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.
### Table S2. Characteristics of the selected studies.

| Exposure (BP) | Score |
|---------------|-------|
| 1. Location of BP Measurement is reported | 7.0 |
| 2. Position when BP Measurement parameters are reported | 0.0 |
| 3. Resting period before BP measurement is reported | 0.0 |
| 4. Number of BP readings is reported | 0.0 |
| 5. Time intervals between BP readings is reported | 0.0 |
| 6. Hypertension was defined by two criteria | 0.0 |

### Comparability (confounder) | Score |
|----------------------------|-------|
| 1. Confounders controlled in analyses | 1.0 |

### Outcome | Score |
|----------------------|-------|
| 1. Measurement of brain volume/segmentation | 0.0 |
| Study            | Study Design                  | N   | Age M (SD) | Sex (% female) | BP Methods | SBP M (SD) | DBP M (SD) | %HT | %AHT | Brain Region | Magnet / Segmentation | Covariables                                      |
|------------------|-------------------------------|-----|------------|----------------|------------|------------|------------|------|------|--------------|------------------------|------------------------------------------------|
| Alkan et al 2019[36] | Cross-sectional               | 164 | 60.1 (7.8) | 59.1           | Occasional | 129.6 (16.9) | 79.5 (19.2) |      | 54.5 | NR           | 1.5 T/Semi-automated    | WMLS | Age, education, BMI, WC, cholesterol, FBG, triglyceride, HDL-C, LDL-C, SBP, DBP, and number of MetS |
| Allan et al 2015[17] | Cross-sectional and Longitudinal | 190 | 69.3 (5.4) | 18.4           | Occasional | 152.6 (1.3) | 82.4 (1.1)  | 52.2 | NR   | WMLS, HCV   | 1.5 T/Semi-automated    | 3 T/Semi-automated | Age and sex                                      |
| Bender et al 2012[25] | Cross-sectional               | 22  | 49.0 (17.3) | 0              | Occasional | 122.3 (10.2) | 75.6 (8.6)  | 0    | 0    | HCV, IP FC, pFW M | 4 T/Manual            | NR | Age, sex, treatment status     |
| Brickman et al 2010[27] | Cross-sectional             | 50  | 50.4 (12.9) | 100            | Occasional | 119.6 (12.8) | 73.1 (6.5)  | 100  | 65.5 |                  | 1.5 T/Manual            | NR | Age, sex, education, and brain atrophy       |
| Burns et al 2005[27] | Cross-sectional             | 88  | 76.9 (8.2)  | 70.5           | Occasional | 135.8 (19.2) | 72.2 (10.3) | 39.8 | NR   | WMLS         | 1.5 T/Semi-automated    | Age, sex, education, and brain atrophy       |
| Cherbuin et al 2015[37] | Cross-sectional              | 144 | 70.4 (1.4)  | 0              | Occasional | 150.3 (19.9) | 82.4 (10)   | 51.4 | NR   | WM/GM regions | Semi-automated (VBM) | Age, sex, BMI, depression, and alcohol consumption |
| DeCarli et al 1995[38] | Cross-sectional             | 51  | 52 (20)    | 49.0           | Occasional | 124 (14)   | 78 (9)      | 0    | NR   | WMLS         | 0.5 T/NR               | Age and education       |
| De Jong et al 2014[39] | Cross-sectional and Longitudinal | 368 | 75.5 (5.3) | 59.0           | Occasional | 143.1 (19.2) | 74.5 (9.8)  | 54.0 | 59.0 | MTL, BG      | 1.5 T/Semi-automated    | Age, sex, and ICV       |
| Den Heijer et al 2005[2] | Cross-sectional and Longitudinal | 511 | 73.4 (8)   | 49.1           | Occasional | 145.8 (20.3) | 76.5 (11.6) | 54.0 | NR   | HCV, Amygdala | 1.5 T/Manual            | Age, sex and CVD factors          |
| Den Heijer et al 2012[29] | Longitudinal                | 518 | 73.5 (7.9) | 0              | Occasional | 145.9 (20.6) | 76.7 (11.5) | 53.0 | 39.0 | lifte and right HCV | 1.5 T/Semi-automated    | Age, sex                     |
| Dickie et al 2016[40] | Cross-sectional             | 681 | 72.7 (0.7) | 47.0           | Occasional | 146 (18)   | 79 (9)      | 48.2 | NR   | WMLS         | 1.5 T/Semi-automated    | Sex, BMI, and CVD history |
