Association of Plasma ADMA Levels With MRI Markers of Vascular Brain Injury
Framingham Offspring Study

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Background and Purpose—Asymmetrical dimethylarginine (ADMA), an inhibitor of endothelial nitric oxide synthase, is a marker of endothelial dysfunction. Elevated circulating ADMA concentrations have been associated with systemic and carotid atherosclerosis, an elevated risk of developing stroke, and magnetic resonance imaging white-matter hyperintensities (WMHs). The relation of plasma ADMA to subclinical vascular brain injury has not been previously studied in a middle-aged, community-based sample.

Methods—In 2013 stroke-free Framingham offspring (mean±SD age, 58±9.5 years; 53% women), we related baseline plasma ADMA levels (1995–1998) to subsequent brain magnetic resonance imaging measures (1999–2004) of subclinical vascular injury: presence of silent brain infarcts (SBIs) and large white-matter hyperintensity volumes (LWMHs; defined as >1 SD above the age-specific mean).

Results—Prevalences of SBIs and LWMHs were 10.7% and 12.6%, respectively. In multivariable analyses adjusting for age, sex and traditional stroke risk factors, higher ADMA levels were associated with an increased risk of prevalent SBIs (odds ratio [OR] per 1-SD increase in ADMA 1.16; 95% CI, 1.01 to 1.33; \( P = 0.04 \)). We observed that participants in the upper 3 age-specific quartiles (Qs) of plasma ADMA values had an increased prevalence of SBIs (OR for Q2–Q4 vs Q1 1.43; 95% CI, 1.00 to 2.04; \( P < 0.05 \)). The prevalence of SBIs in Q1 and Q2–Q4 was 8.3% and 11.6%, respectively. The prevalence of LWMHs did not differ according to ADMA concentrations.

Conclusions—Higher plasma ADMA values were associated with an increased prevalence of SBIs, after adjustment for traditional stroke risk factors. Thus, ADMA may be a potentially useful new biomarker of subclinical vascular brain injury, which is an important correlate of vascular cognitive impairment and risk of stroke. (Stroke. 2009;40:2959-2964.)

Key Words: ADMA ■ endothelial dysfunction ■ silent cerebral infarct

Nitric oxide (NO), also called the “endogenous antiatherosclerotic molecule,” is a key mediator of normal endothelial function. Endothelial dysfunction is emerging as a marker of preclinical atherosclerosis. Asymmetrical dimethylarginine (ADMA) is a major endogenous inhibitor of endothelial NO synthase (eNOS), whereas its symmetrical isomer, symmetrical dimethylarginine (SDMA), does not inhibit eNOS. Accumulation of ADMA results in decreased NO bioavailability, supporting a proatherogenic role for ADMA. Elevated plasma ADMA concentrations have been associated with the presence of numerous traditional and novel stroke risk factors, such as hypertension, diabetes, left ventricular hypertrophy, coronary artery disease, atrial fibrillation, hypercholesterolemia, and hyperhomocysteinemia, as well as with an increased risk of clinical and subclinical carotid and systemic atherosclerosis and intimal-medial thickening. In case-control studies, elevated ADMA concentrations were associated with an increased risk of developing stroke and transient ischemic attack (TIA) and recently with magnetic resonance imaging (MRI) findings of small-vessel disease, specifically with the severity of leukoaraiosis.

White-matter hyperintensities (WMHs) and silent brain infarcts (SBIs) are MRI abnormalities strongly related to stroke risk factors and clinical stroke and are accepted indicators of subclinical macrovascular and microvascular brain injury. Although the pathogenesis of these abnormalities is not fully understood, a diffuse arteriopathy affecting...
the deep, small, perforating cerebral vessels has been proposed as a mechanism underlying chronic ischemia, ischemic demyelination, axonal loss, and gliosis. Various vascular risk factors included in the Framingham Stroke Risk Profile (FSRP), circulating concentrations of inflammatory markers, and homocysteine have each been related to these MRI measures of subcortical vascular brain injury. However, the relation of ADMA, a putative novel biomarker of stroke risk, to subcortical vascular brain injury has not been studied in a community-based sample. Thus, we related plasma ADMA and SDMA levels to MRI measures of subcortical vascular brain injury in our middle-aged, community sample.

