Association of blood pressure with brain ages: a cohort study of grey and white matter ageing discrepancy in mid-to-older adults from UK Biobank

Short title: high blood pressure, grey and white matter ages

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Total word count: 6676

Novelty and Relevance

What is New?

Using brain age gaps for elevating grey matter and white matter health, this study compared the vulnerability of white matter and grey matter to elevated blood pressure.

What is Relevant?

Compared to grey matter, the white matter was more susceptible to the high blood pressure. The association between high blood pressure and cognitive decline, especially processing speed and executive function, was mainly through the impairment of white matter.

Clinical/Pathophysiological Implications?

Our study provided convincing evidence that clinical attention should be focused more on addressing white matter damage in individuals with hypertension.

Abstract

Background: Grey matter (GM) and white matter (WM) impairments are both associated with raised blood pressure (BP), while whether elevated BP are differentially associated with the GM and WM ageing process remains inadequately examined. **Methods:** We included 37,327 participants with diffusion weighted imaging (DWI) and 39,630 participants with T1-weighted scans from UK Biobank. BP was classified into four categories: normal BP, high-normal BP, Grade 1 and Grade 2 hypertension. Brain age gaps for GM (BAG_{GM}) and WM (BAG_{WM}) were derived from DWI and T1 scans separately using 3D-convolutional neural network deep learning techniques. **Results:** There was an increase in both BAG_{GM} and BAG_{WM} with raised BP ($p<0.05$). BAG_{WM} was significantly larger than BAG_{GM} at high-normal BP (0.195 years older, $p = 0.006$), Grade 1 hypertension (0.174 years older, $p = 0.004$) and Grade 2 hypertension (0.510 years older, $p < 0.001$), but not for normal BP.

Mediation analysis revealed that association between hypertension and cognitive decline was primarily mediated by WM impairment. Mendelian randomisation analysis suggested a causal relationship between hypertension and WM ageing acceleration (unstandardised B = 1.780, p = 0.016) but not for GM (p > 0.05). Sliding-window analysis indicated the association between hypertension and brain ageing acceleration was moderated by chronological age, showing stronger correlations in mid-life but weaker associations in the older age. **Conclusions:** Compared with GM, WM was more vulnerable to raised BP. Our study provided compelling evidence that concerted efforts should be directed towards white matter damage in hypertensive individuals in clinical practice.

Keywords: Blood pressure, white matter brain age, grey matter brain age; deep learning networks

Nonstandard Abbreviations and Acronyms	
BAG	brain age gap
BAG_{GM}	grey matter brain age gap
BAG_{WM}	white matter brain age gap
DWI	diffusion weighted imaging
3D-CNN	3D-convolutional neural network
MAE	mean absolutely error
MLP	multilayer perceptron
ReLU	rectified linear unit

1. Introduction

Accumulating evidence has been firmly established that high blood pressure (BP) is linked to both cerebral grey matter (GM) and white matter (WM) injuries[1,2], aggravating the risk of many neurodegenerative and neurovascular disorders [3] [4]. However, owing to the fact that the number of pial arterioles supplying the GM is almost eight times the penetrating arterioles that supply WM [5], WM might be more susceptible to ischemia than GM when affected by hypertension[6]. It is also frequently observed in the clinical practice that many hypertensive patients show greater propensity for WM lesions as opposed to GM. However, the extent to which GM and WM respond differentially to raised BP is difficult to be accurately quantified. Although previous studies[7-9] have incorporated diverse magnetic resonance imaging (MRI) measures to investigate the associations of hypertension with GM (such as cortical volume and thickness) and WM (such as WM volume, fractional anisotropy), a unified neuroimaging biomarker for comparing GM and WM health simultaneously is still absent.

Brain age is an emerging neuroimaging derived measure using deep learning techniques that has gained significant attention. It is considered as a powerful index for estimating the underlying biological health of the brain[10,11]. We define the brain age gap (BAG) as the difference between the predicted age and chronological age (predicted age – chronological age). 'Older appearing' brain with increased BAG suggests an accelerated ageing trajectory or a brain with stroke[12] or Alzheimer's disease[13]. Most studies have examined a general predicted age for the whole brain. In this context, we argue that it is imperative to examine their ageing trajectories separately and quantitively since hypertension is likely to differentially affect GM and WM.

2. Materials and Methods

All demographics or neuroimaging data used in this study are available from the UK Biobank website (https://www.ukbiobank.ac.uk/). All source code and the pretrained model can now be found on Github for reproducibility (https://github.com/Yuangang-Pan/Association-of-blood-pressure-with-brain-ages).

2.1 Participants

We analysed data from participants in the UK Biobank[14], a large-scale population-based cohort. Participants with diffusion weighted imaging (DWI) scans (n = 37,327) and T1-weighted scans (n = 39,630) were included in this study. Figure 1 shows the procedure of allocating these participants to training, validation and testing datasets. The same participants (~20%) were allocated to the testing sets for both GM and WM deep learning models. The remaining participants were then randomly chosen as training set (~60%) and validation set (~20%). Finally, 11,431 testing participants with T1 weighted scans and 11,168 testing participants with DWI weighted scans (11,159 had both) were used for subsequent analyses.

The UK Biobank has been approved by the North West Multi-centre Research Ethics Committee (MREC), UK, and written informed consent was provided by each participant. This study was conducted under Application No. 45262.

2.2 Brain MRI acquisition and pre-processing

Raw T1 and DWI scans were downloaded from UK biobank imaging data pool and were then processed. Details can be found in Supplementary Methods. A T1-derived GM probability map and five DWI-derived WM tensor maps including FA (fractional anisotropy), MD (mean

diffusivity), AxD (axial diffusivity), RD (radial diffusivity) and MO (tensor mode) maps were finally generated for the GM age and WM age calculation, respectively.

2.3 Computation of GM and WM brain ages

The computation of GM and WM brain ages was performed using the 3D-convolutional neural network (3D-CNN) deep learning model, shown in Figure 2. A glossary explaining the terminology used for the deep learning model can be found in Supplementary Table S1

To make a fair comparison, the same spatial resolution of $2 \times 2 \times 2$ mm^3 for both the GM map and the DWI-derived maps were used. The similar network architecture (same network design and same convolution filters) as in our previous WM brain age study was adopted[15]. In particular, the feature extractor consisted of six 3D convolutional layers $Conv3D(32,3,1,2) - Conv3D(64,3,1,2) - Conv3D(128,3,1,2) - Conv3D(256,3,1,2) - Conv3D(256,3,1,2) - Conv3D(64,3,1,2)$ followed by a two-layer Multilayer perceptron (MLP) with dimensions $d - 100 - 1$, where $Conv3D(m,n,p,q)$ denoted a three-dimensional convolutional layer with channel number m, kernel size n, padding size p, stride length q, and d was the dimension of the flattened 3D-CNN output. We applied 3D batch normalization after each convolutional layer, followed by 3D max-pooling and the Rectified Linear Unit (ReLU) activation sequentially except for the last convolutional layer. Other relevant parameters such as sex, scanner, and intracranial volume (ICV) of each participant were integrated into the model by modifying the last MLP through simple concatenation, i.e., $d - (100 + 3) - 1$. We have kept the same experiment setting for all types of data. To be specific, the mean squared error (MSE) was adopted as the loss function. The optimizer was Adam [16] with no weight decay. The neural network weight was initialized using a uniform distribution following [17]. The learning rate was 1e-3 and the training epoch

was 350. The batch size was set to 32. The number of workers were set to 10 for the data loader. The hold-out validation dataset was used for model configuration, i.e., the loss function, the type of data augmentation, training epoch and the learning rate. Bias correction procedures have been adopted to account for the dependence of brain age gap on the chronological age, full details can be found in Supplementary Methods.

2.4 Evaluation of blood pressure

An Omron HEM-7015IT device was used to automatically evaluate the seated blood pressure twice at the imaging visit; two measures of blood pressure were taken a few moments apart. A manual sphygmometer was used if the automated device was not available. The mean blood pressure of systolic BP (SBP) and diastolic BP (DBP) for each individual was computed by averaging the repeated two measurements, respectively. Pulse pressure was calculated as the difference between SBP and DBP. Antihypertensive medication status was recorded as either taking medication for BP control or not.

The 2020 International Society of Hypertension (ISH)[18] practice guidelines were used to classify blood pressure into four categories: *Normal BP*, where SBP is < 130 mmHg and DBP < 85 mmHg; *High-normal BP*, where SBP is 130 - 139 mmHg, and/or DBP is 80 - 89 mmHg; *Grade 1 hypertension*, SBP is 140 - 159 mmHg and/or DBP is 90 - 99 mmHg; *Grade 2 hypertension*, where the SBP ≥ 160 mmHg and/or DBP is ≥ 100 mmHg.

2.5 Evaluation of other risk factors, education and cognition

All other confounding risk factors, including diabetes, hypercholesterolemia, obesity, smoking and Apolipoprotein E (APOE) ε4 carrier status were treated as binary variables. Details can be found in Supplementary Methods. Seven cognitive tests at two brain MRI

visits were performed, viz. Reaction Time, Trail Making Test A and B, Symbol Digit Substitution, Numeric Memory, Pairs Matching Test and Fluid Intelligence Test. All raw scores were standardised into z scores against baseline healthy sample, and grouped into three cognitive domains, namely, processing speed, executive function and memory. Higher scores indicated better cognitive performance.

2.6 Mediation analysis using structural equation modelling

Structural equation modelling was conducted to test the mediation effects of BAGs on the cross-sectional associations between BP and cognitive performance using lavaan package (https://cran.r-project.org/web/packages/lavaan/). In the model, BP status was dummy coded with the normal BP being the reference category, BAG_{GM} and BAG_{WM} were specified as the mediators, and cognitive domain scores as the outcomes. The covariates listed above were controlled in the analyses, with education additionally controlled for cognition. Indirect effects were tested using bootstrapping with 5,000 samples. Missing data were handled by Full Information Maximum Likelihood (FIML). Comparative fit index (CFI) and root mean square error of approximation (RMSEA) were used to evaluate the model fit, with CFI > 0.90 and RMSEA < 0.06 indicating good fit[19].

2.7 One-sample Mendelian randomisation analysis

To determine whether there is a causal relationship between high BP and BAGs (BAG_{GM} or BAG_{WM}), one-sample Mendelian randomisation (1SMR) analysis was performed in the individual-level data from 10,507 White British participants using hypertension polygenetic risk score (PRS) as the genetic instrument. UK Biobank Data Field 22020 was used to restrict a subset of unrelated (to the 3rd degree) individuals who were not sex discordant or outliers for missingness or heterozygosity (n = 8,379)[20]. The schematic representation of this MR

analysis can be found in Supplementary Figure S1. The PRS was calculated using 157 SNPs based on a GWAS study of hypertension[21] (Supplementary Table S2). Unweighted rather than weighted allele scores were applied to minimize risk of weak instrument bias. PLINK 2 with call threshold 0.01 was used to ensure that none of the SNPs were in linkage disequilibrium. The causal effect between hypertension and BAGs was examined using the two-stage least-squares (2SLS) method. Full steps of the MR analysis and its sensitivity analysis can be found in Supplementary Methods.

2.8 Sliding-window analysis

To further examine whether and how chronological age moderates the association between hypertension and grey/white matter ageing acceleration, sliding window analysis was conducted for BAG_{GM} and BAG_{WM} separately. The window was defined with the width of 10 years starting from 45.49 years old; and was shifted forward by one year at a time. Altogether 29 windows were finally generated covering the full chronological age range (45.49 to 82.32 years). In each window, we regressed the effect of hypertension on the BAGs, fully controlling for all covariates. Bonferroni correction was performed for the multiple windows (n = 29).

2.9 Statistical analysis

Statistical analyses were performed using R 4.1.3 and SPSS 26.0. Continuous variables were described as mean (SD, standard deviation), and categorical variables as frequencies (percentages). Repeated measures ANCOVA (analysis of covariance) was employed to examine the difference of BAG_{GM} and BAG_{WM} across four BP categories with BAGs being the within-subjects factor and BP categories the between-subjects factor, controlling for

chronological age, sex, scanner, and all other covariates. The difference between BAG_{WM} and BAG_{GM} across four BP categories was further compared using contrast coding.

To examine the specific contributions of SBP and DBP, linear ($y = a_1x + c_1$) and quadratic association analyses ($y = b_2x^2 + a_2x + c_2$) were conducted to determine the independent relationships between systolic/diastolic BPs (x) and BAGs (y). To avoid multicollinearity, mean centering was performed for both SBP and DBP. Given that no quadratic relationship was found for SBP, the subsequent mediation analyses were carried out using mean centered SBP (C_SBP), DBP (C_DBP) and square of DBP (C_DBP^2) as predictors. Linear and quadratic associations between pulse pressure and BAGs were also examined.

The two tailed $p < 0.05$ was considered as statistically significant. All p values-were adjusted for multiple comparisons using Bonferroni correction based on each specific model.

3. Results

3.1 Sample characteristics

Descriptions of demographics, risk factors, cognition, and brain ages for each BP group are reported in Table 1 and Supplementary Table S3.

3.2 Model performance in GM and WM training, validation and testing

Mean absolute error (MAE) and Pearson's r were applied to evaluate the performances of the two deep learning models, the detailed results in Supplementary Table S4. Briefly, after bias correction, the MAEs for GM and WM healthy test samples were 2.727 and 2.754 years, and

Pearson's correlation coefficient (r) between chronological age and GM brain age in the healthy test sample was 0.910, and 0.908 for WM brain age.

3.3 Associations between BP categories and BAGs

Significant interactions between BP categories and BAGs were found ($F = 6.103$, $p < 0.001$), after fully controlling for all covariates. Both BAG_{GM} and BAG_{WM} showed a stepwise increase with each elevated BP (Figure 3A-3C). The detailed statistical results of pair-wise comparisons can be found in Supplementary Tables S5.

Moreover, significant differences between BAG_{WM} and BAG_{GM} were present (Figure 3A). Specifically, for high-normal BP, BAG_{WM} was 0.195 ± 0.071 years older than BAG_{GM} ($p = 0.006$, 95% CI = 0.056 ~ 0.335); for Grade 1 hypertension, BAG_{WM} was 0.174 ± 0.060 years older than BAG_{GM} ($p = 0.004$, 95% CI = 0.056 ~ 0.292); for Grade 2 hypertension, BAG_{WM} was 0.510 ± 0.101 years older than BAG_{GM} ($p < 0.001$, 95% CI = 0.313 ~ 0.708). With the elevated BP categories, the differences between BAG_{WM} and BAG_{GM} became increasingly larger (Figure 3D). Specifically, the difference at Grade 2 hypertension was observed to be significantly larger than that at normal BP ($p < 0.001$, 95% CI = 0.181 ~ 0.815) and Grade 1 hypertension ($p = 0.022$, 95% CI = 0.031 ~ 0. 641). The detailed statistical results are in Supplementary Table S6.

