mmHg, (P25, P75)]	140(130,149)	140(125,150)	148(135,160)	143(130,152)	6.7837	0.0791
DBP [mmHg, (P25, P75)]	80(79,90)	86(80,90)	90(80,93)	82.5(80,91)	2.9371	0.4014
Glu(mmol/L)	5.67(5.03–6.78)	5.3(5.01–6.43)	5.6(4.93–6.79)	5.73(5.2–7.05)	1.3578	0.7155
TG(mmol/L)	1.68(0.98–2.52)	1.41(1.05–2.05)	1.18(1-1.59)	1.38(0.98–1.97)	4.0099	0.2604
T-CH(mmol/L)	4.49(3.92–5.23)	4.89(3.79–5.38)	4.51(3.87–5.16)	4.43(4.11–5.18)	0.4909	0.9209
LDL-C(mmol/L)	2.88(2.3–3.3)	2.94(2.46–3.44)	3.07(2.21–3.78)	2.84(2.47–3.28)	1.3651	0.7137
HDL-C(mmol/L)	1.14(0.94–1.39)	1.09(0.92–1.29)	1.09(0.89–1.36)	1.21(1.03–1.46)	3.8144	0.2822
BUN(mmol/L)	5.51(4.27–6.59)	5.87(5.03–7.11)	5.81(5.01–6.91)	6.03(4.79–7.15)	4.8004	0.1870
Cr(umol/L)	78.05(64-89.1)	82.6(70.5-101.7)	81.6(69.5–96.2)	80.7(67.9–86.6)	3.8094	0.2828
ALT(U/L)	18(13–26)	12(8–18)[a]	16(12–22)[b]	19.5(15–28)[b]	19.9436	0.0002*
AST(U/L)	17(13–23)	13(12–17)[a]	15(13–22)	18.5(15–23)[b]	11.6288	0.0088*
WBC (10^9/L)	7.1(5.9–8.1)	7(6.2–9.2)	6.9(5.2–8.2)	7.25(6-8.1)	1.1415	0.7671
CRP(mg/L)	1.57(0.94–3.65)	2.68(1.43–6.07)[a]	1.56(0.67–3.27)[b]	2.03(0.81–6.35)	8.2707	0.0407*
ADMA concentration(umol/L)	50.15 ± 12.81	54.74 ± 13.18	52.85 ± 13.4	55.36 ± 11.68	1.7428	0.1602
GFR(ml/min)	58.79(36.2-94.33)	71.59(38.52–93.32)	66.6(38.66–98.99)	63.2(34.09–89.7)	0.5184	0.9148
Ccr(ml/min)	76.8(61.43–95.78)	58.11(39.54–76.48)[a]	70.21(51.79–88.35)	75.13(61.12–85.78)[b]	14.1433	0.0027*
MMSE score (P25, P75)	27(26,28)	17(15,19)[a]	22(21,23)[ab]	24(24,25)[abc]	155.540	< 0.0001*
MoCA score	21.18 ± 3.7	10.38 ± 3.79[a]	15.35 ± 3.92[ab]	18.33 ± 3.94[abc]	65.3297	< 0.0001*
Adjustive MMSE (Based on education) (P25, P75)	28(27,29)	18(16,20)[a]	23(22,24)[ab]	25(25,26)[abc]	159.460	< 0.0001*
Adjustive MoCA (Based on education)	22 ± 3.54	11.3 ± 3.74[a]	16.19 ± 3.67[ab]	19.12 ± 3.74[abc]	69.9711	< 0.0001*

Note compared with level 1 group, [a]$P<0.05$; compared with level 2 group, [b]$P<0.05$; compared with level 3 group, [c]$P<0.05$

normal group exhibited the lowest serum ADMA concentration, while serum ADMA concentration levels in groups 1–4 of MoCA score exhibited a gradual increase ($P = 0.0383$) (Table 4).

Analysis of influencing factors of ADMA

In the analysis of univariate linear regression, it was observed that age ($P = 0.0005$), a past medical history of stroke or cerebral infarction ($P = 0.0219$), and endogenous creatinine clearance ($P = 0.0228$) were identified as distinct risk factors for serum ADMA concentration. The regression coefficients of age and stroke history or cerebral infarction were found to have a positive correlation with ADMA. However, no significant correlation was observed among the other risk factors ($P > 0.05$), as depicted in Tables 5 and 6.

