Higher blood pressure is associated with greater white matter lesions and brain atrophy: a systematic review with meta-analysis acronym defined

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Appendix A. Supplemental results

1. Magnetic resonance imaging

All studies included in the systematic review were adjusted to account for variation in head size, either in the statistical model or during image processing, by normalization against intracranial volume (ICV, 46 studies), average head size (two studies) [1,2], or skull size (two studies) [3,4].

2. BP assessment

Outcome measures included SBP (45%), DBP (39%), PP (8%) and MAP (6.9%). Apart from BP cut-off values, some studies used different values, namely i.e. ≥140/90,(n=) 150/90 (n = 1) [5] 160/95 (n = 1) [2] 160/100 (n = 2) [6,7] or 160-179/90-99 (n = 1) [8] as clinical measures and 135/85 for ABP [9]. Hypertensive participants were below 25% in (29.8% of studies), between 26% to 50% in (49% of studies), and above 50% in (21% of studies).

3. BP brain volumes and Age

3.1. BP associations in young adults

Five studies reported association between BP and brain volumes in young adults (18-40 years) [10–14]. Higher BP (SBP, n = 15; DBP, n = 12) was associated with greater WMLs (n = 2[13,14]) and smaller brain volumes (TBV, n = 3 [10,13,14]; GMV, n = 2 [10,12]; WMV, n = 1[10]; HCV, n = 4[10–13]; amygdala, n = 1[11]; Insula, n = 2[11]). None of the association was significant in young adults.

3.2. Brain volumes in middle age

Twelve studies reported association between BP and brain volumes in middle-aged adults (50-60 years) [13,15–25]. Higher BP was (SBP, n = 17%; DBP, n = 9%; MAP, n = 7%; PP, n = 6%) was associated with larger WMLS (n = 6) [13,15,17–19], and smaller brain volumes including (TBV, n = 6 [13,17,18,20,21,26]; GMV, n = 1[26]; WMV, n = 1[26]; HCVs, n = 2 [13,17].

3.3. BP associations in older age

Fifteen studies reported association between BP and brain volumes in older adults (≥70 years). [2,4,5,13,16,17,27–35]. Higher BP was associated with larger WMLSCV (n= 8) [5,17,27,28,32–35]. Lower BP (DBP, n = 3; SBP, n = 1) was associated with smaller TBV ( n = 1) [30] HCV (n = 2) [2,29] Higher SBP was associated with larger HCV [16]. However, higher BP was associated with smaller TBV (n = 2 [13,30]; HCV, n = 6[13,30,31]).

Table S1. Adjusted Newcastle-Ottawa Quality Assessment Scale for Studies.
| 1. Representative of the general population | i. Generally representative | ☆ |
| | ii. Somewhat representative | ½☆ |
| | iii. Selected group | 0 |
| | iv. No description of the derivation of the cohort | 0 |

