



## RESEARCH ARTICLE

# Circulating asymmetric dimethylarginine and cognitive decline: A 4-year follow-up study of the 1936 Aberdeen Birth Cohort

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**Background:** The underlying mechanisms leading to dementia and Alzheimer's disease (AD) are unclear. Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase, may be associated with cognitive decline, but population-based evidence is lacking.

**Methods:** Change in cognitive performance was assessed in participants of the Aberdeen Birth Cohort of 1936 using longitudinal Raven's progressive matrices (RPM) between 2000 and 2004. Multiple linear regression was used to estimate the association between ADMA concentrations in 2000 and change in cognitive performance after adjustment for potential confounders.

**Results:** A total of 93 participants had complete information on cognitive performance between 2000 and 2004. Mean plasma ADMA concentrations were approximately 0.4  $\mu\text{mol/L}$  lower in those participants with stable or improved RPM scores over follow-up compared with participants whose cognitive performance worsened. In confounder-adjusted analysis, one SD (0.06  $\mu\text{mol/L}$ ) increase in ADMA at 63 years of age was associated with an average reduction in RPM of 1.26 points (95% CI 0.14-2.26) after 4 years.

**Conclusion:** Raised plasma ADMA concentrations predicted worsening cognitive performance after approximately 4 years in this cohort of adults in late-middle age. These findings have implications for future research, including presymptomatic diagnosis or novel therapeutic targets for dementia and AD.

## KEYWORDS

Alzheimer's disease, asymmetric dimethylarginine, biomarkers, cognitive decline, diagnosis, nitric oxide

## 1 | INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterised by a rapid decline in cognition in old age, which is distinct from the normal ageing process. The causes of late onset AD are largely unknown and despite extensive research, there is still no clear consensus on

blood-based biomarkers or effective treatments.<sup>1,2</sup> The vast majority of research has focused on a set of histopathological hallmarks which are often present in diseased brains. However, evidence from observational studies suggests a poor correlation between plaque density and degree of dementia in AD,<sup>3,4</sup> and multiple pharmacological interventions targeting these histopathological hallmarks have proven ineffective.<sup>5</sup>

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There is growing observational evidence for an overlap of risk factors in AD and cardiovascular disease. For example, diabetes is associated with a 2- to 3-fold increased risk of vascular events<sup>6,7</sup> but also a 50% increased risk of dementia<sup>8</sup> and a 20% increase in the rate of cognitive decline.<sup>9-11</sup> Furthermore, large genomewide association studies have confirmed associations between 'vascular risk' genes and the development of AD,<sup>12</sup> with the strongest known genetic risk factor being a mutation in the apolipoprotein E4 gene, which encodes a cholesterol transporter protein.<sup>13</sup> Vascular endothelial dysfunction, an abnormality that is associated with the presence of virtually all known cardiovascular risk factors, is frequently seen in AD. Despite this evidence, there is a lack of population-based research investigating the roles of vascular changes, oxidative stress, lipid metabolism and inflammation in AD pathogenesis.<sup>14,15</sup>

Nitric oxide (NO) has an established role as a mediator in the pathogenesis of cardiovascular disease<sup>16</sup> but also potentially in AD.<sup>17,18</sup> Impaired NO release from dysfunctional endothelial cells precedes reduced blood flow and regional metabolic deficiency. This may result in hypoxic events, leading to activation of the immune response and resultant cell death.<sup>17</sup> In support of this hypothesis, recent interventions to increase the concentrations of endogenously produced NO have halted AD pathogenesis in mice.<sup>19</sup> Furthermore, abnormal NO signalling has been reported in the brains of both human sufferers and animal models of AD.<sup>20,21</sup>

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase (NOS), an essential enzyme for the synthesis of NO.<sup>17</sup> Therefore, ADMA may play an important pathophysiological role in the abnormal NO signalling observed in both CVD and AD and could be a potential target for novel therapeutic interventions.