Discussion

In this study, we specifically selected factors potentially linked to cognitive impairment.The results of the study indicated that the risk factors varied among different scale groups. Specifically, age, education level, systolic blood pressure, ALT, AST, and endogenous creatinine clearance showed an influence on cognitive impairment

Table 4 Comparison of indicators in different MoCA score groups

Variable	1(*n* = 62)	2(*n* = 37)	3(*n* = 31)	4(*n* = 42)	χ2/F	*P*	Variable
Age[y, (P25, P75)]	61.5(52,64)	73(63,80)[a]	70(62,76)[a]	62(56,74)[bc]	62(56,65)[bc]	24.3821	< 0.0001*
Sex(male/female)	4(40)/6(60)	21(48.84)/22(51.16)	24(61.54)/15(38.46)	30(63.83)/17(36.17)	20(60.61)/13(39.39)	3.5748	0.4489
Education level (y)(≥12)	6(60)	41(95.35)a	37(94.87)a	40(85.11)	20(60.61)bcd	24.9557	< 0.000*
Hypertension	3(30)	31(72.09)	26(66.67)	35(74.47)	19(57.58)	9.0705	0.0594
Coronary heart disease	4(40)	16(37.21)	12(30.77)	22(46.81)	12(36.36)	2.4599	0.6518
Diabetes mellitus	0(0)	12(27.91)	7(17.95)	11(23.4)	4(12.12)	5.9498	0.2029
Smoking	2(20)	21(48.84)	16(41.03)	27(57.45)	14(42.42)	5.8712	0.2090
Drinking	4(40)	17(39.53)	15(38.46)	23(48.94)	11(33.33)	2.1702	0.7045
Stroke or cerebral infarction	3(30)	25(58.14)	23(58.97)	24(51.06)	12(36.36)	6.4494	0.1680
Hypohepatia	3(30)	4(9.3)	2(5.13)	3(6.38)	0(0)	--	0.0369*
Renal dysfunction	2(20)	5(11.63)	2(5.13)	2(4.26)	4(12.12)	--	0.2932
Thyroid dysfunction	0(0)	4(9.3)	4(10.26)	1(2.13)	3(9.09)	--	0.4567
Family history of dementia	1(10)	2(4.65)	5(12.82)	5(10.64)	6(18.18)	--	0.4205
Other family history	8(80)	13(30.23)a	19(48.72)	25(53.19)b	18(54.55)b	10.6144	0.0313*
Hight [cm, (P25, P75)]	163.5(160,175)	165(158,170)	166(160–170)	165(160–170)	169(160–175)	6.6330	0.1566
Weight(kg)	60(58–75)	60(54–70)	69.5(60–71)	70(60–75)	70(60–75)	9.1741	0.0569
SBP [mmHg, (P25, P75)]	128(120,140)	140(121,150)	147(140,160)[ab]	142(130,160)[a]	140(130,140)[c]	11.0435	0.0261*
DBP [mmHg, (P25, P75)]	80(78,90)	85(80,90)	90(80,91)	83(80,96)	80(80,90)	3.3197	0.5058
Glu(mmol/L)	5.63(5.23–5.78)	5.48(4.95–7.05)	5.35(4.93–6.57)	6.43(5.08–7.93)	5.67(5.14–6.4)	4.4125	0.3530
TG(mmol/L)	1.34(0.93–1.8)	1.2(0.98–2.05)	1.14(0.94–1.94)	1.59(1.07–2.13)	1.4(1.14–2.16)	2.8574	0.5820
T-CH(mmol/L)	4.38(3.74–5.16)	4.95(3.92–5.39)	4.39(3.64–5.09)	4.42(4.07–4.85)	4.75(4.25–5.34)	4.3797	0.3571
LDL-C(mmol/L)	2.46(1.84–3.22)	3.07(2.48–3.6)	2.6(2.21–3.65)	2.93(2.56–3.26)	2.89(2.58–3.36)	4.6499	0.3251
HDL-C(mmol/L)	1.18(0.87–1.66)	1.1(0.95–1.33)	1.1(0.88–1.38)	1.16(0.94–1.36)	1.16(1.04–1.38)	2.4658	0.6508
BUN(mmol/L)	5.01(4.21–5.59)	5.81(4.73–6.89)	5.73(4.76–6.97)	6.21(4.95–7.08)	5.01(4.34–7.15)	8.0485	0.0898
Cr(umol/L)	73.3(55.9–84.4)	80(66.8–96.9)	84.4(69-96.4)	82.3(67.9–96)	73.6(64.7–89.1)	3.8055	0.4330
ALT(U/L)	19.5(16–35)	12(8–20)[a]	18(12–23)[b]	19(13–26)[b]	17(14–25)[b]	13.1867	0.0104*
AST(U/L)	20.5(15–30)	13(11–17)[a]	17(13–22)[b]	18(13–23)[b]	17(13–22)[b]	13.1339	0.0106*
WBC (109/L)	7.15(4.1-8)	7(6.2–8.2)	7.4(5.6–8.2)	7.4(6.1–8.8)	6.7(5.8–8.2)	2.2924	0.6821
CRP(mg/L)	1.51(0.67–1.59)	2.28(1.39–4.95)	1.83(0.65–6.35)	2.35(0.94–4.85)	1.55(0.83–2.42)	7.1093	0.1302
ADMA concentration(umol/L)	43.65(36.17–53.74)	56.76(47.65–65.74)[a]	58.49(42.94–66.13)[a]	55.51(46.13–60.63)	47.9(37.93–57.63)[bc]	10.1315	0.0383*
GFR(ml/min)	52.61(24.56–84.16)	58.23(37.75–82.17)	75.27(35.39–96.12)	73.49(37.56-100.39)	62.75(37.98–97.35)	3.3183	0.5060
Ccr(ml/min)	83.26 ± 22.28	61.72 ± 22.7[a]	68.46 ± 21.15	74.26 ± 21.7[b]	83.32 ± 26.25[bc]	5.1816	0.0006*
MMSE score(P25, P75)	29.5(29,30)	18(15,22)[a]	23(21,25)[ab]	25(24,27)[abc]	26(26,27)[abcd]	103.030	< 0.0001*
MoCA score(P25, P75)	26(25,28)	10(9,12)[a]	15(14,16)[ab]	19(18,20)[abc]	23(23,24)[abcd]	161.500	< 0.0001*
Adjustive MMSE	30(29–30)	19(16–23)[a]	24(22–26)[ab]	26(25–27)[abc]	27(26–28)[abcd]	96.3713	< 0.0001*
(Based on years of schooling)	26.5(26–29)	11(10–13)[a]	16(15–17)[ab]	20(19–21)[abc]	24(23–25)[abcd]	162.270	< 0.0001*

