Supplementary Material

Associations Between Brain Volumes and Cognitive Tests with Hypertensive Burden in UK Biobank

Supplementary Methods

This section includes further information regarding variables used, how they were processed and links for further information https://www.ukbiobank.ac.uk/.

UK Biobank received ethical approval from the Research Ethics Committee (11/NW/0382). Volunteers gave informed consent for their participation.

Brain MRI

All brain MRI data were acquired on a Siemens Skyra 3 T scanner with a standard Siemens 32-channel head coil.

Cognitive tests

Further information of the cognitive function tests can be found on the UKBiobank website (https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=100026) and additional publications [1]. At baseline, there were a bespoke battery of cognitive tests administered including verbal–numerical reasoning, pairs matching and reaction time.

Verbal and numerical reasoning

A task with thirteen logic/reasoning-type questions and a two-minute time limit was labelled as ‘fluid intelligence’ in the UK Biobank protocol but is now referred to as ‘verbal-numerical reasoning’; http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20016). The maximum score is 13.
Pairs matching

A visual memory test was administered, labelled ‘pairs-matching’ ([http://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=100030](http://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=100030)). Participants were asked to memorize the positions of six card pairs, and then match them from memory while making as few errors as possible. Scores on the pairs-matching test are for the number of errors that each participant made; therefore, higher scores reflect poorer cognitive function. The Pairs matching task had two versions: 3-pair and 6-pair. We used 6-pair version for this work.

Reaction time

Participants completed a timed test of symbol matching, similar to the common card game ‘Snap’ ([http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20023](http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20023)). The score on this task was the mean response time in milliseconds across trials which contained matching pairs.

From 2016 at the imaging visit additional validated cognitive tests were administered including Matrix Pattern, Symbol-Digit Substitution tower rearranging and Trail-Making Tests (TMT) B and A. For the pairs matching, values over 30 were capped at 30 [2], and only participants who completed the task were included in the analysis (n = 641 excluded). In this work, we used TMT B – A. Subtracting TMT A from TMT B removes the individual variance in speed of response and is considered a useful tool in clinical practice for dementia [3]. Individuals who scored >250 s for TMT B were excluded (n = 27) as well as participants with a TMT B - TMT A score less than 0 (n=145) and greater than 150 s were also excluded (n=126). Compared to those who had completed the original battery of cognitive tests only 63-66% also had data for these newer cognitive tests at the imaging visit. In this work, in the main results we only
analyzed the cognitive tests from individuals who also had brain-imaging data. This was to investigate if any associations found between hypertension and brain volumes also reflected similar observations in the cognitive tests in the same people.

**Blood pressure**

Specific details of how blood pressure readings were acquired can be found under the following link: https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/Bloodpressure.pdf.

**Covariates**

Age at assessment date was recorded in whole years and gender was self-reported as male or female. Educational qualifications were self-reported, and for this study were dichotomized according to whether participants held a university/college degree. Self-reported ethnicity was grouped categorically as white or non-white. Assessment center was a multi label category consisting of the different assessment centers for the imaging visit. BMI was constructed from height and weight measurements obtained during the imaging assessment visit. Smoking status was self-reported and was dichotomized into never smoked or ever smoker (current or former). For diabetes diagnosis a combination of self-reported, hospital data were used and for hyperlipidemia self-reported information was used to define if participants had a diagnosis of these co morbidities. ‘Do not know’ and ‘Prefer not to answer’ responses for covariates were treated as missing (<1%) and was not imputed. Multicollinearity between the demographic variables was assessed using variance inflation factor (VIF) values. All variables had VIF less than 10, with the majority with VIF values less than 2 apart from two of the MRI scanner
variables. Despite the higher VIF variables of these MRI scanner variables both were included as recommended by UK Biobank and related published work [4].

REFERENCES

[1] Fawns-Ritchie C, Deary IJ (2020) Reliability and validity of the UK Biobank cognitive tests. PLoS One 15, e0231627.

[2] Hagenaars SP, Harris SE, Davies G, Hill WD, Liewald DC, Ritchie SJ, Marioni RE, Fawns-Ritchie C, Cullen B, Malik R; META-STROKE Consortium, International Consortium for Blood Pressure GWAS; SpiroMeta Consortium; CHARGE Consortium Pulmonary Group, CHARGE Consortium Aging and Longevity Group, Worrall BB, Sudlow CL, Wardlaw JM, Gallacher J, Pell J, Mcintosh AM, Smith DJ, Gale CR, Deary IJ (2016) Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank (N=112151) and 24 GWAS consortia. Mol Psychiatry 21, 1624-1632.