| Study                     | Study Design | N   | Age M (SD) | Sex (% female) | BP Methods | SBP M (SD) | DBP M (SD) | %HT | %AHT | Brain Region | Magnet / Segmentation | Covariables                          |
|--------------------------|--------------|-----|------------|----------------|-------------|------------|------------|------|------|--------------|------------------------|----------------------------------------|
| Firbank et al 2007[5]    | Cross-sectional | 41  | 76 (4)     | 31.7           | Occasional  | 133 (12)  | 73 (8)     | 0    | 0    | Semiautomated | WML, TBV                 |                                        |
| Gattringer et al 2012[3] | Cross-sectional | 287 | 66.6 (6.6) | 49.8           | Occasional  | 141.6 (21.8) | 85.3 (9.7) | 52.3 | NR   | 1.5 T/ Semi-automated | WML, TBV, HCV | Age                                    |
| Gianaros et al 2006[41]  | Longitudinal  | 76  | 61.3 (5)   | 0              | Occasional  | 132.4 (15.3) | 79.3 (8.7) | 38.0 | NR   | Regional GMV | 1.5 T/ Semi-automated | Age and TBV                           |
|                          |              | 58  | 59.9 (5.1) | 100            |             | 128.8 (15) | 76.6 (9.3) | 22.0 |      |              | NR/ Semi-automated | Age, sex, education, APOE4 allele    |
| Glodzik et al 2014[24]   | Cross-sectional | 77  | 63.4 (9.4) | 46.0           | Occasional  | NR         | NR         | 39.0 | 0    |              | 1.5 T Manual/ TR blinded to information |                                        |
| Goldstein et al 2002[42] | Longitudinal  | 155 | 66.2 (6)   | 53.9           | ABP         | NR         | NR         | 0    | 0    |              | TBV, lateral Ventricles           |                                        |
| Goldstein et al 2005[18] | Longitudinal  | 121 | 66.2 (6)   | 57.0           | Occasional  | 119.3 (13.8) | 72.2 (8.9) | 5.8  | NR   |              | 1.5 T Manual/ TR blinded to information | Age                                    |
| Habes et al 2016[43]     | Cross-sectional | 2367| 52.4 (13.7)| 56.7           | Occasional  | 127.3 (17.6) | NR         | NR   | 32.7 | WMLS         | NR/ Semi-automated | Age, sex and education                  |
| Hajjar et al 2010[9]     | Cross-sectional | 43  | 68 (1)     | 56.0           | Occasional  | 129 (2)    | 66 (1)     | 51.0 | 93.0 | GMV/WM       | 3 T/ Semi-automated | Age, sex, race, BMI, and AHT medication |
| Haring et al 2019[23]    | Longitudinal  | 558 | 78.3 (3.6) | 100            | Variability | 122 (1)    | 73 (7)     | 48.0 | NR   | Regional GMV | 3 T/ Semi-automated | Age, education, APOE4 allele          |
| Hoogendam et al 2012[20] | Longitudinal  | 3962| 60.1 (8.5) | 54.4           | Occasional  | 135.3 (19.5) | 81.8 (10.7) | 53.9 | 0    |              | 1.5 T/ Semi-automated | Age, sex, and ICV                             |
| Ikram et al 2008[6]      | Cross-sectional | 490 | 73.4 (7.9) | 50.8           | Occasional  | NR         | NR         | 51.0 | 0    | TBV, GMV, WMV | 1.5 T/ Manual/ TR blinded to information | Age and sex.                             |
| Jeerakathil et al 2004[44]| Longitudinal  | 1814| 53 (9.5)   | 53.0           | Occasional  | 124.5 (18.2) | NR         | 18.3 | 0    | WMLS         | 1 T/ Manual/ TR blinded to information | Age and sex                            |
| Kern et al 2017[45]      | Cross-sectional | 64  | 72 (7)     | 67.2           | Occasional  | NR         | NR         | 32.8 | 34.4 | Regional GMV | 1.5 T/ Semi-automated | Age, sex, education and general intellectual ability |
| Study                  | Study Design      | N  | Age (SD) | Sex (% female) | BP Methods | SBP M (SD) | DBP M (SD) | %HT | %AHT | Brain Region | Magnet / Segmentation | Covariables                                                                 |