Associations between BP categories and BAGs stratified by different antihypertensive medication status were also investigated using ANCOVA. For those who did not take antihypertensive medication, a higher BP category was found to be associated with the increasing BAG_{GM} and BAG_{WM}. However, for those who were on antihypertensive

277 medication, no significant difference was found across BP groups. All the results were shown
278 in Supplementary Results and Figure S2.
279
280 **3.4 Linear associations between SBP and BAGs but quadratic associations between**
281 **DBP and BAGs**
282 After fully controlling for the covariates, significant linear associations between SBP and
283 both BAG_{GM} (unstandardised B = 0.010, p = 0.001, 95% CI = 0.004 ~ 0.016) and BAG_{WM}
284 (unstandardised B = 0.022, p = 0.001, 95% CI = 0.016 ~ 0.028) were found (Figures 3E-F),
285 whereas no significant linear associations were found between DBP and BAG_{GM}
286 (unstandardised B = 0.008, p = 0.102, 95% CI = -0.002 ~ 0.019) and BAG_{WM} (unstandardised
287 B = 0.001, p = 0.833, 95% CI = -0.009 ~ 0.012). However, quadratic relationships were
288 observed between DBP and BAG_{GM} ($p = 0.004$) and BAG_{WM} ($p < 0.001$), but not for SBP and
289 BAG_{GM} and BAG_{WM} (all p values > 0.05). The optimal DBP that associated with the smallest
290 BAG_{GM} were 70.75 mmHg, and 78.36 mmHg for $BAG_{WM.}$ (Figures 3G-H). No significant
291 quadratic association but linear associations were found between pulse pressure and BAG_{GM}
292 (unstandardised B = 0.011, $p < 0.001$) and BAG_{WM} (unstandardised B = 0.025, $p < 0.001$),
293 respectively (Supplementary Figure S3).
294
295 **3.5 Relationships between blood pressure, brain age and cognition by mediation**
296 **analysis**
297 No direct associations between hypertension category and cognition were found, and the
298 association between high BP and cognition was mainly mediated by accelerated ageing of
299 WM (Figure 4). The significant indirect association was mainly found between BP categories
300 and processing speed mediated through BAG_{WM} (Figure 4A) with acceptable model fit: CFI =
301 0.916 and RMSEA = 0.054. However, no significant associations between BP categories and

memory were observed either directly or indirectly. Moreover, the mediation model using SBP and BDP showed adequate model fit: CFI = 0.934 and RMSEA = 0.056. We found that SBP was associated more with the brain damage and cognitive decline than DBP (square term) (Figure 4B). An increase of 10 mmHg SBP was associated with 0.004 z-score decline in processing speed ($p < 0.001$) and 0.003 z-score decline in executive function ($p = 0.001$), via increase in BAG_{WM}.

3.6 One-sample MR analysis

The 1SMR analysis gave the evidence that causal relationship existed between hypertension and WM ageing acceleration but not GM. The presence of hypertension caused about 1.78 years increase of BAG_{WM} (unstandardised B = 1.780, p = 0.016, 95% CI = 0.336 ~ 3.223); but for BAG_{GM}, no significant causal relationship was observed (unstandardised B = 0.759, p = 0.279, 95% CI = -0.616 ~ 2.133). Sensitivity analyses showed that the F-statistic for WM was 175.27, power 0.05; significant association between hypertension PRS and hypertension status was found ($p < 0.001$) while no significant associations were found between the PRS and confounders (all p values > 0.05). The 1SMR sensitivity analyses using two-sample MR (2SMR) methods support a causal association between hypertension and WM ageing. 2SMR sensitivity analyses, especially IVW estimates and weighted median analysis, suggested consistent causal relationship between hypertension and BAG_{WM} with that in the main analyses, and neither the MR-Egger regression nor MR PRESSO methods revealed any pleiotropy (Supplementary Tables S7-9).

3.7 Longitudinal analysis

The demographics of the longitudinal subset are summarised in Supplementary Table S10. No significant longitudinal mediation effect for change of BAGs between BP categories and change of cognitions (all p values > 0.05) was found, see Supplementary Figure S3.

3.8 Sliding-window analysis

After Bonferroni correction, significant associations were found between hypertension and BAG_{GM} and BAG_{WM} (Supplementary Table S11) in each window from 46 to 78 years old. The inversed U-shape was observed for both BAG_{GM} and BAG_{WM}; for BAG_{GM}, the coefficients decreased from around 64 years old; for BAG_{WM}, the coefficients decreased from around 68 years old. In addition, BAG_{WM} showed higher correlation with hypertension than BAG_{GM}, especially between 50 and 67 years old (Figure 5).

4. Discussion

Four main findings were as follows. First, both GM and WM impairments were found to be associated with elevated BP. Second, WM showed greater impairment than GM starting from high-normal BP, and the difference between BAG_{WM} and BAG_{GM} was increasingly larger with higher BP. Third, the associations between BP and processing speed and executive function were mainly mediated through BAG_{WM} rather than BAG_{GM}. Moreover, high systolic BP (SBP) was linearly associated with brain damage and cognitive decline, whereas diastolic BP (DBP) showed a quadratic association with the BAGs, with 71 mmHg and 78 mmHg the optimal DBPs for keeping the smallest BAG_{GM} and $BAG_{WM,}$ respectively. Finally, high BP showed a significant detrimental effect on the brain impairment, but this association was weakened in the late life.

In this study, it is intriguing to note that WM impairment was discovered to be more pronounced than GM, starting early from high-normal hypertension throughout to Grade 2 hypertension. Several meta-analyses[22,23] have also reported an increased prevalence of cardiovascular and cerebrovascular diseases in individuals with BP at high-normal stage, suggesting the subtle impairment on the cerebral microstructures. Additional MR analysis strengthened our hypothesis, indicating the causal relationship between hypertension and ageing acceleration of WM but not GM. The mechanism accounting for the difference in BAG_{GM} and BAG_{WM} remains unclear, but may be attributed to their distinct vascularization patterns. The arterial network is notably intricate along the pial surface, while WM, especially in deep regions, is primarily supplied by long penetrating arteries. The blood flow responsible for supplying glucose and oxygen is therefore not uniform throughout the brain, and is even less in WM when the small perforating arteries are affected by hypertension[24]. On the other hand, the myelin sheaths covering the WM axons, which are highly energy-demanding for efficient signal transmission, is particularly susceptible to the hypoperfusion caused by hypertension.

Mediation analyses in our study revealed that only indirect associations existed between high BP and cognitive decline, which were mainly mediated through the impairment of WM compared with GM. This finding supported our hypothesis that WM was more vulnerable to raised BP, and provided evidence that the WM impairment played the major role in mediating the path from hypertension to vascular cognitive decline. Processing speed and executive function are considered to be more involved in the early stage of the cerebrovascular disorders, whereas memory is relatively preserved[25]. The effect size between BP and memory is also usually reported as smaller than that for processing speed and executive function[26,27]. Consistently, no direct or indirect relationships were found between

BP categories and memory in this study. The increased BAG_{WM} could potentially serve as a promising biomarker to aid in the diagnosis of vascular dementia in future clinical practice.

Our findings demonstrated significant linear associations between SBP and BAGs, while quadratic association was only observed for DBP. Previous studies have shown conflicting findings regarding the association between SBP/DBP and brain disorders[28,29]. The challenge remains to determine the range of SBP/DBP for optimal brain perfusion. Our findings suggest that SBP showed stronger association with WM impairment and cognitive decline than DBP. Although SBP and DBP usually has a strong correlation, SBP was recognised with a stronger association with the disease outcome[30]. Epidemiological studies also demonstrated that SBP was a more related antihypertensive therapeutic target than DBP[31]. The non-linear relationship (especially the U-shape and J-shape) has been widely observed between the diastolic blood pressure and increased volume of white matter intensity[32], dementia[33], cardiovascular disease[34] and mortality[35]. In line with our findings, a cohort study also suggested that lowering diastolic blood pressure to less than 60 mmHg was associated with increased risk of cardiovascular events, and the diastolic blood pressure value between 70 and 80 mmHg was an optimum target.[36] The mechanism underlying this U-shaped relationship is still not well clarified but may involve the impairment of cerebrovascular autoregulation[37]. The brain's autoregulation capacity was compromised when the DBP was outside the optimal range, and lead to potential brain damage, such as the high DBP related atherosclerosis and the low DBP related hypoperfusion.

The findings in sliding-window analysis suggested that chronological age could moderate the association between hypertension and brain ageing acceleration, showing higher correlation between hypertension and BAGs in mid-life but weaker association in the older age.

Consistently, previous studies have reported that chronological age was a risk factor that moderated the association between high blood pressure and cognitive dysfunction [4], which demonstrated the age-dependent U-shaped association between hypertension and cognitive decline, with detrimental effect of midlife hypertension but potential protective effect of late-life hypertension on the cognition[38,39]. This finding suggested that BP management should be concentrated based on specific age groups; aggressive BP control might not be beneficial to individuals with older age. However, this finding should also be interpreted with caution due to the "time lag" effect. Since hypertension is a chronic condition, the observational brain structural and functional damage might not appear until 1-2 decades later for the individuals of mid-age. In addition, the number of the participants in older age groups is relatively smaller than the younger age groups, which may also contribute to this U-shaped pattern.

A notable strength of this study lies in the intuitive MRI-derived metric to evaluate the discrepancy of GM and WM ageing patterns when affected by high BP. Although volumetric measures can be derived from GM and WM, the simple comparison of them is less meaningful since GM and WM have different anatomical compositions, proportions and distributions. Several limitations should also be acknowledged in this study. First, the deep learning model applied in this study is data sensitive, and applying this model to other datasets may need transfer learning. Moreover, we did not find any longitudinal associations between hypertension, brain damage and cognitive decline, which should be further investigated and addressed in the future studies with more participants and longer follow-up time.

5. Perspective

WM might be particularly more vulnerable to the high BP, and the association between high BP and processing speed, as well as the executive function, is largely mediated by the WM impairment. Maintaining the lowest SBP and keeping DBP within an optimal range would be beneficial for preserving the brain health, with 71 mmHg and 78 mmHg identified as the optimal DBPs for GM and WM health. These findings provided potential evidence for the BP management and emphasised the importance that more attention should be paid to the WM impairment in individuals with hypertension.

6. Acknowledgement

This research was undertaken with the assistance of resources and services from the National Computational Infrastructure (NCI), which is supported by the Australian Government. We also thank Angie Russell for helping with the preparation of the manuscript.

7. Source of Fundings

This study was supported by the National Health and Medical Research Council (NHMRC) of Australia Program Grants ID350833, ID568969, ID1093083 and ID630593; Jiyang Jiang was supported by John Holden Family Foundation.

8. Disclosures

The authors declare no conflict of interest.

9. Author contribution

Writing – JD, YP, PSS, JJ, YL, WW, Conception of idea – JD, JJ, WW. Computation and coding – YP, IWT, JJ, WW. Statistics/Analysis – JD, BL. Cognition – JD, BL. PRS computation – YL. Comments/edits – all.

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Figure legends

Figure 1. Flowchart of allocating participants into training, validation and test sets.

Figure 2 Structure of 3D-CNN model. Inputs for WM model are pre-processed 3D FA/MD/AxD/RD/MO maps; Inputs for GM model is GM probability map. Abbreviations: 3D-CNN = 3D convolution neural network; Conv = convolution; Batchnorm = batch normalisation; ReLU = rectified linear unit; WM = white matter; GM = grey matter; FA = fractional anisotropy; MD = mean diffusivity; AxD = axial diffusivity; RD = radial diffusivity; MO = anisotropy mode, DWI = diffusion weighted imaging.

Figure 3 Associations between BAGs and BP. Difference between BAG_{GM} and BAG_{WM} at each BP status (Figure 3A) and group difference within GM (Figure 3B) and WM (Figure 3C; Difference between BAG_{GM} and BAG_{WM} across BP status (3D); Linear association between SBP and BAG_{WM} (Figure 3E) and BAG_{GM} (Figure 3F); Quadratic association between DBP and BAG_{WM} (Figure 3G) and BAG_{GM} (Figure 3H). Abbreviations: BAG_{GM} = grey matter brain age gap; BAG_{WM} = white matter brain age gap; SBP = systolic blood pressure; DBP = diastolic blood pressure.
** indicates $p < 0.001$ and * indicates $p < 0.05$ after Bonferroni correction.

Figure 4 Mediation analyses for BP, BAGs and cognition. Predictors for Figure 4A are the three dummy variables in reference to the normal BP; predictors for Figure 4B are SBP, mean centered BDP (C_DBP) and the square term of mean centered DBP (C_DBP^2). a*b indicate the indirect effect mediated by BAG_{WM}; d*e indicate the indirect effect mediated by BAG_{GM}; c1-9 indicate the average direct effect between predictors and cognition; solid lines indicate significant paths while dash lines indicate the non-significant paths; the thickness indicated the size effect. Abbreviations: BP = blood pressure; SBP = systolic blood pressure; C_DBP^2 = square term of mean centered diastolic blood pressure; BAG_{GM} = grey matter brain age gap; BAG_{WM} = white matter brain age gap; RMSEA = Root mean square error of approximation; CFI = comparative fit index. * indicates the $p < 0.05$, ** indicates the $p < 0.001$.

Figure 5 Sliding window analysis. X axis indicated the chronological age, Y axis indicated the regression coefficient of the hypertension on the BAG_{WM} (blue dash line) and BAG_{GM} (green dash line). The blue circle marks and green triangle marks indicated the corresponding significance of the regression coefficient for BAG_{WM} and BAG_{GM} separately. Abbreviations: BAG_{GM} = grey matter brain age gap; BAG_{WM} = white matter brain age gap.