A number of small-scale studies have investigated the association between ADMA concentrations and cognitive decline in older adults.<sup>22-25</sup> However, no study has adjusted for childhood intelligence, which explains up to 50% of cognitive decline in old age.<sup>26-28</sup> Investigating the association between ADMA and cognitive decline with full adjustment for potential confounders could have implications for presymptomatic diagnosis of AD and may reveal novel drug targets. This study aims to investigate the relationship between plasma ADMA concentrations and the change in cognitive performance across four years in the 1936 Aberdeen Birth Cohort (ABC36) study.

## 2 | METHODS

### 2.1 | Study population

The ABC36 is a well-studied cohort population described in greater depth elsewhere.<sup>29,30</sup> Briefly, 506 volunteers were recruited from Aberdeen in 2000, each of whom were born in 1936 and had completed the Moray House mental survey (MHT), a measure of cognitive performance, in 1947. A total of 986 MHT scores matched with records of local medical practice members. Of these, 647 were invited to participate in a longitudinal study of cognitive ageing and health, of

### Key points

- This cohort study investigated the association between serum ADMA levels and change in cognitive performance in late-middle age (from 63 to 67 years) for the first time using a prospective cohort study design.
- Circulating ADMA levels displayed strong, linear and inverse associations with cognitive function after 4 years. Therefore, blood-based ADMA has potential to aid the early detection of cognitive decline in late-middle age and must be explored using larger studies.
- These findings suggest a potential role of nitric oxide impairment in the pathophysiology underlying cognitive impairment and possible progression to AD, with implications for presymptomatic diagnosis or novel therapy.

which 506 (78%) agreed to participate. Of these, baseline cognitive assessments were undertaken on 480 (74%) participants who were all in good health and living independently aged approximately 63 years. Of these, 246 individuals had complete information on all baseline assessments, including blood measurements (Supplementary Table 1). A total of 93 study participants completed all waves (WII and WIII) of resurvey assessments in 2002 and 2004, aged approximately 65 and 67 years, respectively.

### 2.2 | Study procedures

Assessment interviews were conducted in three stages, carried out by a trained research nurse. The first section comprised assessment of demographic and clinical data, which included smoking and alcohol history, family history of dementia, diabetes or stroke and a physical examination including measurement of body mass index (BMI). Written informed consent was obtained from all participants at the start of the interview. All study procedures were approved by the Grampian Research Ethics Committee (GREC).

Occupation, deprivation scores and years of formal education were used as a composite measure of socioeconomic status (SES). Occupation was categorised in accordance with the Standard Occupational Classification issued by the Scottish Government.<sup>31</sup> Each participant was given a deprivation code corresponding to the postcode of their home address in accordance with the Scottish Index of Multiple Deprivation ranking system.<sup>32</sup> During the physical examination, blood pressure readings were recorded (sitting). Hypertension was identified when mean systolic pressure was above 144 mmHg or when mean diastolic pressure was above 94 mmHg. Subjects receiving medication for the treatment of hypertension were included in the hypertensive category. Subjects were asked to disclose smoking habits into the following classifications: never smoked, previous smoker and current

smoker. As an additional assessment, hippocampal volumes were analyzed through MRI imaging assessment at WIII. The MR acquisition procedure has been described in greater depth elsewhere.<sup>33</sup>

## 2.3 | Childhood intelligence

All children born in 1936 in Scottish schools were included in a survey of mental ability on the 4 June 1947, an initiative led by the Scottish Council for Research in Education. All children took version number 12 of the MHT, comprised of 71 questions with 76 being the maximum attainable score. The results of this test have been found to directly correlate with Stanford-Binet IQ scores.<sup>34</sup>

## 2.4 | Baseline cognitive ability and follow-up

A measure of cognitive ability was assessed using standard Raven's Progressive Matrices (RPM) tests during three waves (WI to WIII) of assessments in 2000 to 2001, 2002 to 2003 and 2003 to 2004, respectively. The test is comprised of five sets of 12 questions, which become increasingly difficult, hence greater cognitive ability is associated with a higher score.<sup>35</sup> For the purposes of this study, scores from WI and WIII were used to measure cognitive trajectories, with the difference between the two scores being the primary outcome measure. For the primary analyses, subjects were grouped into three categories based on change in cognition from WI to WIII. Participants were categorised as rapid decliners if their RPM scores had decreased by 7 points or more from baseline assessment (WI).