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<td>2. Position when BP Measurement parameters are reported</td>
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<td>4. Number of BP readings is reported</td>
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<td>iii. No description</td>
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<td>5. Time intervals between BP readings is reported</td>
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<td>7. Number of BP assessment sessions</td>
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<td>ii. Average of multiple BP measurements taken over a day or longer e.g., BP variability</td>
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<td>iii. Repeated occasional BP measures over time</td>
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<td>i. Analyses control for age and sex</td>
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<td>ii. Analyses control for additional confounders</td>
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<td>ii. Measurement conducted without knowledge of the exposure (e.g. semiautomated segmentation)</td>
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<td>iii. Measurement done with knowledge of the exposure (Manual)</td>
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Table S2. Characteristics of the selected studies.
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<th>Age M (SD)</th>
<th>Sex (% female)</th>
<th>BP Methods</th>
<th>SBP M (SD)</th>
<th>DBP M (SD)</th>
<th>%HT</th>
<th>%AHT</th>
<th>Brain Region</th>
<th>Magnet / Segmentation</th>
<th>Covariables</th>
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<td>Alkan et al 2019[36]</td>
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<td>164</td>
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<td>129.6 (16.9)</td>
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<td>54.5</td>
<td>NR</td>
<td>WMLS</td>
<td>1.5 T/ Semi-automated</td>
<td>Age, education, BMI, WC, cholesterol, FBG, triglyceride, HDL-C, LDL-C, SBP, DBP, and number of MetS</td>
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<td>Age, sex, education, and brain atrophy</td>
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<td>Magnet / Segmentation</td>
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**Notes:**
- **BP Methods:**Occasional
- **%HT %AHT:**0
- **Brain Region:**WMLS, TBV
- **Magnet / Segmentation:**NR
- **Covariables:**Age, sex, education, AHT medication
- **Kern et al 2017[45]** Age, sex, education and general intellectual ability
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<th>Study Design</th>
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<th>Sex (% Female)</th>
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<th>SBP M (SD)</th>
<th>DBP M (SD)</th>
<th>%HT</th>
<th>%AHT</th>
<th>Brain Region</th>
<th>Magnet / Segmentation</th>
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<td>3 T/Semi-automated (VBM)</td>
<td>Age, sex and ICV</td>
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<td>Launer et al 2015</td>
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<td>WMLS</td>
<td>3 T/Semi-automated</td>
<td>Age, sex, race, height, CVD factors, depression, and physical activity</td>
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<td>64.5 (0.8)</td>
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<td>139.9 (1.5)</td>
<td>79.5 (0.9)</td>
<td>32.2</td>
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<td>WMLS, TBV</td>
<td>1.5 T/Semi-automated (VBM)</td>
<td>Age within this narrow age range sample.</td>
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<td>Age, sex, education and CVD factors</td>
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<tr>
<td>Muller et al 2016[48]</td>
<td>Longitudinal</td>
<td>1348</td>
<td>50 (6)</td>
<td>58.0</td>
<td>Occasional</td>
<td>NR</td>
<td>NR</td>
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<td>0</td>
<td>WMLS, TBV, GMV, WMV</td>
<td>1.5 T/Semi-automated</td>
<td>Age, sex, education, and late-life CVD.</td>
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<tr>
<td>Nation et al 2016[21]</td>
<td>Longitudinal</td>
<td>549</td>
<td>59.6 (2.7)</td>
<td>53.2</td>
<td>Occasional</td>
<td>124 (16)</td>
<td>75 (9)</td>
<td>37.9</td>
<td>0</td>
<td>WMLS, TBV, HCV</td>
<td>1.5 T/Semi-automated</td>
<td>Age, sex, and education</td>
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<tr>
<td>Paganini-Hill et al 2019[28]</td>
<td>Longitudinal</td>
<td>97</td>
<td>92.4 (0.3)</td>
<td>60</td>
<td>ABP</td>
<td>142 (1.5)</td>
<td>71 (1)</td>
<td>65.0</td>
<td>NA</td>
<td>WMLS</td>
<td>3 T/Semi-automated</td>
<td>Age, sex, education, smoking and histories of CVD and cerebral vascular diseases</td>
</tr>
<tr>
<td>Pase et al 2016[22]</td>
<td>Cross-sectional</td>
<td>332</td>
<td>62.9 (10.2)</td>
<td>54.0</td>
<td>IDSBP</td>
<td>134 (19)</td>
<td>76 (10)</td>
<td>38.7</td>
<td>35.0</td>
<td>WMLS, TBV</td>
<td>1 T or 1.5 T/NR</td>
<td>Age, sex, and age</td>
</tr>
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<td>N</td>
<td>Age M (SD)</td>
<td>Sex (% female)</td>
<td>BP Methods</td>
<td>SBP M (SD)</td>
<td>DBP M (SD)</td>
<td>%HT</td>
<td>%AHT</td>
<td>Brain Region</td>
<td>Magnet / Segmentation</td>
<td>Covariables</td>
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<td>---------------------------</td>
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<td>------</td>
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<td>Power et al 2016[49]</td>
<td>Cross-sectional and Longitudinal</td>
<td>1678</td>
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<td>Occasional</td>
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<td>66 (3.6)</td>
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<td>72.0</td>
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<td>3 T/Semi-automated</td>
<td>Age, sex, race, education, ICV, BMI, DM, cholesterol, and smoking status</td>
</tr>
<tr>
<td>Sabayan et al 2013[4]</td>
<td>Longitudinal</td>
<td>553</td>
<td>74.9 (3.2)</td>
<td>43.6</td>
<td>Variability</td>
<td>156.1 (16.4)</td>
<td>85.1 (7.3)</td>
<td>63.1</td>
<td>NR</td>
<td>Gray Matter Volume (GMV), White Matter Volume (WMV)</td>
<td>1.5 T/Semi-automated</td>
<td>Average BP and CVD factors</td>
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<tr>
<td>Schaare et al 2019[50]</td>
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<td>27.7 (5.3)</td>
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<td>Occasional</td>
<td>123.2 (12.2)</td>
<td>73.4 (8.5)</td>
<td>11.0</td>
<td>0</td>
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<td>3 T/Semi-automated</td>
<td>Age, sex, and ICV</td>
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<tr>
<td>Scott et al 2015[32]</td>
<td>Cross-sectional</td>
<td>150</td>
<td>73.7 (6.3)</td>
<td>48.7</td>
<td>Occasional</td>
<td>136 (16)</td>
<td>75 (10)</td>
<td>44.0</td>
<td>NR</td>
<td>Whole-Brain Measures (WMLS)</td>
<td>3 T/NR</td>
<td>Age, sex, time between examination cycle and MRI, smoking, DM, APOE e4 genotype status, use of AHT medication; and serum homocysteine</td>
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<td>Spartano et al 2016[51]</td>
<td>Longitudinal</td>
<td>1094</td>
<td>40 (9)</td>
<td>53.9</td>
<td>Exercise</td>
<td>166 (25.0)</td>
<td>74 (9)</td>
<td>28.3</td>
<td>17.7</td>
<td>Tubular Blood Volume (TBV)</td>
<td>1.5 T/NR</td>
<td>Age, sex, education, BMI, and history of smoking, DM and CVD.</td>
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<td>Suzuki et al 2017[26]</td>
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<td>Occasional</td>
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<td>74.5 (7.1)</td>
<td>0</td>
<td>0</td>
<td>Tubular Blood Volume (TBV), Hippocampus (HCV), White Matter Volume (WMV)</td>
<td>3 T/Semi-automated</td>
<td>Age, sex, education, BMI, and history of smoking, DM and CVD.</td>
</tr>
<tr>
<td>Taki et al 2004[52]</td>
<td>Cross-sectional</td>
<td>769</td>
<td>47.4 (13.5)</td>
<td>53.8</td>
<td>Occasional</td>
<td>NR</td>
<td>NR</td>
<td>11.9</td>
<td>82.0</td>
<td>Regional Gray Matter (GMV)</td>
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<td>Sex, ICV, SBP, and BMI</td>
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<tr>
<td>Taki et al 2013[53]</td>
<td>Longitudinal</td>
<td>381</td>
<td>51.2 (11.8)</td>
<td>59.0</td>
<td>Occasional</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Regional Gray Matter (GMV)</td>
<td>0.5 T/Semi-automated</td>
<td>Sex, ICV, SES, and BMI</td>
</tr>
<tr>
<td>Trotman et al 2019[11]</td>
<td>Cross-sectional</td>
<td>40</td>
<td>19.1 (0.2)</td>
<td>100</td>
<td>Reactivity</td>
<td>122 (11.7)</td>
<td>77 (8.6)</td>
<td>NR</td>
<td>NR</td>
<td>Hippocampus, Amygdala, Insula</td>
<td>3 T/Semi-automated</td>
<td>Age, ICV, SES, and BMI</td>
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<tr>
<td>vanVelsen et al 2013[7]</td>
<td>Cross-sectional</td>
<td>1022</td>
<td>68.4 (7.3)</td>
<td>52.3</td>
<td>Occasional</td>
<td>144.5 (18.6)</td>
<td>80.3 (10.3)</td>
<td>47.4</td>
<td>0</td>
<td>Cortical thickness</td>
<td>1.5 T/Semi-automated</td>
<td>Age and sex.</td>
</tr>
<tr>
<td>Verhaaren et al 2013[54]</td>
<td>Cross-sectional</td>
<td>65</td>
<td>61.6 (5)</td>
<td>52.0</td>
<td>Occasional</td>
<td>138 (19)</td>
<td>78 (10)</td>
<td>25.9</td>
<td>22.0</td>
<td>Whole-Brain Measures (WMLS)</td>
<td>1.5 T/Semi-automated</td>
<td>Age, sex, and ICV, CVD factors</td>
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### Table S3. Methodological quality of studies.