Table 1 Baseline sample descriptions

	All test sample (n = 10561)	**Normal BP** (n = 3598)	**High-normal BP** (n = 2330)	**Grade 1 hypertension** (n = 3393)	**Grade 2 hypertension** (n = 1240)
Demographics					
Chronological age, mean (SD)	63.81 (7.51)	61.44 (7.37)	63.47 (7.41)	65.25 (7.07)	67.37 (6.96)
Sex (male, %)	4847 (45.9)	1181 (32.80)	1118 (48.00)	1844 (54.30)	704 (56.80)
Education (college, %)	4957 (49.3)	1799 (52.30)	1107 (49.60)	1513 (47.00)	538 (46.20)
Risk factors					
Diabetes (%)	579 (5.5)	123 (3.40)	148 (6.40)	235 (7.00)	73 (5.90)
Hypercholesterolemia (%)	2591 (24.7)	616 (17.30)	564 (24.40)	1030 (30.60)	381 (31.00)
Obesity (%)	2022 (19.3)	481 (13.50)	461 (19.90)	777 (23.10)	303 (24.90)
Smoking (%)	3993 (38.1)	1331 (37.20)	869 (37.60)	1278 (38.00)	515 (41.90)
APOE ε4 carriers (%)	2429 (27.6)	801 (26.80)	536 (27.30)	784 (27.80)	308 (30.00)
Antihypertensive medication (%)	2517 (24.0)	476 (13.40)	527 (22.80)	1058 (31.40)	456 (37.00)
Brain ages					
GM brain age, mean (SD)	63.87 (8.31)	61.15 (8.06)	63.38 (8.25)	65.51 (7.87)	68.03 (7.55)
WM brain age, mean (SD)	64.02 (8.35)	61.18 (8.22)	63.58 (8.19)	65.74 (7.81)	68.41 (7.30)
BAG_{GM}, mean (SD)	0.06 (3.49)	-0.30 (3.40)	-0.08 (3.52)	0.27 (3.46)	0.64 (3.54)
BAG_{WM}, mean (SD)	0.21 (3.61)	-0.27 (3.58)	0.12 (3.68)	0.50 (3.53)	1.02 (3.56)
Cognition					
Processing speed, mean (SD)	0.08 (0.98)	0.28 (0.92)	0.13 (0.95)	0.04 (0.95)	-0.12 (1.01)
Executive function, mean (SD)	0.08 (0.99)	0.19 (0.96)	0.08 (0.97)	0.05 (0.99)	-0.12 (0.99)
Memory, mean (SD)	0.05 (1.00)	0.11 (1.00)	0.10 (1.01)	0.08 (0.99)	-0.06 (0.95)
Global cognition, mean (SD)	0.09 (0.98)	0.25 (0.95)	0.14 (0.95)	0.08 (0.94)	-0.11 (0.96)

Abbreviations: BP = blood pressure; SD = standard deviation; APOE = apolipoprotein E; GM = grey matter; WM = white matter; BAG_{GM} = grey matter brain age gap; BAG_{WM} = white matter brain age gap.

Supplementary

Association of blood pressure with brain ages: a cohort study of grey and white matter ageing discrepancy in mid-to-older adults from UK Biobank

Short title: high blood pressure, grey and white matter ages

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Supplementary Methods

Imaging acquisition and processing

T1 weighted imaging and DWI scans were obtained from three different imaging centres (Cheadle Greater Manchester, Newcastle and Reading, UK), with the identical scanner (3T Siemens Skyra scanner with a standard Siemens 32-channel head coil) and protocols. Briefly, T1-weighted magnetisation-prepared rapid acquisition with gradient echo (MPRAGE) scans were collected with the resolution of 1 × 1 × 1 mm and field-of-view of 208 × 256 × 256 matrix; DWI scans were acquired with the resolution of 2 × 2 × 2 mm, field-of-view of 104 × 104 × 72 matrix, 5b = 5 and 50b = 1000 s/mm^2 and 50b=2000 s/mm^2 (all 100 directions are distinct).

Computational Anatomy Toolbox (CAT12) [1] was used to generate modulated GM of the whole brain in the Dartel space with the voxel size of 1.5 × 1.5 × 1.5 mm^3. Briefly, the original 3D T1-weighted MRI scans were interpolated, normalized using an affine followed by non-linear registration, denoised, corrected for bias field inhomogeneities, and then segmented into GM, WM, and cerebral spinal fluid (CSF) components; only GM segments were used in further computation of GM age. To be comparable to the spatial resolution of DWI scans, we downsized the GM maps to 2× 2 × 2 mm^3. Pre-processing of DWI scans including eddy currents and distortions correction was conducted preliminarily by the UK Biobank imaging team. Volumes with b = 1000 s/mm^2 were extracted for the subsequent diffusion tensor imaging (DTI) model fit. Five DWI maps in native space were generated: FA (fractional anisotropy), MD (mean diffusivity), AxD (axial diffusivity), RD (radial diffusivity) and MO (tensor mode). FLIRT (FMRIB's linear Image Registration Tool) and FNIRT (FMRIB's Nonlinear Image Registration Tool) were then used to warp all native DWI maps nonlinearly to MNI-152 standard space with spatial resolution of 2 × 2 × 2 mm^3.

Bias correction of brain ages

A well-described systematic age-related bias has been observed in many brain age studies[2-4], showing that older participants are estimated with a younger brain age while younger participants are estimated with an older brain age. To solve this problem, bias-correction procedures have been adopted to account for the dependence of brain age gap on the chronological age. Based on the techniques proposed by Smith et al[4], the linear bias correction was conducted to the predicated age, where y and $\hat{y}$ denote the chronological age and predicted age, respectively. We fit a linear regression $\hat{y} = \alpha y + \beta$ on the left-out validation set with known chronological age. Applying the learned coefficients (α, β), the corrected predicted age $\hat{y}_{co}$ for test set can be estimated by

$$\hat{y}_{co} = \frac{\hat{y} - \beta}{\alpha}$$

where we assume the coefficients (α, β) can be generalised to the test set.

Evaluation of other risk factors and education

Diabetes mellitus and hypercholesterolemia were assessed via the medication history. Body mass index (BMI) was calculated as weight (kg)/height^2 (m); BMI over 30 was diagnosed as obesity. Smoking status was defined as current/previous smoking or not. Apolipoprotein E (APOE) ε4 carrier status was evaluated and was treated as a binary variable (with one/two ε4 alleles or none). More information about APOE genotyping can be found in our previous study that used UK Biobank data[5]. Education was assessed by binarizing the qualifications into two categories (college degree or not).

Sensitivity analysis for one-sample Mendelian randomisation analysis

The sensitivity analysis was conducted to evaluate whether the instrumental variable assumptions are satisfied. The three assumptions are (1) the hypertension PRS is associated with hypertension; (2) the hypertension is not associated with confounders including the chronological age, sex scanner; and (3) the hypertension PRS would only affect the BAGs through its effect on the hypertension.

Four steps were carried out for the sensitivity analyses:

1. Investigating the instrument strength. Statistical power estimate for this 1SMR was carried out using an online instrument (https://shiny.cnsgenomics.com/mRnd/) to generate the F-statistics[6] and power values.
2. To satisfy the independence assumption, we restricted our MR analysis in British White population (Field ID 21000) and controlled for the first 10 genetic principal components.
3. Linear regression model was used to assess the horizontal pleiotropy, i.e. the association between hypertension PRS and the cofounders, including chronological age, sex and scanner.
4. We then regressed the SNP-outcomes associations against the SNP-exposure associations, and meta-analysed across all SNPs in the genetic variants. we mimicked two-sample MR (2SMR) approaches by regressing the SNP-outcomes associations against the SNP-exposure associations, and meta-analysing across all SNPs in the genetic variants. “TwoSampleMR” package was used to perform the analysis[7]. Multiple methods were applied in the 2SMR setting to report the results, including fixed-effects inverse-variance weighted (IVW), random-effects IVW, MR Egger and weighted median. The intercept term in MR Egger regression and MR-PRESSOR [8] were used to indicate directional horizontal pleiotropy.

Supplementary Analysis and Results

Associations between BP categories and BAGs stratified by antihypertensive medication status

Associations between BP categories and BAGs stratified by different antihypertensive medication status were investigated using ANCOVA. The results were shown in Supplementary Figure S2. After controlling for chronological age, sex, scanner, diabetes, hypercholesterolemia, obesity, smoking and APOE status, for those who were not on antihypertensive drugs, both GM and WM showed increased BAGs with elevated BP. As shown in Figure S2A, BAG_{GM} at Grade 2 hypertension had a brain 0.792 ± 0.157 years older than normal BP ($p < 0.001$, 95% CI = 0.378 ~ 1.207), and 0.667 ± 0.164 years older than high-normal BP ($p < 0.001$, 95% CI = 0.235 ~ 1.100). Participants with BAG_{GM} at Grade 1 hypertension showed 0.499 ± 0.107 years larger than normal BP ($p < 0.001$, 95% CI = 0.216 ~ 0.783), and 0.374 ± 0.119 years older than high-normal BP ($p = 0.010$, 95% CI = 0.060 ~ 0.687). For BAG_{WM} (Figure S2B), participants who were not on medication showed 1.443 ± 0.162 years larger BAG_{WM} at Grade 2 hypertension than normal BP ($p < 0.001$, 95% CI = 1.015 ~ 1.872), 1.156 ± 0.170 years older than high-normal BP ($p < 0.001$, 95% CI = 0.708 ~ 1.604), and 0.774 ± 0.163 years older than Grade 1 hypertension ($p < 0.001$, 95% CI = 0.344 ~ 1.204). BAG_{WM} at Grade 1 hypertension was 0.669 ± 0.111 years older than normal BP ($p < 0.001$, 95% CI = 0.375 ~ 0.963), and 0.382 ± 0.124 years larger than high-normal BP ($p = 0.012$, 95% CI = 0.056 ~ 0.708). However, regarding those participants who were on medication, both GM and WM showed positive BAGs and no significant differences of BAGs were found across all four groups (all p values > 0.05). In addition, BAG_{GM} for participants with antihypertensive medication history at each BP category was significantly larger than those without medication (all p values < 0.001). BAG_{WM} showed the similar results from normal BP to Grade 1 hypertension (all p values < 0.001) except for Grade 2 hypertension ($p = 0.188$).

Supplementary Figure S2 here

Different associations between BP status and BAGs were observed when we stratified the antihypertensive medication status. For those who did not take antihypertensive medication, a higher BP category was found to be associated with the increasing BAG_{GM} and BAG_{WM}. However, in this study, for those who were on antihypertensive medication, increasing trends of BAGs were observed with the raised BP, however, it was not statistically significant. This result suggested that the brain impairment was not alleviated even the BP was controlled to normal or high-normal categories after antihypertensive medication. In addition, those who were on antihypertensive medicine still have relatively older brain age than those who were not on medication at each BP category, which might provide further evidence that the beneficial effect of antihypertensive medication on reducing structural brain impairment was limited. This finding may be against the existed literature that good control of high BP can be an effective therapeutic strategy associated with reduced risk of stroke and myocardial infarction[9], and also incident dementia and Alzheimer's disease[10]. However, given that limited studies have investigated the association between antihypertensive medication and an intermediate outcome, i.e. brain structural changes, whether the antihypertensive medication is beneficial to reverse brain structural impairment continues to be inclusive[11]. Some have reported that intensive BP control can reduce the acceleration of WMH progression[12, 13], whereas some studies also observed no effect of antihypertensive medication on the brain atrophy[14]. The duration of taking medication and the subtypes of antihypertensive drugs may also affect the results. Further subgroup analyses might provide more insights into this research question.

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Supplementary Tables

Table S1 Glossary of the terminology used for the deep learning model

Full name	Meaning
Adaptive Momentum (Adam)	A powerful gradient descent method.
Batch normalization	A common operator on the input or output of the activation functions, which can speed training and reduce overfitting.
Batch size	The number of samples used in one training iteration.
Data loader	An operator wraps an iterable around the dataset to enable easy access to the samples
Data augmentation	A series of operators which rotate, stretch, and reflect each sample to produce many variants of the original sample, enriching the training set to enable excellent training.
Epoch	The number of full training passes over the entire training set.
Loss function	a measure of how far a model's prediction is from its target.
Learning rate	A multiplier that controls the degree to which each gradient descent increases or decreases the model weights. Training will take longer if it is too small or cannot convergence if it is very large high.
Mean squared error (MSE)	A loss function that calculates the average of the square of the difference between target values and the model predication over a set of samples.
Multilayer perceptron (MLP)	A kind of neural network architecture for learning from 1-dimensional data or simple 2-dimensional data.
Optimizer	A specific implementation of the gradient descent algorithm, e.g., AdaGrad and Adam.
Rectified Linear Unit (ReLU)	An activation function which outputs zero if input is negative or zero, and outputs the input itself if input is positive, which enables a neural network to learn nonlinear relationships.
Validation dataset	A hold-out subset of the dataset that performs initial evaluation against a trained model.
Workers	A parameter enables multi-process data loading with the specified number of loader worker processes
weight decay	A regularization technique by adding a small penalty to the loss function to avoid overfitting.
3D-convolutional neural network (3D-CNN)	A kind of neural network architecture for learning from complex 3-dimensional data, e.g., medical images