[3] Rasmusson DX, Zonderman AB, Kawas C, Resnick SM (1998) Effects of age and dementia on the trail making test. Clin Neuropsychol 12, 169–178.

[4] Alfaro-Almagro F, McCarthy P, Afyouni S, Andersson JLR, Bastiani M, Miller KL, Nichols TE, Smith SM (2020) Confound modelling in UK Biobank brain imaging. Neuroimage 224, 117002.
**Supplementary Table 1.** Self-reported health variables codes used for exclusion criteria on initial population

| Condition                                      | Code |
|------------------------------------------------|------|
| Dementia or Alzheimer’s disease                | 1263 |
| Parkinson’s disease                            | 1262 |
| Chronic degenerative neurological              | 1258 |
| Guillain-Barré syndrome                        | 1256 |
| Multiple Sclerosis                             | 1261 |
| Other demyelinating disease                    | 1397 |
| Stroke or ischemic stroke                      | 1081 |
| Brain cancer                                   | 1032 |
| Brain hemorrhage                               | 1491 |
| Brain/intracranial abscess                     | 1245 |
| Cerebral aneurysm                              | 1425 |
| Cerebral palsy                                 | 1433 |
| Encephalitis                                   | 1246 |
| Epilepsy                                       | 1264 |
| Head injury                                    | 1266 |
| Infections of the nervous system               | 1244 |
| Ischemic stroke                                | 1583 |
| Meningeal cancer                               | 1031 |
| Meningioma (benign)                            | 1659 |
| Meningitis                                     | 1247 |
| Motor Neuron Disease                           | 1259 |
| Neurological injury/trauma                     | 1240 |
| Spina bifida                                   | 1524 |
| Subdural hematoma                              | 1083 |
| Subarachnoid hemorrhage                        | 1086 |
| Transient ischemic attack                      | 1082 |
### Supplementary Table 2. UKBiobank Field codes for all variables used in manuscript

| Variable                      | Code                                      |
|-------------------------------|-------------------------------------------|
| **Hypertension variables**    |                                           |
| Self reported                 | Field ID 20002, Code 1065, 1072           |
| Self reported taking bp medication | 6177/6153                                |
| Age when high bp first diagnosed | 2966                                      |
| Ever told by a doctor they have high BP | 6150                                      |
| Systolic blood pressure       | 4080                                      |
| Diastolic blood pressure      | 4079                                      |
| **Neuroimaging**              |                                           |
| Total Brain Volume            | 25010                                     |
| Total Grey Matter             | 25006                                     |
| Total White Matter            | 25008                                     |
| White matter hyperintensities | 25781                                     |
| Ventricular CSF               | 25004                                     |
| Hippocampus (L+R)             | 25019/20                                  |
| Thalamus (L+R)                | 25011/12                                  |
| Caudate (L+R)                 | 25013/14                                  |
| Putamen (L+R)                 | 25015/16                                  |
| Pallidum (L+R)                | 25017/18                                  |
| Amygdala (L+R)                | 25021/22                                  |
| Accumbens (L+R)               | 25023/24                                  |
| gFA (fractional anisotropy)   | 25488-25514                               |
| gMD (mean diffusivity)        | 25515-25541                               |
| **Cognitive Tests**           |                                           |
| Symbol-Digit                  | 23324                                     |
| Matrix Reasoning              | 6373                                      |
| Verbal and Numeric Reasoning  | 20016                                     |
| Reaction Time                 | 20023                                     |
| Pairs Matching                | 399                                       |
| TMT A                         | 6348                                      |
| TMT B                         | 6350                                      |
| Tower Rearranging             | 21004                                     |
| **Confounding Variables**     |                                           |
| Education                     | 6138                                      |
| Smoking Status                | 20116                                     |
| Gender                        | 31                                        |
| Age at Assessment             | 21300                                     |
| Assessment Centre             | 54                                        |
| BMI                           | 21001                                     |
| Ethnicity                     | 21000                                     |
| Diabetes                      | Field ID 20002: Code 1220, 1222, 1223 & Field IDs 130708, 130708, 130710, 130712, 130712, 6177, 6153 |
| High Cholesterol              | Field ID 20002, Code 1473 & Field IDs 6177, 6153 |
| Head size                     | 25000                                     |
| Scanner Position X            | 25756                                     |
| Scanner Position Y            | 25757                                     |
| Scanner Position Z            | 25758                                     |
| Scanner Position              | 25759                                     |