Subjects and Methods

Study Sample

The Framingham Study is a community-based, ongoing cohort study. In 1971, the offspring of the original Framingham cohort and their spouses were enrolled in the Framingham Offspring Study. These participants have been assessed once every 4 years with medical histories, physical examinations, and laboratory tests and are currently undergoing their ninth examination. All persons have been under continuous surveillance for incident stroke and TIA. A total of 3532 offspring survived this sixth offspring examination (1995–1998), and blood drawn at this examination was used for ADMA estimation in 3453 participants. All participants were invited to participate in brain MRI. A subset of 2072 participants who did not have known contraindications to MRI underwent volumetric brain MRI between 1999 and 2004. From this subset, we excluded 59 persons with prevalent stroke, dementia, or other neurologic illness (such as multiple sclerosis or brain tumor) that could affect MRI. Although plasma ADMA and SDMA levels were not measured at the same time when brain MRI was performed, the MRI changes of interest (SBIs and WMHs) accumulate over time; hence, prior exposure to elevated levels of these markers is more likely to be related to MRI markers of subcortical disease, as previously shown for the association of plasma total homocysteine (tHcy) with SBIs. Although plasma ADMA and SDMA levels were not measured at the same time when brain MRI was performed, the MRI changes of interest (SBIs and WMHs) accumulate over time; hence, prior exposure to elevated levels of these markers is more likely to be related to MRI markers of subcortical disease, as previously shown for the association of plasma total homocysteine (tHcy) with SBIs. Our study sample comprises 2013 persons (53% female), with a mean ± SD age of 58 ± 9.5 years. This study was approved by the institutional review board at Boston University Medical Center and the ethics committee of the Hamburg Board of Physicians. All participants gave informed consent.

Measurement of Plasma ADMA and SDMA Concentrations

Plasma ADMA and SDMA concentrations were measured on stored samples by liquid chromatography–tandem mass spectroscopy techniques. The details of the assay and its excellent reproducibility, with coefficients of variation of 3.2% and 3.4% for ADMA and SDMA, respectively, have been described in prior publications. Although SDMA is primarily eliminated by renal excretion, ADMA is mainly metabolized in kidneys by dimethylarginine dimethylaminohydrolase to citrulline and dimethylamine.

Brain Imaging

MRI acquisition and measurement techniques and interrater reliability have been detailed previously. MRI acquisition and measurement techniques and interrater reliability have been detailed previously. MRI acquisition and measurement techniques and interrater reliability have been detailed previously. In brief, the images were acquired on a 1- or 1.5-T Siemens Magnetom and transferred to the centralized reading center at the University of California-Davis Medical Center. The images were analyzed by operators blinded to the participant’s identity, age, sex, plasma ADMA level, and their exposure to stroke risk factors. Brain volume was determined by manual demarcation of the intracranial vault to establish the total cranial volume, followed by subsequent mathematical modeling to determine parenchymal volume. The volume of abnormal WMHs was determined by previously described semiautomated methods. WMH volume was corrected for a measure of head size, the total intracranial volume. Subjects were categorized as having extensive WMHs when the logarithm of WMH volume/total cranial volume was >1 SD above the age-specific mean in this cohort. The presence or absence of an MRI infarct was determined manually by the operator, based on the size (>3 mm), location, and imaging characteristics of the lesion. The lesion was required to have the density of cerebrospinal fluid on the subtraction image; when embedded within the basal ganglia, it was further required to be distinctly isolated from the circle of Willis vessels to avoid confusion with dilated Virchow spaces. MRI infarcts were classified as SBIs if the person had not had a clinically documented stroke at any time before MRI. All images were evaluated by 3 different raters, with κ values for agreement ranging between 0.73 and 0.90.

Definition of Covariates

The components of the previously described and validated FSRP were used as baseline covariates. The FSRP provides an estimate of the 10-year risk of stroke for a given subject, based on age, sex, and measurements of several cardiovascular risk factors, including systolic blood pressure, antihypertensive therapy, diabetes, smoking status, history of cardiovascular disease, and the presence of atrial fibrillation. Blood pressure was recorded as the average of 2 physician-recorded measurements. Diabetes mellitus was defined by a recorded fasting blood glucose value ≥126 mg/dL (7 mmol/L), a previous diagnosis of diabetes mellitus, or the use of oral hypoglycemic agents or insulin. Smoking status was categorized as “current smoker” or “current nonsmoker.” Prior cardiovascular disease events included a diagnosis of coronary heart disease, congestive heart failure, or peripheral arterial disease. The diagnosis of atrial fibrillation was based on ECG documentation of the arrhythmia on a standard 12-lead ECG obtained at the heart study examination or elsewhere. Additional covariates in our analysis were serum creatinine, measured by a modified Jaffe method, and plasma tHcy, which was estimated by a previously validated method. Plasma tHcy levels influence plasma ADMA levels through inhibition of dimethylaminohydrolase, an enzyme that regulates NOS and hydrolyzes ADMA, and these have been associated with the risk of SBIs. All covariates were measured at the same time that blood was drawn for ADMA and SDMA measurements.