<table>
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<tr>
<th>Studies</th>
<th>Total Rating</th>
<th>Methodological quality</th>
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</thead>
<tbody>
<tr>
<td>Alkan et al 2019[36]</td>
<td>9.0/10.5</td>
<td>(85.7%) High</td>
</tr>
<tr>
<td>Allan et al 2015[17]</td>
<td>6.5/10.5</td>
<td>(61.9%) Moderate</td>
</tr>
<tr>
<td>Bender et al 2012[25]</td>
<td>6.5/10.5</td>
<td>(61.9%) Moderate</td>
</tr>
<tr>
<td>Brickman et al 2010[27]</td>
<td>7.5/10.5</td>
<td>(71.4%) High</td>
</tr>
<tr>
<td>Burns et al 2005[27]</td>
<td>2.0/10.5</td>
<td>(19%) Low</td>
</tr>
<tr>
<td>Cherbuin et al 2015[37]</td>
<td>8.0/10.5</td>
<td>(76.2%) High</td>
</tr>
<tr>
<td>DeCarli et al 1995[38]</td>
<td>0.5/10.5</td>
<td>(76.2%) Low</td>
</tr>
<tr>
<td>De Jong et al 2014[39]</td>
<td>3.5/10.5</td>
<td>(33.3%) Low</td>
</tr>
<tr>
<td>Den Heijer et al 2005[2]</td>
<td>2.5/10.5</td>
<td>(23.8%) Low</td>
</tr>
<tr>
<td>Den Heijer et al 2012[29]</td>
<td>6.5/10.5</td>
<td>(61.9%) Moderate</td>
</tr>
<tr>
<td>Dickie et al 2016[40]</td>
<td>5.0/10.5</td>
<td>(47.6%) Moderate</td>
</tr>
<tr>
<td>Firbank et al 2007[5]</td>
<td>8.0/10.5</td>
<td>(76.2%) High</td>
</tr>
<tr>
<td>Gianaras et al 2006[41]</td>
<td>8.0/10.5</td>
<td>(76.2%) High</td>
</tr>
<tr>
<td>Glodzik et al 2014[24]</td>
<td>5.5/10.5</td>
<td>(52.4%) Moderate</td>
</tr>
<tr>
<td>Goldstein et al 2002[42]</td>
<td>7.0/10.5</td>
<td>(66.7%) Moderate</td>
</tr>
<tr>
<td>Goldstein et al 2005[18]</td>
<td>6.0/10.5</td>
<td>(57.1%) Moderate</td>
</tr>
<tr>
<td>Habes et al 2016[43]</td>
<td>8.0/10.5</td>
<td>(76.2%) High</td>
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</table>
Meta-analysis results