Note compared with level 1 group, [a]$P<0.05$; compared with level 2 group, [b]$P<0.05$; compared with level 3 group, [c]$P<0.05$; compared with level 4 group, [d]$P<0.05$

Table 5 Analysis of influencing factors of ADMA (univariate linear regression)

Variable	Parameter estimation	Standard error	t	*P*
Sex	0.9632	1.9816	0.4861	0.6275
Education level	-1.5326	2.6522	-0.5779	0.5641
Hypertension	3.7184	2.0534	1.8109	0.0719
Coronary heart disease	1.3881	2.0126	0.6897	0.4913
Diabetes mellitus	0.3529	2.4608	0.1434	0.8862
Smoking	-0.3953	1.9647	-0.2012	0.8408
Drinking	-0.3196	1.9948	-0.1602	0.8729
Stroke or cerebral infarction	4.4654	1.9301	2.3135	0.0219*
Hypohepatia	-5.6961	3.8222	-1.4902	0.1380
Renal dysfunction	-6.7434	3.4350	-1.9632	0.0513
Thyroid dysfunction	5.0154	3.8278	1.3102	0.1919
Family history of dementia	-1.4055	3.1247	-0.4498	0.6534
Other family history	-0.7730	1.9604	-0.3943	0.6939
Age	0.3363	0.0949	3.5453	0.0005*
MMSE score	-0.4130	0.2137	-1.9321	0.0550
MoCA score	-0.4787	0.1725	-2.7753	0.0061*
Height	-0.1310	0.1293	-1.0132	0.3124
Weight	0.0302	0.0854	0.3537	0.7240
SBP	0.0122	0.0543	0.2240	0.8230
DBP	-0.0566	0.0924	-0.6123	0.5412
Glu	0.0025	0.4016	0.0063	0.9950
TG	-0.6309	0.7256	-0.8695	0.3858
T-CH	-0.5699	0.9476	-0.6015	0.5483
LDL-C	-1.1090	1.2533	-0.8848	0.3775
HDL-C	-0.0548	2.4519	-0.0223	0.9822
BUN	0.7722	0.4551	1.6969	0.0915
Cr	0.0408	0.0412	0.9917	0.3228
ALT	-0.0151	0.0746	-0.2020	0.8402
AST	-0.0699	0.1032	-0.6767	0.4995
WBC	-0.4787	0.4200	-1.1398	0.2560
CRP	0.2962	0.2649	1.1182	0.2651
GFR	0.0038	0.0217	0.1760	0.8605
Ccr	-0.0931	0.0405	-2.2969	0.0228*
Adjustive MMSE	-0.4351	0.2185	-1.9911	0.0481*
Adjustive MoCA	-0.5102	0.1765	-2.8908	0.0043*