Field IDs obtained only for imaging visit apart from Ethnicity where baseline visit information was also used
**Supplementary Table 3.** Cross-sectional characteristics of UK Biobank participants at imaging visit stratified by hypertensive state.

|                        | Normotensive (n = 14,317) | Hypertensive & No self reported (n = 8,434) | Hypertensive & self reported (n = 87,62) | n    |
|------------------------|---------------------------|---------------------------------------------|-----------------------------------------|------|
| **Demographics**       |                           |                                             |                                         |      |
| Age, y (mean (SD))     | 61.16 (7.39)              | 64.75 (7.16)                                | 65.99 (6.97)                            | 31,513|
| Gender (Male (%))      | 5,423 (37.9)              | 4314 (51.2)                                 | 5,083 (58.0)                            | 31,513|
| BMI, kg/m² (mean (SD)) | 25.35 (3.88)              | 26.73 (4.29)                                | 28.14 (4.71)                            | 31,227|
| Ethnicity (White (%))  | 13,820 (96.8)             | 8,235 (97.9)                                | 8,446 (96.7)                            | 31,429|
| Education – Degree (%) | 7,541 (53.1)              | 3,930 (47.2)                                | 3,801 (43.7)                            | 31,231|
| Assessment Centre (%)  |                           |                                             |                                         | 31,513|
| Cheadle                | 9,927 (69.3)              | 5,381 (63.8)                                | 5,909 (67.4)                            |      |
| Reading                | 1,898 (13.3)              | 784 (9.3)                                   | 1,047 (11.9)                            |      |
| Newcastle              | 2,492 (17.4)              | 2,269 (26.9)                                | 1,806 (20.6)                            |      |
| Smoking Status (Ever/Current (%)) | 5,015 (35.3) | 2,989 (35.8)                                | 3,610 (41.5)                            | 31,260|
| Diastolic Blood Pressure, mm Hg (mean (SD)) | 73.29 (7.57) | 84.44 (9.00)                                | 81.67 (10.23)                           | 31,513|
| Systolic Blood Pressure, mm Hg (mean (SD)) | 124.17 (10.09) | 152.89 (12.29)                              | 146.77 (18.04)                          | 31,513|
| Hypercholesterolemia (N (%)) | 1,818 (12.7) | 1,495 (17.7)                                | 4,290 (49.0)                            | 31,513|
| Diabetes (N (%))       | 362 (2.5)                 | 283 (3.4)                                   | 1,065 (12.2)                            | 31,513|
| Length of Hypertension, y (mean (SD)) | - | -                                       | 12.27 (9.28)                           | 7,142 |

**Brain Volumes (Voxels)**

|                           |                           |                                             |                                         |      |
|---------------------------|---------------------------|---------------------------------------------|                                         |      |
| Total Brain Volume mm³ (mean (SD)) | 1,165,040.96 (110,430.33) | 1,160,807.05 (112,612.46) | 1,160,539.44 (110,864.83) | 31,506|
| WMH mm³ (mean (SD))       | 3,249.73 (3635.94)        | 4,723.55 (4735.64)                         | 5,958.29 (5627.74)                     | 30,013|
| Ventricular CSF mm³ (mean (SD)) | 32,800.50 (14472.97)   | 36,818.68 (15601.07)                       | 39,989.74 (17,090.97)                  | 31,354|
| Grey Matter mm³ (mean (SD)) | 620,528.85 (54781.27)   | 614,022.80 (55892.68)                     | 609,705.18 (55,859.08)                 | 31,508|
| Hippocampus mm³ (mean (SD)) | 3,874 (424)              | 3,841 (440)                                | 3,803 (439)                            | 31,473|
| Accumbens mm³ (mean (SD)) | 459 (103)                | 438 (104)                                  | 421 (104)                              | 31,498|
| Amygdala mm³ (mean (SD))  | 1,246 (215)              | 1,250 (219)                                | 1,251 (217)                            | 31,493|
| Pallidum mm³ (mean (SD))  | 1,783 (213)              | 1,781 (227)                                | 1,767 (231)                            | 31,443|
| Putamen mm³ (mean (SD))   | 4,828 (555)              | 4,789 (575)                                | 4,774 (580)                            | 31,470|
| Caudate mm³ (mean (SD))   | 3,470 (412)              | 3,471 (424)                                | 3,480 (425)                            | 31,468|
| Thalamus mm³ (mean (SD))  | 7,722 (728)              | 7,645 (729)                                | 7,593 (715)                            | 31,449|
| gFA Std units M (SD)      | 0.09 (0.52)              | -0.03 (0.56)                               | -0.13 (0.59)                           | 29,686|
| gMD Std units M (SD)      | -0.10 (0.41)             | 0.02 (0.46)                                | 0.14 (0.50)                            | 29,686|