Participants were allocated into the slow decline category if WIII RPM scores had decreased anywhere between 0 and 6 points below baseline scores. The maintainers and improvers had either maintained cognitive function or improved their RPM score between WI and WII assessments.

## 2.5 | Plasma ADMA levels

Blood samples were taken at baseline (WI) in 2000 and measurement of serum lipids undertaken. A random subset of blood samples were centrifuged at 4°C for 10 minutes at 2500 rpm to obtain plasma which was then frozen at -80°C. Samples were thawed at a later date and plasma ADMA concentrations were measured using hydrophilic-interaction liquid chromatography-electrospray tandem mass spectrometry as described previously.<sup>36</sup>

## 2.6 | Statistical analysis

To investigate population sample characteristics, chi-square tests and tests for linearity were employed to compare the means between each subgroup of cognitive trajectory profile and selected characteristics at baseline. The corresponding significance value for each test was presented in the results.

The adjusted mean values (and corresponding 95% confidence intervals) of baseline ADMA were estimated for each category of change in RPM from baseline to WIII assessment using a direct standardization technique. The adjusted association between plasma

**TABLE 1** Baseline characteristics of study population, by cognitive performance category

Baseline characteristics	Difference in RPM score after 4 years			P <sub>trend/het</sub>	All
	Rapid decliners	Slow decliners	Maintainers/improvers		
Total n (% of 93)	15 (16)	43 (46)	35 (38)		93
Age, years (mean [SD])	63.3 (0.6)	63.3 (0.6)	63.2 (0.4)	.699	63.3 (0.5)
Sex, n (%)				.707	
Male	6 (40)	26 (60)	19 (54)		51 (55)
Female	9 (60)	17 (40)	16 (46)		42 (45)
Formal education (years), n (%)				.891	
0–10	8 (53)	27 (63)	22 (63)		57 (62)
11–13	6 (40)	9 (21)	5 (14)		20 (21)
>14	1 (7)	7 (16)	8 (23)		16 (17)
Current smoker, % (mean)	26.6% (46)	18.6% (39)	20.0% (41)	.588	20.4% (41)
Alcohol consumption, units/week (mean [SD])	7.1 (8.5)	5.3 (6.9)	5.5 (7.0)	.497	5.7 (7.2)
RPM score at first visit (mean [SD])	41.9 (6.4)	38.4 (8.3)	36.7 (8.5)	<.001*	38.3 (8.2)
Childhood MHT score (mean [SD])	42.9 (10.7)	42.8 (11.8)	47.8 (9.9)	.794	44.7 (11.1)

Note: Categories of cognitive performance correspond to the following differences in RPM score between baseline and follow-up assessments: Rapid decliners = RPM score decrease by ≥7 points; slow decliners = RPM score decrease between 0 and 6 points; maintainers/improvers = RPM score remained unchanged or increased across follow-up.