White matter lesions volume (WMLS)

<table>
<thead>
<tr>
<th>Study</th>
<th>LogLik</th>
<th>deviance</th>
<th>AIC</th>
<th>BIC</th>
<th>AICc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hajjar et al 2010[9]</td>
<td>8.0/10.5</td>
<td>(81%) High</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Haring et al 2019[23]</td>
<td>9.0/10.5</td>
<td>(85.7%) High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoogendam et al 2012[20]</td>
<td>7.0/10.5</td>
<td>(66.7%) Moderate</td>
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<tr>
<td>Ikram et al 2008[6]</td>
<td>5.5/10.5</td>
<td>(52.4%) Moderate</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Jeerakathil et al 2004[44]</td>
<td>3.0/10.5</td>
<td>(28.6%) Low</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Kern et al 2017[45]</td>
<td>9.0/10.5</td>
<td>(85.7%) High</td>
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<tr>
<td>Kobuch et al 2020[46]</td>
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<tr>
<td>Korf et al 2004[31]</td>
<td>3.0/10.5</td>
<td>(28.6%) Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lane et al 2019[13]</td>
<td>9.0/10.5</td>
<td>(85.7%) High</td>
<td></td>
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<td></td>
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<tr>
<td>Launer et al 2015[14]</td>
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<td>(61.9%) Moderate</td>
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<td></td>
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<tr>
<td>Mahinrad et al 2019[47]</td>
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<td>(95.2%) High</td>
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</tr>
<tr>
<td>McNeil et al 2018[16]</td>
<td>6.5/10.5</td>
<td>(61.9%) Moderate</td>
<td></td>
<td></td>
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<tr>
<td>Muller et al 2014[30]</td>
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<td>(57.1%) Moderate</td>
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</tr>
<tr>
<td>Muller et al 2016[48]</td>
<td>5.0/10.5</td>
<td>(47.6%) Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nation et al 2016[21]</td>
<td>8.0/10.5</td>
<td>(76.2%) High</td>
<td></td>
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</tr>
<tr>
<td>Paganini-Hill et al 2019[28]</td>
<td>4.0/10.5</td>
<td>(38.1%) Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pase et al 2016[22]</td>
<td>8.0/10.5</td>
<td>(76.2%) High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Power et al 2016[49]</td>
<td>5.0/10.5</td>
<td>(47.6%) Moderate</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sabayan et al 2013[4]</td>
<td>5.0/10.5</td>
<td>(47.6%) Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schaare et al 2019[50]</td>
<td>10.0/10.5</td>
<td>(95.2%) High</td>
<td></td>
<td></td>
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<tr>
<td>Scott et al 2015[32]</td>
<td>2.0/10.5</td>
<td>(19%) Low</td>
<td></td>
<td></td>
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<tr>
<td>Spartano et al 2016[51]</td>
<td>4.0/10.5</td>
<td>(38.1%) Low</td>
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<td>Suzuki et al 2017[26]</td>
<td>9.0/10.5</td>
<td>(85.7%) High</td>
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<tr>
<td>Taki et al 2004[52]</td>
<td>4.5/10.5</td>
<td>(42.9%) Moderate</td>
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<td>Taki et al 2013[53]</td>
<td>5.5/10.5</td>
<td>(52.4%) Moderate</td>
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<td>Trotman et al 2019[11]</td>
<td>2.5/10.5</td>
<td>(23.8%) Low</td>
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<td>Tsao et al 2016[19]</td>
<td>6.0/10.5</td>
<td>(57.1%) Moderate</td>
<td></td>
<td></td>
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<tr>
<td>vanVelsen et al 2013[7]</td>
<td>5.0/10.5</td>
<td>(47.6%) Moderate</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Verhaaren et al 2013[54]</td>
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<td>(81.0%) High</td>
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<td>Wardlaw et al 2014[35]</td>
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<td>(47.6%) Moderate</td>
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<tr>
<td>White et al 2011[34]</td>
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<td>(61.9%) Moderate</td>
<td></td>
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<tr>
<td>Wiseman et al 2004[8]</td>
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<td>(42.9%) Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolfson et al 2013[33]</td>
<td>9.0/10.5</td>
<td>(85.7%) High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yano et al 2017[10]</td>
<td>9.5/10.5</td>
<td>(90.5%) High</td>
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</table>

Figure S1. Association between SBP and White matter lesions from cross-sectional studies A. Forest plots; B. Sensitivity Analysis; trim and fill.

