Received: 8 January 2020 | Accepted: 17 May 2020

DOI: 10.1002/gps.5355

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry WILEY

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

Deborah E. Malden[1] | Arduino A. Mangoni[2,3] | Richard J. Woodman[4] | Frank Thies[5] | Chris McNeil[6] | Alison D. Murray[6] | Roy L. Soiza[7]

[1]Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health (NDPH), University of Oxford, Oxford, UK

[2]Discipline of Clinical Pharmacology, College of Medicine and Public Health, Flinders University and Flinders Medical Centre, Adelaide, Australia

[3]Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

[4]Flinders Centre for Epidemiology and Biostatistics, College of Medicine and Public Health, Flinders University, Adelaide, Australia

[5]Rowett institute, University of Aberdeen, Aberdeen, UK

[6]Aberdeen Biomedical Imaging Centre, University of Aberdeen, Aberdeen, UK

[7]Ageing Clinical & Experimental Research (ACER), University of Aberdeen, Aberdeen, UK

Correspondence
Deborah E. Malden, Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health (NDPH), University of Oxford, Oxford, UK.
Email: deborah.malden@trinity.ox.ac.uk

Funding information
NHS Grampian R&D Endowments, Grant/Award Number: 11/08; Scottish government; Rural and Environment Science and Analytical Services Division

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 μmol/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 μmol/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.[1,2] 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,[3,4] and multiple pharmacological interventions targeting these histopathological hallmarks have proven ineffective.[5]

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[6,7] but also a 50% increased risk of dementia[8] and a 20% increase in the rate of cognitive decline.[9-11] Furthermore, large genomewide association studies have confirmed associations between 'vascular risk' genes and the development of AD,[12] with the strongest known genetic risk factor being a mutation in the apolipoprotein E4 gene, which encodes a cholesterol transporter protein.[13] 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.[14,15]

Nitric oxide (NO) has an established role as a mediator in the pathogenesis of cardiovascular disease[16] but also potentially in AD.[17,18] 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.[17] In support of this hypothesis, recent interventions to increase the concentrations of endogenously produced NO have halted AD pathogenesis in mice.[19] Furthermore, abnormal NO signalling has been reported in the brains of both human sufferers and animal models of AD.[20,21]

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase (NOS), an essential enzyme for the synthesis of NO.[17] 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.[22-25] However, no study has adjusted for childhood intelligence, which explains up to 50% of cognitive decline in old age.[26-28] 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.

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 de/sign.
- 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.

2 | METHODS

2.1 | Study population

The ABC36 is a well-studied cohort population described in greater depth elsewhere.[29,30] 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 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.[31] 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.[32] 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.[33]

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.[34]

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.[35] 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.[36]

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

	Difference in RPM score after 4 years				
Baseline characteristics	**Rapid decliners**	**Slow decliners**	**Maintainers/improvers**	$P_{trend/het}$	**All**
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 (β) 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

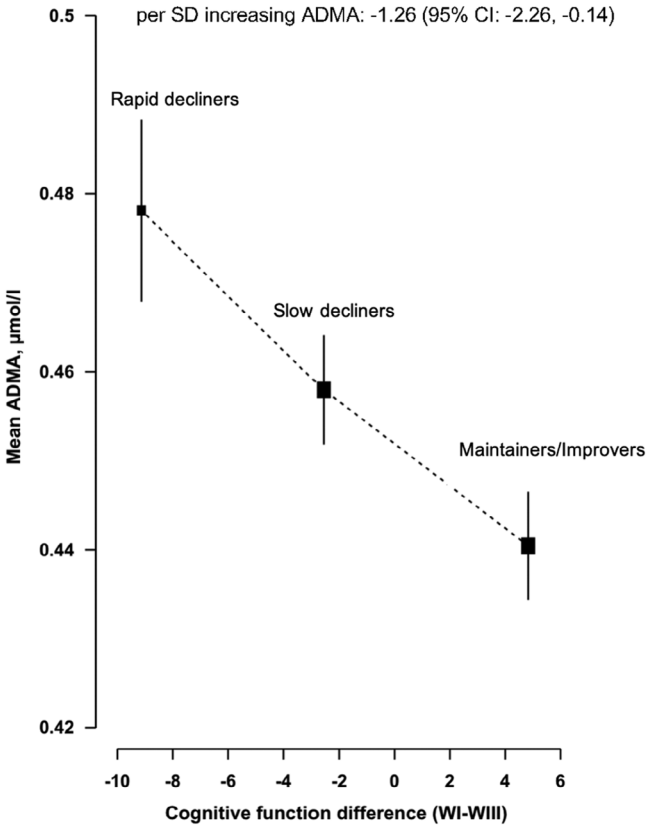

FIGURE 1 Association between baseline ADMA across categories of cognitive function scores between baseline and 4-year repeat assessment. Mean values (95% confidence intervals) were adjusted for gender, smoking, social deprivation, education and hippocampal volume. Areas of point estimates are inversely 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 ±0.5 SDs from the mean value of ADMA