Table S2 Summary of genetic variants used for calculating hypertension PRS

SNP	chrom	pos	effect allele	other allele	beta	se	pval
rs10061297	5	88170007	T	C	-0.05415	0.008824	8.45E-10
rs10077410	5	122450771	A	G	0.052941	0.007993	3.50E-11
rs10265221	7	151414329	C	T	0.039065	0.006065	1.19E-10
rs10504744	8	82790203	C	G	-0.03565	0.005549	1.32E-10
rs10749408	10	122967526	T	C	-0.03336	0.005886	1.45E-08
rs1077394	6	31610384	T	C	0.043141	0.005846	1.59E-13
rs10926978	1	243431654	C	T	0.035123	0.005863	2.09E-09
rs10995307	10	64552242	C	T	-0.03007	0.005502	4.63E-08
rs11039216	11	47406592	T	C	0.042323	0.005504	1.48E-14
rs11064885	12	110498432	A	C	-0.05448	0.009143	2.55E-09
rs11072508	15	75062397	T	C	-0.05427	0.005888	3.07E-20
rs11099098	4	81169912	T	G	0.098227	0.006037	1.58E-59
rs111663960	6	26082220	G	A	0.060009	0.008291	4.55E-13
rs11168327	12	48345975	T	C	0.036041	0.006241	7.71E-09
rs1116969	2	159312164	C	G	-0.04086	0.006168	3.50E-11
rs11191580	10	104906211	C	T	-0.08873	0.010362	1.10E-17
rs11231711	11	63929215	A	G	0.072015	0.011811	1.08E-09
rs115262049	2	43196694	T	A	-0.05724	0.009779	4.82E-09
rs11556924	7	129663496	T	C	-0.03824	0.005621	1.02E-11
rs11774829	8	105978368	A	T	-0.06677	0.009357	9.56E-13

rs11864054	16	30846134	A	G	0.03911 6	0.00568 4	5.92E-12
rs11866219	16	69549749	C	A	-0.03197	0.00566	1.61E-08
rs1186699	2	61662555	A	C	-0.03437	0.00574 5	2.20E-09
rs12035750	1	89332099	C	T	0.04148 4	0.00565 2	2.14E-13
rs12258967	10	18727959	G	C	-0.05301	0.00601 1	1.17E-18
rs12413195	10	18470329	C	T	0.04391 1	0.00647 6	1.19E-11
rs12426667	12	54433483	C	A	-0.04561	0.00604 7	4.60E-14
rs12482030	21	37718587	T	G	0.04917 3	0.00828 2	2.90E-09
rs12514965	5	11398889 3	C	T	0.04712 1	0.00646 2	3.05E-13
rs12753716	1	11928641	C	T	-0.06912	0.01133 8	1.09E-09
rs1275988	2	26914364	T	C	-0.0737	0.00565 1	7.11E-39
rs1278719	3	13596156 9	A	G	0.04401 6	0.00649 8	1.25E-11
rs12925388	16	81616668	G	A	0.04602 9	0.00555 8	1.21E-16
rs12948326	17	43188117	G	T	0.03274 2	0.00578 4	1.50E-08
rs12978472	19	7257990	G	C	-0.09645	0.00833 8	6.07E-31
rs13112725	4	10691174 2	C	G	0.04561	0.00642 6	1.27E-12
rs13150093	4	15651673 0	A	G	-0.03002	0.00549 4	4.65E-08
rs1436138	17	75316880	G	A	-0.0393	0.00576 9	9.64E-12
rs1507154	6	79503700	T	C	0.03600 1	0.00548 9	5.42E-11
rs1558902	16	53803574	A	T	0.03761 3	0.00558 7	1.67E-11
rs1650581	5	15751675 3	G	C	0.05206 6	0.00628 4	1.17E-16
rs16853173	3	16883283 5	T	C	-0.07026	0.01063 2	3.90E-11
rs16895971	4	17884986	C	T	0.04630 8	0.00795 9	5.94E-09
rs169080	19	4980864	C	T	-0.03588	0.00574 2	4.13E-10
rs1717200	15	41368334	G	A	0.03804 8	0.0055	4.59E-12

rs17264887	2	183213152	G	A	-0.03382	0.005541	1.04E-09
rs17335134	2	43753906	G	A	-0.04247	0.006187	6.70E-12
rs17608766	17	45013271	C	T	0.060999	0.007689	2.14E-15
rs17747401	10	76400164	T	C	-0.03358	0.005753	5.33E-09
rs1801253	10	115805056	C	G	0.06183	0.006309	1.10E-22
rs1882961	21	16556367	T	C	0.036485	0.006007	1.25E-09
rs188315257	2	25241386	G	T	-0.06238	0.009625	9.11E-11
rs2014590	3	169146497	T	C	-0.03847	0.005492	2.47E-12
rs2046823	3	56779011	A	G	-0.03729	0.006296	3.16E-09
rs2238280	14	72425522	C	T	0.034914	0.006387	4.60E-08
rs2298359	21	33671140	C	T	-0.06678	0.011099	1.78E-09
rs2306363	11	65405600	T	G	-0.04649	0.006795	7.85E-12
rs2327429	6	134209837	C	T	-0.04081	0.006058	1.63E-11
rs2443708	3	11545719	C	T	0.036046	0.005942	1.30E-09
rs2493136	1	230851536	T	C	0.035433	0.005597	2.44E-10
rs2521501	15	91437388	T	A	0.067602	0.005939	5.10E-30
rs2643826	3	27562988	T	C	0.049387	0.005532	4.33E-19
rs2681485	12	90025622	A	G	0.054497	0.005596	2.05E-22
rs268263	2	164954174	A	T	0.03739	0.006485	8.13E-09
rs2735357	10	89662504	G	A	0.036088	0.006323	1.15E-08
rs2760061	1	228191075	A	T	0.038194	0.00561	9.85E-12
rs2820290	1	201783682	G	A	0.030449	0.005533	3.74E-08
rs28416181	8	25905963	G	T	-0.04314	0.006372	1.28E-11
rs28431893	9	113174023	A	G	0.094363	0.014895	2.37E-10
rs28667801	4	26785356	T	A	0.04547	0.005644	7.89E-16

rs2906163	7	2516594	T	C	-0.04207	0.00576 5	2.92E-13
rs34869093	16	51757242	G	A	0.03344 4	0.00568 3	3.99E-09
rs35429	12	11555586 7	G	A	-0.04783	0.00564 2	2.27E-17
rs35479618	1	15366242 3	A	G	0.13227 2	0.02073 1	1.76E-10
rs35593046	3	53553923	T	G	-0.05088	0.00637 2	1.40E-15
rs36071027	5	15844427 4	T	C	-0.04061	0.00572 8	1.34E-12
rs3790604	1	11304687 9	A	C	0.10022 7	0.01047	1.04E-21
rs3796205	3	12463934 4	C	G	-0.03337	0.00577 1	7.37E-09
rs3796581	4	15664288 4	G	A	-0.06493	0.00709 1	5.33E-20
rs3802228	8	14399221 8	G	A	-0.03053	0.00550 1	2.86E-08
rs3803266	13	30154349	C	G	-0.04423	0.00649 5	9.75E-12
rs3858446	11	32450890	G	A	0.03170 3	0.00573	3.16E-08
rs3863248	8	81407872	G	C	-0.03906	0.00651 5	2.04E-09
rs3902740	2	37506166	C	T	-0.03123	0.00563 6	2.99E-08
rs3918226	7	15069017 6	T	C	0.13022 8	0.01023	4.04E-37
rs3936510	5	55860866	T	G	0.04282 2	0.00681 3	3.28E-10
rs42038	7	92243719	T	C	-0.03307	0.00601	3.75E-08
rs426570	11	16907008	T	C	0.03788 4	0.00599 2	2.58E-10
rs4277405	17	61548918	T	C	-0.04341	0.00566 8	1.88E-14
rs4363897	17	46815947	C	G	0.07602 8	0.01294 5	4.28E-09
rs4375757	18	48784953	T	C	0.06524 2	0.00973 5	2.06E-11
rs448385	1	25395133	A	G	0.03457 9	0.00552 9	3.99E-10
rs4609031	6	51145245	A	G	0.03782 5	0.00666 8	1.40E-08
rs4690774	4	14408532 7	T	A	-0.03489	0.00549 2	2.13E-10
rs4755737	11	43791865	A	G	-0.04079	0.00549 9	1.21E-13

rs4785581	16	89699664	A	C	-0.03481	0.00558 7	4.68E-10
rs483071	13	22294117	T	C	0.04442 6	0.0058	1.87E-14
rs4833586	4	11139113 9	G	A	-0.05151	0.00769 2	2.13E-11
rs4873492	8	51947549	T	C	0.04483 1	0.00735 4	1.09E-09
rs4910498	11	9765503	T	A	0.04406 9	0.00572 8	1.43E-14
rs4942041	13	41931507	A	T	0.05805 5	0.01047 8	3.01E-08
rs516246	19	49206172	T	C	0.03528 1	0.00549 9	1.40E-10
rs56163207	18	57939298	G	A	0.03296 5	0.00593 7	2.82E-08
rs56393506	6	16108930 7	T	C	0.04468 5	0.00753	2.95E-09
rs56403963	7	1946130	G	C	-0.04196	0.00733 9	1.08E-08
rs569550	11	1887068	G	T	0.05971 1	0.00565 1	4.24E-26
rs57139556	6	15099851 1	G	A	-0.09828	0.01072 6	5.07E-20
rs57748895	1	11582616 9	T	A	0.13351 1	0.02052	7.70E-11
rs57866767	10	96023077	C	T	-0.04392	0.00553 6	2.13E-15
rs57946343	10	63499951	C	T	-0.09669	0.00769 5	3.27E-36
rs6031431	20	42795152	G	A	0.04055 1	0.00556 8	3.27E-13
rs604723	11	10061054 6	C	T	0.07725 5	0.00623 5	2.93E-35
rs61056117	7	27245997	T	A	0.08180 3	0.01051 9	7.44E-15
rs6108168	20	8626271	A	C	-0.05017	0.00629 9	1.66E-15
rs6108787	20	10967214	G	T	0.05444 6	0.00549	3.48E-23
rs6119758	20	30649661	G	A	0.04090 9	0.00623 8	5.46E-11
rs61772626	1	57015668	G	A	0.05519 1	0.00832 7	3.40E-11
rs62481856	7	10641208 2	A	G	0.05156 8	0.00686 9	6.03E-14
rs6271	9	13652227 4	T	C	-0.06438	0.01053 2	9.76E-10
rs6445597	3	53734531	A	G	0.04038 8	0.00592 4	9.25E-12

rs6488549	12	12890168	T	A	-0.03477	0.00556 4	4.13E-10
rs6812640	4	38387900	G	C	-0.03443	0.00559 6	7.66E-10
rs6860901	5	12787175 0	T	C	0.04682 1	0.00593 6	3.09E-15
rs6923071	6	12718850 2	T	C	0.06416 5	0.00556 8	9.90E-31
rs6932812	6	16618094 7	G	C	-0.06181	0.01103 6	2.13E-08
rs6961048	7	27328187	G	C	0.06794 7	0.00909 4	7.90E-14
rs6985028	8	30822094	A	G	-0.03514	0.00551 3	1.83E-10
rs7129204	11	12252721 2	C	G	0.05096 7	0.00841 3	1.38E-09
rs7174222	15	81018543	T	C	0.05129 8	0.00550 4	1.16E-20
rs7233089	18	42422069	G	A	-0.03452	0.00615 7	2.07E-08
rs72762705	16	4020732	T	C	-0.0444	0.00702 4	2.59E-10
rs7302981	12	50537815	G	A	-0.04214	0.00566 1	9.67E-14
rs73046792	19	49605705	A	G	-0.04983	0.00739 1	1.56E-11
rs73105845	12	48135607	C	T	-0.0549	0.00978 8	2.03E-08
rs7310615	12	11186504 9	G	C	-0.0628	0.00553 1	7.14E-30
rs74439044	17	7781019	C	T	0.05972 2	0.00923	9.79E-11
rs74884762	2	54797113	A	C	0.03951 6	0.00703 6	1.95E-08
rs74900445	8	95268903	C	T	0.05271 4	0.00844 1	4.23E-10
rs751984	11	61278246	C	T	-0.04787	0.00875 2	4.50E-08
rs75511781	7	13132371 0	G	A	0.08155	0.01344 9	1.33E-09
rs7700842	5	15782418 3	C	T	-0.05715	0.00568 9	9.57E-24
rs7733331	5	32828846	C	T	0.06547 3	0.00561 5	2.01E-31
rs7764523	6	43349795	A	G	0.04423 9	0.00586 8	4.74E-14
rs7768871	6	22109189	T	C	0.03244 8	0.00557 2	5.77E-09
rs77924615	16	20392332	A	G	-0.06392	0.00703 7	1.05E-19

rs7837979	8	10198534	T	C	0.042687	0.005596	2.38E-14
rs78953748	20	57715798	G	T	0.103806	0.008831	6.63E-32
rs79044887	20	47427831	G	C	-0.04772	0.00775	7.40E-10
rs7972957	12	20164203	G	C	0.044241	0.006174	7.71E-13
rs7981842	13	73830609	C	T	-0.07045	0.01292	4.97E-08
rs800981	7	74196364	T	C	0.03746	0.00687	4.95E-08
rs8061324	16	3541490	G	T	-0.04088	0.006324	1.02E-10
rs8102879	19	1832317	A	G	-0.05	0.006809	2.09E-13
rs880315	1	10796866	C	T	0.065575	0.005856	4.16E-29
rs9798571	20	62438415	A	G	-0.04734	0.006527	4.08E-13
rs9844972	3	150097635	C	G	0.069874	0.011008	2.19E-10
rs9848655	3	138108352	A	G	0.044977	0.00745	1.57E-09

Table S3 Sample sizes of demographics, risk factors, brain ages and cognition for each BP group using ISH guideline

	Normal BP (n = 3598)	**High-normal BP** (n = 2330)	**Grade 1 hypertension** (n = 3393)	**Grade 2 hypertension** (n = 1240)
Demographics				
Chronological age	n = 3598	n = 2330	n = 3393	n = 1240
Sex	n = 3598	n = 2330	n = 3393	n = 1240
Education	n = 3442	n = 2233	n = 3217	n = 1164
Risk factors				
Diabetes	n = 3582	n = 2319	n = 3377	n = 1233
Hypercholesterolemia	n = 3564	n = 2308	n = 3367	n = 1231
Obesity	n = 3563	n = 2313	n = 3365	n = 1219
Smoking	n = 3574	n = 2314	n = 3363	n = 1230
APOE ε4 carriers	n = 2990	n = 1966	n = 2825	n = 1026
Anti-hypertensive medication	n = 3564	n = 2308	n = 3367	n = 1231
Brain ages				
GM brain age	n = 3598	n = 2330	n = 3393	n = 1240
BAG_{GM}	n = 3598	n = 2330	n = 3393	n = 1240
WM brain age	n = 3516	n = 2253	n = 3304	n = 1216
BAG_{WM}	n = 3516	n = 2253	n = 3304	n = 1216
Cognition				
Processing speed	n = 2227	n = 1523	n = 2223	n = 848
Executive function	n = 2172	n = 1478	n = 2136	n = 811
Memory	n = 2292	n = 1556	n = 2285	n = 871
Global cognition	n = 2224	n = 1520	n = 2219	n = 846

This table shows the total numbers of the participants for each measure in analysis. Abbreviations: ISH = International Society of Hypertension; BP = blood pressure; SD = standard deviation; APOE = apolipoprotein E; GM = grey matter; WM = white matter; BAG_{GM} = grey matter brain age gap; BAG_{WM} = white matter brain age gap.