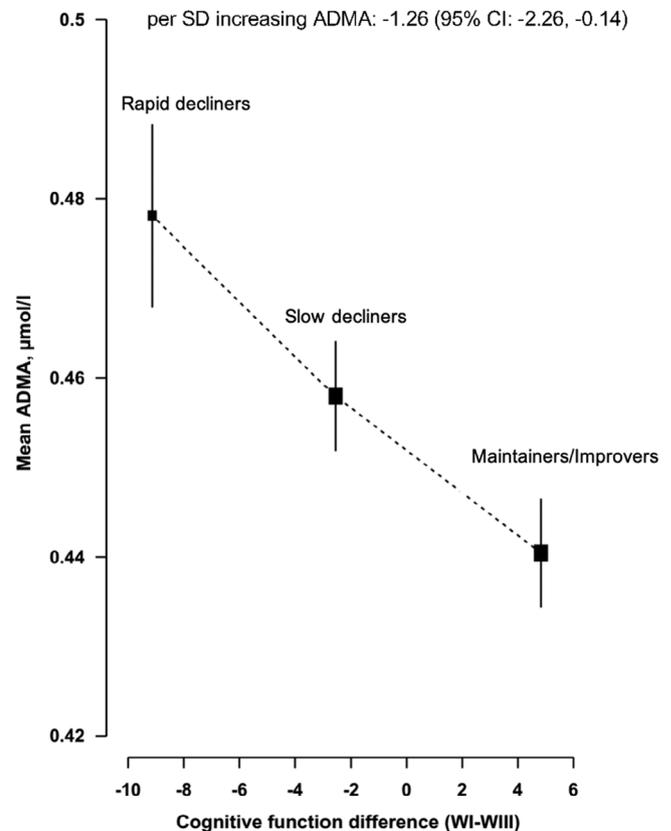
Abbreviations: MHT = Moray house test; RPM = Ravens progressive matrix score.

\*P < .05 for linear trend.

ADMA concentrations and change from baseline RPM score to WIII RPM score was investigated using multiple linear regression analysis. The model was adjusted for gender, smoking status, systolic blood pressure, SES, RPM score at baseline, childhood mental ability and hippocampal volume as potential confounding variables. The results were expressed as beta ( $\beta$ ) coefficients and corresponding 95% CI representing the difference in RPM score between WI and WIII per one SD increasing ADMA at baseline. All variables contained no outliers, and each was tested for homoscedasticity of residuals, a normal sampling distribution and independence, thereby meeting the criteria for multiple linear regression analysis. All statistical analyses were conducted using STATA version 16.0 and R version 3.5.2.

### 3 | RESULTS

A total of 93 participants with complete information at baseline and all subsequent assessments contributed to the main analyses (Table 1). Across the four year follow-up period, the majority of study participants ( $n = 43$ ) showed a slow decline in cognitive performance, 15 participants showed a rapid decline, and 35 participants maintained or improved their cognition scores. On average, participants were 63.3 (SD 0.5) years at baseline, and just over half of participants (55%) were men. Although not statistically significant, a slightly larger proportion of participants with declining cognitive performance across follow-up were men (60%). Similarly, prior to confounder adjustment, no significant differences in baseline age, years of education, childhood MHT score, smoking habits, or alcohol consumption were observed between participants who improved or maintained their cognitive performance scores. Participants showing a decline in RPM score from baseline to follow-up had significantly lower baseline SBP values and raised RPM scores compared with participants who maintained or improved their RPM score (Table 2). However, baseline ADMA, DBP, cholesterol concentrations and BMI were similar across



**FIGURE 1** Association between baseline ADMA across categories of cognitive function scores between baseline and 4-year repeat assessment. Mean values (95% confidence intervals) were adjusted for gender, smoking, social deprivation, education and hippocampal volume. Areas of point estimates are inversely proportional to the variance of the coefficient. Participants were categorised as maintainers or improvers if they did not achieve a lower score at wave III (WIII) compared with wave I (WI). Similarly, participants were categorised as slow decliners if they achieved between 1 and 7 points below their baseline levels, and rapid decliners if performance at WIII was greater than 7 points below the baseline RPM score. The y-axis is standardised to represent  $\pm 0.5$  SDs from the mean value of ADMA