**Cognitive Tests**

|                           |                           |                                             |                                         |      |
|---------------------------|---------------------------|---------------------------------------------|                                         |      |
| Pairs Matching -incorrect matches (mean (SD)) | 3.51 (2.78)             | 3.70 (2.89)                                | 3.85 (2.97)                            | 29,241|
| Verbal and Numerical Reasoning – Correct answers (mean (SD)) | 6.78 (2.06)             | 6.59 (2.04)                                | 6.55 (2.07)                            | 29,182|
| Reaction Time, s (mean (SD)) | 585.21 (106.45)        | 595.46 (108.70)                            | 602.63 (110.36)                        | 29,628|
| Trail-Making Test B – A, s (mean (SD)) | 314.41 (178.04)        | 343.22 (192.28)                            | 361.87 (206.13)                        | 18,801|
Matrix Reasoning – Correct answers (mean (SD))
8.21 (2.10) 7.94 (2.09) 7.75 (2.18) 19,478
Symbol-Digit Substitution – Correct answers (mean (SD))
19.94 (5.16) 18.71 (5.07) 17.96 (5.25) 19,503
Tower Rearranging – Correct answers (mean (SD))
10.17 (3.22) 9.89 (3.20) 9.65 (3.23) 19,310

p values are adjusted for multiple tests using FDR, one-way analysis of variance and Chi-square testing to compare normotensive and hypertensive state on continuous and categorical variables
Supplementary Table 4. Main and age interactive effects between hypertensive and normotensive participants with brain volumes

| Description                                      | Standardized β | Upper   | Lower   | p      |
|--------------------------------------------------|----------------|---------|---------|--------|
| Total Brain Volume: Main Effect (n = 30778)      | -0.0114        | -0.0215 | -0.0013 | 0.036  |
| Total Brain Volume: Age Interaction              | 0.0157         | -0.0215 | 0.0056  | 0.004  |
| Total Grey Matter: Main Effect (n = 30781)       | -0.0345        | -0.046  | -0.023  | < 0.001|
| Total Grey Matter: Age Interaction               | 0.0041         | -0.0075 | 0.0156  | 0.49   |
| WMH: Main Effect (n = 29322)                     | 0.1978         | -0.0157 | 0.2184  | < 0.001|
| WMH: Age Interaction                             | 0.0051         | -0.0157 | 0.0259  | 0.662  |
| Ventricular CSF: Main Effect (n = 30631)         | 0.0411         | 0.0218  | 0.0605  | < 0.001|
| Ventricular CSF: Age Interaction                 | -0.0087        | -0.0281 | 0.0108  | 0.422  |
| gFA: Main Effect (n = 28997)                     | -0.0962        | -0.1096 | -0.0829 | < 0.001|
| gFA: Age Interaction                             | -0.0273        | -0.0407 | -0.0138 | < 0.001|
| gMD: Main Effect (n = 28997)                     | 0.0983         | 0.088   | 0.1086  | < 0.001|
| gMD: Age Interaction                             | 0.0241         | 0.0137  | 0.0345  | < 0.001|
| Hippocampus: Main Effect (n = 30745)             | -0.0176        | -0.0389 | 0.0036  | 0.199  |
| Hippocampus: Age Interaction                     | 0.0065         | -0.0149 | 0.0278  | 0.683  |
| Thalamus: Main Effect (n = 30722)                | -0.0263        | -0.0428 | -0.0097 | 0.003  |
| Thalamus: Age Interaction                        | 0.0419         | 0.0253  | 0.0586  | < 0.001|
| Caudate: Main Effect (n = 30741)                 | 0.0327         | 0.0124  | 0.053   | 0.004  |
| Caudate: Age Interaction                         | 0.0211         | 7.00E-04| 0.0415  | 0.059  |
| Putamen: Main Effect (n = 30742)                 | -0.0044        | -0.023  | 0.0142  | 0.846  |
| Putamen: Age Interaction                         | 0.0128         | -0.0059 | 0.0314  | 0.271  |
| Pallidum: Main Effect (n = 30716)                | -0.0066        | -0.0276 | 0.0143  | 0.591  |
| Pallidum: Age Interaction                        | 0.0178         | -0.0033 | 0.0388  | 0.121  |
| Amygdala: Main Effect (n = 30765)                | -0.0355        | -0.058  | -0.0131 | 0.005  |
| Amygdala: Age Interaction                        | -0.0171        | -0.0396 | 0.0055  | 0.1934 |
| Accumbens: Main Effect (n = 30770)               | -0.062         | -0.0831 | -0.041  | < 0.001|
| Accumbens: Age Interaction                       | 0.0175         | -0.0306 | 0.0387  | 0.129  |

