Association of Retinopathy and Retinal Microvascular Abnormalities With Stroke and Cerebrovascular Disease

Alun D. Hughes, PhD; Emanuela Falaschetti, MSc; Nicholas Witt, MSc; Sumangali Wijetunge, PhD; Simon A. McG. Thom, MD; Therese Tillin, MSc; Steve J. Aldington, FBIPP; Nish Chaturvedi, MD

Background and Purpose—Abnormalities of the retinal circulation may be associated with cerebrovascular disease. We investigated associations between retinal microvascular abnormalities and (1) strokes and subclinical cerebral infarcts and (2) cerebral white matter lesions in a UK-based triethnic population-based cohort.

Methods—A total of 1185 participants (age, 68.8±6.1 years; 77% men) underwent retinal imaging and cerebral magnetic resonance imaging. Cerebral infarcts and white matter hyperintensities were identified on magnetic resonance imaging, retinopathy was graded, and retinal vessels were measured.

Results—Higher retinopathy grade (odds ratio [OR], 1.40 [95% confidence interval (95% CI), 1.16–1.70]), narrower arteriolar diameter (OR, 0.98 [95% CI, 0.97–0.99]), fewer symmetrical arteriolar bifurcations (OR, 0.84 [95% CI, 0.75–0.95]), higher arteriolar optimality deviation (OR, 1.16 [95% CI, 1.00–1.34]), and more tortuous venules (OR, 1.20 [95% CI, 1.09–1.32]) were associated with strokes/infarcts and white matter hyperintensities. Associations with quantitative retinal microvascular measures were independent of retinopathy.

Conclusions—Abnormalities of the retinal microvasculature are independently associated with stroke, cerebral infarcts, and white matter lesions. (Stroke. 2016;47:2862-2864. DOI: 10.1161/STROKEAHA.116.014998.)

Key Words: cerebral infarction ■ cerebrovascular disorders ■ retinal vessels ■ stroke ■ white matter

Stroke is a leading cause of death and disability worldwide; however, symptomatic strokes represent only a small fraction of the burden of cerebrovascular disease. White matter lesions may also be indicative of cerebrovascular disease and stroke risk. Retinopathy is associated with incident and prevalent stroke, subclinical infarcts, and white matter lesions; however, associations with quantitative retinal microvascular measures have been inconsistent. This study investigated associations between retinal microvascular abnormalities and (1) cerebral infarcts/stroke and (2) white matter lesions in a UK-based triethnic population-based cohort and if associations with quantitative measures were independent of retinopathy status.

Methods

Participants

Southall and Brent Revisited is a population-based triethnic cohort (Europeans, South Asians, and African Caribbeans). Surviving participants attended for reinvestigation between 2008 and 2011. Ethics approval was granted by St Mary’s Hospital Research Ethics Committee (07/H0712/109), and written informed consent was obtained.

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and potential confounders plus retinopathy for quantitative measures (model 3).

**Results**

A higher retinopathy grade was associated with higher OR for cerebral infarcts and stroke (Table 1) and WMH (Table 2). Narrower arteriolar diameter, fewer symmetrical arteriolar bifurcations, higher venular tortuosity, and lower AVR were also significantly associated with greater OR for cerebral infarct and strokes (Table 1) and WMH (Table 2). Adjustment for confounders had little or no effect. Further adjustment for urinary microalbuminuria had minimal effects on associations (not shown).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1 OR (95% CI)</th>
<th>P Value</th>
<th>Model 2 OR (95% CI)</th>
<th>P Value</th>
<th>Model 3 OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
<td>NR</td>
<td>...</td>
</tr>
<tr>
<td>R0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R1</td>
<td>1.47 (1.08–2.00)</td>
<td>0.015</td>
<td>1.41 (1.01–1.96)</td>
<td>0.04</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>R2</td>
<td>3.62 (1.75–7.48)</td>
<td>0.001</td>
<td>2.79 (1.30–5.99)</td>
<td>0.008</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Trend</td>
<td>...</td>
<td>&lt;0.001</td>
<td>...</td>
<td>0.004</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