**TABLE 2** Body size and biomarker characteristics at baseline assessment, by cognitive performance category

Baseline characteristics	Difference in RPM score after 4 years			$P_{\text{trend}}$	All
	Rapid decliners	Slow decliners	Maintainers/improvers		
ADMA, $\mu\text{mol/L}$ (mean [SD])	0.464 (0.061)	0.458 (0.065)	0.446 (0.065)	.807	0.455 (0.064)
BMI, $\text{kg/m}^2$	26.0 (4.2)	27.4 (4.6)	26.5 (4.2)	.261	26.8 (4.4)
SBP, mm Hg (mean [SD])	135.3 (26.8)	142.8 (20.8)	147.6 (24.7)	<b>.008*</b>	143.4 (23.5)
DBP, mm Hg (mean [SD])	79.3 (11.4)	78.5 (8.7)	77.5 (10.1)	.975	78.3 (9.6)
HDL, mmol/L (mean [SD])	1.46 (0.37)	1.33 (0.40)	1.45 (0.35)	.108	1.39 (0.38)
LDL, mmol/L (mean [SD])	3.66 (0.83)	3.23 (0.84)	3.43 (0.92)	.104	3.37 (0.87)
Nonfasting triglycerides, mmol/L (mean [SD])	2.03 (1.30)	1.97 (0.92)	2.10 (1.30)	.720	2.03 (1.13)

Categories of cognitive performance correspond to the following differences in RPM score between baseline and follow-up assessments: rapid decliners = RPM score decrease by  $\geq 7$  points; slow decliners = RPM score decrease between 0 and 6 points; maintainers/improvers = RPM score remained unchanged or increased across follow-up.

ADMA = asymmetric dimethylarginine; BMI = body-mass index; DBP = diastolic blood pressure; HDL = high density lipoprotein; LDL = low density lipoprotein; SBP = systolic blood pressure.

\* $P < .05$  for linear trend.

RPM performance categories before adjustment for potential confounders.

In confounder adjusted analysis, ADMA concentrations were negatively and linearly associated with an improvement in cognitive performance approximately four years after baseline (Figure 1). On average, one SD (roughly equivalent to 0.06  $\mu\text{mol/L}$ ) increase in ADMA at baseline was associated with a reduction in cognitive performance score of 1.26 (95% CI 0.14–2.26) points from baseline to Will assessment.

## 4 | DISCUSSION

After full adjustment for potential confounders, higher plasma ADMA concentrations were associated with a decline in cognitive performance approximately four years later. This finding supports conclusions drawn from several previous studies.<sup>22–25</sup> Poor cognitive performance, in the absence of a clinical syndrome such as mild cognitive impairment (MCI) or dementia, is a risk factor for the development of dementia. Therefore, plasma ADMA concentrations may predict dementia at older age.

### 4.1 | Comparison with previous observational evidence

To our knowledge, no study has investigated the prospective association between ADMA concentrations and cognitive decline trajectories in longitudinal population studies to date. In a cross-sectional study, mean plasma ADMA concentrations were approximately 0.1  $\mu\text{mol/L}$  higher among 80 AD patients compared with 80 matched controls.<sup>22</sup> Similarly, in a smaller case-control study of 25 AD patients and 25 matched controls, plasma ADMA concentrations were approximately 0.4  $\mu\text{mol/L}$  higher among AD patients vs controls.<sup>25</sup> However, beyond matching on age and sex, these studies were unable to adjust for other important confounding factors. In the Hunter Community study, a cohort of 483 healthy elderly Australians, participants in the top quarter of ADMA distribution had 1.82 (95% CI: 1.04–3.18) greater odds of memory impairment compared to the lowest group after adjusting for age, education and sex.<sup>23</sup> The Barcelona-AsIA Neuropsychology Study, including over 740 adults aged 51 to 79 years, reported that higher plasma ADMA concentrations were associated with a reduction in verbal memory after adjusting for age, gender, years of education and depressive symptoms.<sup>24</sup> However, all of these studies were cross-sectional in nature, which limits the ability to infer causation. Furthermore, we are unable to rule out the effects of reverse causality (ie, AD patients may have altered their behavior as a result of the disease, potentially influencing plasma ADMA levels). A number of studies have reported similar effects of ADMA concentrations on cognitive deficits in animal models.<sup>37</sup>

### 4.2 | Underlying mechanisms

The exact cause of the association between plasma ADMA concentrations and cognitive function is unknown. However, a number of

mechanisms have been suggested previously.<sup>38</sup> The observed positive association may be the result of impaired endothelial-derived NO synthesis, which may influence the onset and progression of cognitive decline and AD through two main mechanisms: (a) increased atherosclerosis and vasoconstriction, leading to subsequent impaired cerebral blood flow regulation and cognitive function and (b) enhanced oxidative stress and reduced neuroprotection of astrocytes.

