Cognitive Impairment Before Intracerebral Hemorrhage Is Associated With Cerebral Amyloid Angiopathy

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Background and Purpose—Although the association between cerebral amyloid angiopathy (CAA) and cognitive impairment is increasingly recognized, it is not clear whether this is because of the impact of recurrent intracerebral hemorrhage (ICH) events, disruptions caused by cerebral small vessel damage, or both. We investigated this by considering whether cognitive impairment before ICH was associated with neuroimaging features of CAA on magnetic resonance imaging.

Methods—We studied 166 patients with neuroimaging-confirmed ICH recruited to a prospective multicentre observational study. Preexisting cognitive impairment was determined using the Informant Questionnaire on Cognitive Decline in the Elderly (IQQCODE). Magnetic resonance imaging markers of cerebral small vessel disease, including CAA, were rated by trained observers according to consensus guidelines.

Results—The prevalence of cognitive impairment before ICH was 24.7% (n=41) and, in adjusted analyses, was associated with fulfilling the modified Boston criteria for probable CAA at presentation (odds ratio, 4.01; 95% confidence interval, 1.53–10.51; P=0.005) and a higher composite CAA score (for each point increase, odds ratio, 1.42; 95% confidence interval, 1.03–1.97; P=0.033). We also found independent associations between pre-ICH cognitive decline and the presence of cortical superficial siderosis, strictly lobar microbleeds, and lobar ICH location, but not with other neuroimaging markers, or a composite small vessel disease score.

Conclusions—CAA (defined using magnetic resonance imaging markers) is associated with cognitive decline before symptomatic ICH. This provides evidence that small vessel disruption in CAA makes an independent contribution to cognitive impairment, in addition to effects due to brain injury caused directly by ICH.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT02513316.

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Key Words: cerebral amyloid angiopathy ■ cerebral hemorrhage ■ cerebral small vessel diseases ■ cognitive dysfunction ■ prevalence ■ siderosis

Although the associations between dementia and ischemic stroke have been comprehensively described,1 fewer data are available for spontaneous intracerebral hemorrhage (ICH), in part because of its high case fatality.2,3 Cognitive impairment often develops in survivors of ICH who were previously dementia free, particularly if the ICH is lobar, and has been associated with baseline neuroimaging markers of cerebral amyloid angiopathy (CAA).2 In those presenting with ICH, cognitive impairment before the event is common, with an estimated pooled incidence of 16.7%,4 suggesting that the underlying neurovascular and neuroradiological processes that result in cognitive impairment after ICH might already be present at the time of initial presentation with ICH.5,6 However, it is not clear to what extent subsequent cognitive impairment after ICH is mediated by direct damage.
from the index ICH, the effects of recurrent ICH, or the impact of the underlying small vessel disease (SVD)1–4; understanding the contribution of these mechanisms is potentially important in developing rational dementia prevention strategies.

We therefore investigated whether neuroimaging evidence of CAA (specifically, meeting the modified Boston criteria for probable CAA at presentation, and increases in a composite CAA score5) was associated with the presence of cognitive impairment before ICH. We then performed further analyses investigating the associations between individual magnetic resonance imaging (MRI) neuroimaging markers of SVD and cognitive impairment before ICH.