Statistical Analysis

We used multivariable logistic-regression models to examine the cross-sectional associations between plasma ADMA or SDMA (independent variable) and MRI phenotypes (SBIs and WMHs; dependent variables) after adjusting for covariates known to influence these variables. Plasma ADMA and SDMA values were analyzed as continuous and categorical variables with age-specific quartiles (Qs), defined within 10-year age groups. We additionally examined the trend across quartiles of plasma ADMA (or SDMA) for the MRI phenotypes and also compared persons in the upper 3 quartiles with those in the lowest quartile. In initial analyses, we adjusted only for age, sex, and time interval between ADMA/SDMA and MRI measurements. We next additionally adjusted for components of the FSRP score. Finally, to explore whether the effect of ADMA was independent of serum creatinine and plasma tHcy levels and use of statin and antithrombotic therapies, we individually adjusted for each in separate models. We did not adjust for carotid intimal-medial thickening or carotid stenosis, as these phenotypes may lie along the causal pathway between ADMA concentrations and vascular brain injury. All analyses were performed with the SAS (SAS Institute Inc, Cary, NC).

Results

Table 1 presents the age-specific cutpoints for each of the 4 quartiles (Qs) of plasma ADMA in our sample. The distributions of demographic and vascular risk factor characteristics and other covariate data recorded at the baseline examination, as well as the prevalence of SBIs and large WMHs (LWMHs), are summarized in Table 2. In our sample, men were more likely to have higher mean systolic blood pressure, to be...
taking antihypertensive medication, to have diabetes, to have a history of cardiovascular disease and atrial fibrillation, and to have higher plasma tHcy and serum creatinine levels. Plasma ADMA and tHcy levels were correlated (Spearman correlation coefficient = 0.10; P < 0.001). The prevalences of SBIs and LWMHs were 10.7% and 12.6%, respectively.

In Table 3 and supplemental Table I (available online at http://stroke.ahajournals.org) we present results of the multivariable analysis relating plasma ADMA (modeled as a continuous and categorical variable) to the prevalence of SBIs and WMHs on brain MRI. In the initial analysis, ADMA concentrations were associated with an increased risk of prevalent SBI (odds ratio [OR] per 1-SD increase in ADMA = 1.15; 95% CI, 1.00 to 1.32; P = 0.04). Across ADMA quartiles, we observed a trend such that participants in the upper 3 age-specific quartiles of plasma ADMA concentrations had an increased prevalence of SBIs compared with persons in the lowest quartile (OR for Q2–Q4 vs Q1 = 1.46; 95% CI, 1.02 to 2.07; P = 0.04). After further adjustment for traditional stroke risk factors, this association remained robust (OR per 1-SD increment in ADMA concentration and increased prevalence of SBIs was present after adjusting for the use of statin and antithrombotic therapies (OR per 1-SD increase in ADMA = 1.15; 95% CI, 1.00 to 1.32; P = 0.04). Moreover, after adjustment for serum creatinine (OR per 1-SD increase in ADMA = 1.15; 95% CI, 1.00 to 1.33; P = 0.05) or for plasma tHcy concentrations (OR for Q2–Q4 vs Q1 = 1.43; 95% CI, 1.00 to 2.04; P = 0.05), an association between plasma ADMA concentration and increased prevalence of SBIs was present. An association between plasma ADMA concentration and increased prevalence of SBIs was present after adjusting for the use of statin and antithrombotic therapies (OR per 1-SD increase in ADMA = 1.15; 95% CI, 1.00 to 1.32; P = 0.04). Moreover, after adjustment for serum creatinine (OR per 1-SD increase in ADMA = 1.15; 95% CI, 1.00 to 1.33; P = 0.05) or for plasma tHcy concentrations (OR for Q2–Q4 vs Q1 = 1.43; 95% CI, 1.00 to 2.04; P = 0.05), the association remained significant. The prevalences of SBIs in Q1 and Q2–Q4 were 8.3% and 11.6%, respectively. The prevalence of LWMHs did not differ according to ADMA concentration in any of the analyses. In addition, we did not observe a significant association between plasma SDMA concentrations and the brain MRI measures of subclinical vascular brain injury (data presented in supplemental Table II).