Note * represents $P<0.05$, the effect of variables on ADMA was statistically significant

Table 6 Analysis of influencing factors of ADMA (multifactor linear regression)

Variable	Parameter estimation	Standard error	F	*P*
Intercept term	30.0370	6.3393	22.4508	< 0.0001
Stroke or cerebral infarction	3.7452	1.8879	3.9352	0.0489
Age	0.3148	0.0947	11.0522	0.0011

as assessed by MoCA. It is known that ADMA is significantly increased in End-stage renal disease, as well as in progression of kidney failure and renal fibrosis [14–16]. After controlling for endogenous creatinine clearance, it was observed that the serum ADMA concentration progressively rose as the MoCA score decreased. ON the other hand, age, ALT, AST, CRP, and endogenous creatinine clearance were found to have an impact on cognitive impairment as evaluated by MMSE. Nevertheless, patients with cognitive impairment can be encouraged to engage in cognitive activities and learning endeavors to potentially slow down or prevent the occurrence of cognitive decline. The results of this study also revealed that when the risk factors were divided based on MoCA and MMSE scores, there was a notable difference in liver function between the groups ($P<0.05$). Surprisingly, among individuals with low cognitive scores, aminotransferase levels were lower than expected. This unexpected finding suggests that in these patients, liver cells may have poor function and consequently release fewer enzymes, while the unaffected liver cells exhibit normal function. It is likely that more transaminase is released after liver damage.In another study by Ciećko-Michalska et al., [17] which involved 138 patients, memory function was assessed in patients with cirrhosis using a simple mental state checklist. The findings revealed that compared to normal individuals, patients with cirrhosis showed a clear tendency towards memory errors. Consequently, protecting liver function and regulating transaminase levels could potentially slow down or prevent the occurrence of cognitive impairment. This results of this study revealed significant variations in endogenous creatinine clearance ($P=0.002$) among the groups based on MoCA and MMSE scores. Generally, the body produces approximately 300 μmol of ADMA within 24 h, with about 50 μmol of ADMA being eliminated through the kidneys [15]. When glomerular filtration function declines, leading to reduced endogenous creatinine clearance, ADMA is not efficiently cleared through the kidneys. Consequently, this reduces NO levels, causing endothelial dysfunction and indirectly contributing to the onset and progression of cognitive impairment [18]. Kurella et al. further corroborated this by observing that patients with chronic kidney disease exhibited significantly prolonged EEG latency, and as the EEG latency increased, their cognitive scores declined. This observation also provides indirect evidence that renal dysfunction can be linked to the development of cognitive impairment [19]. ADMA has a unique inhibitory effect on endothelial NO synthase, which can inhibit the impact of NO on vascular dilation and endothelial function. By reducing cerebral blood flow or exacerbating oxidative stress and inflammation, it promotes the occurrence and development of cerebral small-vessel diseases [20]. After controlling for

age, gender, vascular risk factors, and creatinine clearance, the number of lacunes is not significantly associated with ADMA levels, but the severity of white matter hyperintensities is related to ADMA [21]. ADMA and endothelial cells dysfunction play a significant role in the early pathological development of CSVD [22]. Gao Qiang et al. from our research group found ADMA are elevated in SVD, and are associated with cognitive impairment in patients with LA lesions [6].

In the current study, we observed notable distinctions in systolic blood pressure across all groups, as indicated by the MoCA score ($P = 0.0261$). However, the MMSE score did not display any significant differences, possibly due to the limited sensitivity of MMSE in assessing cognitive function. The relationship between systolic blood pressure and cognitive score was depicted as an inverted U-shaped curve. The inconsistency in the relationship between SBP and cognitive dysfunction in the two scales might be attributed to specific factors: Firstly, 62 patients in the MMSE group were classified as normal, and the overall mean SBP was 139.1 ± 19.5 mmHg. This suggests that MMSE may not be sufficiently sensitive to detect mild cognitive impairment, and even when MoCA indicates cognitive decline (score of 2 to 3), the MMSE score may still be considered normal. Moreover, higher SBP in these cases could lead to false negative results.