Materials and Methods

Patient Selection

We included patients recruited to a prospective multicentre observational cohort study of symptomatic patients with confirmed ICH (The Clinical Relevance of Microbleeds In Stroke Study; CROMIS-2). Those aged ≥18 years with an ICH confirmed on brain imaging (either computed tomography or MRI) were eligible, providing that there was no evidence that the ICH was because of an underlying structural cause or secondary to head trauma. This study has been preregistered, and the full details of the study protocol have been published previously.6 The study was approved by the National Research Ethics Service (IRAS reference 10/H0716/61). Written informed consent was obtained from each patient. The primary and substudy analyses for the CROMIS-2 study are ongoing; once all of these analyses are completed, the hemispheres contralateral to the ICH was preferentially rated. White matter hyperintensities (WMH; also termed leukoaraiosis) were rated (K.O.-B.A.) on T2 and FLAIR sequences using the Fazekas scale.7,18 Cortical superficial siderosis (cSS) was identified on blood-sensitive sequences and classified (D.W.) as either focal (involving ≤3 sulci) or disseminated (involving ≥4 sulci), in keeping with previously described terminology.19 Medial temporal atrophy (MTA) was rated (G.B.) on T1 or FLAIR coronal images using the Scheltens visual scale.20,21 Global cortical atrophy (GCA) was rated (G.B.) using the Pasquier scale on axial T1 or FLAIR images. In cases where these sequences were not available, T2 images were used. For both MTA and GCA, there was good agreement between all sequences used (MTA κ=0.77; GCA κ=1.00). For both MTA and GCA, the hemisphere contralateral to the ICH was preferentially rated.

ICH location was defined as infratentorial, deep, or lobar, with the latter in cortical or cortical–subcortical regions and not involving any of the deep grey matter structures. Hematoma volume was calculated (S.L.) using a previously described validated semiautomated planimetric method.22 A clinico-radiological diagnosis of probable CAA was based on meeting the modified Boston criteria.6

The CAA score was calculated from a previously described 6-point scale.23 This scale awards 1 point for CSO-PVS rating of

| Table 1. Baseline Demographic and Clinical Characteristics |
|-----------------|---------|-----------------|-----------------|-----------------|
|                  | All     | IQCODE ≤3.3     | IQCODE >3.3     | Mean or Proportion Difference (95% CI) | P Value   |
| n (%)            | 166     | 125 (75.3)      | 41 (24.7)       | …                | …         |
| Age, y, mean (SD)| 68.9 (12.9) | 67.0 (13.1) | 74.5 (10.9) | −7.5 (−11.9 to −3.0) | 0.0012 |
| Sex, male, n (%)| 104 (62.7) | 76 (60.8)  | 28 (68.3)  | −7.5 (−24.1 to 9.1) | 0.389    |
| Hypertension, presence, n (%)| 96 (58.1) | 75 (60.5)  | 21 (51.2)  | 9.3 (−8.3 to 26.8) | 0.297    |
| Hypercholesterolemia, presence, n (%)| 58 (35.8) | 37 (30.6)  | 21 (51.2)  | −20.6 (−38.0 to −3.3) | 0.017    |
| Diabetes mellitus, presence, n (%)| 20 (12.1) | 11 (8.9)   | 9 (22.0)   | −13.1 (−26.7 to 0.5) | 0.026    |
| Atrial fibrillation, presence, n (%)| 33 (21.3) | 22 (19.0)  | 11 (28.2)  | −9.2 (−25.1 to 6.6) | 0.223    |
| Previous ischemic stroke or TIA, presence, n (%)| 29 (18.1) | 18 (14.8)  | 11 (28.9)  | −14.2 (−29.9 to 1.5) | 0.047    |
| Previous ICH, presence, n (%)| 9 (5.5)  | 4 (3.2)    | 5 (12.5)   | −9.3 (−20.0 to 1.4) | 0.025    |

Percentage values were calculated using the total number of patients for whom data was available as the denominator. P values are from χ² and independent t tests. Proportion differences and their confidence intervals are given as percentages. CI indicates confidence intervals; ICH, intracerebral hemorrhage; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; and TIA, transient ischemic attack.

Imaging Acquisition and Analysis

Imaging was undertaken at each study center according to local protocols, and all brain imaging performed as part of the participant’s standard clinical care was sent to the study’s coordinating center in anonymized DICOM format.

Imaging analysis was performed by 2 clinical research associates (D.W., G.B.) and 2 MSc students (K.O.-B.A., S.L.), all of whom were trained in neuroimaging rating and blinded to the participant clinical details. All structural imaging markers of cerebral SVD were rated in accordance with the Standards for Reporting Vascular Changes on Neuroimaging consensus criteria.16 Only those with an available MRI and all of the necessary sequences for cerebral SVD rating (ie, axial T2, axial or coronal fluid-attenuated inversion recovery (FLAIR), and a blood-sensitive sequence) were included in the neuroimaging marker analysis.