Random-Effects Model (k = 7; tau^2 estimator: REML)

<table>
<thead>
<tr>
<th>logLik</th>
<th>deviance</th>
<th>AIC</th>
<th>BIC</th>
<th>AICc</th>
</tr>
</thead>
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<td>3.6850</td>
<td>-7.3700</td>
<td>-3.3700</td>
<td>-3.7865</td>
<td>0.6300</td>
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</tbody>
</table>
\[ \text{tau}^2 \text{ (estimated amount of total heterogeneity): 0.0102 (SE = 0.0073)} \]
\[ \text{tau} \text{ (square root of estimated tau}^2 \text{ value): 0.1010} \]
\[ I^2 \text{ (total heterogeneity / total variability): 99.06\%} \]
\[ H^2 \text{ (total variability / sampling variability): 106.59} \]

**Test for Heterogeneity:**
\[ Q(\text{df} = 6) = 506.2446, \ p-\text{val} < .0001 \]

**Model Results:**
<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
</table>
| 0.1081   | 0.0435 | 2.4882 | 0.0128 | 0.0230 | 0.1933 *

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

**Sensitivity Analysis**

Estimated number of missing studies on the left side: 0 (SE = 1.8715)
Random-Effects Model (k = 7; tau^2 estimator: REML)
\[ \text{tau}^2 \text{ (estimated amount of total heterogeneity): 0.0102 (SE = 0.0073)} \]
\[ \text{tau} \text{ (square root of estimated tau}^2 \text{ value): 0.1010} \]
\[ I^2 \text{ (total heterogeneity / total variability): 99.06\%} \]
\[ H^2 \text{ (total variability / sampling variability): 106.59} \]

**Test for Heterogeneity:**
\[ Q(\text{df} = 6) = 506.2446, \ p-\text{val} < .0001 \]

**Model Results:**
<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
</table>
| 0.1081   | 0.0435 | 2.4882 | 0.0128 | 0.0230 | 0.1933 *

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

**Figure S2.** Association between SBP and White matter lesions from longitudinal studies. A. Forest plots; B. Sensitivity Analysis.

**Random-Effects Model** (k = 3; tau^2 estimator: REML)

<table>
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<tr>
<th>logLik</th>
<th>deviance</th>
<th>AIC</th>
<th>BIC</th>
<th>AICc</th>
</tr>
</thead>
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<tr>
<td>5.3344</td>
<td>-10.6687</td>
<td>-6.6687</td>
<td>-9.2824</td>
<td>5.3313</td>
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</tbody>
</table>
\[ \text{tau}^2 \text{ (estimated amount of total heterogeneity): 0 (SE = 0.0006)} \]
tau (square root of estimated tau^2 value): 0
I^2 (total heterogeneity / total variability): 0.00%
H^2 (total variability / sampling variability): 1.00

Test for Heterogeneity:
Q(df = 2) = 0.1372, p-val = 0.9337

Model Results:

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0138</td>
<td>0.0138</td>
<td>0.3181</td>
<td>-0.0133</td>
<td>0.0408</td>
<td></td>
</tr>
</tbody>
</table>

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Sensitivity Analysis

Estimated number of missing studies on the left side: 0 (SE = 1.4967)
Random-Effects Model (k = 3; tau^2 estimator: REML)
tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.0006)
tau (square root of estimated tau^2 value): 0
I^2 (total heterogeneity / total variability): 0.00%
H^2 (total variability / sampling variability): 1.00

Test for Heterogeneity:
Q(df = 2) = 0.1372, p-val = 0.9337

Model Results:

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0138</td>
<td>0.0138</td>
<td>0.3181</td>
<td>-0.0133</td>
<td>0.0408</td>
<td></td>
</tr>
</tbody>
</table>

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Figure S3. Association between DBP and White matter lesions from longitudinal studies. A. Forest plots; B. Sensitivity Analysis; trim and fill.

Random-Effects Model (k = 3; tau^2 estimator: REML)

logLik  deviance  AIC  BIC  AICc
1.9996  -3.9992  0.0008  -2.6129  12.0008
tau^2 (estimated amount of total heterogeneity): 0.0047 (SE = 0.0067)
tau (square root of estimated tau^2 value): 0.0683
I^2 (total heterogeneity / total variability): 95.69%
H^2 (total variability / sampling variability): 23.21

Test for Heterogeneity:

Q(df = 2) = 52.3723, p-val < .0001

Model Results:

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0725</td>
<td>0.0475</td>
<td>1.5283</td>
<td>0.1264</td>
<td>-0.0205</td>
<td>0.1656</td>
</tr>
</tbody>
</table>

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Sensitivity Analysis

Estimated number of missing studies on the left side: 0 (SE = 1.8715)

Random-Effects Model (k = 7; tau^2 estimator: REML)
tau^2 (estimated amount of total heterogeneity): 0.0102 (SE = 0.0073)
tau (square root of estimated tau^2 value): 0.1010
I^2 (total heterogeneity / total variability): 99.06%
H^2 (total variability / sampling variability): 106.59

Test for Heterogeneity:

Q(df = 6) = 506.2446, p-val < .0001

Model Results:

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1081</td>
<td>0.0435</td>
<td>2.4882</td>
<td>0.0128</td>
<td>0.0230</td>
<td>0.1933</td>
</tr>
</tbody>
</table>

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Total brain volume (TBV)

Figure S4. Association between SBP and total brain volume from cross-sectional studies. A. Forest plots; B. Sensitivity Analysis; trim and fill.