|-----------------------|-------------------|----|----------|----------------|------------|------------|------------|------|------|--------------|------------------------|-----------------------------------------------------------------------------|
| Kobuch et al 2020[46] | Cross-sectional   | 54 | 78.8 (1.5)| 31.5          | Occasional | NR         | NR         | NR   | NR   | Regional GMV| 3 T/Semi-automated (VBM) | Age, sex and ICV                                                          |
| Korf et al 2004[31]   | Longitudinal      | 543| 81.6 (5.0)| 0             | Occasional | NR         | NR         | 25.8 | NR   | HCV          | 1.5 T/Manual            | Age, education, ApoE, smoking, alcohol, and dementia.                        |
| Cross-sectional and Longitudinal |                 | 441| 81.6 (5.0)| 0             | Occasional | 120.2 (13.7)| 78.4 (9.5) | 16.0 | 2.0  | WMLS, TBV, HCV| 3 T/Semi-automated       | Sex, APOE ε4 status, AHT medication, and BP at 69 years of age.            |
| Lane et al 2019[13]   | Cross-sectional and Longitudinal | 441| 69.0     | 49.0          | 120.2 (13.7)| 78.4 (9.5) | 16.0 | 2.0  | WMLS, TBV, HCV| 3 T/Semi-automated       | Age, sex, and race.                                                       |
| Launer et al 2015     | Cross-sectional   | 680| 50.3 (3.5)| 52.2          | Occasional | 139.9 (1.5)| 79.5 (0.9) | 32.2 | NR   | WMLS, TBV   | 3 T/Semi-automated       | Age, sex, education, CVD factors                                           |
| Mahinradet et al 2019[47] | Longitudinal ral | 144| 56 (4)   | 42.0          | Occasional | 107 (10)  | 65 (10)   | 48.6 | 30   | WMLS        | 3 T/Semi-automated       | Age within this narrow age range sample.                                    |
| McNeil et al 2018[16] | Cross-sectional   | 227| 64.5 (0.8)| 52.0          | Occasional | 139.9 (1.5)| 79.5 (0.9) | 32.2 | NR   | WMLS        | 1.5 T/Semi-automated     | Age, sex, education, CVD factors                                           |
| Muller et al 2014[30] | Longitudinal      | 4057| 50 (6)  | 59.0          | Occasional | 142 (13)  | 74 (6)    | 34.0 | 6.0  | WMLS, TBV, GMV| 1.5 T/Semi-automated     | Age, sex, education, and late-life CVD.                                     |
| Muller et al 2016[48] | Longitudinal      | 1348| 50 (6)  | 58.0          | Occasional | NR         | NR         | 35.0 | 0    | WMLS, TBV, GMV| 1.5 T/Semi-automated     | Age, sex, and education                                                   |
| Nation et al 2016[21] | Longitudinal      | 549| 59.6 (2.7)| 53.2          | Occasional | 124 (16)  | 75 (9)    | 37.9 | 0    | WMLS, TBV, HCV| 1.5 T/Semi-automated     | Age, sex, education, smoking and histories of CVD and cerebral vascular diseases |
| Paganin-Hill et al 2019[28] | Longitudinal      | 97 | 92.4 (0.3)| 60            | ABP        | 142 (1.5) | 71 (1)    | 65.0 | NA   | WMLS        | 3 T/Semi-automated       | Age, sex, education, smoking and histories of CVD and cerebral vascular diseases |
| Pase et al 2016[22]   | Cross-sectional   | 332| 62.9 (10.2)| 54.0          | IDSBP      | 134 (19)  | 76 (10)   | 38.7 | 35.0 | WMLS, TBV   | 1 T or 1.5 T/NR           | Age, sex, and age                                                        |
| Study | Study Design | N   | Age (SD) | Sex (% female) | BP Methods | SBP (SD) | DBP (SD) | %HT | %AHT | Brain Region | Magnet/Segmentation | Covariables |
|-------|--------------|-----|----------|----------------|------------|----------|----------|------|------|--------------|---------------------|-------------|
| Power et al 2016[49] | Cross-sectional and Longitudinal | 1678 | 52.0 | 61.0 | Occasional | 130 (5.9) | 66 (3.6) | 23.0 | 72.0 | Brain lobes | 3 T/Semi-automated | Age, sex, race, education, ICV, BMI, DM, cholesterol, and smoking status |