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

	Difference in RPM score after 4 years				
Baseline characteristics	**Rapid decliners**	**Slow decliners**	**Maintainers/improvers**	P_{trend}	**All**
ADMA, µmol/L (mean [SD])	0.464 (0.061)	0.458 (0.065)	0.446 (0.065)	.807	0.455 (0.064)
BMI, 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)	**.008***	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 ≥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 μmol/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 WIII 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.[22-25] 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 μmol/L higher among 80 AD patients compared with 80 matched controls.[22] Similarly, in a smaller case-control study of 25 AD patients and 25 matched controls, plasma ADMA concentrations were approximately 0.4 μmol/L higher among AD patients vs controls.[25] 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.[23] 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.[24] 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.[37]

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.[38] 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 subacute 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 Ca^{++} and resultant cell death, as well as activating neuroprotective proteins and important antioxidant precursors.[38] 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.[18,39]

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,[40] 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.[41] 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,[42] 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),[43] 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.[44]

Various cohort studies have confirmed associations between higher ADMA concentrations and a number of chronic diseases, including type 2 diabetes, cardiovascular disease and stroke.[45-47] 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.[48] 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.[49] 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.[42,50] 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,[26-28] 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.[51,52] 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.[53] 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.[50] 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.[54]

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.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge all participants of the ABC36 study. They acknowledge their colleagues, Prof Lawrence Whalley, Prof Ian Deary and the late Prof John Starr who developed the study. F.T. acknowledges support by the Rural and Environment Science and Analytical Services Division of the Scottish government (RESAS).

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.