Random-Effects Model (k = 4; tau^2 estimator: REML)

<table>
<thead>
<tr>
<th>logLik</th>
<th>deviance</th>
<th>AIC</th>
<th>BIC</th>
<th>AICc</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.6975</td>
<td>-5.3950</td>
<td>-1.3950</td>
<td>-3.1977</td>
<td>10.6050</td>
</tr>
</tbody>
</table>

tau^2 (estimated amount of total heterogeneity): 0.0007 (SE = 0.0010)
tau (square root of estimated tau^2 value): 0.0269
I^2 (total heterogeneity / total variability): 94.33%
H^2 (total variability / sampling variability): 17.63

Test for Heterogeneity:
Q(df = 3) = 55.4156, p-val < .0001

Model Results:
```plaintext
estimate  se   zval   pval   ci.lb   ci.ub
-0.0223  0.0190 -1.1762  0.2395 -0.0596  0.0149
```
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Sensitivity Analysis
Estimated number of missing studies on the right side: 1 (SE = 1.5779)
Random-Effects Model (k = 5; tau^2 estimator: REML)
tau^2 (estimated amount of total heterogeneity): 0.0007 (SE = 0.0010)
tau (square root of estimated tau^2 value): 0.0268
I^2 (total heterogeneity / total variability): 92.53%
H^2 (total variability / sampling variability): 13.38

Test for Heterogeneity:
Q(df = 4) = 57.6540, p-val < .0001

Model Results:
```plaintext
estimate  se   zval   pval   ci.lb   ci.ub
-0.0205  0.0189 -1.0834  0.2786 -0.0575  0.0166
```
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Random-Effects Model (k = 4; tau^2 estimator: REML)
```
logLik deviance AIC  BIC  AICc
1.9396   -3.8792   0.1208   -1.6820   12.1208
```
tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.0004)
tau (square root of estimated tau^2 value): 0
I^2 (total heterogeneity / total variability): 0.00%
H^2 (total variability / sampling variability): 1.00

Test for Heterogeneity:
Q(df = 3) = 5.3948, p-val = 0.1451

---

**Figure S5.** Association between DBP and total brain volume from cross-sectional studies. A. Forest plots; B. Sensitivity Analysis; trim and fill.
Model Results:

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.0010</td>
<td>0.0010</td>
<td>-1.0361</td>
<td>0.3002</td>
<td>-0.0030</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Signif. codes: 0 "***" 0.001 "**" 0.01 "*" 0.05 "." 0.1 " " 1

Sensitivity Analysis

Estimated number of missing studies on the right side: 1 (SE = 1.6103)

Random-Effects Model (k = 5; tau^2 estimator: REML)

\[ \text{tau}^2 \text{ (estimated amount of total heterogeneity): 0 (SE = 0.0004)} \]
\[ \text{tau} \text{ (square root of estimated tau}^2 \text{ value): 0} \]
\[ \text{I}^2 \text{ (total heterogeneity / total variability): 0.00\%} \]
\[ \text{H}^2 \text{ (total variability / sampling variability): 1.00} \]

Test for Heterogeneity:

\[ Q(\text{df} = 4) = 10.4280, \ p\text{-val} = 0.0338 \]

Model Results:

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.0010</td>
<td>0.0010</td>
<td>-1.0174</td>
<td>0.3090</td>
<td>-0.0030</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Signif. codes: 0 "***" 0.001 "**" 0.01 "*" 0.05 "." 0.1 " " 1

Random-Effects Model (k = 3; tau^2 estimator: REML)

\[ \text{logLik} \quad \text{deviance} \quad \text{AIC} \quad \text{BIC} \quad \text{AICc} \]
\[ -2.7216 \quad 5.4432 \quad 9.4432 \quad 6.8295 \quad 21.4432 \]
\[ \text{tau}^2 \text{ (estimated amount of total heterogeneity): 0.2601 (SE = 0.6657)} \]
\[ \text{tau} \text{ (square root of estimated tau}^2 \text{ value): 0.5100} \]
\[ \text{I}^2 \text{ (total heterogeneity / total variability): 39.31\%} \]
\[ \text{H}^2 \text{ (total variability / sampling variability): 1.65} \]

Test for Heterogeneity:

\[ Q(\text{df} = 2) = 2.7519, \ p\text{-val} = 0.2526 \]

Figure S6. Association between SBP variability and total brain volume from longitudinal studies. A. Forest plots; B. Sensitivity Analysis; trim and fill.
Model Results:

\[
\begin{array}{cccccc}
\text{estimate} & \text{se} & \text{zval} & \text{pval} & \text{ci.l} \text{b} & \text{ci.u} \text{b} \\
-0.3862 & 0.4342 & -0.8895 & 0.3738 & -1.2371 & 0.4648 \\
\end{array}
\]