### Discussion

In the community-based, middle-aged Framingham Offspring Study sample, we observed an independent, cross-sectional association between higher plasma ADMA levels and increased prevalence of SBIs, even after adjustment for traditional risk factors. Our findings demonstrate that plasma ADMA levels may be related not only to the risk of clinical stroke, as suggested by prior studies, but also to the risk of subclinical vascular brain injury. Plasma SDMA was not associated with SBIs or WMHs.

ADMA, SDMA, and monomethyl-l-arginine (l-NMMA) are methylarginines produced during the degradation of methylated proteins. ADMA and l-NMMA are both competitive inhibitors of eNOS, but circulating levels of l-NMMA are low, suggesting that ADMA is the major endogenous inhibitor of eNOS.8,26,27 Accumulation of ADMA would thus decrease NO production. ADMA, a reasonably stable biomarker, may therefore be a true causal risk factor for endothelial dysfunction.8 However, it could be merely a risk marker, as it has been associated with numerous traditional and novel vascular risk factors, such as plasma tHcy levels,3–10 and with subclinical cerebrovascular disease.14 In a small double-blind, vehicle-controlled study of 20 healthy subjects, intravenously administered ADMA reduced vessel compliance and decreased cerebral blood flow measured by perfusion MRI.28 This interesting observation suggests that circulating levels of ADMA may impact the pathogenesis of subclinical and/or clinical cerebrovascular disease by influencing cerebral autoregulation and arterial vasomotor reactivity; this effect may also be mediated by NO pathways.

Although the pathogenesis of cerebral small-vessel disease (lacunar infarcts and leukoaraiosis) remains poorly understood, several studies have suggested that chronic endothelial dysfunction has a significant role in mediating impaired cerebral autoregulation and could contribute to the breakdown of the blood–brain barrier, which has been observed in small cerebral vessel disease.29 As already mentioned, studies have suggested that cerebral small-vessel disease includes a clinicopathologic and radiologic spectrum with different underlying mechanisms contributing to lacunar infarcts on one hand and to diffuse WM injury on the other. Chronic endothelial dysfunction of small, perforating, cerebral vessels could result in poor WM irrigation and accumulation of WM injury,30 even in the absence of clinical events.

SBIs are defined as vascular brain lesions confirmed by computed tomography or MRI but without an apparent clinical correlate, and most of them (74% to 86%) are lacunar infarcts.31

### Table 1. Age-Specific Quartiles of Plasma ADMA Levels in Framingham Offspring

<table>
<thead>
<tr>
<th>Age, y</th>
<th>n</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>49</td>
<td>0.18–0.45</td>
<td>0.45–0.51</td>
<td>0.52–0.56</td>
<td>0.57–0.78</td>
</tr>
<tr>
<td>40–49</td>
<td>363</td>
<td>0.19–0.44</td>
<td>0.44–0.50</td>
<td>0.50–0.59</td>
<td>0.60–1.02</td>
</tr>
<tr>
<td>50–59</td>
<td>692</td>
<td>0.20–0.45</td>
<td>0.45–0.52</td>
<td>0.52–0.60</td>
<td>0.60–1.08</td>
</tr>
<tr>
<td>60–69</td>
<td>548</td>
<td>0.21–0.47</td>
<td>0.47–0.55</td>
<td>0.55–0.63</td>
<td>0.63–1.01</td>
</tr>
<tr>
<td>70+</td>
<td>253</td>
<td>0.27–0.49</td>
<td>0.49–0.56</td>
<td>0.57–0.65</td>
<td>0.65–1.10</td>
</tr>
</tbody>
</table>

Plasma ADMA units are in μmol/L.