Table S4 Deep learning model performances

	GM brain age					WM brain age			
	Before bias correction		After bias correction			Before bias correction		After bias correction	
	MAE	Pearson's r	MAE	Pearson's r		MAE	Pearson's r	MAE	Pearson's r
Training set (n = 21149)	0.329	0.999	-	-	Training set (n = 19546)	0.334	0.999	-	-
Validation set (n = 7050)	2.470	0.912	-	-	Validation set (n = 6515)	2.525	0.909	-	-
Healthy test set (n = 6506)	2.462	0.910	2.727	0.910	Healthy test set (n = 7769)	2.511	0.908	2.754	0.908
All test set (n = 11431)	2.502	0.908	2.767	0.908	All test set (n = 11168)	2.572	0.902	2.839	0.902

Abbreviations: GM = grey matter; WM = white matter; MAE = mean absolute error; Pearson's r = Pearson's correlation coefficient.

Table S5 Pairwise comparison across each ISH group at different BAG levels

BAGs	(I) ISHgroup	(J) ISHgroup	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[b]	
						Lower Bound	Upper Bound
BAG_{GM}	1	2	-0.090	0.104	1	-0.363	0.184
		3	-0.430*	0.097	p < 0.001	-0.685	-0.174
		4	-0.737*	0.134	p < 0.001	-1.090	-0.385
	2	1	0.090	0.104	1	-0.184	0.363
		3	-0.340*	0.104	0.006	-0.614	-0.066
		4	-0.648*	0.138	p < 0.001	-1.011	-0.285
	3	1	0.430*	0.097	p < 0.001	0.174	0.685
		2	0.340*	0.104	0.006	0.066	0.614
		4	-0.307	0.129	0.101	-0.647	0.032
	4	1	0.737*	0.134	p < 0.001	0.385	1.090
		2	0.648*	0.138	p < 0.001	0.285	1.011
		3	0.307	0.129	0.101	-0.032	0.647
BAG_{WM}	1	2	-0.273	0.106	0.062	-0.553	0.008
		3	-0.592*	0.099	p < 0.001	-0.854	-0.330
		4	-1.235*	0.137	p < 0.001	-1.597	-0.873
	2	1	0.273	0.106	0.062	-0.008	0.553
		3	-0.319*	0.107	0.017	-0.600	-0.038
		4	-0.963*	0.141	p < 0.001	-1.335	-0.59
	3	1	0.592*	0.099	p < 0.001	0.330	0.854
		2	0.319*	0.107	0.017	0.038	0.600
		4	-0.643*	0.132	p < 0.001	-0.992	-0.295
	4	1	1.235*	0.137	p < 0.001	0.873	1.597
		2	0.963*	0.141	p < 0.001	0.590	1.335
		3	0.643*	0.132	p < 0.001	0.295	0.992

Based on estimated marginal means; * indicated the mean difference is significant at the 0.05 level. a indicated the adjustment for multiple comparisons: Bonferroni. 1, 2, 3, 4 indicated the

four ISH categories, from Normal BP to Normal-high BP to Grade 1 hypertension and Grade 2 hypertension.
Abbreviations: ISH = International Society of Hypertension; BAG_{GM} = grey matter brain age gap; BAG_{WM} = white matter brain age gap.

Table S6 Pairwise comparison between BAG_{GM} and BAG_{WM} at different ISH levels

ISHgroup	(I) BAG_{GM}	(J) BAG_{WM}	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[b]	
						Lower Bound	Upper Bound
Normal	1	2	-0.012	0.060	0.836	-0.130	0.105
High-Normal	1	2	-0.195*	0.071	0.006	-0.335	-0.056
Grade 1 hypertension	1	2	-0.174*	0.060	0.004	-0.292	-0.056
Grade 2 hypertension	1	2	-0.510*	0.101	p < 0.001	-0.708	-0.313

Based on estimated marginal means; * indicated the mean difference is significant at the 0.05 level. a indicated the djustment for multiple comparisons: Bonferroni. 1 and 2 indicated the BAG_{GM} and BAG_{WM} separately.
Abbreviations: ISH = International Society of Hypertension; BAG_{GM} = grey matter brain age gap; BAG_{WM} = white matter brain age gap.

Table S7 Sensitivity analysis and pleiotropy analysis for causal effect of hypertension on brain ageing in 2SMR method

	IVW		MR Egger		Weighted median		MR PRESSO		Horizontal pleiotropy	
	beta	p value	beta	p value	beta	p value	Global test P	Correct P*	Egger Intercept P	
BAG_{GM}	1.078347	0.014752	1.033	0.172668	0.545368	0.396132	170.9439	NA	0.000583	0.940908
BAG_{WM}	1.807963	0.000109	1.194	0.1349	1.341693	0.049622	172.8107	NA	0.007901	0.340486

Abbreviations: IVW = inverse-variance weighted; MR= Mendelian randomisation; 2SMR = two-sample MR; BAG_{WM} = white matter brain age gap.

Table S8 Summary of genetic variants used to estimate the effect of hypertension on GM ageing in 2SMR methods

exposure	outcome	SNP	effect allele	beta_exposure	se_exposure	pval_exposure	beta_outcome	se_outcome	pval_outcome
Hypertension	BAG_{GM}	rs10061297	T	-0.01441	0.01081	1.83E-01	-0.00811	0.075753	9.15E-01
Hypertension	BAG_{GM}	rs10077410	A	0.027112	0.009772	5.54E-03	0.018241	0.068275	7.89E-01
Hypertension	BAG_{GM}	rs10265221	C	0.001239	0.007399	8.67E-01	0.036625	0.0517	4.79E-01
Hypertension	BAG_{GM}	rs10504744	C	0.006014	0.006701	3.70E-01	0.052765	0.047029	2.62E-01
Hypertension	BAG_{GM}	rs10749408	C	0.014499	0.007158	4.28E-02	0.094818	0.050073	5.83E-02
Hypertension	BAG_{GM}	rs1077394	C	-0.00495	0.007041	4.82E-01	0.009081	0.049279	8.54E-01
Hypertension	BAG_{GM}	rs10926978	C	0.002467	0.0072	7.32E-01	-0.04608	0.050266	3.59E-01
Hypertension	BAG_{GM}	rs10995307	C	-0.0029	0.006723	6.66E-01	0.021481	0.046926	6.47E-01
Hypertension	BAG_{GM}	rs11039216	C	-0.01503	0.006626	2.33E-02	-0.01031	0.046412	8.24E-01
Hypertension	BAG_{GM}	rs11064885	A	-0.01217	0.010746	2.57E-01	0.045648	0.075378	5.45E-01
Hypertension	BAG_{GM}	rs11072508	C	0.013433	0.007181	6.14E-02	0.053991	0.050371	2.84E-01
Hypertension	BAG_{GM}	rs11099098	T	0.012127	0.007428	1.03E-01	0.048093	0.05193	3.54E-01
Hypertension	BAG_{GM}	rs111663960	G	0.018237	0.010355	7.82E-02	-0.02595	0.072565	7.21E-01
Hypertension	BAG_{GM}	rs11168327	T	0.009869	0.007603	1.94E-01	0.110493	0.053137	3.76E-02
Hypertension	BAG_{GM}	rs1116969	C	-0.00245	0.007625	7.48E-01	0.000683	0.053268	9.90E-01

Hypertension	BAG_{GM}	rs11191580	C	-0.01426	0.012315	2.47E-01	-0.06479	0.085948	4.51E-01
Hypertension	BAG_{GM}	rs11231711	A	0.001775	0.01397	8.99E-01	-0.04025	0.098185	6.82E-01
Hypertension	BAG_{GM}	rs115262049	T	-0.02122	0.012037	0.077896	-0.09782	0.084783	0.248616
Hypertension	BAG_{GM}	rs11556924	T	-0.0102	0.006832	0.135544	0.035755	0.047833	0.454782
Hypertension	BAG_{GM}	rs11774829	A	-0.00417	0.011416	0.714621	0.042906	0.079991	0.591702
Hypertension	BAG_{GM}	rs11864054	G	-0.00686	0.006926	0.321779	0.010918	0.048569	0.822149
Hypertension	BAG_{GM}	rs11866219	A	-9.1E-05	0.00693	0.989544	0.103133	0.048425	0.033217
Hypertension	BAG_{GM}	rs1186699	A	-0.00891	0.006941	0.199376	-0.09522	0.04861	0.050162
Hypertension	BAG_{GM}	rs12035750	C	-0.00696	0.006896	0.31296	-0.03108	0.048186	0.518938
Hypertension	BAG_{GM}	rs12258967	G	-0.01785	0.007302	0.014494	-0.00931	0.051154	0.855628
Hypertension	BAG_{GM}	rs12413195	C	-0.00672	0.007797	0.388471	0.008964	0.05467	0.869768
Hypertension	BAG_{GM}	rs12426667	C	-0.01543	0.007392	0.036836	0.010286	0.051657	0.842166
Hypertension	BAG_{GM}	rs12482030	T	0.011755	0.010227	0.250394	0.013745	0.071264	0.84706
Hypertension	BAG_{GM}	rs12514965	C	-0.00624	0.00781	0.424577	0.000751	0.05469	0.989042
Hypertension	BAG_{GM}	rs12753716	C	-0.03507	0.01361	0.009994	0.252208	0.095631	0.008368
Hypertension	BAG_{GM}	rs1275988	C	0.017667	0.006892	0.010385	-0.03189	0.048176	0.508015
Hypertension	BAG_{GM}	rs1278719	G	-0.00801	0.007934	0.312905	0.015968	0.055513	0.77362
Hypertension	BAG_{GM}	rs12925388	A	-0.00072	0.006779	0.915945	-0.04422	0.047397	0.35088
Hypertension	BAG_{GM}	rs12948326	G	0.009655	0.007052	0.171041	-0.20501	0.049318	3.25E-05
Hypertension	BAG_{GM}	rs12978472	G	-0.0167	0.009962	0.093645	-0.06353	0.069488	0.36064
Hypertension	BAG_{GM}	rs13112725	G	-0.00974	0.007779	0.210824	0.057576	0.054508	0.290863
Hypertension	BAG_{GM}	rs13150093	A	-0.00633	0.006667	0.342418	-0.00237	0.046492	0.959427
Hypertension	BAG_{GM}	rs1436138	G	-0.00144	0.007017	0.837929	-0.09486	0.049195	0.053856
Hypertension	BAG_{GM}	rs1507154	T	0.008232	0.006607	0.212857	0.10045	0.046282	0.03
Hypertension	BAG_{GM}	rs1558902	A	-0.0031	0.0068	0.648847	0.052271	0.04769	0.273073
Hypertension	BAG_{GM}	rs1650581	G	-0.00056	0.007688	0.942097	0.037485	0.053889	0.486692
Hypertension	BAG_{GM}	rs16853173	T	-0.0014	0.012568	0.91133	0.037983	0.087567	0.664472

Hypertension	BAG_{GM}	rs16895971	C	-0.01157	0.009627	0.22956	0.006394	0.067376	0.92439
Hypertension	BAG_{GM}	rs169080	T	0.006882	0.006999	0.325473	-0.0705	0.048758	0.14822
Hypertension	BAG_{GM}	rs1717200	G	-0.00264	0.00673	0.694556	-0.0165	0.04704	0.725812
Hypertension	BAG_{GM}	rs17264887	G	-0.00232	0.006794	0.732554	-0.02678	0.047508	0.57299
Hypertension	BAG_{GM}	rs17335134	G	-0.00316	0.007564	0.67658	0.041527	0.052789	0.431496
Hypertension	BAG_{GM}	rs17608766	C	0.015221	0.009402	0.105517	0.175741	0.065943	0.007708
Hypertension	BAG_{GM}	rs17747401	T	-0.02213	0.007009	0.001598	-0.06512	0.049032	0.184197
Hypertension	BAG_{GM}	rs1801253	G	-0.01424	0.007652	0.062734	0.002126	0.053524	0.96831
Hypertension	BAG_{GM}	rs1882961	T	0.000418	0.007348	0.9546	-0.00405	0.051316	0.937168
Hypertension	BAG_{GM}	rs188315257	G	-0.0096	0.011637	0.409446	-0.09431	0.081309	0.246101
Hypertension	BAG_{GM}	rs2014590	T	-0.01103	0.006668	0.098205	0.049974	0.04666	0.284183
Hypertension	BAG_{GM}	rs2046823	A	-0.02033	0.007667	0.008014	0.072229	0.05364	0.17815
Hypertension	BAG_{GM}	rs2238280	T	0.003892	0.00778	0.616947	-0.00032	0.054613	0.995325
Hypertension	BAG_{GM}	rs2298359	C	-0.00768	0.013634	0.573386	0.113829	0.095064	0.231178
Hypertension	BAG_{GM}	rs2306363	T	-0.01327	0.00824	0.10739	-0.06749	0.05769	0.242107
Hypertension	BAG_{GM}	rs2327429	C	-0.00848	0.007367	0.249456	0.091219	0.051686	0.077612
Hypertension	BAG_{GM}	rs2443708	T	0.002322	0.00728	0.749757	0.046371	0.050917	0.362464
Hypertension	BAG_{GM}	rs2493136	T	0.018054	0.00687	0.008607	-0.00701	0.048107	0.884105
Hypertension	BAG_{GM}	rs2521501	T	0.006727	0.007294	0.356429	0.017186	0.050978	0.736028
Hypertension	BAG_{GM}	rs2643826	T	0.004006	0.006749	0.552801	0.003247	0.047138	0.945087
Hypertension	BAG_{GM}	rs2681485	G	-0.01959	0.006773	0.003836	-0.09914	0.047346	0.036295
Hypertension	BAG_{GM}	rs268263	T	-0.01683	0.007805	0.031032	-0.03079	0.054647	0.573193
Hypertension	BAG_{GM}	rs2735357	A	-0.00724	0.007691	0.346747	0.046862	0.053568	0.381699
Hypertension	BAG_{GM}	rs2760061	A	0.005453	0.006836	0.425068	0.038509	0.047892	0.421364
Hypertension	BAG_{GM}	rs2820290	A	0.000882	0.006697	0.89517	0.059259	0.046813	0.20559
Hypertension	BAG_{GM}	rs28416181	G	-0.01138	0.007685	0.138653	0.005689	0.053723	0.915674
Hypertension	BAG_{GM}	rs28431893	A	0.007838	0.01803	0.663785	-0.09758	0.126603	0.440882