**Quantitative measures**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1 OR (95% CI)</th>
<th>P Value</th>
<th>Model 2 OR (95% CI)</th>
<th>P Value</th>
<th>Model 3 OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriolar diameter</td>
<td>0.98 (0.97–0.99)</td>
<td>0.04</td>
<td>0.97 (0.96–0.99)</td>
<td>0.003</td>
<td>0.97 (0.96–0.99)</td>
<td>0.002</td>
</tr>
<tr>
<td>No. of arterioles</td>
<td>0.94 (0.87–1.01)</td>
<td>0.08</td>
<td>0.94 (0.87–1.02)</td>
<td>0.1</td>
<td>0.93 (0.86–1.01)</td>
<td>0.09</td>
</tr>
<tr>
<td>No. of symmetrical arteriolar bifurcations</td>
<td>0.84 (0.75–0.95)</td>
<td>0.004</td>
<td>0.83 (0.73–0.94)</td>
<td>0.003</td>
<td>0.82 (0.73–0.93)</td>
<td>0.002</td>
</tr>
<tr>
<td>Arteriolar tortuosity</td>
<td>1.05 (0.98–1.12)</td>
<td>0.2</td>
<td>1.04 (0.97–1.12)</td>
<td>0.3</td>
<td>1.04 (0.97–1.12)</td>
<td>0.3</td>
</tr>
<tr>
<td>Log arteriolar optimality deviation</td>
<td>1.16 (1.00–1.34)</td>
<td>0.05</td>
<td>1.13 (0.97–1.32)</td>
<td>0.1</td>
<td>1.13 (0.97–1.32)</td>
<td>0.1</td>
</tr>
<tr>
<td>Venular diameter</td>
<td>1.00 (0.99–1.01)</td>
<td>&gt;0.9</td>
<td>0.99 (0.98–1.01)</td>
<td>0.3</td>
<td>0.99 (0.98–1.01)</td>
<td>0.3</td>
</tr>
<tr>
<td>No. of venules</td>
<td>0.97 (0.90–1.04)</td>
<td>0.3</td>
<td>0.99 (0.92–1.07)</td>
<td>0.8</td>
<td>0.99 (0.92–1.07)</td>
<td>0.8</td>
</tr>
<tr>
<td>Venular tortuosity</td>
<td>1.20 (1.09–1.32)</td>
<td>&lt;0.001</td>
<td>1.17 (1.05–1.29)</td>
<td>0.003</td>
<td>1.16 (1.05–1.29)</td>
<td>0.004</td>
</tr>
<tr>
<td>Arteriovenous ratio</td>
<td>0.29 (0.08,1.01)</td>
<td>0.05</td>
<td>0.25 (0.07–0.93)</td>
<td>0.04</td>
<td>0.23 (0.06–0.85)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, sex, ethnicity; model 2: model 1 plus adjustment for hypertension, body mass index, HbA1c (glycated hemoglobin), diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, log C-reactive protein, coronary artery disease, years of education, and smoking habit; model 3, model 2 plus adjustment for the presence of retinopathy. CI indicates confidence interval; NR, not relevant; and OR, odds ratio.