Epidemiological studies have demonstrated a correlation between high blood pressure and dementia [23], with a particular study in Europe on systolic hypertension (Syst-Eur) showing a 55% reduction in dementia occurrence after two years of high blood pressure treatment. However, the evidence for blood pressure treatment reducing the incidence of vascular cognitive impairment is inconclusive, as only 2 out of 32 patients with new vascular dementia were diagnosed in that study [24]. Another study revealed that the relative risk of developing vascular dementia was approximately one-third lower in the blood pressure treatment group compared to the control group [25]. Furthermore, the hypertension in the very elderly trial cognitive function assessment (HYVET-COG), which involved Chinese participation, was a multicenter study. A meta-analysis of its results combined with findings from three similar studies indicated that lowering blood pressure could enhance the occurrence of dementia [26].

A pooled data analysis indicated that a mild reduction in blood pressure (< 5/3 mmHg, where 1 mm Hg = 0.133 kPa) was associated with improved MMSE scores, as well as better immediate and delayed logical recall [27]. These research outcomes collectively suggest that antihypertensive treatment may potentially improve cognitive function or help prevent cognitive decline, ultimately reducing the risk of cognitive impairment. Previous research has indicated that cognitive decline is more pronounced in patients with higher levels of CRP in their blood serum [28]. The reason for this could be the activation of the complement system, which may result in dysfunction of the endothelial cells, alterations in cerebrovascular structures, and disruption of subcortical brain circuits, ultimately leading to cognitive issues [29].

In cerebrovascular diseases, elevated CRP levels may hinder the growth of new blood vessels by reducing the production of nitric oxide, encouraging the accumulation of monocytes, promoting cell proliferation and vascular smooth muscle migration, thereby contributing to cognitive dysfunction [30]. Moreover, CRP may also have detrimental effects on neurons, further exacerbating cognitive impairment [31].

To mitigate the impact of the inflammatory response and minimize its damage to the vascular endothelium, it becomes crucial to promote the formation of new blood vessels. By doing so, it would be possible to potentially prevent or delay the onset of cognitive impairment.

The results of this study demonstrated significant differences in serum ADMA concentration across all groups based on MoCA scores ($P = 0.0383$), with the serum ADMA levels increasing gradually as the MoCA scores decreased. Conversely, there was no notable difference in serum ADMA concentration among groups categorized by MMSE scores ($P = 0.1602$). This may be attributed to the fact that the average ADMA level among 62 normal patients in the MMSE group was 50.15 ± 12.81 umol/L, which was higher than that of the MoCA1 group. As a result, MMSE may not be sensitive enough to detect cognitive impairment and fails to recognize mild cognitive impairment. Consequently, cases with cognitive function at the MoCA1 level may be labeled as normal MMSE, even though their ADMA levels are elevated, leading to no significant statistical difference among the groups.

In another clinical study, ADMA was administered intravenously to healthy volunteers in a randomized, double-blind, placebo-controlled manner. This led to a significant reduction in cerebral perfusion and vascular compliance compared to the placebo group, suggesting that ADMA might play a role in the onset of dementia [32]. Also there were notable statistical variances in serum ADMA levels across all groups based on their MoCA scores ($P = 0.0383$). Moreover, it was observed that the serum ADMA concentration progressively rose as the MoCA score decreased.

In the serum of the groups categorized based on MMSE score, ADMA, functioning as an internal inhibitor of NOS, did not impede the production of NO. Moreover, it did not trigger an elevation in the creation of harmful oxygen free radicals, nor did it induce processes such as platelet activation and aggregation [33], monocyte adhesion [34], or acceleration of endothelial cell apoptosis, which could potentially lead to endothelial dysfunction.

The preservation of normal cerebral vascular endothelial cells is crucial for maintaining the self-regulation function of cerebral blood flow and preserving the integrity of the blood-brain barrier [35].

At present, the impairment of the blood-brain barrier, dysregulation of cerebral blood flow autoregulation, and chronic hypoperfusion are recognized as significant factors contributing to leukoencephalopathy, which leads to cognitive dysfunction. White et al. [36] conducted a study on effects of NOS inhibitors on cerebral blood flow autoregulation and found that NO plays a role in regulating cerebral blood flow. When released, NO reduces the self-regulation of damaged cerebral blood flow and may slow down cerebral blood flow.

Corzo et al. [37] discovered that NO, mediated by HDL-cholesterol, aids in slowing down the progression of dementia. The exact mechanism is not yet fully understood, but it is suggested that HDL may stimulate the activation of kinase cascade and calcium ion, leading to the formation of reactive astrocytes, which, in turn, induces iNOS. Consequently, decreased NO levels can exacerbate cerebral blood flow dysfunction, synaptic destruction, and increase oxidative stress, indirectly promoting the development of dementia.