Hypertension	BAG_{GM}	rs28667801	T	-0.00176	0.006842	0.797489	0.10613	0.047888	0.026698
Hypertension	BAG_{GM}	rs2906163	C	0.011432	0.007099	0.10732	-0.01814	0.049704	0.715133
Hypertension	BAG_{GM}	rs34869093	G	0.006115	0.006975	0.380681	0.060049	0.048736	0.217928
Hypertension	BAG_{GM}	rs35429	G	0.001284	0.006858	0.851454	-0.05369	0.04785	0.261853
Hypertension	BAG_{GM}	rs35479618	A	-0.02624	0.024346	0.281118	0.095027	0.172317	0.581324
Hypertension	BAG_{GM}	rs35593046	T	2.24E-05	0.007796	0.997709	0.039287	0.054551	0.471427
Hypertension	BAG_{GM}	rs36071027	T	-0.0056	0.007006	0.42376	-0.00672	0.049027	0.891046
Hypertension	BAG_{GM}	rs3790604	A	0.001584	0.012742	0.901074	0.038708	0.089317	0.664751
Hypertension	BAG_{GM}	rs3796205	C	0.003366	0.007014	0.631292	0.109042	0.048957	0.025948
Hypertension	BAG_{GM}	rs3796581	G	-0.00861	0.00847	0.309543	-0.01328	0.059576	0.823668
Hypertension	BAG_{GM}	rs3802228	A	0.013425	0.006718	0.045718	-0.00713	0.046987	0.879441
Hypertension	BAG_{GM}	rs3803266	G	0.005919	0.007933	0.455595	0.021716	0.055339	0.694754
Hypertension	BAG_{GM}	rs3858446	G	0.006336	0.006972	0.36352	0.050635	0.048777	0.299249
Hypertension	BAG_{GM}	rs3863248	G	-0.00789	0.007771	0.310148	-0.00917	0.05436	0.866073
Hypertension	BAG_{GM}	rs3902740	T	-0.0023	0.006871	0.738132	-0.08281	0.048024	0.084688
Hypertension	BAG_{GM}	rs3918226	T	0.02062	0.012861	0.108902	0.0045	0.089785	0.960029
Hypertension	BAG_{GM}	rs3936510	T	0.00193	0.008364	0.817558	-0.00491	0.058505	0.933155
Hypertension	BAG_{GM}	rs42038	T	-0.00865	0.007372	0.240783	-0.02348	0.051654	0.649385
Hypertension	BAG_{GM}	rs426570	T	0.010917	0.007338	0.136861	0.089609	0.051315	0.080795
Hypertension	BAG_{GM}	rs4277405	C	0.000249	0.006913	0.971253	0.004169	0.048326	0.931256
Hypertension	BAG_{GM}	rs4363897	C	0.013787	0.015961	0.38775	-0.03376	0.111637	0.762313
Hypertension	BAG_{GM}	rs4375757	T	0.008543	0.012157	0.482241	0.010132	0.085204	0.905341
Hypertension	BAG_{GM}	rs448385	A	0.007813	0.006771	0.248529	0.034986	0.047255	0.459095
Hypertension	BAG_{GM}	rs4609031	A	0.005854	0.008081	0.4688	-0.01284	0.056321	0.819664
Hypertension	BAG_{GM}	rs4690774	T	-0.00171	0.006692	0.798428	-0.0181	0.046712	0.698481
Hypertension	BAG_{GM}	rs4755737	A	-0.00459	0.006708	0.494071	0.064509	0.046862	0.168674
Hypertension	BAG_{GM}	rs4785581	A	0.008722	0.006794	0.199272	0.00037	0.0475	0.993791

Hypertension	BAG_{GM}	rs483071	C	0.003859	0.007011	0.582031	-0.04591	0.049258	0.351367
Hypertension	BAG_{GM}	rs4833586	A	0.009808	0.009289	0.291059	0.075728	0.065012	0.244114
Hypertension	BAG_{GM}	rs4873492	T	-0.00351	0.00893	0.694495	-0.02562	0.062347	0.681147
Hypertension	BAG_{GM}	rs4910498	A	-0.00328	0.006922	0.636114	-0.02803	0.048434	0.562829
Hypertension	BAG_{GM}	rs4942041	T	0.019696	0.012738	0.122093	-0.08767	0.089429	0.32694
Hypertension	BAG_{GM}	rs516246	C	-0.01355	0.006654	0.041754	-0.046	0.046646	0.324045
Hypertension	BAG_{GM}	rs56163207	G	0.000631	0.007217	0.930277	0.038479	0.050534	0.446405
Hypertension	BAG_{GM}	rs56393506	T	0.009271	0.00927	0.317264	-0.00133	0.0646	0.983605
Hypertension	BAG_{GM}	rs56403963	G	0.002065	0.00885	0.815541	-0.02429	0.061894	0.694706
Hypertension	BAG_{GM}	rs569550	G	0.018853	0.006884	0.00618	0.032172	0.04814	0.50396
Hypertension	BAG_{GM}	rs57139556	G	0.006806	0.012558	0.587851	0.009344	0.087867	0.915314
Hypertension	BAG_{GM}	rs57748895	T	0.043684	0.024575	0.075496	-0.01149	0.170392	0.946242
Hypertension	BAG_{GM}	rs57866767	C	-0.00084	0.00667	0.899772	0.13089	0.046683	0.005059
Hypertension	BAG_{GM}	rs57946343	C	-0.01068	0.009424	0.25733	-0.1237	0.065648	0.059541
Hypertension	BAG_{GM}	rs6031431	G	0.010985	0.006802	0.106341	0.010085	0.047334	0.831283
Hypertension	BAG_{GM}	rs604723	T	-0.00956	0.007601	0.208297	0.055737	0.053298	0.295692
Hypertension	BAG_{GM}	rs61056117	A	-0.01001	0.012501	0.423108	-0.12193	0.087267	0.162365
Hypertension	BAG_{GM}	rs6108168	A	-0.00837	0.007659	0.274723	-0.09976	0.053706	0.063274
Hypertension	BAG_{GM}	rs6108787	G	0.009049	0.006671	0.174957	0.032644	0.046722	0.484762
Hypertension	BAG_{GM}	rs6119758	A	-0.00954	0.007618	0.210483	-0.05926	0.053044	0.263925
Hypertension	BAG_{GM}	rs61772626	G	0.022487	0.010025	0.024904	0.006127	0.070258	0.930506
Hypertension	BAG_{GM}	rs62481856	A	-0.0016	0.008422	0.849701	-0.00951	0.058811	0.871607
Hypertension	BAG_{GM}	rs6271	T	-0.0202	0.012455	0.104861	0.032036	0.087461	0.714154
Hypertension	BAG_{GM}	rs6445597	A	0.008683	0.007139	0.223893	0.018195	0.050052	0.71622
Hypertension	BAG_{GM}	rs6488549	T	-0.00206	0.006771	0.760695	-0.02706	0.047366	0.567838
Hypertension	BAG_{GM}	rs6812640	C	0.007466	0.006845	0.275367	-0.01773	0.047854	0.71099
Hypertension	BAG_{GM}	rs6860901	T	0.01101	0.007381	0.135807	0.038914	0.051662	0.451324

Hypertension	BAG_{GM}	rs6923071	T	0.004051	0.006776	0.549925	-0.00381	0.04743	0.936058
Hypertension	BAG_{GM}	rs6932812	G	-0.01539	0.013205	0.243995	-0.07528	0.092533	0.415904
Hypertension	BAG_{GM}	rs6961048	G	0.009783	0.011151	0.38031	0.061296	0.077999	0.431968
Hypertension	BAG_{GM}	rs6985028	G	0.0078	0.006704	0.244617	0.046998	0.046845	0.315761
Hypertension	BAG_{GM}	rs7129204	C	-0.01963	0.01035	0.057894	-0.07861	0.072441	0.277883
Hypertension	BAG_{GM}	rs7174222	T	0.018475	0.006726	0.006027	0.005915	0.047177	0.900225
Hypertension	BAG_{GM}	rs7233089	A	-0.00044	0.007439	0.953047	-0.07366	0.05198	0.156462
Hypertension	BAG_{GM}	rs72762705	T	-5.4E-05	0.008472	0.994898	-0.05516	0.059203	0.351499
Hypertension	BAG_{GM}	rs7302981	A	0.018803	0.006915	0.006556	-0.04141	0.048346	0.391673
Hypertension	BAG_{GM}	rs73046792	A	-0.01965	0.009017	0.029352	-0.07757	0.06318	0.219564
Hypertension	BAG_{GM}	rs73105845	C	0.004917	0.011502	0.66905	-0.07042	0.080638	0.382546
Hypertension	BAG_{GM}	rs7310615	C	0.0111	0.006778	0.101513	0.013682	0.047325	0.772506
Hypertension	BAG_{GM}	rs74439044	C	-0.0029	0.01143	0.800037	0.225406	0.079558	0.004616
Hypertension	BAG_{GM}	rs74884762	A	0.005122	0.008587	0.550868	-0.00618	0.059778	0.917693
Hypertension	BAG_{GM}	rs74900445	C	0.00371	0.010277	0.718064	0.018369	0.071863	0.798261
Hypertension	BAG_{GM}	rs751984	C	-0.01976	0.010684	0.064437	-0.07783	0.07481	0.298194
Hypertension	BAG_{GM}	rs75511781	G	0.021487	0.016323	0.188085	-0.03776	0.114091	0.74066
Hypertension	BAG_{GM}	rs7700842	C	-0.00791	0.006901	0.252031	-0.02248	0.048347	0.641948
Hypertension	BAG_{GM}	rs7733331	T	-0.01416	0.006826	0.038026	-0.06359	0.047787	0.183303
Hypertension	BAG_{GM}	rs7764523	A	0.011879	0.007091	0.093926	-0.01695	0.049602	0.732572
Hypertension	BAG_{GM}	rs7768871	T	0.009789	0.006794	0.149671	-0.0068	0.04761	0.886393
Hypertension	BAG_{GM}	rs77924615	A	-0.00552	0.008569	0.519842	-0.02801	0.05998	0.640553
Hypertension	BAG_{GM}	rs7837979	T	0.004376	0.006865	0.523847	-0.04414	0.047943	0.357204
Hypertension	BAG_{GM}	rs78953748	G	0.026638	0.010995	0.015422	0.062348	0.076867	0.417318
Hypertension	BAG_{GM}	rs79044887	G	-0.0074	0.009314	0.426747	0.02595	0.065166	0.690486
Hypertension	BAG_{GM}	rs7972957	C	0.00023	0.007528	0.975576	0.000371	0.052628	0.994373
Hypertension	BAG_{GM}	rs7981842	T	-0.00302	0.015842	0.848859	-0.00868	0.11092	0.937611

Hypertension	BAG_{GM}	rs800981	T	-0.01006	0.008432	0.232659	-0.04951	0.058804	0.399847
Hypertension	BAG_{GM}	rs8061324	T	0.01096	0.00765	0.151993	-0.01296	0.053689	0.80925
Hypertension	BAG_{GM}	rs8102879	A	-0.00381	0.008231	0.643445	0.016692	0.057579	0.7719
Hypertension	BAG_{GM}	rs880315	C	0.008464	0.007142	0.23599	0.00418	0.049998	0.933381
Hypertension	BAG_{GM}	rs9798571	A	-0.00926	0.007949	0.244058	-0.08504	0.055562	0.125892
Hypertension	BAG_{GM}	rs9844972	C	0.023054	0.013598	0.090028	0.117664	0.09445	0.212873
Hypertension	BAG_{GM}	rs9848655	A	0.008785	0.009061	0.332311	-0.08431	0.063368	0.18341

Table S9 Summary of genetic variants used to estimate the effect of hypertension on WM ageing in 2SMR methods

exposure	outcome	SNP	effect allele	beta_exposure	se_exposure	pval_exposure	beta_outcome	se_outcome	pval_outcome
Hypertension	BAG_{WM}	rs10061297	T	-0.01441	0.01081	1.83E-01	-0.01643	0.079273	8.36E-01
Hypertension	BAG_{WM}	rs10077410	A	0.027112	0.009772	5.54E-03	0.021893	0.071492	7.59E-01
Hypertension	BAG_{WM}	rs10265221	C	0.001239	0.007399	8.67E-01	-0.00751	0.054226	8.90E-01
Hypertension	BAG_{WM}	rs10504744	C	0.006014	0.006701	3.70E-01	0.066427	0.049343	1.78E-01
Hypertension	BAG_{WM}	rs10749408	C	0.014499	0.007158	4.28E-02	0.125665	0.052538	1.68E-02
Hypertension	BAG_{WM}	rs1077394	C	-0.00495	0.007041	4.82E-01	0.049663	0.051628	3.36E-01
Hypertension	BAG_{WM}	rs10926978	C	0.002467	0.0072	7.32E-01	-0.03007	0.052778	5.69E-01
Hypertension	BAG_{WM}	rs10995307	C	-0.0029	0.006723	6.66E-01	0.086995	0.049163	7.68E-02
Hypertension	BAG_{WM}	rs11039216	C	-0.01503	0.006626	2.33E-02	-0.09429	0.048656	5.27E-02
Hypertension	BAG_{WM}	rs11064885	A	-0.01217	0.010746	2.57E-01	-0.08276	0.079073	2.95E-01
Hypertension	BAG_{WM}	rs11072508	C	0.013433	0.007181	6.14E-02	0.034312	0.052812	5.16E-01
Hypertension	BAG_{WM}	rs11099098	T	0.012127	0.007428	1.03E-01	0.023673	0.054412	6.64E-01
Hypertension	BAG_{WM}	rs111663960	G	0.018237	0.010355	7.82E-02	0.117604	0.076087	1.22E-01
Hypertension	BAG_{WM}	rs11168327	T	0.009869	0.007603	1.94E-01	0.033055	0.055741	5.53E-01
Hypertension	BAG_{WM}	rs1116969	C	-0.00245	0.007625	7.48E-01	0.025976	0.055912	6.42E-01
Hypertension	BAG_{WM}	rs11191580	C	-0.01426	0.012315	2.47E-01	-0.0256	0.090029	7.76E-01