Lacunes were identified and counted (D.W.) on T2 and FLAIR sequences.12 Cerebral microbleeds were rated (D.W.) using blood-sensitive (T2* weighted or susceptibility weighted images) sequences and the validated Microbleed Anatomical Rating Scale.13 MRI-visible perivascular spaces (PVS) in the centrum semiovale (CSO-PVS) and basal ganglia (BG-PVS) were defined and rated (G.B.) on T2 and FLAIR sequences using a validated 4-point visual rating scale14,15 on a single predefined slice (first slice above the anterior commissure for the basal ganglia, and the first slice above the level of the lateral ventricles for the centrum semiovale). The hemisphere contralateral to the ICH was preferentially rated. White matter hyperintensities (WMH; also termed leukoaraiosis) were rated (K.O.-B.A.) on T2 and FLAIR sequences using the Fazekas scale.7,17 Cortical superficial siderosis (cSS) was identified on blood-sensitive sequences and classified (D.W.) as either focal (involving ≤3 sulci) or disseminated (involving ≥4 sulci), in keeping with previously described terminology.19 Medial temporal atrophy (MTA) was rated (G.B.) on T1 or FLAIR coronal images using the Scheltens visual scale.20,21 Global cortical atrophy (GCA) was rated (G.B.) using the Pasquier scale on axial T1 or FLAIR images. In cases where these sequences were not available, T2 images were used. For both MTA and GCA, there was good agreement between all sequences used (MTA κ=0.77; GCA κ=1.00). For both MTA and GCA, the hemisphere contralateral to the ICH was preferentially rated.

ICH location was defined as infratentorial, deep, or lobar, with the latter in cortical or cortical–subcortical regions and not involving any of the deep grey matter structures. Hematoma volume was calculated (S.L.) using a previously described validated semiautomated planimetric method.22

A clinico-radiological diagnosis of probable CAA was based on meeting the modified Boston criteria.6

The CAA score was calculated from a previously described 6-point scale.23 This scale awards 1 point for CSO-PVS rating of

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frequent-to-severe grades (ie, presence of >20 CSO-PVS) and WMH that is either Fazekas grade 3 if periventricular, or Fazekas grade ≥2 if deep.22 Additional points are awarded for the presence of lobar microbleeds (1 point if 2–4 are present; 2 points if there are ≥5) and cSS (1 point if focal; 2 points if disseminated).7

The SVD score was determined using a previously described 4-point scale.22,23 This scale awards 1 point for the presence of lacunes, microbleeds, BG-PVS rating of moderate-to-severe grades (ie, presence of >10 BG-PVS), and WMH that is either Fazekas grade 3 if periventricular or Fazekas grade ≥2 if deep.22

Statistics
We investigated for selection bias within our final cohort by comparing the characteristics of people with appropriate MRI and those without. IQCODE was dichotomized using a cutoff of 3.3, and baseline characteristics were compared (Table 1) for those with scores ≥3.3 (ie, with cognitive impairment) and those with scores ≤3.3. Continuous data were reviewed for normality, and if normally distributed we used the independent t test. Where continuous variables were not normally distributed, we used the (nonparametric) Mann–Whitney U test. We used the χ2 tests for categorical variables. The independent t test (normally distributed continuous data) and the 2-sample test of proportion (categorical data) were used to compare means and proportions, respectively.

Univariate comparisons were used to identify potential confounders for inclusion in the multivariable models; all variables with P<0.05 were included. We then performed adjusted logistic regression analyses, adjusting for significant associations identified in univariate analyses (Table 2). In further analyses (Table 3), we investigated associations with other neuroimaging markers suggestive of CAA (the presence of strictly lobar microbleeds, and presentation with lobar ICH), as well as a composite SVD score and its component elements. In these analyses, each neuroimaging marker was considered individually (ie, each adjusted model included only 1 neuroimaging marker at a time). Given that these analyses were exploratory, we did not make an adjustment for multiple testing.