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Sensitivity Analysis

Estimated number of missing studies on the right side: 2 (SE = 1.4881)
Random-Effects Model (k = 5; \(\tau^2\) estimator: REML)
\(\tau^2\) (estimated amount of total heterogeneity): 0.1990 (SE = 0.4248)
\(\tau\) (square root of estimated \(\tau^2\) value): 0.4461
\(I^2\) (total heterogeneity / total variability): 32.73%
\(H^2\) (total variability / sampling variability): 1.49

Test for Heterogeneity:
\[Q(\text{df} = 4) = 5.7247, p\text{-val} = 0.2207\]

Model Results:

\[
\begin{array}{cccccc}
\text{estimate} & \text{se} & \text{zval} & \text{pval} & \text{ci.l} \text{b} & \text{ci.u} \text{b} \\
-0.0490 & 0.3470 & -0.1412 & 0.8877 & -0.7290 & 0.6310 \\
\end{array}
\]

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Random-Effects Model (k = 3; \(\tau^2\) estimator: REML)
\[
\begin{array}{cccccc}
\text{logLik} & \text{deviance} & \text{AIC} & \text{BIC} & \text{AICc} \\
\end{array}
\]

\(\tau^2\) (estimated amount of total heterogeneity): 0.1079 (SE = 1.2247)
\(\tau\) (square root of estimated \(\tau^2\) value): 0.3285
\(I^2\) (total heterogeneity / total variability): 6.96%
\(H^2\) (total variability / sampling variability): 1.07

Test for Heterogeneity:

Figure S7. Association between DBP variability and total brain volume from longitudinal studies. A. Forest plots; B. Sensitivity Analysis; trim and fill.
Q(df = 2) = 1.2944, p-val = 0.5235

Model Results:

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>z val</th>
<th>p val</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.1526</td>
<td>0.3365</td>
<td>-0.4536</td>
<td>0.6501</td>
<td>-0.8121</td>
<td>0.5069</td>
</tr>
</tbody>
</table>

Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Sensitivity Analysis

Estimated number of missing studies on the left side: 0 (SE = 1.4967)
Random-Effects Model (k = 3; tau^2 estimator: REML)
tau^2 (estimated amount of total heterogeneity): 0.1079 (SE = 1.2247)
tau (square root of estimated tau^2 value): 0.3285
I^2 (total heterogeneity / total variability): 6.96%
H^2 (total variability / sampling variability): 1.07

Test for Heterogeneity:
Q(df = 2) = 1.2944, p-val = 0.5235

Model Results

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>z val</th>
<th>p val</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.1526</td>
<td>0.3365</td>
<td>-0.4536</td>
<td>0.6501</td>
<td>-0.8121</td>
<td>0.5069</td>
</tr>
</tbody>
</table>

Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Hippocampal volume (HCV)

<table>
<thead>
<tr>
<th>logLik</th>
<th>deviance</th>
<th>AIC</th>
<th>BIC</th>
<th>AICc</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6525</td>
<td>-1.3049</td>
<td>2.6951</td>
<td>0.0813</td>
<td>14.6951</td>
</tr>
</tbody>
</table>

tau^2 (estimated amount of total heterogeneity): 0.0211 (SE = 0.0310)
tau (square root of estimated tau^2 value): 0.1453
I^2 (total heterogeneity / total variability): 83.80%
H^2 (total variability / sampling variability): 6.17

Test for Heterogeneity:
Q(df = 2) = 14.1697, p-val = 0.0008

Figure S8. Association between DBP and hippocampal volume from cross-sectional studies. A. Forest plots; B. Sensitivity Analysis; trim and fill.

Random-Effects Model (k = 3; tau^2 estimator: REML)

logLik  deviance  AIC   BIC   AICc
0.6525  -1.3049  2.6951  0.0813 14.6951
tau^2 (estimated amount of total heterogeneity): 0.0211 (SE = 0.0310)
tau (square root of estimated tau^2 value): 0.1453
I^2 (total heterogeneity / total variability): 83.80%
H^2 (total variability / sampling variability): 6.17

Test for Heterogeneity:
Q(df = 2) = 14.1697, p-val = 0.0008
Model Results:

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.1193</td>
<td>0.1012</td>
<td>-1.1787</td>
<td>0.2385</td>
<td>-0.3177</td>
<td>0.0791</td>
</tr>
</tbody>
</table>

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Sensitivity Analysis

Estimated number of missing studies on the left side: 2 (SE = 1.4881)
Random-Effects Model (k = 5; tau^2 estimator: REML)
tau^2 (estimated amount of total heterogeneity): 0.0432 (SE = 0.0413)
tau (square root of estimated tau^2 value): 0.2078
I^2 (total heterogeneity / total variability): 90.88%
H^2 (total variability / sampling variability): 10.97

Test for Heterogeneity:
Q(df = 4) = 34.1568, p-val < .0001

Model Results:

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.2500</td>
<td>0.1094</td>
<td>-2.2854</td>
<td>0.0223</td>
<td>-0.4644</td>
<td>-0.0356</td>
</tr>
</tbody>
</table>

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Random-Effects Model (k = 3; tau^2 estimator: REML)