**Table 2. Association Between Retinopathy and Quantitative Retinal Microvascular Measures With White Matter Hyperintensities**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1 OR (95% CI)</th>
<th>P Value</th>
<th>Model 2 OR (95% CI)</th>
<th>P Value</th>
<th>Model 3 OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
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<td>Retinopathy</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
<td>NR</td>
<td>...</td>
</tr>
<tr>
<td>R0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R1</td>
<td>1.14 (0.89–1.46)</td>
<td>0.3</td>
<td>1.03 (0.79–1.33)</td>
<td>0.9</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>R2</td>
<td>5.64 (2.64–12.09)</td>
<td>&lt;0.001</td>
<td>4.35 (1.98–9.56)</td>
<td>&lt;0.001</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Trend</td>
<td>...</td>
<td>0.001</td>
<td>...</td>
<td>0.04</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Arteriolar diameter</td>
<td>0.99 (0.97–1.00)</td>
<td>0.02</td>
<td>0.98 (0.97–0.99)</td>
<td>0.01</td>
<td>0.98 (0.97–0.99)</td>
<td>0.002</td>
</tr>
<tr>
<td>No. of arterioles</td>
<td>0.91 (0.86–0.967)</td>
<td>0.002</td>
<td>0.92 (0.87–0.98)</td>
<td>0.006</td>
<td>0.92 (0.87–0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>No. of symmetrical arteriolar bifurcations</td>
<td>0.90 (0.83–0.98)</td>
<td>0.02</td>
<td>0.88 (0.81–0.97)</td>
<td>0.007</td>
<td>0.88 (0.80–0.96)</td>
<td>0.006</td>
</tr>
<tr>
<td>Arteriolar tortuosity</td>
<td>0.97 (0.92–1.03)</td>
<td>0.4</td>
<td>0.96 (0.90–1.02)</td>
<td>0.2</td>
<td>0.96 (0.90–1.02)</td>
<td>0.2</td>
</tr>
<tr>
<td>Log arteriolar optimality deviation</td>
<td>0.98 (0.88–1.09)</td>
<td>0.7</td>
<td>1.00 (0.90–1.12)</td>
<td>&gt;0.9</td>
<td>1.01 (0.90–1.12)</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>Venular diameter</td>
<td>0.99 (0.99–1.01)</td>
<td>0.9</td>
<td>1.00 (0.99–1.01)</td>
<td>0.6</td>
<td>1.00 (0.99–1.01)</td>
<td>0.6</td>
</tr>
<tr>
<td>No. of venules</td>
<td>0.94 (0.89–0.99)</td>
<td>0.03</td>
<td>0.96 (0.90–1.01)</td>
<td>0.1</td>
<td>0.96 (0.90–1.01)</td>
<td>0.1</td>
</tr>
<tr>
<td>Venular tortuosity</td>
<td>1.14 (1.04–1.23)</td>
<td>0.003</td>
<td>1.11 (1.01–1.21)</td>
<td>0.02</td>
<td>1.11 (1.02–1.21)</td>
<td>0.02</td>
</tr>
<tr>
<td>Arteriovenous ratio</td>
<td>0.40 (0.15–1.04)</td>
<td>0.06</td>
<td>0.32 (0.12–0.86)</td>
<td>0.02</td>
<td>0.31 (0.12–0.84)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, sex, ethnicity; model 2: model 1 plus adjustment for hypertension, body mass index, glycated hemoglobin, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, log C-reactive protein, coronary artery disease, years of education, and smoking habit; model 3, model 2 plus adjustment for presence of retinopathy. CI indicates confidence interval; NR, not relevant; and OR, odds ratio.
Retinopathy and quantitative abnormalities of the retinal microvasculature are associated with prevalent clinical and subclinical cerebrovascular disease in a triethnic population-based cohort. Associations were independent of risk factors, and adjustment for the presence of retinopathy had little effect on associations with quantitative measures. Previous studies examining the retina in relation to cerebral disease have yielded inconsistent results.10–14 Our data provide additional information in a large, well-characterized, triethnic sample including first-generation migrants to the United Kingdom who are at increased risk of stroke.2

This study has many limitations. It is cross-sectional, so the issue of causality cannot be resolved. By design, the majority were men and only 40% of original participants attended for reassessment. People who attended clinic were slightly younger and tended to be healthier than those who failed to attend or who had died in the intervening period. Nevertheless, it seems unlikely that this would substantially influence the validity of cross-sectional associations observed within the sample.

In summary, retinopathy, arteriolar narrowing, reduced density of the retinal arteriolar network (rarefaction), and increased venular tortuosity are associated with cerebral infarcts, stroke, and white matter lesions in an older triethnic cohort. These associations are independent of conventional risk factors, including diabetes mellitus, elevated blood pressure and renal microvascular disease, and associations with quantitative measures were independent of retinopathy.

Acknowledgments
We gratefully acknowledge the assistance of the Southall and Brent Revisited (SABRE) team and participants.

Sources of Funding
The Southall and Brent Revisited (SABRE) eye substudy was funded by the British Heart Foundation (PG/12/29/29497). The main SABRE study received funding from the British Heart Foundation, the Wellcome Trust and Diabetes UK. Drs Hughes and Chaturvedi received support from a National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) Award to University College London Hospitals, SAMcGT received support from a NIHR BRC Award to Imperial College Healthcare National Health Service Trust. The funders played no role in study design, conduct, analyses, or the decision to submit the article for publication.

Discussion

Retinopathy and quantitative abnormalities of the retinal microvasculature are associated with prevalent clinical and subclinical cerebrovascular disease in a triethnic population-based cohort. Associations were independent of risk factors, and adjustment for the presence of retinopathy had little effect on associations with quantitative measures. Previous studies examining the retina in relation to cerebral disease have yielded inconsistent results.10–14 Our data provide additional information in a large, well-characterized, triethnic sample including first-generation migrants to the United Kingdom who are at increased risk of stroke.2

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Disclosures
None.