| Sabayan et al 2013[4] | Longitudinal | 553 | 74.9 (3.2) | 43.6 | Variability | 156.1 (16.4) | 85.1 (7.3) | 63.1 | NR | GMV, WM, HCV | 1.5 T/Semi-automated | Average BP and CVD factors |
| Schaare et al 2019[50] | Cross-sectional | 423 | 27.7 (5.3) | 41.8 | Occasional | 123.2 (12.2) | 73.4 (8.5) | 11.0 | 0 | Regional GMV | 3 T/Semi-automated | Age, sex, and ICV |
| Scott et al 2015[32] | Cross-sectional | 150 | 73.7 (6.3) | 48.7 | Occasional | 136 (16) | 75 (10) | 44.0 | NR | WMLS | 3 T/NR | |
| Spartano et al 2016[51] | Longitudinal | 1094 | 40 (9) | 53.9 | Exercise | 166 (25.0) | 74 (9) | 28.3 | 17.7 | TBV | 1.5 T/NR | Age, sex, time between examination cycle and MRI, smoking, DM, APOE e4 genotype status, use of AHT medication, and serum homocysteine |
| Suzuki et al 2017[26] | Cross-sectional | 1559 | 62.6 (7) | 52.0 | Occasional | 125.6 (9.5) | 74.5 (7.1) | 0 | 0 | TBV, GMV, WMV | 3 T/Semi-automated | Age, sex, education, BMI, and history of smoking, DM and CVD |
| Taki et al 2004[52] | Cross-sectional | 769 | 47.4 (13.5) | 53.8 | Occasional | NR | NR | 11.9 | 82.0 | Regional GMV | 0.5 T/Semi-automated | Sex, ICV, SBP, and BMI |
| Taki et al 2013[53] | Longitudinal | 381 | 51.2 (11.8) | 59.0 | Occasional | NR | NR | NR | NR | Regional GMV | 0.5 T/Semi-automated | |
| Trotman et al 2019[11] | Cross-sectional | 40 | 19.1 (0.2) | 100 | Reactivity | 122 (11.7) | 77 (8.6) | NR | NR | HCV, Amygdala, Insula | 3 T/Semi-automated | Age, ICV, SES, and BMI |
| vanVelsen et al 2013[7] | Cross-sectional | 1022 | 68.4 (7.3) | 52.3 | Occasional | 144.5 (18.6) | 80.3 (10.3) | 47.4 | 0 | Cortical thickness | 1.5 T/Semi-automated | Age and sex. |
| Verhaaren et al 2013[54] | Cross-sectional | 665 | 61.6 (5) | 52.0 | Occasional | 138 (19) | 78 (10) | 25.9 | 22.0 | WMLS | 1.5 T/Semi-automated | Age, sex, and ICV, CVD factors |
| Study                          | Study Design          | N     | Age M (SD) | Sex (% female) | BP Methods | SBP M (SD) | DBP M (SD) | %HT | %AHT | Brain Region | Magnet / Segmentation | Covariables                                                                 |
|-------------------------------|-----------------------|-------|------------|----------------|------------|------------|------------|------|------|--------------|----------------------------|----------------------------------------------------------------------------|
| Wardlaw et al 2014[35]       | Cross-sectional       | 881   | 72.5 (0.7) | 52.0           | Occasional | 120.2 (13.7) | 78.4 (9.5) | 49.0 |      | NR           | 1.5 T/ Semi-automated       | WMLS                                                                      |
| White et al 2011[34]         | Longitudinal          | 72    | 82.1 (3.9) | 56.9           | Occasional | 122 (1.3)   | 73 (7)     | 70   | 64.0 | WMLS         | 3 T/ Semi-automated         | Age and LDL cholesterol levels, Sex                                     |
| Wiseman et al 2004[8]        | Cross-sectional       | 154   | 77.2 (3.7) | 78.6           | Occasional | 150 (16)    | 80 (9)     | 66.9 |      | 16.2         | TBV, HCV                    | 1.5 T/ Semi-automated         | Age and ICV                                                               |
| Wolfson et al 2013[33]       | Cross-sectional and Longitudinal | 67 | 81.7 (3.9) | 61.0           | ASBP       | 138 (14)    | 69 (7)     | NR   | 69.0 | WMLS         | 3 T/ Semi-automated         | Age, sex, and BMI or education                                           |
| Yano et al 2017[10]          | Longitudinal          | 547   | 25.6 (3.4) | 53.9           | Variability | 123.2 (12.2) | 73.4 (8.5) | 51.8 |      | 21.2         | TBV, GMV, WMV, HCV          | 3 T/ Semi-automated         |