Statistical analysis was performed (G.B.) using Stata (Version 11.2).

Results

Cohort Characteristics
The demographic and imaging characteristics of those included (n=166) are shown in Table 1. Patients without MRI (n=588) and those with MRI but with missing or uninterpretable sequences (n=43) were excluded (online-only Data Supplement). When compared with the excluded patients (online-only Data Supplement), those included were younger (mean, 68.9 versus 75.0 years; P<0.00001), less likely to have hypertension (58.2% versus 70.9%; P=0.002), hypercholesterolemia (35.8% versus 47.9%; P<0.006), diabetes mellitus (12.1% versus 19.8%; P=0.024), and atrial fibrillation (12.3% versus 43.5%; P<0.0001), and more likely to have previously had an ischemic stroke or transient ischemic attack (24.7% versus 18.1%; P=0.081), lower Glasgow Coma Scale at presentation (interquartile range, 13–15 versus 14–15; P=0.003) and pre-ICH cognitive decline (38.2% versus 24.7%; P=0.001).

When comparing those with and without pre-ICH cognitive decline, those with (n=41) were older (mean difference, 75.0 versus 73.6 years; P<0.0001), more likely to present with lobar ICH (29.3% versus 2.4%; P<0.0001), and were more likely to have had previous ICH (24.4% versus 5.7%; P<0.001), diabetes mellitus (29.3% versus 4.8%; P<0.001), hypercholesterolemia (29.3% versus 5.1%; P<0.0001), hypertension (46.3% versus 20.0%; P<0.0001), and atrial fibrillation (6.1% versus 0.0%; P<0.0001). When compared to those with pre-ICH cognitive decline, those without cognitive decline were more likely to have had transient ischemic attack (19.5% versus 3.9%; P<0.0001), and were more likely to have ICH in the medial temporal atrophy cluster (MTA) (9.8% versus 2.4%; P<0.001) and cerebral amyloid angiopathy (CAA) (the presence of strictly lobar microbleeds, and presentation with lobar ICH) (12.1% versus 2.4%; P<0.0001).

Table 3. Logistic Regression Models (Univariable and Adjusted), Reviewing Associations Between Cognitive Impairment Before ICH and Individual Structural Markers of Cerebral SVD, and a Composite SVD Score

<table>
<thead>
<tr>
<th></th>
<th>Univariable OR (95% CI)</th>
<th>P Value</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMH; periventricular Fazekas 3 or deep Fazekas ≥2 (presence)</td>
<td>2.31 (1.11–4.79)</td>
<td>0.024</td>
<td>2.03 (0.87–4.74)</td>
<td>0.103</td>
</tr>
<tr>
<td>Lacunes (presence)</td>
<td>1.18 (0.50–2.81)</td>
<td>0.702</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>CSO-PVS (per grade increase)</td>
<td>0.77 (0.53–1.12)</td>
<td>0.168</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>BG-PVS (per grade increase)</td>
<td>0.97 (0.53–1.80)</td>
<td>0.935</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Strictly lobar microbleeds (presence)</td>
<td>2.76 (1.21–6.30)</td>
<td>0.016</td>
<td>2.47 (0.95–6.37)</td>
<td>0.062</td>
</tr>
<tr>
<td>cSS (presence)</td>
<td>4.16 (1.55–11.12)</td>
<td>0.005</td>
<td>4.08 (1.28–13.05)</td>
<td>0.018</td>
</tr>
<tr>
<td>Presentation with lobar ICH</td>
<td>2.07 (1.00–4.28)</td>
<td>0.050</td>
<td>2.29 (0.99–5.31)</td>
<td>0.053</td>
</tr>
<tr>
<td>MTA (per grade increase)</td>
<td>1.33 (0.90–1.97)</td>
<td>0.150</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>GCA (per grade increase)</td>
<td>1.35 (0.88–2.08)</td>
<td>0.169</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Hemorrhage volume, mL</td>
<td>0.98 (0.96–1.01)</td>
<td>0.210</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>SVD score (per point increase)</td>
<td>1.52 (1.06–2.18)</td>
<td>0.021</td>
<td>1.36 (0.89–2.08)</td>
<td>0.150</td>
</tr>
</tbody>
</table>