### Table 2. Baseline Characteristics of the Study Sample

<table>
<thead>
<tr>
<th>Stroke Risk Factors/Other Covariates</th>
<th>N = 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, %</td>
<td>53</td>
</tr>
<tr>
<td>Age, y</td>
<td>58±9.5</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>126±18</td>
</tr>
<tr>
<td>Antihypertensive medication, %</td>
<td>24</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>14</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>9.5</td>
</tr>
<tr>
<td>Prevalent cardiovascular disease, %</td>
<td>7.5</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>1.85</td>
</tr>
<tr>
<td>Log (plasma homocysteine)</td>
<td>2.21±0.29</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>101.7±16.3</td>
</tr>
<tr>
<td>Outcome variables</td>
<td></td>
</tr>
<tr>
<td>SBI</td>
<td>10.7</td>
</tr>
<tr>
<td>LWMH volume</td>
<td>12.6</td>
</tr>
</tbody>
</table>

Values are mean±SD for continuous variables.
SBIs have been associated with an increased risk of subsequent clinical stroke and with cognitive impairment and memory loss.

Several vascular risk factors increase the risk of SBIs, including age, hypertension, diabetes mellitus, smoking, and atrial fibrillation, as well as novel biomarkers such as plasma tHcy and serum cholesterol.

However, prior studies have not examined the association of circulating ADMA and MRI-defined SBIs.

Diffuse WM injury, called “leukoaraiosis,” is a descriptive term referring to a radiologic finding of diffuse, bilateral, periventricular WMHs, which are a consequence of various pathophysiologic mechanisms (ischemic demyelination, gliosis, astrocytic proliferation, and inflammation), and could result from vascular insults, neuronal injury, or both.

A recent case-control study reported an association of plasma ADMA levels with the presence of cerebral small-vessel disease, which was defined by the presence of lacunar stroke and/or leukoaraiosis on brain computed tomography or MRI. The investigators found that higher plasma ADMA levels were associated with leukoaraiosis severity but not with an increased prevalence of clinically evident lacunar strokes. However, silent as opposed to all brain infarcts were not specifically assessed as an outcome in that study. Conversely, in our study, whereas we did observe an association of ADMA with SBIs, this was not true for the risk of prevalent WMHs. Our results for WMHs may differ from those of Khan et al; perhaps our study participants had a lower burden of WMHs and vascular risk factors and lower mean ADMA levels (0.54, vs 0.81 µmol/L in the prior study). The observed differences could also be related to the different MRI techniques used to assess WMHs in the 2 studies: we used a quantitative method, whereas Khan et al used a qualitative technique. Interestingly, other novel risk factors, such as elevated plasma tHcy levels, have also shown an association with prevalent SBIs, but not with WMHs, in the Framingham study sample.

From a clinical perspective, elevated plasma ADMA concentrations may partly explain the elevated risk of incident TIA and stroke that has been associated with SBIs. Several studies have reported an association between elevated plasma ADMA levels and an increased risk for clinical events, although a large population-based study in patients with coronary artery disease found that ADMA was an independent marker predicting the risk of future total cardiovascular events and death, but not the risk of clinical stroke. Perhaps in that study there were too few cerebrovascular events.