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2. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ. 2010;341:c3666.
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http://stroke.ahajournals.org/content/suppl/2016/10/20/STROKEAHA.116.014998.DC1

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SUPPLEMENTAL METHODS

Participants

Southall and Brent REvisited (SABRE) is tri-ethnic cohort (Europeans, South Asians and African Caribbeans) in London, UK. SABRE is a representative community-based sample of men and women aged between 40 and 69 who were recruited without exclusions between 1988 and 1990. Ethnicity was self-assigned, and confirmed by country of birth of all four grandparents. Cohort survivors were invited to attend clinic between 2008 and 2011. Out of 2346 Europeans, 1,711 South Asians and 810 African Caribbeans studied at baseline, 2206 (94%), 1618 (95%) and 679 (85%), respectively, could be traced, and of these a total of 1438 participants attended clinic (684 Europeans (43% of survivors), 522 South Asians (41% of survivors) and 232 African Caribbeans (42% of survivors)). A comparison of participants at baseline and in 2008-2011 is shown in supplemental table I.

Investigations

All participants completed a questionnaire detailing comorbidity, risk factors, health behaviours and medications. Reports of stroke and coronary heart disease were confirmed by health records. Anthropometry was performed to a standardised protocol. Sitting clinic BP was measured three times after 15-min seated rest with an Omron CEP 7050; the mean of the final two readings was used in analysis. Hypertension was defined as use of BP-lowering medication, or patient report confirmed by health records. Known diabetes was based on patient report confirmed by health records. WHO 1999 criteria were used to define diabetes2 and the homeostasis model assessment calculator was used to estimate insulin resistance (HOMA-IR).3 Fasting cholesterol (enzymatic method), glycated haemoglobin (HbA1C; high-pressure liquid chromatography) and C-reactive protein (CRP; automated analyser) were measured. Urinary albumin (enzyme immunoassay) and creatinine (kinetic Jaffé method) were measured in an early morning urine sample. Albumin to creatinine ratio was classified as grade 0 (men ≤ 2.5mg/mmol; women ≤3.5mg/mmol); grade 1 (men > 2.5mg/mmol and ≤70mg/mmol; women >3.5mg/mmol and ≤70mg/mmol); or grade 2 (>70mg/mmol for both sexes).

Retinal imaging

Participants were excluded from retinal photography if they had glaucoma or any condition that prevented adequate imaging of the retina. The fundus of both eyes was imaged using a Zeiss FF450+ fundus camera (30° field) and an Allied Vision Tech Oscar 510C CCD (2588 x 1958 pixels) following administration of 1% (w/v) tropicamide and 2.5% (w/v) phenylephrine eye drops. Refraction was measured using a Nidek AR-310 auto-refractometer. Digital retinal photography was performed on 1205 individuals (84%) and analysable images for retinopathy grading and quantitative microvascular analysis were obtained in 1185 (98%) and 1167 (97%) individuals respectively (Supplemental figure 1). The characteristics of the participants with images suitable for retinopathy grading is shown in Supplemental Table II.

Retinopathy grading was performed using images of 4 fields from both eyes (disc-centred (equating to ETDRS Field 1), macular-centred (ETDRS Field 2), temporal-to-macular (ETDRS Field 3), and superior-temporal (ETDRS Field 4)) according to the NHS Diabetic Eye Screening
Grading was performed in duplicate by separate readers with any disagreements between readers resolved by independent arbitration. For the purposes of analysis, the worst retinopathy grade of either eye was used.

Quantification of the retinal microvasculature was performed on the right eye (98%), unless the image was inadequate, in which case the left eye was used. Quantitative assessment of the retinal microvasculature was performed using a custom-written Matlab (The MathWorks, Inc, USA) program using a validated algorithm with subpixel accuracy." Diameter measurements were corrected for refraction using the Bengtsson factor calculated using the spherical equivalent for the appropriate eye. Vessel tortuosity was calculated from the actual length of the vessel and the straight line distance between bifurcations. Two measures of arteriolar microvascular density were calculated: the number of arteriolar vessels and the number of symmetrical bifurcations (defined as a bifurcation where the squared ratio of the offspring diameters ≥0.4). Arteriolar optimality deviation (AOD) was calculated for symmetrical bifurcations as:

\[
AOD = \left( \frac{d_1^3 + d_2^3}{d_0^3} \right) - \frac{1}{2^3}
\]

where \(d_0\), \(d_1\) and \(d_2\) are the diameters of the parent and offspring branches at a bifurcation respectively.