The results indicate that endothelial dysfunction plays a role in early cognitive impairment, but its effects may only manifest in the late stages if MMSE criteria are met. Therefore, endothelial dysfunction could be involved in the development of cognitive impairment. The results of the multivariate analysis revealed several independent risk factors associated with serum ADMA concentration. These risk factors include age ($P = 0.0005$), stroke history ($P = 0.0219$), and Ccr (creatinine clearance, $P = 0.0228$). Interestingly, we found that both age and stroke history were positively correlated with other risk factors ($P > 0.05$). It is worth noting that other researchers have previously suggested a connection between serum ADMA concentration and various factors such as kidney function, coronary heart disease, hypertension, and stroke [38].

In addressing cognitive screening tools, the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) are the most commonly used methods in cognitive impairment detection in both clinical and research fields. MoCA is a better measure of cognitive function due to lack of ceiling effect and with good detection of cognitive heterogeneity. MCI prevalence is higher using MoCA compared to MMSE. Both tools identify concordantly modifiable factors for MCI, which provide important evidence for establishing intervention measures. So MoCA and MMSE were used to measure the relationship between ADMA concentration and the degree of cognitive impairment. MMSE reflecting verbal episodic memory were less, and the influence was significantly related to the cultural level of the subjects. The scale mainly focuses on memory and language function, and lacks assessment of executive function, visual space, abstract thinking, etc. The emphasis is on instant memory. Low sensitivity, high specificity.

In contrast, in the present study, we observed that serum ADMA concentrations increased with age and history of stroke. However, unlike previous findings, we did not detect a similar increase in ADMA concentrations in relation to kidney function. We speculate that this discrepancy may be due to the intricate interplay of multiple independent variables in their multifactor analysis. Nonetheless, the results of this study support the notion that elevated serum ADMA levels, which can result from conditions like renal insufficiency, contribute to vascular endothelial dysfunction and indirectly affect cognitive function, aligning with findings of other studies [39, 40].

Conclusion

The MoCA scale gauges the susceptibility to early cognitive impairment. In this study, there was a direct relationship between ADMA levels and the extent of cognitive impairment, suggesting that endothelial dysfunction and cognitive impairment were positively linked. Moreover, it was observed that systolic blood pressure contributed to endothelial dysfunction and cognitive decline, following an inverted U-shaped pattern. Based on the results of this study, age, stroke history, and renal insufficiency history were independent risk factors for serum ADMA concentration. By safeguarding renal function, addressing atherosclerotic factors, and preventing strokes, it may be possible to reduce endothelial dysfunction and consequently lower the risk of cognitive impairment.

Abbreviations

ADMA	Asymmetric dimethylarginine
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
NO	Nitric oxide
L-Arg	Arginine
NOS	Nitric oxide synthase
FPG	Fasting plasma glucose
LDL	Lipoprotein cholesterol
TC	Total cholesterol
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
WBC	White blood cells
ELISA	enzyme-linked immunosorbent assay
Syst-Eur	Europe on systolic hypertension

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40359-025-02715-y.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Acknowledgements
We would like to acknowledge the hard and dedicated work of all the staff that implemented the intervention and evaluation components of the study.

Author contributions
Conception and design of the research: Ying Fan, Zhao-Qi Yan, Lei Liu. Acquisition of data: Lei Liu, Jia-Xin Guan, Zhi-Qiang Song. Analysis and interpretation of the data: Lei Liu, Zhi-Qiang Song, Jia-Xin Guan. Statistical analysis: Lei Liu, Qiang Gao, Zhao-Qi Yan. Obtaining financing: Ying Fan, Lei Liu, Qiang GaoWriting of the manuscript: Lei Liu, Su-Jun Cheng. Critical revision of the manuscript for intellectual content: Lei Liu, Su-Jun Cheng. All authors read and approved the final draft.