M = mean; SD = standard deviation; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; ASBP= ambulatory systolic blood pressure; ABP = ambulatory blood pressure; WMLS = White matter lesions; TBV = total brain volume; GMV= grey matter volume; WMV = white matter volume; HCV = Hippocampal volume; ICV = Intracranial volume; IPFC= lateral prefrontal cortex, pFWM = prefrontal white matter. CVD= Cardiovascular disease; Hypertension = HT; ATH = Antihypertensive; BMI = body mass index; DM = DM mellitus; WC = waist circumference, FBG = fasting blood glucose; APOE e4= Apolipoprotein E ; HDL-C= High-density lipoprotein cholesterol; LDL-C= low density lipoprotein-cholesterol, MetS= Metabolic syndrome; SES= socioeconomic status; T = tesla.

Table S3. Methodological quality of studies.
Hajjar et al 2010[9] 8.0 /10.5 (81%) High
Haring et al 2019[23] 9.0 /10.5 (85.7%) High
Hoogendam et al 2012[20] 7.0 /10.5 (66.7%) Moderate
Ikram et al 2008[6] 5.5 /10.5 (52.4%) Moderate
Jeerakathil et al 2004[44] 3.0 /10.5 (28.6%) Low
Kern et al 2017[45] 9.0 /10.5 (85.7%) High
Kobuch et al 2020[46] 5.5 /10.5 (52.4%) Moderate
Korf et al 2004[31] 3.0 /10.5 (28.6%) Low
Lane et al 2019[13] 9.0 /10.5 (85.7%) High
Launer et al 2015[14] 6.5 /10.5 (61.9%) Moderate
Mahinrad et al 2019[47] 10.0 /10.5 (95.2%) High
McNeil et al 2018[16] 6.5 /10.5 (61.9%) Moderate
Muller et al 2014[30] 6.0 /10.5 (57.1%) Moderate
Muller et al 2016[48] 5.0 /10.5 (47.6%) Moderate
Nation et al 2016[21] 8.0 /10.5 (76.2%) High
Paganini-Hill et al 2019[28] 4.0 /10.5 (38.1%) Low
Pase et al 2016[22] 8.0 /10.5 (76.2%) High
Power et al 2016[49] 5.0 /10.5 (47.6%) Moderate
Sabayan et al 2013[4] 5.0 /10.5 (47.6%) Moderate
Schaare et al 2019[50] 10.0 /10.5 (95.2%) High
Scott et al 2015[32] 2.0/10.5 (19%) Low
Spartano et al 2016[51] 4.0 /10.5 (38.1%) Low
Suzuki et al 2017[26] 9.0 /10.5 (85.7%) High
Taki et al 2004[52] 4.5 /10.5 (42.9%) Moderate
Taki et al 2013[53] 5.5 /10.5 (52.4%) Moderate
Trotman et al 2019[11] 2.5 /10.5 (23.8%) Low
Tsao et al 2016[19] 6.0 /10.5 (57.1%) Moderate
vanVelsen et al 2013[7] 5.0 /10.5 (47.6%) Moderate
Verhaaren et al 2013[54] 8.5 /10.5 (81.0%) High
Wardlaw et al 2014[35] 5.0 /10.5 (47.6%) Moderate
White et al 2011[34] 6.5 /10.5 (61.9%) Moderate
Wiseman et al 2004[8] 4.5 /10.5 (42.9%) Moderate
Wolfson et al 2013[33] 9.0 /10.5 (85.7%) High
Yano et al 2017[10] 9.5 /10.5 (90.5%) High