Between- and within-observer reproducibility of retinopathy grading was good (unweighted kappa = 0.73 for both) and reproducibility of quantitative measures was excellent (intraclass correlation coefficient between 0.84 and 0.99 for all measures)

Cerebral MRI

MRI was performed on 1,306 individuals attending clinic (91%) using a previously published protocol. MRI data were not available in 92 individuals who underwent retinal imaging due to claustrophobia (n=39), metal implant or another contraindication for MRI (n=29) or refusal (n=24) (Supplemental Figure 1). Views included standard sagittal T1-weighted images and axial T1-weighted, proton density, and T2-weighted images of 5-mm thickness with no gaps. Thin section 3-mm axial fluid attenuated inversion recovery (FLAIR) and coronal 1.5-mm three-dimensional T1-weighted gradient echo images were also obtained. Cerebral infarcts and strokes were categorised as: 0 = no stroke or large infarct (>3mm); 1 = large infarct + no stroke; 2 = stroke and/or ≥2 large infarcts. Assessment of white matter was performed as previously described, only lesions ≥3 mm were assessed; as smaller lesions are poorly reproducible.

Severity of white matter lesions was scored on a 10-point scale using the Cardiovascular Health Study (CHS) standards, which combine periventricular and subcortical foci. White matter hyperintensities (WMH) were classified into 4 categories: none - no WMH, mild – one WMH; moderate – 2 WMH and severe ≥ 3 WMH. Scans were read masked; inter- and intra-observer agreement for MRI measures have been reported previously and kappa ranged between 0.68 and 0.79.
SUPPLEMENTAL TABLES

**Supplemental Table I.** Comparison of measures in all participants at baseline (1988-1990) with those who attended clinic at between 2008-2011.

<table>
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<tbody>
<tr>
<td>n</td>
<td>4857</td>
<td>1438</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>75</td>
<td>76</td>
<td>0.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Age (y)</td>
<td>52.4±7</td>
<td>50.0±6</td>
<td>&lt;0.0001</td>
<td>0.08</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>75.5±13</td>
<td>75.2±13</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>125±18</td>
<td>121±15</td>
<td>&lt;0.0001</td>
<td>0.8</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79±11</td>
<td>78±11</td>
<td>0.003</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>Fasting HbA1c (%)</td>
<td>5.9±1.0</td>
<td>5.7±0.8</td>
<td>&lt;0.0001</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>14</td>
<td>8</td>
<td>&lt;0.0001</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Values presented are those measured at baseline. Data are mean ± SD for numerical data and (%) for categorical data. SBP systolic blood pressure, DBP diastolic blood pressure.

**Supplemental Table II.** Characteristics of sample (n = 1185)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.8±6.1</td>
</tr>
<tr>
<td>Male, %</td>
<td>77</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>European, %</td>
<td>48</td>
</tr>
<tr>
<td>South Asian, %</td>
<td>37</td>
</tr>
<tr>
<td>African Caribbean, %</td>
<td>15</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.5±4.6</td>
</tr>
<tr>
<td>SBP/DBP, mmHg</td>
<td>140±17 / 77±10</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>6.1(5.4, 6.8)</td>
</tr>
<tr>
<td>Fasting glucose, mmol/l</td>
<td>5.2(4.2, 6.2)</td>
</tr>
</tbody>
</table>
Total cholesterol, mmol/l 4.7±1.1
HDL cholesterol, mmol/l\textsuperscript{a} 1.32(0.88, 1.76)
C-reactive protein, mg/l\textsuperscript{b} 1.51(0.71, 3.24)
Smoking (current/ex/never), % 7/38/56
Education, y 11.8±3.3
Hypertension, % 66.7
Diabetes, % 30
Coronary artery disease, n (%) 24
Cerebrovascular disease, n [%] 20
  1 large infarct + no stroke 11
  Stroke and/or 2+ large infarcts 9
White matter hyperintensity grade
  None, % 2
  Mild, % 36
  Moderate, % 31
  Severe, % 31
Albumin to creatinine ratio grade
  Grade 0, % 88
  Grade 1, % 11
  Grade 2, % 1
Presence of retinopathy, % 34.5
  Retinopathy grade R0, % of total with retinopathy 66.6
  Retinopathy grade R1, % of total with retinopathy 30.6
  Retinopathy grade R2, % of total with retinopathy 2.8
\textsuperscript{a}median and interquartile range
Supplemental Figure I. Diagram indicating the flow of participants through the study.
Supplemental references


10. Shibata D, Tillin T, Beauchamp N, Heasman J, Hughes AD, Park C, et al. African caribbeans have greater subclinical cerebrovascular disease than europeans: This is associated with both their elevated resting and ambulatory blood pressure and their hyperglycaemia. *J. Hypertens.* 2013;31:2391-2399