Funding
Key research and development program project of Heilongjiang Province (2023ZX06C03); The Joint Guidance Project of Heilongjiang Provincial Natural Science Foundation (No. LH2020H051); The Foundation of Harbin Science Technology Bureau (No. 2014RFQGJ042).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study followed the Declaration of Helsinki and was approved by the Ethics Committee of Second Affiliated Hospital of Harbin Medical University. Written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Geriatrics, Second Affiliated Hospital of Harbin Medical University, No. 148 Baojian Road, Harbin 150086, China
[2]Health Management Centre, Second Affiliated Hospital of Harbin Medical University, No. 148 Baojian Road, Harbin 150086, China

Received: 28 December 2023 / Accepted: 8 April 2025
Published online: 18 April 2025

References

1. Wang J, Chen J, Tang Z. The effects of copper on brain microvascular endothelial cells and Claudin via apoptosis and oxidative stress. Biol Trace Elem Res. 2016;174(1):132–41.
2. Karaarslan F, Ozkuk K, Seringec Karabulut S. How does spa treatment affect cardiovascular function and vascular endothelium in patients with generalized osteoarthritis? A pilot study through plasma asymmetric di-methyl arginine (ADMA) and L-arginine/ADMA ratio. Int J Biometeorol. 2018;62(5):833–42.
3. Stephan BCM, Harrison SL, Keage HAD. Cardiovascular disease, the nitric oxide pathway and risk of cognitive impairment and dementia. Curr Cardiol Rep. 2017;19(9):87.
4. Fan Y, Gao Q, Guan JX, Liu L, Hong M, Jun L, Wang L, Ding HF, Jiang LH, Hou BY, Li M, Song ZQ, Sun DQ, Yan CQ, Ma L. DDAH 2 (-449 G/C) G allele is positively associated with leukoaraiosis in Northeastern China: a double-blind, intergroup comparison, case-control study. Neural Regeneration Res. 2021;16(8):1592–7.
5. Guan J, Yan C, Gao Q, Li J, Wang L, Hong M, Zheng X, Song Z, Li M, Liu M, Fan Y, Ma L. Analysis of risk factors in patients with leukoaraiosis. Med (Baltim). 2017;96(8):e6153.
6. Gao Q, Fan Y, Mu LY, Ma L, Song ZQ, Zhang YN. S100B and ADMA in cerebral small vessel disease and cognitive dysfunction. J Neurol Sci. 2015;354(6):27–32.
7. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-9. Erratum in: J Am Geriatr Soc. 2019;67(9):1991.
8. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc. 1992;40(9):922–35.
9. Langa KM, Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. JAMA. 2014;312(23):2551–61.
10. Li JQ, Tan L, Wang HF. Risk factors for predicting progression from mild cognitive impairment to Alzheimer's disease: a systematic review and meta-analysis of cohort studies. J Neurol Neurosurg Psychiatry. 2016;87(5):476–84.
11. Jia X, Wang Z, Huang F, Su C, Du W, Jiang H, Wang H, Wang J, Wang F, Su W, Xiao H, Wang Y, Zhang B. A comparison of the Mini-Mental state examination (MMSE) with the Montreal cognitive assessment (MoCA) for mild cognitive impairment screening in Chinese middle-aged and older population: a cross-sectional study. BMC Psychiatry. 2021;21(1):485.
12. Wu Y, Zhang Y, Yuan X, Guo J, Gao X. Influence of education level on MMSE and MoCA scores of elderly inpatients. Appl Neuropsychol Adult. 2023;30(4):414–8.
13. Miralbell J, López-Cancio E, López-Oloriz J. Cognitive patterns in relation to biomarkers of cerebrovascular disease and vascular risk factors. Cerebrovasc Dis. 2013;36(2):98–105.
14. MacAllister RJ, Vallance P, Williams D, Hoffmann K-H, Ritz E. Concentration of dimethyl-L-arginine in the plasma of patients with end-stage renal failure. Nephrol Dial Transpl. 1996;11:2449–52.
15. Oliva-Damaso E, Oliva-Damaso N, Rodriguez-Esparragon F, Payan J, Baamonde-Laborda E, Gonzalez-Cabrera F, Santana-Estupiñan R, Rodriguez-Perez JC. Asymmetric (ADMA) and symmetric (SDMA) dimethylarginines in chronic kidney disease: A clinical approach. Int J Mol Sci. 2019;20(15):3668.
16. Eiselt J, Rajdl D, Racek J, Vostry M, Rulcova K, Wirth J. Asymmetric dimethylarginine and progression of chronic kidney Disease-a One-Year Follow-Up study. Kidney Blood Press Res. 2014;39:50–7.
17. Ciećko-Michalska I, Wójcik J, Senderecka M. Cognitive functions in patients with liver cirrhosis: a tendency to commit more memory errors. Med Sci Monit. 2013;19(182):283–8.
18. Doğan İ, Eser B, Özkurt S, Yayar Ö, Özgür B, Kayadibi H, Doğan T, Muşmul A, Soydan M. Serum ADMA, endothelial dysfunction, and atherosclerosis in hypervolemic Hemodialysis patients. Turk J Med Sci. 2018;48(5):1041–7.
19. Kurella M, Chertow GM, Luan J. Cognitive impairment in chronic kidneydisease. J Am Geriatr Soc. 2004;52(11):1863–9.
20. Jaime Garcia D,Chagnot A, Wardlaw, JM et al. A scoping review on biomarkers of endothelial dysfunction in small vessel disease: molecular insights from human studies. Int J Mol Sci. 2023;24(17):13114.
21. Khan U, Hassan A, Vallance P, et al. Asymmetric dimethylarginine in cerebral small vessel disease[J]. Stroke. 2007;38(2):411–3.
22. Janes F, Cifù A, Pessa ME, et al. ADMA as a possible marker of endothelial damage. A study in young asymptomatic patients with cerebral small vessel disease[J]. Sci Rep. 2019;9(1):14207.
23. Ou YN, Tan CC, Shen XN, Xu W, Hou XH, Dong Q, Tan L, Yu JT. Blood pressure and risks of cognitive impairment and dementia: A systematic review and Meta-Analysis of 209 prospective studies. Hypertension. 2020;76(1):217–25. Epub 2020 May 26.
24. Tadic M, Cuspidi C, Hering D. Hypertension and cognitive dysfunction in elderly: blood pressure management for this global burden. BMC Cardiovasc Disord. 2016;16(1):208.
25. Hsu PF, Pan WH, Yip BS. C-Reactive protein predicts incidence of dementia in an elderly Asian community cohort. J Am Med Dir Assoc. 2017;18(3):277.
26. Peters R, Beckett N, Forette F. Incident dementia and blood pressure Lowering in the hypertension in the very elderly trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol. 2008;7(8):683–9.
27. Birns J, Morris R, Donaldson N. The effects of blood pressure reduction on cognitive function: a review of effects based on pooled data from clinical trials. J Hypertens. 2006;24(10):1907–14.
28. Zheng F, Xie W. High-sensitivity C-reactive protein and cognitive decline: the english longitudinal study of ageing. Psychol Med. 2018;48(8):1381–9.
29. Fleszar MG, Wiśniewski J, Zboch M, Diakowska D, Gamian A, Krzystek-Korpacka M. Targeted metabolomic analysis of nitric oxide/L-arginine pathway metabolites in dementia: association with pathology, severity, and structural brain changes. Sci Rep. 2019;9(1):13764.
30. Whitfield JF. Can Statins put the brakes on Alzheimer's disease?[J]. Expert Opin Investig Drugs. 2006;15(12):1479–85.