Meta-analysis results

White matter lesions volume (WMLS)

![Figure S1](image-url).

**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)

| logLik | deviance | AIC | BIC | AICc |
|-------|----------|-----|-----|------|
| 3.6850 | -7.3700  | -3.3700 | -3.7865 | 0.6300 |
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:

| estimate | se   | zval  | pval   | ci.lb | ci.ub |
|----------|------|-------|--------|-------|-------|
| 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)
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:

| estimate | se   | zval  | pval   | ci.lb | ci.ub |
|----------|------|-------|--------|-------|-------|
| 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.
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:

| estimate | se  | zval | pval | ci.lb | ci.ub |
|----------|-----|------|------|-------|-------|
| 0.0138   | 0.0138 | 0.9984 | 0.3181 | -0.0133 | 0.0408 |

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:

| estimate | se  | zval | pval | ci.lb | ci.ub |
|----------|-----|------|------|-------|-------|
| 0.0138   | 0.0138 | 0.9984 | 0.3181 | -0.0133 | 0.0408 |

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:

| estimate | se    | zval   | pval   | ci.lb | ci.ub |
|----------|-------|--------|--------|-------|-------|
| 0.0725   | 0.0475| 1.5283 | 0.1264 | -0.0205 | 0.1656 |

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

| estimate | se    | zval   | pval | ci.lb | ci.ub |
|----------|-------|--------|------|-------|-------|
| 0.1081   | 0.0435| 2.4882 | 0.0128| 0.0230| 0.1933 |

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 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)

logLik deviance AIC  BIC  AICc
2.6975 -5.3950  -1.3950  -3.1977  10.6050

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:
| 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:
| 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:

\[
\begin{array}{cccccc}
\text{estimate} & \text{se} & \text{z val} & \text{p val} & \text{ci. lb} & \text{ci. ub} \\
-0.0010 & 0.0010 & -1.0361 & 0.3002 & -0.0030 & 0.0009 \\
\end{array}
\]

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

Sensitivity Analysis

Estimated number of missing studies on the right side: 1 (SE = 1.6103)
Random-Effects Model (k = 5; tau^2 estimator: REML)
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:

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

Model Results:

\[
\begin{array}{cccccc}
\text{estimate} & \text{se} & \text{z val} & \text{p val} & \text{ci. lb} & \text{ci. ub} \\
-0.0010 & 0.0010 & -1.0174 & 0.3090 & -0.0030 & 0.0009 \\
\end{array}
\]

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

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

\[
\begin{array}{cccccc}
\text{logLik} & \text{deviance} & \text{AIC} & \text{BIC} & \text{AICc} \\
-2.7216 & 5.4432 & 9.4432 & 6.8295 & 21.4432 \\
\end{array}
\]

tau^2 (estimated amount of total heterogeneity): 0.2601 (SE = 0.6657)
tau (square root of estimated tau^2 value): 0.5100
I^2 (total heterogeneity / total variability): 39.31%
H^2 (total variability / sampling variability): 1.65

Test for Heterogeneity:

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

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

```
estimate  se     zval  pval    cl.lb    cl.ub
-0.3862  0.4342  -0.8895  0.3738  -1.2371  0.4648
```

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(df = 4) = 5.7247, p-val = 0.2207

**Model Results:**

```
estimate  se     zval  pval    cl.lb    cl.ub
-0.0490  0.3470  -0.1412  0.8877  -0.7290  0.6310
```