Each model is independent, and considers only a single neuroimaging marker at a time. All adjusted models incorporated the following variables: age at event, hypercholesterolemia, presence of diabetes mellitus, previous ischemic stroke or transient ischemic attack, and previous ICH. BG indicates basal ganglia; CI, confidence interval; CSO, centrum semiovale; cSS, cortical superficial siderosis; GCA, global cortical atrophy; ICH, intracerebral hemorrhage; MTA, medial temporal atrophy; OR, odds ratio; PVS, MRI-visible perivascular space; SVD, small vessel disease; and WMH, white matter hyperintensities.
process impairing cognition in CAA. Our findings also contribute to our understanding of the mechanisms by which CAA disrupts cognition, which include hematomata damage (via direct effects on cortical integrity and function) and small vessel mechanisms. The latter may include effects on brain network efficiency, which correlates with cognitive performance and shows disturbances in the non-ICH hemisphere. Our finding that CAA is associated with cognitive impairment before ICH shows that hematomata damage cannot be the only mechanism contributing to cognitive disruption and supports the hypothesis that small vessel mechanisms are important.

A further possibility is that cognitive impairment before ICH is because of coincident Alzheimer’s disease. Although the co-occurrence of CAA and Alzheimer’s disease pathology is well recognized, CAA seems to have a cognitive profile distinct from that seen in Alzheimer’s disease, characterized primarily by deficits in processing speed and executive function. Recent neuropathological work found that CAA makes an independent contribution to cognitive performance in Alzheimer’s disease. Together, this evidence suggests that CAA has a specific neurovascular impact on cognitive performance, independent of coexistent Alzheimer’s pathology. Although we did not find an association between MTA or GCA (as putative imaging markers of Alzheimer’s pathology and pre-ICH cognitive impairment, we acknowledge that our sample size is small and so we cannot rule out missing subtle effects.

The main strength of this study is our detailed neuroimaging description of the structural markers of cerebral SVD in the context of pre-ICH cognitive decline, in a richly phenotyped prospective nationwide cohort of patients. However, our work also has limitations. Those included in our study were younger, with fewer comorbidities and a lower IQCODE than those who did not have an interpretable MRI; additionally, we acknowledge that a suspicion of CAA could increase the likelihood of an MRI being performed (50% of our included patients presented with lobar ICH), and so our final cohort might not be representative of those presenting with a spontaneous ICH to an acute stroke service. Brain imaging at each study center was completed according to local protocols, and so there are unavoidable variations in the nature and manner of the sequences obtained, which could influence our results. In particular, the use of susceptibility-weighted versus T2*-weighted gradient echo sequences may result different microbleed counts, as the former is more sensitive to this; we did not adjust for this in our analyses. There are inherent limitations of using the IQCODE, including variations in the threshold used to define cognitive impairment and the lack of validation against a reference standard for prestroke cognitive impairment. Finally, we acknowledge that our study size is small, and so our results should be interpreted cautiously, particularly the adjusted analyses. As detailed, we chose not to apply an adjustment for multiple testing in order not to miss potential associations of interest. In addition, although our study is powered to detect moderate effect sizes, it may have missed smaller effects.

Cognitive impairment before ICH is common and is associated with imaging findings consistent with an important contribution from CAA. This suggests that any future strategy aiming to reduce the impact of poststroke dementia in ICH will...
need to extend beyond stroke prevention and include strategies that address the small vessel impact of CAA. Further work on the natural history of when and how CAA may influence an individual’s cognitive profile is a priority for future research.