The proposed theory of ADMA-mediated endothelial dysfunction and vascular damage is thought to be the result of vasoconstriction and remodelling which accompanies a reduced availability of NO, thus favouring atherosclerosis. The resulting impairment of cerebral blood flow regulation increases the risk of acute ischemic events and sub-acute or chronic hypoperfusion states, which greatly increase an individual's susceptibility to dementia. The production of NO is known to maintain synaptic plasticity and contribute to neuroprotection through restricting the influx of  $\text{Ca}^{++}$  and resultant cell death, as well as activating neuroprotective proteins and important antioxidant precursors.<sup>38</sup> It is also possible that impaired endothelial-derived NO synthesis leads to the build-up of toxic proteins in the brain, leading to progressive cognitive decline and the onset of AD.<sup>18,39</sup>

### 4.3 | Implications of study findings

Given the observed association, and pending further evidence from large-scale studies, potential clinical uses of ADMA include risk stratification in old age, diagnosis of preclinical AD, or identification of novel therapeutic targets. Dementia is a progressive debilitating condition, costing an estimated US\$800 billion per year globally,<sup>40</sup> and more importantly, costing dementia patients substantial losses in quality of life for extended periods. The global number of people living with dementia more than doubled between 1990 and 2016, and the prevalence is expected to continue rising.<sup>41</sup> Once diagnosed, treatment options are severely limited, mostly due to the late onset of symptoms. Without a breakthrough in early diagnosis and prevention of the disease, the burden on caregivers and geriatric care services will continue to increase rapidly.

Importantly, ADMA concentrations can be modulated by pharmacological interventions,<sup>42</sup> and therefore ADMA may prove valuable as a future prevention strategy for dementia and AD. Endogenous enzymes involved in ADMA metabolism have been suggested as a means for manipulating ADMA levels in vivo. Approximately 80% of endogenous ADMA is metabolized in intracellular compartments by dimethylarginine dimethylaminohydrolase (DDAH),<sup>43</sup> and, pharmacological strategies to reduce endogenous ADMA via up-regulation of DDAH have been previously proposed as a novel treatments for disorders with abnormal NO signalling.<sup>44</sup>

Various cohort studies have confirmed associations between higher ADMA concentrations and a number of chronic diseases, including type 2 diabetes, cardiovascular disease and stroke.<sup>45–47</sup> In addition, a recent review has also highlighted the potential involvement of ADMA in the pathogenesis of other chronic diseases beyond atherosclerotic diseases, including COPD and depression.<sup>48</sup> Together

with a growing ageing population, the increasing prevalence of chronic disease risk factors is leading to rapid increases in multimorbidity and polypharmacy. Adverse drug reactions (ADRs) are themselves a major cause of morbidity, accounting for an estimated 6.5% of unplanned hospital admissions.<sup>49</sup> Therefore, given the overlap of risk factors between AD and other chronic diseases, ADMA could represent a unified novel pathway for future therapeutics targeted at a single pathway for chronic disease prevention.

#### 4.4 | Future research directions

Given the potential for impact, there is a clear rationale for continued research into the association between plasma ADMA and dementia. Large-scale, robust prospective cohort studies are required, with long follow-up, standardised outcome assessments and repeat exposure measurements. Ideally, to establish risk factors, follow-up should cover the window of opportunity to intervene by assessment of dementia risk factors in middle age. Furthermore, the availability of genetic information would allow for the assessment of causality underlying observational associations. Following on from this, pharmacological strategies are required to reveal whether the change in ADMA concentration mediates any beneficial effect of these interventions on clinical end-points such as cognitive function. Encouragingly, studies have confirmed the pharmacokinetics and the short-term safety of arginine metabolite supplementation.<sup>42,50</sup> However, intervention studies investigating clinical end-points, for example, cardiovascular morbidity and mortality, are eagerly awaited.