<table>
<thead>
<tr>
<th>logLik</th>
<th>deviance</th>
<th>AIC</th>
<th>BIC</th>
<th>AICc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2400</td>
<td>-2.4800</td>
<td>1.5200</td>
<td>-1.0937</td>
<td>13.5200</td>
</tr>
</tbody>
</table>

tau^2 (estimated amount of total heterogeneity): 0.0161 (SE = 0.0177)
tau (square root of estimated tau^2 value): 0.1270

Model Results:

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0810</td>
<td>0.0767</td>
<td>1.0554</td>
<td>0.2912</td>
<td>-0.0694</td>
<td>0.2313</td>
</tr>
</tbody>
</table>

Figure S9. Association between DBP and hippocampal volume from cross-sectional studies. A. Forest plots; B. Sensitivity Analysis; trim and fill.
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Random-Effects Model (k = 3; tau^2 estimator: REML)

<table>
<thead>
<tr>
<th>logLik</th>
<th>deviance</th>
<th>AIC</th>
<th>BIC</th>
<th>AICc</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.3265</td>
<td>-14.6529</td>
<td>-10.6529</td>
<td>-13.2667</td>
<td>1.3471</td>
</tr>
</tbody>
</table>

tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.0000)
tau (square root of estimated tau^2 value): 0
I^2 (total heterogeneity / total variability): 0.00%
H^2 (total variability / sampling variability): 1.00

Test for Heterogeneity:
Q(df = 2) = 0.9932, p-val = 0.6086

Model Results:

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>z val</th>
<th>p val</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.0063</td>
<td>0.0027</td>
<td>-2.3603</td>
<td>0.0183</td>
<td>-0.0116</td>
<td>-0.0011</td>
</tr>
</tbody>
</table>

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Sensitivity Analysis
Estimated number of missing studies on the right side: 2 (SE = 1.4881)

Random-Effects Model (k = 5; tau^2 estimator: REML)
tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.0000)
tau (square root of estimated tau^2 value): 0
I^2 (total heterogeneity / total variability): 0.00%
H^2 (total variability / sampling variability): 1.00

Test for Heterogeneity:
Q(df = 4) = 2.4687, p-val = 0.6502

Model Results:

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>z val</th>
<th>p val</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.0050</td>
<td>0.0024</td>
<td>-2.0518</td>
<td>0.0402</td>
<td>-0.0098</td>
<td>-0.0002</td>
</tr>
</tbody>
</table>

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Figure S10. Association between SBP variability and hippocampal volume from longitudinal studies. A. Forest plots; B. Sensitivity Analysis; trim and fill.
**Figure S11.** Association between DBP variability and hippocampal volume from longitudinal studies. A. Forest plots; B. Sensitivity Analysis; trim and fill.

### Random-Effects Model (k = 3; tau^2 estimator: REML)

<table>
<thead>
<tr>
<th>logLik</th>
<th>deviance</th>
<th>AIC</th>
<th>BIC</th>
<th>AICc</th>
</tr>
</thead>
<tbody>
<tr>
<td>-6.1862</td>
<td>-12.3723</td>
<td>-8.3723</td>
<td>-10.9860</td>
<td>3.6277</td>
</tr>
</tbody>
</table>

- \( \tau^2 \) (estimated amount of total heterogeneity): 0 (SE = 0.0001)
- \( \tau \) (square root of estimated \( \tau^2 \) value): 0
- I^2 (total heterogeneity / total variability): 0.00%
- H^2 (total variability / sampling variability): 1.00

**Test for Heterogeneity:**

\[ Q(df = 2) = 0.7764, \ p-val = 0.6783 \]

**Model Results:**

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0017</td>
<td>0.0029</td>
<td>0.5731</td>
<td>0.5666</td>
<td>-0.0040</td>
<td>0.0073</td>
</tr>
</tbody>
</table>

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Estimated number of missing studies on the left side: 2 (SE = 1.4881)

### Random-Effects Model (k = 5; tau^2 estimator: REML)

- \( \tau^2 \) (estimated amount of total heterogeneity): 0 (SE = 0.0001)
- \( \tau \) (square root of estimated \( \tau^2 \) value): 0
- I^2 (total heterogeneity / total variability): 0.00%
- H^2 (total variability / sampling variability): 1.00

**Test for Heterogeneity:**

\[ Q(df = 4) = 1.6569, \ p-val = 0.7985 \]

**Model Results:**

<table>
<thead>
<tr>
<th>estimate</th>
<th>se</th>
<th>zval</th>
<th>pval</th>
<th>ci.lb</th>
<th>ci.ub</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0010</td>
<td>0.0028</td>
<td>0.3562</td>
<td>0.7217</td>
<td>-0.0045</td>
<td>0.0065</td>
</tr>
</tbody>
</table>

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
Figure S12. The Forest plots show the association between SBP and white matter lesions in elderly below or above ~75 years. Given the small number of studies these results should be interpreted with caution. However, the pattern of results appears to indicate that effects are consistent below in younger individuals (mean weighted age ~72 years). In contrast, while still significant in older individuals (mean weighted age 80.6 years) the effect appears much reduced in this age group.

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*BMJ(Clinical Res. ed.)* **2013**, 347, f4600.

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