Standardized betas, 95% CI, and p-values are reported from regression models where hypertension status are regressed onto MRI measures adjusted for age, age*age, sex, sex*age, sex*age^2, education, ethnicity, assessment center, body mass index, smoking status, diabetes, and hyperlipidemia. position MRI confounds and head size. Main Effects: Negative values indicate smaller volumes for hypertensive participants compared with normotensive participants for all volumes apart from WHM, ventricular CSF, and gMD. Age interaction effects: A significant interaction would indicate a different association magnitude at different ages. p values are adjusted using false discovery rate.
### Supplementary Figure 1

Forest plot showing the association of brain volumes with hypertensive participants with and without BP medication use versus normotensive participants.

| Description                  | Standardized Beta               |
|------------------------------|---------------------------------|
| **Total Brain Volume (n =30778)** |                                 |
| Hypertensive - No BP Medications | -0.0055 (-0.0166 to 0.0055)     |
| Hypertensive - BP Medications  | -0.0243 (-0.0378 to -0.0108)    |
| **Total Grey Matter (n =30781)** |                                 |
| Hypertensive - No BP Medications | -0.0167 (-0.0293 to -0.0042)    |
| Hypertensive - BP Medications  | -0.0705 (-0.0858 to -0.0552)    |
| **Ventricular CSF (n =30631)** |                                 |
| Hypertensive - No BP Medications | 0.0240 (0.0028 to 0.0451)       |
| Hypertensive - BP Medications  | 0.0764 (0.0506 to 0.1023)       |
| **WMH (n =29322)**             |                                 |
| Hypertensive - No BP Medications | 0.1575 (0.1350 to 0.1800)       |
| Hypertensive - BP Medications  | 0.2790 (0.2514 to 0.3067)       |
| **gFA (n =28997)**             |                                 |
| Hypertensive - No BP Medications | -0.0668 (-0.0814 to -0.0523)    |
| Hypertensive - BP Medications  | -0.1537 (-0.1715 to -0.1359)    |
| **gMD (n =28997)**             |                                 |
| Hypertensive - No BP Medications | 0.0733 (0.0621 to 0.0845)       |
| Hypertensive - BP Medications  | 0.1472 (0.1334 to 0.1609)       |
| **Hippocampus (n =30745)**     |                                 |
| Hypertensive - No BP Medications | -0.0064 (-0.0296 to 0.0168)     |
| Hypertensive - BP Medications  | -0.0406 (-0.0689 to 0.0122)     |
| **Thalamus (n =30722)**        |                                 |
| Hypertensive - No BP Medications | -0.0220 (-0.0401 to -0.0039)    |
| Hypertensive - BP Medications  | -0.0380 (-0.0601 to -0.0159)    |
| **Caudate (n =30741)**         |                                 |
| Hypertensive - No BP Medications | 0.0286 (0.0064 to 0.0508)       |
| Hypertensive - BP Medications  | 0.0393 (0.0122 to 0.0665)       |
| **Putamen (n =30742)**         |                                 |
| Hypertensive - No BP Medications | -0.0055 (-0.0259 to 0.0148)     |
| Hypertensive - BP Medications  | -0.0030 (-0.0279 to 0.0218)     |
| **Pallidum (n =30716)**        |                                 |
| Hypertensive - No BP Medications | 0.0092 (-0.0137 to 0.0321)      |
| Hypertensive - BP Medications  | -0.0398 (-0.0678 to -0.0118)    |
| **Amygdala (n =30765)**        |                                 |
| Hypertensive - No BP Medications | -0.0235 (-0.0481 to 0.0011)     |
| Hypertensive - BP Medications  | -0.0584 (-0.0884 to -0.0284)    |
| **Accumbens (n =30770)**       |                                 |
| Hypertensive - No BP Medications | -0.0406 (-0.0636 to -0.0176)    |
| Hypertensive - BP Medications  | -0.1064 (-0.1345 to -0.0783)    |
Volumes and age have been standardized (mean = 0 and standard deviations = 1). Hypertensive state 0 = normotensive, 1 = hypertensive