**Table 3. Association of Plasma ADMA and Brain MRI Variables**

<table>
<thead>
<tr>
<th>Model</th>
<th>LWMHs OR (95% CI)</th>
<th>P</th>
<th>SBIs OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1*</td>
<td>1.00 (0.87–1.14)</td>
<td>1.00</td>
<td>1.15 (1.00–1.32)</td>
<td>0.04</td>
</tr>
<tr>
<td>1-SD ↑</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>0.98 (0.67–1.43)</td>
<td>0.90</td>
<td>1.54 (1.02–2.34)</td>
<td>0.04</td>
</tr>
<tr>
<td>Q2</td>
<td>1.13 (0.78–1.63)</td>
<td>0.52</td>
<td>1.34 (0.88–2.05)</td>
<td>0.17</td>
</tr>
<tr>
<td>Q3</td>
<td>0.96 (0.66–1.40)</td>
<td>0.82</td>
<td>1.49 (0.98–2.26)</td>
<td>0.07</td>
</tr>
<tr>
<td>Trend across quartiles</td>
<td>0.98</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2–4 vs Q1</td>
<td>1.02 (0.75–1.39)</td>
<td>0.90</td>
<td>1.46 (1.02–2.07)</td>
<td>0.04</td>
</tr>
<tr>
<td>Model 2†</td>
<td>1.00 (0.87–1.14)</td>
<td>0.95</td>
<td>1.16 (1.01–1.33)</td>
<td>0.04</td>
</tr>
<tr>
<td>1-SD ↑</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>0.98 (0.67–1.44)</td>
<td>0.92</td>
<td>1.56 (1.03–2.37)</td>
<td>0.04</td>
</tr>
<tr>
<td>Q2</td>
<td>1.09 (0.76–1.59)</td>
<td>0.63</td>
<td>1.26 (0.82–1.94)</td>
<td>0.28</td>
</tr>
<tr>
<td>Q3</td>
<td>0.95 (0.65–1.39)</td>
<td>0.80</td>
<td>1.49 (0.98–2.27)</td>
<td>0.06</td>
</tr>
<tr>
<td>Trend across quartiles</td>
<td>0.95</td>
<td>0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2–4 vs Q1</td>
<td>1.01 (0.74–1.37)</td>
<td>0.95</td>
<td>1.43 (1.00–2.04)</td>
<td>0.05</td>
</tr>
<tr>
<td>Model 3‡</td>
<td>1.00 (0.87–1.14)</td>
<td>0.97</td>
<td>1.15 (1.00–1.33)</td>
<td>0.05</td>
</tr>
<tr>
<td>1-SD ↑</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>0.96 (0.66–1.41)</td>
<td>0.84</td>
<td>1.57 (1.03–2.39)</td>
<td>0.04</td>
</tr>
<tr>
<td>Q2</td>
<td>1.06 (0.73–1.54)</td>
<td>0.76</td>
<td>1.24 (0.81–1.91)</td>
<td>0.33</td>
</tr>
<tr>
<td>Q3</td>
<td>0.95 (0.65–1.39)</td>
<td>0.81</td>
<td>1.48 (0.97–2.26)</td>
<td>0.07</td>
</tr>
<tr>
<td>Trend across quartiles</td>
<td>0.94</td>
<td>0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2–4 vs Q1</td>
<td>0.99 (0.73–1.35)</td>
<td>0.95</td>
<td>1.43 (1.00–2.03)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Model 1 was adjusted for age, sex, and time to MRI.
†Model 2=model 1 plus additional adjustment for atrial fibrillation, history of cardiovascular disease, smoking, diabetes mellitus, systolic blood pressure, and antihypertension therapy.
‡Model 3=model 2 plus additional adjustment for serum creatinine. Bold indicates results with P values <0.05.
(n=45) to detect a true association with clinical stroke. In a recent report from the Population Study of Women in Gothenburg, baseline ADMA levels were associated with an ≈30% increase in risk of cardiovascular disease events (myocardial infarction and stroke) during a 24-year follow-up period.24 In our Framingham offspring sample, we have had too few clinical stroke and TIA events to permit an assessment of the association between plasma ADMA levels and clinical stroke.

The strengths of our study are the use of a community-based sample under rigorous surveillance for clinical stroke and TIA, the relatively younger age of our sample, the validated volumetric MRI techniques used, and the recording of MRI measures by radiologists blinded to ADMA levels. In sequential models, we were also able to examine the association after adjustment for concurrent vascular risk factors, use of statin and antithrombotic therapies, and serum creatinine and plasma tHcy levels. The effect of ADMA on risk of SBI was independent of these traditional stroke risk factors. Further studies of this pathway could clarify whether ADMA mediates the observed association of plasma tHcy with SBIs.20

A limitation of our study is the predominantly white ethnicity of the Framingham offspring sample, which could limit the generalizability of our findings to other ethnicities. We have only single-occasion measurements of both plasma ADMA and brain MRI and could not evaluate the impact of changes in plasma ADMA on MRI phenotypes or assess the relation between baseline plasma ADMA levels and the risk of incident SBIs or longitudinal changes in WMHs; moreover, we do not know whether the observed MRI changes preceded or followed the baseline examination wherein ADMA levels were assessed. Thus, our cross-sectional analysis does not permit us to confirm or refute a causal role for ADMA.

Additional molecular and experimental studies are required to assess the role of ADMA in brain injury. Nevertheless, our findings raise the possibility that elevated ADMA levels may represent a target for therapeutic interventions. Further prospective studies will clarify whether baseline ADMA levels have an additive value in stroke risk stratification when combined with other traditional and novel biomarkers.

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Disclosures

Dr R. Böger, Schwedhelm, and Maas are named as inventors on patents relating to analytical assays for methylarginines and receive royalties from these. No other authors have reported financial disclosures.

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