Hypertension	BAG_{WM}	rs11231711	A	0.001775	0.01397	8.99E-01	0.170931	0.102801	9.64E-02
Hypertension	BAG_{WM}	rs115262049	T	-0.02122	0.012037	0.077896	-0.01747	0.088786	0.844035
Hypertension	BAG_{WM}	rs11556924	T	-0.0102	0.006832	0.135544	-0.07262	0.050229	0.14828
Hypertension	BAG_{WM}	rs11774829	A	-0.00417	0.011416	0.714621	-0.09431	0.083879	0.260873
Hypertension	BAG_{WM}	rs11864054	G	-0.00686	0.006926	0.321779	-0.08767	0.050987	0.085546
Hypertension	BAG_{WM}	rs11866219	A	-9.1E-05	0.00693	0.989544	0.068377	0.050768	0.178059
Hypertension	BAG_{WM}	rs1186699	A	-0.00891	0.006941	0.199376	-0.05946	0.05099	0.243634
Hypertension	BAG_{WM}	rs12035750	C	-0.00696	0.006896	0.31296	-0.07028	0.050542	0.16438
Hypertension	BAG_{WM}	rs12258967	G	-0.01785	0.007302	0.014494	-0.05254	0.053697	0.327863
Hypertension	BAG_{WM}	rs12413195	C	-0.00672	0.007797	0.388471	0.042426	0.057369	0.459606
Hypertension	BAG_{WM}	rs12426667	C	-0.01543	0.007392	0.036836	-0.04973	0.054154	0.358454
Hypertension	BAG_{WM}	rs12482030	T	0.011755	0.010227	0.250394	0.015554	0.075064	0.835848
Hypertension	BAG_{WM}	rs12514965	C	-0.00624	0.00781	0.424577	0.058542	0.057305	0.307001
Hypertension	BAG_{WM}	rs12753716	C	-0.03507	0.01361	0.009994	0.143272	0.100625	0.154529
Hypertension	BAG_{WM}	rs1275988	C	0.017667	0.006892	0.010385	-0.05682	0.05053	0.260811
Hypertension	BAG_{WM}	rs1278719	G	-0.00801	0.007934	0.312905	0.044165	0.058233	0.448213
Hypertension	BAG_{WM}	rs12925388	A	-0.00072	0.006779	0.915945	-0.09451	0.049644	0.056968
Hypertension	BAG_{WM}	rs12948326	G	0.009655	0.007052	0.171041	-0.16393	0.051848	0.001573
Hypertension	BAG_{WM}	rs12978472	G	-0.0167	0.009962	0.093645	0.002616	0.072872	0.971364
Hypertension	BAG_{WM}	rs13112725	G	-0.00974	0.007779	0.210824	-0.05067	0.057252	0.376154
Hypertension	BAG_{WM}	rs13150093	A	-0.00633	0.006667	0.342418	-0.03777	0.048826	0.439185
Hypertension	BAG_{WM}	rs1436138	G	-0.00144	0.007017	0.837929	-0.14513	0.051542	0.004875
Hypertension	BAG_{WM}	rs1507154	T	0.008232	0.006607	0.212857	0.081974	0.048553	0.091375
Hypertension	BAG_{WM}	rs1558902	A	-0.0031	0.0068	0.648847	-0.02527	0.050051	0.613608
Hypertension	BAG_{WM}	rs1650581	G	-0.00056	0.007688	0.942097	0.109573	0.056464	0.052335
Hypertension	BAG_{WM}	rs16853173	T	-0.0014	0.012568	0.91133	-0.01166	0.092188	0.899359
Hypertension	BAG_{WM}	rs16895971	C	-0.01157	0.009627	0.22956	-0.03577	0.07073	0.613054

Hypertension	BAG_{WM}	rs169080	T	0.006882	0.006999	0.325473	-0.09859	0.051198	0.054178
Hypertension	BAG_{WM}	rs1717200	G	-0.00264	0.00673	0.694556	-0.05865	0.049323	0.234399
Hypertension	BAG_{WM}	rs17264887	G	-0.00232	0.006794	0.732554	-0.01569	0.049777	0.752603
Hypertension	BAG_{WM}	rs17335134	G	-0.00316	0.007564	0.67658	0.026689	0.055342	0.62963
Hypertension	BAG_{WM}	rs17608766	C	0.015221	0.009402	0.105517	0.087852	0.069342	0.205201
Hypertension	BAG_{WM}	rs17747401	T	-0.02213	0.007009	0.001598	-0.03295	0.051451	0.521918
Hypertension	BAG_{WM}	rs1801253	G	-0.01424	0.007652	0.062734	-0.06342	0.056149	0.258726
Hypertension	BAG_{WM}	rs1882961	T	0.000418	0.007348	0.9546	0.104479	0.053847	0.052369
Hypertension	BAG_{WM}	rs188315257	G	-0.0096	0.011637	0.409446	-0.23306	0.085154	0.006213
Hypertension	BAG_{WM}	rs2014590	T	-0.01103	0.006668	0.098205	-0.05145	0.04896	0.293385
Hypertension	BAG_{WM}	rs2046823	A	-0.02033	0.007667	0.008014	0.020367	0.056285	0.717475
Hypertension	BAG_{WM}	rs2238280	T	0.003892	0.00778	0.616947	0.060377	0.057407	0.292944
Hypertension	BAG_{WM}	rs2298359	C	-0.00768	0.013634	0.573386	0.022427	0.099849	0.822289
Hypertension	BAG_{WM}	rs2306363	T	-0.01327	0.00824	0.10739	-0.02659	0.060537	0.660524
Hypertension	BAG_{WM}	rs2327429	C	-0.00848	0.007367	0.249456	0.016103	0.054185	0.766332
Hypertension	BAG_{WM}	rs2443708	T	0.002322	0.00728	0.749757	0.027729	0.0534	0.603581
Hypertension	BAG_{WM}	rs2493136	T	0.018054	0.00687	0.008607	-0.03058	0.050387	0.543893
Hypertension	BAG_{WM}	rs2521501	T	0.006727	0.007294	0.356429	0.058386	0.053607	0.276111
Hypertension	BAG_{WM}	rs2643826	T	0.004006	0.006749	0.552801	-0.0216	0.049504	0.66257
Hypertension	BAG_{WM}	rs2681485	G	-0.01959	0.006773	0.003836	-0.06911	0.049671	0.164165
Hypertension	BAG_{WM}	rs268263	T	-0.01683	0.007805	0.031032	-0.09194	0.057426	0.109421
Hypertension	BAG_{WM}	rs2735357	A	-0.00724	0.007691	0.346747	-0.0002	0.056203	0.997209
Hypertension	BAG_{WM}	rs2760061	A	0.005453	0.006836	0.425068	0.021601	0.050245	0.667276
Hypertension	BAG_{WM}	rs2820290	A	0.000882	0.006697	0.89517	0.006769	0.049106	0.89036
Hypertension	BAG_{WM}	rs28416181	G	-0.01138	0.007685	0.138653	-0.0092	0.0563	0.870244
Hypertension	BAG_{WM}	rs28431893	A	0.007838	0.01803	0.663785	-0.17109	0.132906	0.19803
Hypertension	BAG_{WM}	rs28667801	T	-0.00176	0.006842	0.797489	0.042453	0.050329	0.398961

Hypertension	BAG_{WM}	rs2906163	C	0.011432	0.007099	0.10732	-0.02159	0.052143	0.678883
Hypertension	BAG_{WM}	rs34869093	G	0.006115	0.006975	0.380681	-0.01821	0.051103	0.721625
Hypertension	BAG_{WM}	rs35429	G	0.001284	0.006858	0.851454	-0.04829	0.050161	0.335701
Hypertension	BAG_{WM}	rs35479618	A	-0.02624	0.024346	0.281118	-0.08873	0.182748	0.627299
Hypertension	BAG_{WM}	rs35593046	T	2.24E-05	0.007796	0.997709	-0.02777	0.057319	0.628106
Hypertension	BAG_{WM}	rs36071027	T	-0.0056	0.007006	0.42376	-0.05977	0.051491	0.24572
Hypertension	BAG_{WM}	rs3790604	A	0.001584	0.012742	0.901074	-0.07908	0.094021	0.400286
Hypertension	BAG_{WM}	rs3796205	C	0.003366	0.007014	0.631292	0.11414	0.05143	0.026486
Hypertension	BAG_{WM}	rs3796581	G	-0.00861	0.00847	0.309543	-0.06915	0.062518	0.268714
Hypertension	BAG_{WM}	rs3802228	A	0.013425	0.006718	0.045718	0.011214	0.049281	0.819996
Hypertension	BAG_{WM}	rs3803266	G	0.005919	0.007933	0.455595	0.002285	0.058142	0.968645
Hypertension	BAG_{WM}	rs3858446	G	0.006336	0.006972	0.36352	0.04741	0.05116	0.35411
Hypertension	BAG_{WM}	rs3863248	G	-0.00789	0.007771	0.310148	-0.00508	0.056963	0.928886
Hypertension	BAG_{WM}	rs3902740	T	-0.0023	0.006871	0.738132	-0.00551	0.05037	0.912945
Hypertension	BAG_{WM}	rs3918226	T	0.02062	0.012861	0.108902	0.035733	0.094197	0.704437
Hypertension	BAG_{WM}	rs3936510	T	0.00193	0.008364	0.817558	0.008585	0.061478	0.888944
Hypertension	BAG_{WM}	rs42038	T	-0.00865	0.007372	0.240783	-0.00219	0.054168	0.967809
Hypertension	BAG_{WM}	rs426570	T	0.010917	0.007338	0.136861	0.070568	0.053717	0.188977
Hypertension	BAG_{WM}	rs4277405	C	0.000249	0.006913	0.971253	0.00078	0.050714	0.98773
Hypertension	BAG_{WM}	rs4363897	C	0.013787	0.015961	0.38775	0.1657	0.11702	0.156808
Hypertension	BAG_{WM}	rs4375757	T	0.008543	0.012157	0.482241	0.134341	0.089261	0.132347
Hypertension	BAG_{WM}	rs448385	A	0.007813	0.006771	0.248529	0.092736	0.049627	0.0617
Hypertension	BAG_{WM}	rs4609031	A	0.005854	0.008081	0.4688	-0.05602	0.059058	0.34287
Hypertension	BAG_{WM}	rs4690774	T	-0.00171	0.006692	0.798428	-0.09601	0.049026	0.050228
Hypertension	BAG_{WM}	rs4755737	A	-0.00459	0.006708	0.494071	-0.05724	0.049198	0.244653
Hypertension	BAG_{WM}	rs4785581	A	0.008722	0.006794	0.199272	-0.01301	0.049954	0.79451
Hypertension	BAG_{WM}	rs483071	C	0.003859	0.007011	0.582031	-0.02425	0.051634	0.638555

Hypertension	BAG_{WM}	rs4833586	A	0.009808	0.009289	0.291059	-0.04773	0.068303	0.484683
Hypertension	BAG_{WM}	rs4873492	T	-0.00351	0.00893	0.694495	-0.03564	0.065393	0.58575
Hypertension	BAG_{WM}	rs4910498	A	-0.00328	0.006922	0.636114	-0.12822	0.050847	0.011691
Hypertension	BAG_{WM}	rs4942041	T	0.019696	0.012738	0.122093	-0.10091	0.093577	0.280874
Hypertension	BAG_{WM}	rs516246	C	-0.01355	0.006654	0.041754	-0.02127	0.048934	0.663749
Hypertension	BAG_{WM}	rs56163207	G	0.000631	0.007217	0.930277	-0.00032	0.052962	0.995114
Hypertension	BAG_{WM}	rs56393506	T	0.009271	0.00927	0.317264	-0.06697	0.067831	0.323553
Hypertension	BAG_{WM}	rs56403963	G	0.002065	0.00885	0.815541	-0.02216	0.064894	0.732695
Hypertension	BAG_{WM}	rs569550	G	0.018853	0.006884	0.00618	0.066612	0.050526	0.187406
Hypertension	BAG_{WM}	rs57139556	G	0.006806	0.012558	0.587851	-0.02527	0.091907	0.783382
Hypertension	BAG_{WM}	rs57748895	T	0.043684	0.024575	0.075496	-0.00316	0.179033	0.985932
Hypertension	BAG_{WM}	rs57866767	C	-0.00084	0.00667	0.899772	0.078254	0.048976	0.110118
Hypertension	BAG_{WM}	rs57946343	C	-0.01068	0.009424	0.25733	-0.13202	0.068873	0.055286
Hypertension	BAG_{WM}	rs6031431	G	0.010985	0.006802	0.106341	0.091296	0.049855	0.067096
Hypertension	BAG_{WM}	rs604723	T	-0.00956	0.007601	0.208297	0.010759	0.055723	0.8469
Hypertension	BAG_{WM}	rs61056117	A	-0.01001	0.012501	0.423108	-0.05899	0.09153	0.519262
Hypertension	BAG_{WM}	rs6108168	A	-0.00837	0.007659	0.274723	-0.0414	0.056427	0.463203
Hypertension	BAG_{WM}	rs6108787	G	0.009049	0.006671	0.174957	0.065441	0.048978	0.181539
Hypertension	BAG_{WM}	rs6119758	A	-0.00954	0.007618	0.210483	-0.08133	0.05571	0.144351
Hypertension	BAG_{WM}	rs61772626	G	0.022487	0.010025	0.024904	-0.02598	0.073993	0.725535
Hypertension	BAG_{WM}	rs62481856	A	-0.0016	0.008422	0.849701	0.086051	0.061694	0.163105
Hypertension	BAG_{WM}	rs6271	T	-0.0202	0.012455	0.104861	-0.02494	0.091843	0.785936
Hypertension	BAG_{WM}	rs6445597	A	0.008683	0.007139	0.223893	-0.01045	0.052597	0.842512
Hypertension	BAG_{WM}	rs6488549	T	-0.00206	0.006771	0.760695	-0.02781	0.049604	0.575105
Hypertension	BAG_{WM}	rs6812640	C	0.007466	0.006845	0.275367	0.047799	0.050239	0.341406
Hypertension	BAG_{WM}	rs6860901	T	0.01101	0.007381	0.135807	-0.02344	0.054256	0.665773
Hypertension	BAG_{WM}	rs6923071	T	0.004051	0.006776	0.549925	0.019803	0.049717	0.690401