**Supplementary Figure 2.** Age interactive plot between hypertensive and normotensive participants with total brain volume, Thalamus and latent factors for latent measures of white matter fractional anisotropy (gFA) and mean diffusivity (gMD).
Supplementary Figure 3. Forest plot showing the association of brain volumes with hypertensive participants with and without self-report and stratification by BP medication use versus normotensive participants.
Supplementary Figure 4. Forest plot showing the association with different brain volumes with length of hypertension in hypertensive participants split into quartiles with people with hypertension less than 5 years as reference level. Black dots indicate standardized beta < 0.05 FDR p value. Standardized betas, 95% CI, and p-values are reported from regression models where hypertension status is regressed onto each brain volume adjusted for age, age², sex, sex*age, sex*age², education, ethnicity, assessment center, body mass index, smoking status, diabetes, hyperlipidemia, head size, and MRI scanner position. Negative values indicate smaller volumes for hypertensive participants compared with normotensive participants for all volumes apart from WHM, ventricular CSF, and gMD. p values are adjusted using false discovery rate.
Supplementary Figure 5. Forest plot showing the association of cognition tests with hypertensive participants with and without BP medication use versus normotensive participants.
**Supplementary Table 5.** Main and age interactive effects between hypertensive and normotensive participants with cognitive tests at imaging visit.

| Description                                      | Standardized β | 95% CI        | p   |
|--------------------------------------------------|----------------|---------------|-----|
| Reaction Time: Main Effect (n = 30,778)          | -0.025         | -0.049, -0.001| 0.073|
| Reaction Time: Age Interaction                  | -0.010         | -0.034, 0.014 | 0.477|
| Verbal & Numerical Reasoning: Main Effect (n = 30,781) | -0.027         | -0.051, -0.003| **0.045** |
| Verbal & Numerical Reasoning: Age Interaction   | 0.006          | -0.018, 0.030 | 0.702|
| Pairs Matching: Main Effect (n = 29,322)        | 0.019          | -0.006, 0.044 | 0.275|
| Pairs Matching: Age Interaction                 | 0.003          | -0.023, 0.028 | 0.933|
| TMTB-TMTA: Main Effect (n = 18,394)             | 0.007          | -0.024, 0.037 | 0.747|
| TMTB-TMTA: Age Interaction                      | 0.010          | -0.021, 0.040 | 0.679|
| Matrix Pattern: Main Effect (n = 19,053)        | -0.014         | -0.043, 0.016 | 0.439|
| Matrix Pattern: Age Interaction                 | -0.001         | -0.031, 0.029 | 0.946|
| Symbol digit matches: Main Effect (n = 19,074)   | -0.017         | -0.045, 0.011 | 0.346|
| Symbol digit matches: Age Interaction           | 0.027          | -0.002, 0.055 | 0.126|
| Tower Arranging: Main Effect (n = 18,895)       | -0.024         | -0.055, 0.006 | 0.174|
| Tower Arranging: Age Interaction                | -0.005         | -0.036, 0.026 | 0.787|
| TMTB-TMTA: Main Effect (n = 18,394)             | -0.025         | -0.049, -0.001| 0.073|
| TMTB-TMTA: Age Interaction                      | -0.010         | -0.034, 0.014 | 0.477|

Standardized betas, 95% CI, and p-values are reported from regression models where hypertension status*age are regressed onto cognitive test measures adjusted for age, age*age, sex, sex*age, sex*age^2, education, ethnicity, assessment center, body mass index, smoking status, diabetes, and hyperlipidemia. For the cognitive tests, negative values indicate better cognitive function for reaction time, pairs matching, TMT B-A, whereas positive scores indicate better cognitive scores for verbal and numerical reasoning, matrix pattern, symbol digit substitution and tower rearranging. Age interaction effects: A significant interaction would indicate a different association magnitude at different ages. p values are adjusted using false discovery rate.
In Supplementary Figure 6, we present the associations between hypertensives compared to normotensives individuals using information from the original baseline visit. Individuals with no valid BP measures and pre-existing medical conditions as stated in Supplementary Table 1. For this analysis, there were 255,625 hypertensive individuals and 197,889 normotensive individuals as defined using BP, self-reported hypertension, and BP medication use. The results show that compared to normotensives, individuals with hypertension have slower reaction times, poorer verbal and numerical reasoning and made more errors on the pairs matching test.