31. Kuo HK, Yen CJ, Chang CH. Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population: systematic review and meta-analysis[J]. Lancet Neurol. 2005;4(6):371–80.
32. Kielstein JT, Donnerstag F, Gasper S. ADMA increases arterial stiffness and decreases cerebral blood flow in humans. Stroke. 2006;37(8):2024–9.
33. Stoessel A, Paliege A, Theilig F. Indolent course of tubulointerstitial disease in a mouse model of subpressor, low-dose nitric oxide synthase Inhibition. Am J Physiol. 2008;295(3):F717–25.
34. Chen M, Li Y, Yang T. ADMA induces monocyte adhesion via activation of chemokine receptors in cultured THP-1 cells. Cytokine. 2008;43(2):149–59.
35. Markus HS. Genes, endothelial function and cerebral small vessel disease in man. Exp Physiol. 2008;93(1):121–7.
36. White RP, Vallance P, Markus HS. Effect of Inhibition of nitric oxide synthase on dynamic cerebral autoregulation in humans. Clin Sci. 2000;99(6):555–60.
37. Corzo L, Zas R, Rodríguez S. Decreased levels of serum nitric oxide in different forms of dementia. Neurosci Lett. 2007;420(3):263–7.
38. Nishiyama Y, Otsuka T, Ueda M. Asymmetric dimethylarginine is related to the predicted stroke risk in middle-aged Japanese men. J Neurol Sci. 2014;338(1–2):87–91.
39. Petersen RC. Mild cognitive impairment:transition between aging and Alzheimer's disease. Neurologia. 2000;15(3):93–101.
40. Bollenbach A, Schutte AE, Kruger R, Tsikas D. An ethnic comparison of arginine dimethylation and cardiometabolic factors in healthy black and white youth: the ASOS and African-PREDICT studies. J Clin Med. 2020;9(3):844.

Publisher's note