ORCID

Deborah E. Malden https://orcid.org/0000-0003-0567-8294

REFERENCES

1. Shi L, Baird AL, Westwood S, et al. A decade of blood biomarkers for Alzheimer's disease research: an evolving field, improving study designs, and the challenge of replication. *J Alzheimers Dis*. 2018;62(3):1181-1198.
2. Olsson B, Lautner R, Andreasson U, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *Lancet Neurol*. 2016;15(7):673-684.
3. Holmes C, Boche D, Wilkinson D, et al. Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. *Lancet*. 2008;372(9634):216-223.
4. Fagan AM, Mintun MA, Shah AR, et al. Cerebrospinal fluid tau and ptau181 increase with cortical amyloid deposition in cognitively normal individuals: implications for future clinical trials of Alzheimer's disease. *EMBO Mol Med*. 2009;1:371-380.
5. Makin S. The amyloid hypothesis on trial. *Nature*. 2018;559:S4-S7.
6. Liu G, Yao L, Liu J, et al. Cardiovascular disease contributes to Alzheimer's disease: evidence from large-scale genome-wide association studies. *Neurobiol Aging*. 2014;35(4):786-792.
7. Sarwar N, Gao P, Kondapally Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375:2215-2222.
8. Chatterjee S, Peters SAE, Woodward M, et al. Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. *Diabetes Care*. 2016;39:300-307.
9. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol*. 2006;5:64-74.
10. Feinkohl I, Price JF, Strachan MW, Frier BM. The impact of diabetes on cognitive decline: potential vascular, metabolic, and psychosocial risk factors. *Alzheimers Res Ther*. 2015;7:46.
11. Rawlings AM, Sharrett AR, Schneider AL, et al. Diabetes in midlife and cognitive change over 20 years: a cohort study. *Ann Intern Med*. 2014;161:785-793.
12. Rocchi A, Orsucci D, Tognoni G, Ceravolo R, Siciliano G. The role of vascular factors in late-onset sporadic Alzheimer's disease. Genetic and molecular aspects. *Curr Alzheimers Res*. 2009;6:224-237.
13. Kamboh MI, Demirci FY, Wang X, et al. Genome-wide association study of Alzheimer's disease. *Transl Psychiatry*. 2012;2:e117.
14. Jo WK, Law AC, Chung SK. The neglected co-star in the dementia drama: the putative roles of astrocytes in the pathogeneses of major neurocognitive disorders. *Mol Psychiatry*. 2014;19(2):159-167.
15. Shineman DW, Basi GS, Bizon JL, et al. Accelerating drug discovery for Alzheimer's disease: best practices for preclinical animal studies. *Alzheimers Res Ther*. 2011;3(5):28.
16. Huang PL, Huang Z, Mashimo H, et al. Hypertension in mice lacking the gene for endothelial nitric oxide synthase. *Nature*. 1995;377(6546):239-242.
17. Togo T, Katsuse O, Iseki E. Nitric oxide pathways in Alzheimer's disease and other neurodegenerative dementias. *Neurol Res*. 2004;26(5):563-566.
18. Wang J, Zhu W, Xu Z, et al. Pin1, endothelial nitric oxide synthase, and amyloid-β form a feedback signaling loop involved in the pathogenesis of Alzheimer's disease, hypertension, and cerebral amyloid angiopathy. *Med Hypotheses*. 2014;82:145-150.
19. Kan MJ, Lee JE, Wilson JG, et al. Arginine deprivation and immune suppression in a mouse model of Alzheimer's disease. *J Neurosci*. 2015;35(15):5969-5982.
20. Steinert JR, Chernova T, Forsythe ID. Nitric oxide signaling in brain function, dysfunction, and dementia. *Neuroscientist*. 2010;16:435-452.
21. Hurtado MO, Kohler I, De Lange ECM. Next-generation biomarker discovery in Alzheimer's disease using metabolomics—from animal to human studies. *Bioanalysis*. 2018;10(18):1525-1546.
22. Arlt S, Schulze F, Eichenlaub M, et al. Asymmetrical dimethylarginine is increased in plasma and decreased in cerebrospinal fluid of patients with Alzheimer's disease. *Dement Geriatr Cogn Disor*. 2008;26:58-64.
23. McEvoy M, Schofield P, Smith W, et al. Memory impairment is associated with serum Methylarginines in older adults. *Curr Alzheimers Res*. 2014;11:97-106.
24. Miralbell J, López-Cancio E, López-Oloriz J, et al. Cognitive patterns in relation to biomarkers of cerebrovascular disease and vascular risk factors. *Cerebrovascu Dis*. 2013;36:98-105.
25. Selley ML. Increased concentrations of homocysteine and asymmetric dimethylarginine and decreased concentrations of nitric oxide in the plasma of patients with Alzheimer's disease. *Neurobiol Aging*. 2003;24:903-907.
26. Deary IJ, Whalley LJ, Lemmon H, Crawford JR, Starr JM. The stability of individual differences in mental ability from childhood to old age. *Dermatol Int*. 2000;31:85-92.
27. Deary IJ, Corley J, Gow AJ, et al. Age-associated cognitive decline. *Br Med Bull*. 2009;92(1):135-152.
28. Starr JM, Deary IJ, Macintyre S. Associations with successful ageing in the "healthy old people in Edinburgh" cohort: being well, fit and healthy. *Aging Clin Exp Res*. 2003;15(4):336-342.
29. Murray AD, Staff RT, McNeil CJ, et al. Brain lesions, hypertension and cognitive ageing in the 1921 and 1936 Aberdeen birth cohorts. *Age*. 2012;34:451-459.
30. Whalley LJ, Fox HC, Deary IJ, Starr JM. Childhood IQ, smoking, and cognitive change from age 11 to 64 years. *Addict Behav*. 2005;30:77-88.
31. Government TS. *Standard Occupational Classification* March 16, 2000; 2015. http://www.statistics.gov.uk/methodsquality/nssec/soc2000.asp
32. Government TS. *Scottish Index of Multiple Deprivation 2012: A National Statistics Publication for Scotland*; 2012.
33. Mustafa N, Ahearn TS, Waiter GD, Murray AD, Whalley LJ, Staff RT. Brain structural complexity and life course cognitive change. *Neuroimage*. 2012;61:694-701.
34. Scottish Council for Research in Education. *The intelligence of Scottish children: A national survey of an age-group*. London, UK: University of London Press; 1933.
35. Raven J, Summers B, Birchfield M, et al. *Manual for Raven's Progressive Matrices and Vocabulary Scales. . American and International Norms*. Vol 3. 2nd ed. Oxford, UK: Oxford Psychologists Press; 1990.
36. Schwedhelm E, Tan-Andresen J, Maas R, Riederer U, Schulze F, Böger RH. Liquid chromatography-tandem mass spectrometry method for the analysis of asymmetric dimethylarginine in human plasma. *Clin Chem*. 2005;51:1268-1271.