#### 4.5 | Strengths and limitations

This study presents with a number of strengths. First, the prospective study design enabled us to study the association between ADMA concentrations and change in cognition for the first time, which has not been conducted to date. In addition, as discussed previously, childhood intelligence is one of the strongest predictors of cognition in old age,<sup>26-28</sup> and therefore the availability of childhood intelligence in ABC36 offered an unparalleled opportunity to study the longitudinal cognitive ageing, independent of childhood cognition. Furthermore, as all participants were born within the same year, any observed changes were unlikely to be the result of differences in age, or cohort effects, which is a common challenge when interpreting epidemiological evidence. Another important strength is the use of hydrophilic-interaction liquid chromatography-electrospray tandem mass spectrometry techniques for ADMA measurements. Since these are gold-standard techniques, the effect of measurement error in the exposure is reduced in the current analyses.

However, when interpreting the results presented here, it is important to consider a number of potential limitations. First, the sample size is relatively small, with 15 participants showing evidence of rapid cognitive decline after four years. Therefore, the results of this study are

hypothesis-generating, and they should be interpreted with caution. Additional prospective studies with larger sample sizes and longer durations of follow-up are required to confirm the association between plasma ADMA and a change in cognitive performance. Second, only a single measure of plasma ADMA per participant was used in this investigation. Although plasma ADMA is thought to remain relatively stable, there are known physiological conditions whereby measured ADMA concentrations may be misrepresentative of normal circulating levels.<sup>51,52</sup> Also, although studies have reported that cerebrospinal fluid ADMA concentrations are lower than plasma ADMA concentrations in AD patients, no information is available regarding the strength of the correlation between plasma and cerebrospinal fluid concentrations.<sup>53</sup> Therefore, additional research is required to investigate whether peripheral ADMA concentrations adequately reflect the concentrations of this metabolite in the central nervous system.

A common source of bias in longitudinal studies of cognitive ageing is the retention of volunteer participants, as participants who drop out tend to score lower during initial cognitive tests, a group who are at greater risk of dementia.<sup>50</sup> With this knowledge, practitioners may have inflicted bias into the present study through inviting rapid decliners back for follow-up assessments earlier than nondecliners. Moreover, refusal to participate was significantly associated with low childhood mental ability (MHT) scores ( $P < .05$ ), reported as a source of bias elsewhere.<sup>54</sup>

Furthermore, although we adjusted for multiple important factors, it is not possible to rule out the effects of residual confounding. Importantly, no measure of renal function was included in the analyses. ADMA is removed from the body through a combination of intracellular metabolism and renal excretion, and hence renal function is an important confounding variable, which would explain some of the variance in plasma ADMA levels. However, this may have been less important in this present study since renal function is generally not altered in healthy individuals at age 63 years. Of these limitations, some were unavoidable consequences of observational research.

#### 4.6 | Conclusion

In summary, the results from this study suggest that ADMA concentrations are associated with cognitive decline in older age. Therefore, plasma ADMA, or correlates thereof, may be involved in the pathogenesis underlying cognitive decline and progression to AD. However, larger studies investigating this association are warranted. Possible future implications include the discovery of novel drug targets or presymptomatic biomarkers for AD.

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

**DATA AVAILABILITY STATEMENT**

The data are not publicly available due to privacy or ethical restrictions. The data that support the findings of this study are available on request from the Steering Committee which is responsible for the future preservation of Aberdeen Birth Cohort databases. Further details can be found online: <https://www.abdn.ac.uk/birth-cohorts/1936/for-researchers/data-access>.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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