Appendix

The CROMIS-2 Collaborators: Louise Shaw, MD; Jane Sword, MD; Azlisham Mohd Nor, MD; Pankaj Sharma, PhD; Roland Veltkamp MD; Deborah Kelly, MD; Frances Harrington, MD; Marc Randell, MD; Matthew Smith, MD; Karim Mahawish, MD; Abdellabeset Elmarim, MD; Bernard Essi, MD; Claire Cullen, MD; Arumug Nallasivam, MD; Christopher Price, MD; Adrian Barry, MD; Christine Roffe, MD; John Coyle, MD; Ahamad Hassan, MD; Caroline Lovelock, DPhil; Jonathan Birns, MD; David Cohen, MD; L. Sekaran, MD; Adrian Parry-Jones, PhD; Anthea Parry, MD; David Hargroves, MD; Harald Proschel, MD; Prabel Datta, MD; Khaled Darawil, MD; Aravindakshan Manoj, MD; Mathew Burn, MD; Chris Patterson, MD; Elio Giallombardo, MD; Nigel Smyth, MD; Syed Mansoor, MD; Iaj Anwar, MD; Rachel Marsh, MD; Sissi Isopoglou, MD; Dinesh Chadha, MD; Mathuri Prabhakaran, MD; Sanjeevikumar Meenakishundaram, MD; Janice O’Connell, MD; Jon Scott, MD; Vinodh Krishnamurthy, MD; Prasanna Agboram, MD; Michael McCormick, MD; Paul O’Mahony, MD; Martin Cooper, MD; Lillian Choy, MD; Peter Wilkinson, MD; Simon Leach, MD; Sarah Caine, MD; Ise Burger, MD; Gunaratam Gunathilagam, MD; Paul Guyler, MD; Hedley Emsley, MD; Michelle Davis, MD; Dulka Manawadu, MD; Kath Pasco, MD; Maam Mamun, MD; Robert Luder, MD; Mahmud Sahid, MD; Iaj Anwar, MD; James Okwera, MD; Julie Staals, PhD; Elizabeth Warburton, MD; Kari Saastamoinen, MD; Timothy England, MD; Janet Putterill, MD; Enrico Flossman, MD; Michael Power, MD; Krishna Dani, MD; David Mangion, MD; Appu Suman, MD; John Corrigan, MD; Enas Lawrence, MD; and Djamil Valihasa, MD.

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Disclosures

Dr Cohen has received institutional research support from Bayer; honoraria for lectures and an Advisory Board from Bayer, diverted to a local charity; and travel/accommodation expenses for participation in scientific meetings covered by Bayer and Boehringer Ingelheim. G.H.Y. Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Biotronik, Portola, and Boehringer Ingelheim and has been on the speakers’ bureau for Bayer, BMS/ Pfizer, Boehringer Ingelheim, and Sanofi-Aventis. The other authors report no conflicts.

References


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SUPPLEMENTARY MATERIAL

Supplementary Table
Baseline characteristics of those included and excluded subjects. P values are from chi-squared and independent t-tests, except where indicated († for Mann-Whitney U test).

<table>
<thead>
<tr>
<th></th>
<th>All with IQCODE</th>
<th>Included in final analysis</th>
<th>Excluded</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>797</td>
<td>166</td>
<td>631</td>
<td>-</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>73.7 (12.1)</td>
<td>68.9 (12.9)</td>
<td>75.0 (11.6)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>328 (41.2)</td>
<td>62 (37.4)</td>
<td>266 (42.2)</td>
<td>0.263</td>
</tr>
<tr>
<td>Hypertension, presence, n (%)</td>
<td>539 (68.2)</td>
<td>96 (58.2)</td>
<td>443 (70.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypercholesterolaemia, presence, n (%)</td>
<td>351 (45.4)</td>
<td>58 (35.8)</td>
<td>293 (47.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>Diabetes mellitus, presence, n (%)</td>
<td>144 (18.2)</td>
<td>20 (12.1)</td>
<td>124 (19.8)</td>
<td>0.024</td>
</tr>
<tr>
<td>Atrial fibrillation, presence, n (%)</td>
<td>285 (38.8)</td>
<td>33 (21.3)</td>
<td>252 (43.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Previous ischaemic stroke or TIA, presence, n (%)</td>
<td>176 (23.3)</td>
<td>29 (18.1)</td>
<td>147 (24.7)</td>
<td>0.081</td>
</tr>
<tr>
<td>Previous intracerebral haemorrhage, presence, n (%)</td>
<td>38 (4.9)</td>
<td>9 (5.5)</td>
<td>29 (4.7)</td>
<td>0.683</td>
</tr>
<tr>
<td>GCS, median (IQR)</td>
<td>15 (14 – 15)</td>
<td>15 (14 – 15)</td>
<td>15 (13 – 15)</td>
<td>0.003†</td>
</tr>
<tr>
<td>IQCODE, median (IQR)</td>
<td>3.12 (3.0 – 3.5)</td>
<td>3.0 (3.0 – 3.3)</td>
<td>3.13 (3.0 – 3.5)</td>
<td>&lt;0.00001†</td>
</tr>
<tr>
<td>IQCODE &gt; 3.3</td>
<td>282 (35.4)</td>
<td>41 (24.7)</td>
<td>241 (38.2)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abbreviations: GCS, Glasgow Coma Scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; IQR, interquartile range; SD, standard deviation; TIA, transient ischaemic attack.
Supplementary Figure
Description of the study population. Only those with an available MRI and the necessary sequences for cerebral small vessel disease rating (i.e. axial T2, axial and/or coronal FLAIR, and a blood sensitive sequence) were included in the neuroimaging marker analysis.