**Supplementary Figure 6.** Forest plot showing the association with different cognitive tests between hypertensive and normotensive individuals at baseline only (n = 453,516). Standardized betas, 95% CI, and p-values are reported from regression models where hypertension status is regressed onto each cognitive test adjusted for age, age², sex, sex*age, sex*age², education, ethnicity, assessment center, body mass index, smoking status, diabetes, and hyperlipidemia. For the cognitive tests, negative values indicate better cognitive scores for reaction time, pairs matching whereas positive scores indicate better cognitive scores for verbal and numerical reasoning. p values are adjusted using false discovery rate.
Supplementary Figure 7. Forest plot showing the association of cognition tests with hypertensive participants with and without self reported hypertension stratified by BP medication use.

In Supplementary Figure 8, we present the associations between hypertensives self-reported and not self-reported compared to normotensives individuals using information from the original baseline visit. For this analysis, there were 115038 hypertensive individuals with no self-reported hypertension, 140587 hypertensive individuals who also self-reported they had hypertension and 197889 normotensive individuals as defined using BP, self-reported hypertension and BP medication use. The results show that compared to normotensives, individuals with hypertension who also self-reported hypertension have slower reaction times, poor verbal and numerical reasoning and made more errors on the pairs matching test. Furthermore, for verbal and numerical
reasoning individuals who were hypertensive but did not self-report a hypertension diagnosis also had poor cognitive function compared to normotensives.

Supplementary Figure 8. Forest plot showing the association with different cognitive tests between hypertensive self reported and not self reported and normotensive individuals at baseline only (n = 453,516). Standardized betas, 95% CI, and p-values are reported from regression models where hypertension status is regressed onto each cognitive test adjusted for age, age², sex, sex*age, sex*age², education, ethnicity, assessment center, body mass index, smoking status, diabetes, and hyperlipidemia. For the cognitive tests, negative values indicate better cognitive scores for reaction time, pairs matching whereas positive scores indicate better cognitive scores for verbal and numerical reasoning. p values are adjusted using false discovery rate.

Supplementary Table 6. Association between length of hypertension with cognitive function tests in hypertensive participants at baseline.

| Cognitive Tests       | Standardized β | 95% CI     | p    | n    |
|-----------------------|----------------|------------|------|------|
|                       | Standardized β | Lower      | Upper |      |      |
| Reaction Time         | 0.011          | 0.005      | 0.017 | 0.001| 103,362|
| Verbal & Numeric Reasoning | 0.016        | 0.006      | 0.025 | 0.002| 36,794 |
| Pairs Matching        | 0.003          | -0.004     | 0.009 | 0.506| 101,133|

Standardized betas, 95% CI, and p-values are reported from regression models where hypertension status is regressed onto cognitive test measures adjusted for age, age², sex, sex*age, sex*age², education, ethnicity, assessment center, body mass index, smoking status, diabetes, and hyperlipidemia. For the cognitive tests, negative values indicate better cognitive function for reaction time, pairs matching, whereas positive scores indicate better cognitive scores for verbal and numerical reasoning. p values are adjusted using false discovery rate.
Supplementary Figure 9. Forest plot showing the association with different cognitive tests between quartiles of length of hypertension and normotensive individuals at baseline only (n = 453,516). Standardized betas, 95% CI, and p-values are reported from regression models where hypertension status is regressed onto each cognitive test adjusted for age, age^2, sex, sex*age, sex*age^2, education, ethnicity, assessment center, body mass index, smoking status, diabetes, and hyperlipidemia. For the cognitive tests, negative values indicate better cognitive scores for reaction time, pairs matching whereas positive scores indicate better cognitive scores for verbal and numerical reasoning. p values are adjusted using false discovery rate. Reference level normotensive participants (n = 107,383).