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

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

```
logLik  deviance  AIC  BIC  AICc
-3.6756  7.3513  11.3513  8.7376  23.3513
```
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:**

| estimate | se    | z val | p val | ci lb  | ci ub   |
|----------|-------|-------|-------|--------|---------|
| -0.1526  | 0.3365| -0.4536| 0.6501| -0.8121| 0.5069  |

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)

\[ \tau^2 = 0.1079 \] (SE = 1.2247)

\[ \tau = 0.3285 \]

\[ I^2 = 6.96\% \]

\[ H^2 = 1.07 \]

**Test for Heterogeneity:**

Q(df = 2) = 1.2944, p-val = 0.5235

**Model Results**

| estimate | se    | z val | p val | ci lb  | ci ub   |
|----------|-------|-------|-------|--------|---------|
| -0.1526  | 0.3365| -0.4536| 0.6501| -0.8121| 0.5069  |

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

**Hippocampal volume (HCV)**

\[ \log L = 0.6525 \]

\[ \text{deviance} = -1.3049 \]

\[ \text{AIC} = 2.6951 \]

\[ \text{BIC} = 0.0813 \]

\[ \text{AICc} = 14.6951 \]

\[ \tau^2 = 0.0211 \] (SE = 0.0310)

\[ \tau = 0.1453 \]

\[ I^2 = 83.80\% \]

\[ H^2 = 6.17 \]

**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.
Model Results:

| estimate | se   | zval  | pval  | ci.lb  | ci.ub  |
|----------|------|-------|-------|--------|--------|
| -0.1193  | 0.1012 | -1.1787 | 0.2385 | -0.3177 | 0.0791 |

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:

| estimate | se   | zval  | pval  | ci.lb  | ci.ub  |
|----------|------|-------|-------|--------|--------|
| -0.2500  | 0.1094 | -2.2854 | 0.0223 | -0.4644 | -0.0356 * |

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

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

| logLik  | deviance | AIC | BIC | AICc |
|--------|----------|-----|-----|------|
| 1.2400 | -2.4800  | 1.5200 | -1.0937 | 13.5200 |

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

Model Results:

| estimate | se   | zval  | pval  | ci.lb  | ci.ub  |
|----------|------|-------|-------|--------|--------|
| 0.0810   | 0.0767 | 1.0554 | 0.2912 | -0.0694 | 0.2313 |

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

Figure S10. Association between SBP 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)

|       | logLik | deviance | AIC   | BIC   | AICc  |
|-------|--------|----------|-------|-------|-------|
|       | 7.3265 | -14.6529 | -10.6529 | -13.2666 | 1.3471 |

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:

| estimate | se   | zval  | pval   | ci.lb | ci.ub |
|----------|------|-------|--------|-------|-------|
| -0.0063  | 0.0027 | -2.3603 | 0.0183 | -0.0116 | -0.0011  |

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:

| estimate | se   | zval  | pval   | ci.lb | ci.ub |
|----------|------|-------|--------|-------|-------|
| -0.0050  | 0.0024 | -2.0518 | 0.0402 | -0.0098 | -0.0002  |

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

|            | logLik  | deviance | AIC    | BIC     | AICc   |
|------------|---------|----------|--------|---------|--------|
|            | 6.1862  | -12.3723 | -8.3723| -10.9860| 3.6277 |

- \( \tau^2 \) (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:**

| estimate | se   | zval  | pval | ci.lb | ci.ub |
|----------|------|-------|------|-------|-------|
| 0.0017   | 0.0029| 0.5731| 0.5666| -0.0040| 0.0073 |

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)**

|            | logLik  | deviance | AIC    | BIC     | AICc   |
|------------|---------|----------|--------|---------|--------|
|            | 6.1862  | -12.3723 | -8.3723| -10.9860| 3.6277 |

- \( \tau^2 \) (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:**  
\( Q(df = 2) = 1.6569, p-val = 0.7985 \)

**Model Results:**

| estimate | se   | zval  | pval | ci.lb | ci.ub |
|----------|------|-------|------|-------|-------|
| 0.0010   | 0.0028| 0.3562| 0.7217| -0.0045| 0.0065 |

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