37. Huang L, Chen C, Sheen J, Chen Y, Hsieh C, Tain Y. The interaction between high ammonia diet and bile duct ligation in developing rats: assessment by spatial memory and asymmetric dimethylarginine. *Int J Dev Neurosci*. 2010;28:169-174.
38. Zundorf G, Reiser G. Calcium dysregulation and homeostasis of neural calcium in the molecular mechanisms of neurodegenerative diseases provide multiple targets for neuroprotection. *Antioxid Redox Signal*. 2011;14(7):1275-1288.
39. Kelleher RJ, Soiza RL. Evidence of endothelial dysfunction in the development of Alzheimer's disease: is Alzheimer's a vascular disorder? *Am J Cardiovascu Dis*. 2013;3(4):197-226.
40. Prince M, Wimo A, Guerchet M, Ali GC, Wu YT, Prina M. *World Alzheimer Report 2015—The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends*. England: Alzheimer's Disease International; 2015. https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf.
41. GBD Dementia Collaborators. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the global burden of disease study 2016. *Lancet Neurol*. 2019;18(1):88-106.
42. Marin M, Manez S. Pharmacological interventions on asymmetric dimethylarginine, a clinical marker of vascular disease. *Curr Med Chem*. 2011;18(5):714-724.
43. Leiper JM, Santa Maria J, Chubb A, et al. Identification of two human dimethylarginine dimethylaminohydrolases with distinct tissue distributions and homology with microbial arginine deiminases. *Biochemistry*. 1999;343:209-214.
44. Leiper J, Nandi M. The therapeutic potential of targeting endogenous inhibitors of nitric oxide synthesis. *Nat Rev Drug Discov*. 2011;10(4):277-291.
45. Huang S, Xu Y, Peng W-F, et al. A correlational study between serum asymmetric dimethylarginine level and impaired glucose tolerance patients associated with obesity. *J Cell Physiol*. 2019;234(7):10640-10645.
46. Lee W, Lee HJ, Jang HB, et al. Asymmetric dimethylarginine (ADMA) is identified as a potential biomarker of insulin resistance in skeletal muscle. *Nat Sci Rep*. 2018;8(1):2133
47. Khan U, Hassan A, Vallance P, Markus HS. Asymmetric dimethylarginine in cerebral small vessel disease. *Stroke*. 2007;38(2):411-413.
48. Mangoni AA, Rodionov RN, Mcevoy M, Zinellu A, Carru C, Sotgia S. New Horizons in Arginine Metabolism, Ageing and Chronic Disease States. *Age Ageing*. 2019;48(6):776-782.
49. Pirohanned M, James S, Meakin S, et al. Adverse drug reactions as a cause of admission to hospital: prospective analysis of 18,820 patients. *BMJ*. 2004;15:329.
50. Matthews FE, Chatfield M, Brayne C. An investigation of whether factors associated with short-term attrition change or persist over ten years: data from the Medical Research Council cognitive function and ageing study (MRC CFAS). *BMC Public Health*. 2006;6:185
51. Osanai T, Saitoh M, Sasaki S, Tomita H, Matsunaga T, Okumura K. Effect of shear stress on asymmetric Dimethylarginine release from vascular endothelial cells. *Hypertension*. 2003;42:985-990.
52. Ueda S, Kato S, Matsuoka H, et al. Regulation of cytokine-induced nitric oxide synthesis by asymmetric dimethylarginine: role of dimethylarginine dimethylaminohydrolase. *Circ Res*. 2003;92:226-233.
53. Arlt S, Schulze F, Eichenlaub M, et al. Asymmetrical dimethylarginine is increased in plasma and decreased in cerebrospinal fluid of patients with Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2008;26(1):58-64.
54. Whalley LJ, Sharma S, Fox HC, et al. Anticholinergic drugs in late life: adverse effects on cognition but not on progress to dementia. *J Alzheimers Dis*. 2012;30:253-261.

SUPPORTING INFORMATION

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

How to cite this article: Malden DE, Mangoni AA, Woodman RJ, et al. Circulating asymmetric dimethylarginine and cognitive decline: A 4-year follow-up study of the 1936 Aberdeen Birth Cohort. *Int J Geriatr Psychiatry*. 2020;35:1181–1188. https://doi.org/10.1002/gps.5355