Abbreviations: CROMIS-2, Clinical Relevance of Microbleeds in Stroke Study; ICH, intracerebral haemorrhage; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly.
STROBE Statement—checklist of items that should be included in reports of observational studies

<table>
<thead>
<tr>
<th>Item No</th>
<th>Recommendation</th>
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| **Title and abstract** | 1. (a) Indicate the study’s design with a commonly used term in the title or the abstract  
2. (b) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | |
| **Background/rationale** | 2. Explain the scientific background and rationale for the investigation being reported |
| **Objectives** | 3. State specific objectives, including any prespecified hypotheses |
| **Methods** | |
| **Study design** | 4. Present key elements of study design early in the paper |
| **Setting** | 5. Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| **Participants** | 6. (a) **Cohort study**—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  
(b) **Case-control study**—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  
(c) **Cross-sectional study**—Give the eligibility criteria, and the sources and methods of selection of participants  
(b) **Cohort study**—For matched studies, give matching criteria and number of exposed and unexposed  
(c) **Case-control study**—For matched studies, give matching criteria and the number of controls per case |
| **Variables** | 7. Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| **Data sources/measurement** | 8* For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| **Bias** | 9. Describe any efforts to address potential sources of bias |
| **Study size** | 10. Explain how the study size was arrived at |
| **Quantitative variables** | 11. Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| **Statistical methods** | 12. (a) Describe all statistical methods, including those used to control for confounding  
(b) Describe any methods used to examine subgroups and interactions  
(c) Explain how missing data were addressed  
(d) **Cohort study**—If applicable, explain how loss to follow-up was addressed  
(e) **Case-control study**—If applicable, explain how matching of cases and controls was addressed  
(f) **Cross-sectional study**—If applicable, describe analytical methods taking account of sampling strategy  
(g) Describe any sensitivity analyses |

Continued on next page
Results

Participants 13*  
(a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed  
(b) Give reasons for non-participation at each stage  
(c) Consider use of a flow diagram

Descriptive data 14*  
(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders  
(b) Indicate number of participants with missing data for each variable of interest  
(c) **Cohort study**—Summarise follow-up time (e.g., average and total amount)

Outcome data 15*  
**Cohort study**—Report numbers of outcome events or summary measures over time  
**Case-control study**—Report numbers in each exposure category, or summary measures of exposure  
**Cross-sectional study**—Report numbers of outcome events or summary measures

Main results 16  
(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included  
(b) Report category boundaries when continuous variables were categorized  
(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses 17  
Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses

Discussion

Key results 18  
Summarise key results with reference to study objectives

Limitations 19  
Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

Interpretation 20  
Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence

Generalisability 21  
Discuss the generalisability (external validity) of the study results

Other information

Funding 22  
Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.