Hypertension	BAG_{WM}	rs6932812	G	-0.01539	0.013205	0.243995	-0.08145	0.096989	0.401078
Hypertension	BAG_{WM}	rs6961048	G	0.009783	0.011151	0.38031	0.102612	0.081801	0.209722
Hypertension	BAG_{WM}	rs6985028	G	0.0078	0.006704	0.244617	-0.01968	0.049168	0.688961
Hypertension	BAG_{WM}	rs7129204	C	-0.01963	0.01035	0.057894	-0.02584	0.076007	0.733898
Hypertension	BAG_{WM}	rs7174222	T	0.018475	0.006726	0.006027	0.04505	0.049526	0.363033
Hypertension	BAG_{WM}	rs7233089	A	-0.00044	0.007439	0.953047	-0.00907	0.054517	0.867847
Hypertension	BAG_{WM}	rs72762705	T	-5.4E-05	0.008472	0.994898	0.004653	0.062135	0.940306
Hypertension	BAG_{WM}	rs7302981	A	0.018803	0.006915	0.006556	-0.01256	0.050699	0.804269
Hypertension	BAG_{WM}	rs73046792	A	-0.01965	0.009017	0.029352	-0.09495	0.066278	0.15199
Hypertension	BAG_{WM}	rs73105845	C	0.004917	0.011502	0.66905	-0.04532	0.084436	0.591429
Hypertension	BAG_{WM}	rs7310615	C	0.0111	0.006778	0.101513	-0.02406	0.049626	0.627876
Hypertension	BAG_{WM}	rs74439044	C	-0.0029	0.01143	0.800037	0.165255	0.083416	0.047605
Hypertension	BAG_{WM}	rs74884762	A	0.005122	0.008587	0.550868	-0.08632	0.062671	0.168442
Hypertension	BAG_{WM}	rs74900445	C	0.00371	0.010277	0.718064	-0.02135	0.075175	0.776447
Hypertension	BAG_{WM}	rs751984	C	-0.01976	0.010684	0.064437	-0.03584	0.078502	0.648049
Hypertension	BAG_{WM}	rs75511781	G	0.021487	0.016323	0.188085	-0.15238	0.11989	0.203766
Hypertension	BAG_{WM}	rs7700842	C	-0.00791	0.006901	0.252031	0.06567	0.050713	0.195368
Hypertension	BAG_{WM}	rs7733331	T	-0.01416	0.006826	0.038026	-0.06768	0.050168	0.177317
Hypertension	BAG_{WM}	rs7764523	A	0.011879	0.007091	0.093926	-0.01528	0.051959	0.768724
Hypertension	BAG_{WM}	rs7768871	T	0.009789	0.006794	0.149671	-0.02156	0.049722	0.664603
Hypertension	BAG_{WM}	rs77924615	A	-0.00552	0.008569	0.519842	0.047444	0.062775	0.449803
Hypertension	BAG_{WM}	rs7837979	T	0.004376	0.006865	0.523847	-0.009	0.050241	0.85782
Hypertension	BAG_{WM}	rs78953748	G	0.026638	0.010995	0.015422	0.067472	0.080635	0.402748
Hypertension	BAG_{WM}	rs79044887	G	-0.0074	0.009314	0.426747	0.017054	0.068387	0.803078
Hypertension	BAG_{WM}	rs7972957	C	0.00023	0.007528	0.975576	0.046407	0.055199	0.400523
Hypertension	BAG_{WM}	rs7981842	T	-0.00302	0.015842	0.848859	0.068597	0.116687	0.556628
Hypertension	BAG_{WM}	rs800981	T	-0.01006	0.008432	0.232659	0.049578	0.061712	0.421777

Hypertension	BAG_{WM}	rs8061324	T	0.01096	0.00765	0.151993	-0.01175	0.056207	0.834374
Hypertension	BAG_{WM}	rs8102879	A	-0.00381	0.008231	0.643445	-0.10305	0.060353	0.087769
Hypertension	BAG_{WM}	rs880315	C	0.008464	0.007142	0.23599	0.033936	0.052464	0.517742
Hypertension	BAG_{WM}	rs9798571	A	-0.00926	0.007949	0.244058	-0.09827	0.05825	0.091613
Hypertension	BAG_{WM}	rs9844972	C	0.023054	0.013598	0.090028	-0.01516	0.098657	0.877892
Hypertension	BAG_{WM}	rs9848655	A	0.008785	0.009061	0.332311	0.011831	0.066491	0.858778

Table S10 Longitudinal sample descriptions of each BP group

	Normal (n = 493)		**High-normal** (n = 309)		**Grade 1 hypertension** (n = 456)		**Grade 2 hypertension** (n = 141)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Demographics								
Chronological age, mean (SD)	60.86 (7.19)	63.11 (7.19)	63.71 (6.99)	65.97 (6.99)	63.90 (6.71)	66.15 (6.70)	66.26 (6.86)	68.52 (6.85)
Sex (male, %)	173 (35.1)	-	151 (48.9)	-	261 (57.2)	-	96 (68.1)	-
Education (college, %)	257 (25.4)	-	137 (44.6)	-	222 (49.0)	-	61 (43.6)	-
Risk factors								
Diabetes (%)	16 (3.3)	-	19 (6.2)	-	23 (5.1)	-	7 (5.0)	-
Hypercholesterolemia (%)	62 (12.7)	-	72 (23.5)	-	122 (26.9)	-	41 (29.1)	-
Obesity (%)	54 (11.0)	-	56 (18.4)	-	86 (18.9)	-	35 (35.0)	-
Smoking (%)	134 (27.3)	-	110 (35.9)	-	154 (33.9)	-	58 (41.1)	-
APOE ε4 carriers (%)	132 (32.0)	-	76 (28.7)		108 (28.2)	-	30 (25.6)	-
Anti-hypertensive medication (%)	49 (10.0)	-	65 (21.2)	-	134 (29.6)	-	44 (31.2)	-
Brain ages								
GM brain age, mean (SD)	60.38 (7.91)	62.43 (8.04)	63.46 (8.19)	65.64 (8.12)	63.83 (7.67)	66.03 (7.53)	66.90 (7.64)	69.04 (7.23)
WM brain age, mean (SD)	60.24 (8.08)	62.51 (8.16)	63.44 (7.76)	65.80 (7.84)	64.05 (7.42)	66.50 (7.35)	67.34 (7.06)	69.61 (7.02)
BAG_{GM}, mean (SD)	-0.48 (3.34)	-0.68 (3.32)	-0.25 (3.67)	-0.32 (3.64)	-0.07 (3.54)	-0.12 (3.43)	0.64 (3.74)	0.52 (3.74)
BAG_{WM}, mean (SD)	-0.62 (3.32)	-0.60 (3.29)	-0.26 (3.55)	-0.16 (3.48)	0.15 (3.35)	0.35 (3.40)	1.09 (3.59)	1.10 (3.59)
Cognition								

Processing speed, mean (SD)	0.41 (0.90)	0.36 (0.97)	0.26 (0.91)	0.10 (0.96)	0.22 (0.89)	0.11 (1.00)	0.06 (0.99)	-0.04 (1.04)
Executive function, mean (SD)	0.34 (0.96)	0.29 (0.95)	0.21 (0.89)	0.06 (0.95)	0.20 (0.98)	0.10 (1.00)	0.02 (0.96)	-0.06 (1.01)
Memory, mean (SD)	0.20 (0.96)	0.23 (0.97)	0.20 (0.93)	0.08 (0.95)	0.13 (0.98)	0.06(0.98)	-0.02 (1.04)	-0.22 (1.01)
Global cognition, mean (SD)	0.40 (0.92)	0.37 (0.96)	0.29 (0.87)	0.11 (0.94)	0.23 (0.96)	0.12 (0.98)	0.03 (0.97)	-0.13 (1.03)

Abbreviations: BP = blood pressure; SD = standard deviation; APOE = apolipoprotein E; GM = grey matter; WM = white matter; BAG_{GM} = grey matter brain age gap; BAG_{WM} = white matter brain age gap

Table S11 Statistical details of sliding window analysis

			BAG_{GM}			BAG_{WM}		
Windows (years)	Averaged age (years)	Number of participants	Regression coefficient	p	Corrected p	Regression coefficient	p	Corrected p
45.49-55	50	1557	0.4783	0.0080	0.2324	0.5605	0.0054	0.1574
46-56	51	1910	0.5922	0.0004	0.0109*	0.8309	0.0000	0.0002*
47-57	52	2256	0.5452	0.0004	0.0111*	0.7686	0.0000	0.0002*
48-58	53	2572	0.4531	0.0019	0.0558	0.7224	0.0000	0.0002*
49-59	54	2864	0.4748	0.0007	0.0217*	0.7636	0.0000	P < 0.0001*
50-60	55	3116	0.5170	0.0002	0.0052*	0.7947	0.0000	P < 0.0001*
51-61	56	3315	0.5291	0.0001	0.0028*	0.8826	0.0000	P < 0.0001*
52-62	57	3546	0.4709	0.0004	0.0104*	0.8145	0.0000	P < 0.0001*
53-63	58	3668	0.5045	0.0001	0.0030*	0.8951	0.0000	P < 0.0001*
54-64	59	3790	0.4694	0.0002	0.0072*	0.8093	0.0000	P < 0.0001*
55-65	60	3974	0.4458	0.0004	0.0102*	0.8008	0.0000	P < 0.0001*
56-66	61	4108	0.3890	0.0014	0.0403*	0.7644	0.0000	P < 0.0001*
57-67	62	4220	0.4131	0.0006	0.0170*	0.7537	0.0000	P < 0.0001*

58-68	63	4321	0.4698	0.0001	0.0020*	0.7536	0.0000	P < 0.0001*
59-69	64	4386	0.5211	0.0000	0.0002*	0.7997	0.0000	P < 0.0001*
60-70	65	4494	0.4903	0.0000	0.0004*	0.7529	0.0000	P < 0.0001*
61-71	66	4573	0.5014	0.0000	0.0001*	0.6827	0.0000	P < 0.0001*
62-72	67	4505	0.4894	0.0000	0.0002*	0.6205	0.0000	P < 0.0001*
63-73	68	4470	0.5217	0.0000	P < 0.0001*	0.5499	0.0000	P < 0.0001*
64-74	69	4330	0.4707	0.0000	0.0003*	0.4925	0.0000	0.0001*
65-75	70	4112	0.4396	0.0000	0.0014*	0.5037	0.0000	0.0001*
66-76	71	3836	0.4375	0.0001	0.0022*	0.4234	0.0001	0.0035*
67-77	72	3529	0.4031	0.0004	0.0112*	0.4111	0.0002	0.0067*
68-78	73	3198	0.3800	0.0012	0.0357*	0.3885	0.0008	0.0221*
69-79	74	2847	0.2956	0.0173	0.5022	0.2161	0.0734	2.1293
70-80	75	2429	0.2889	0.0289	0.8370	0.1461	0.2558	7.4169
71-81	76	1974	0.1853	0.1948	5.6482	0.1075	0.4383	12.7102
72-82	77	1577	0.2540	0.1073	3.1103	0.1764	0.2500	7.2513
73-82.32	78	1207	0.0681	0.7033	20.3961	0.0811	0.6455	18.7182

Abbreviations: BAG_{GM} = grey matter brain age gap; BAG_{WM} = white matter brain age gap; corrected p indicated the adjusted p value after Bonferroni correction.

Supplementary Figures

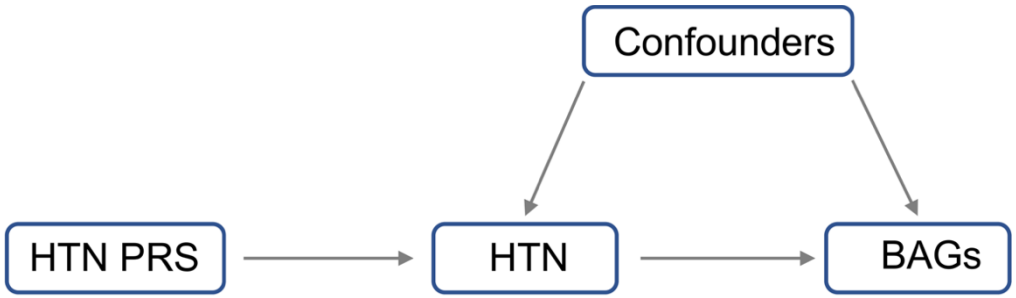


Figure S1 Schematic representation of MR analysis. The two-stage MR analysis was conducted with HTN PRS as the genetic instrument using individual-level data from 11056 UK Biobank participants. This analysis was restricted in White British Ancestry. Confounders including chronological age, sex, scanner and four genetic principal components were adjusted in the first and second stage. Abbreviations: MR = Mendelian randomization; HTN = hypertension; PRS = polygenetic risk score; BAGs = BAG_{GM} or $BAG_{WM.}$

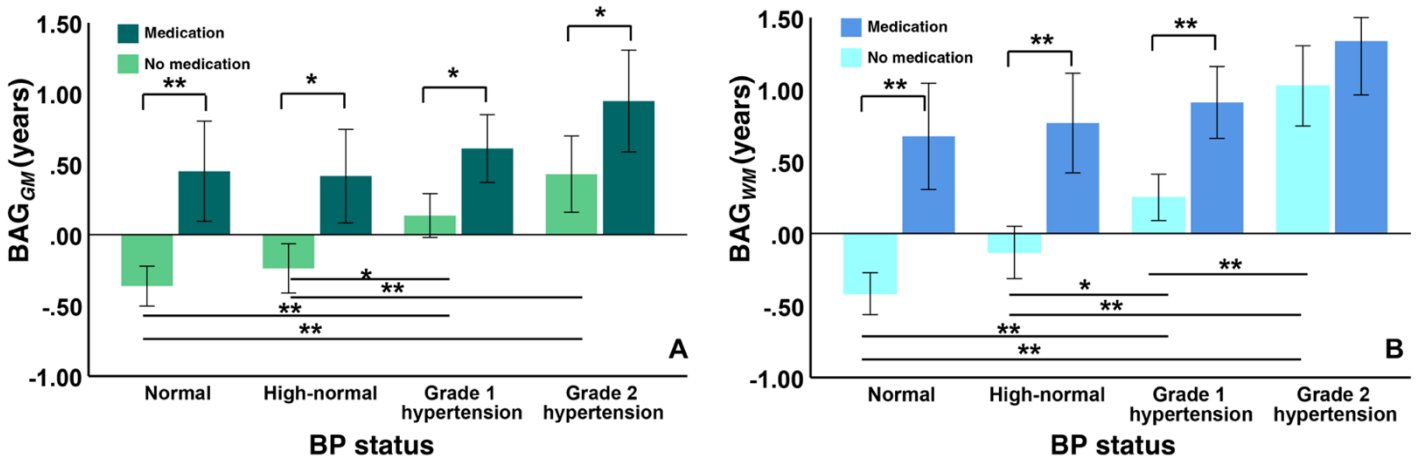


Figure S2 Association between BP and BAG$_{GM}$ (Figure S2A) and BAG$_{WM}$ (Figure S2B) stratified by anti-hypertensive medication status. Abbreviations: BAG$_{GM}$ = grey matter brain age gap; BAG$_{WM}$ = white matter brain age gap; BP = blood pressure. ** indicates $p < 0.001$ after Bonferroni correction.

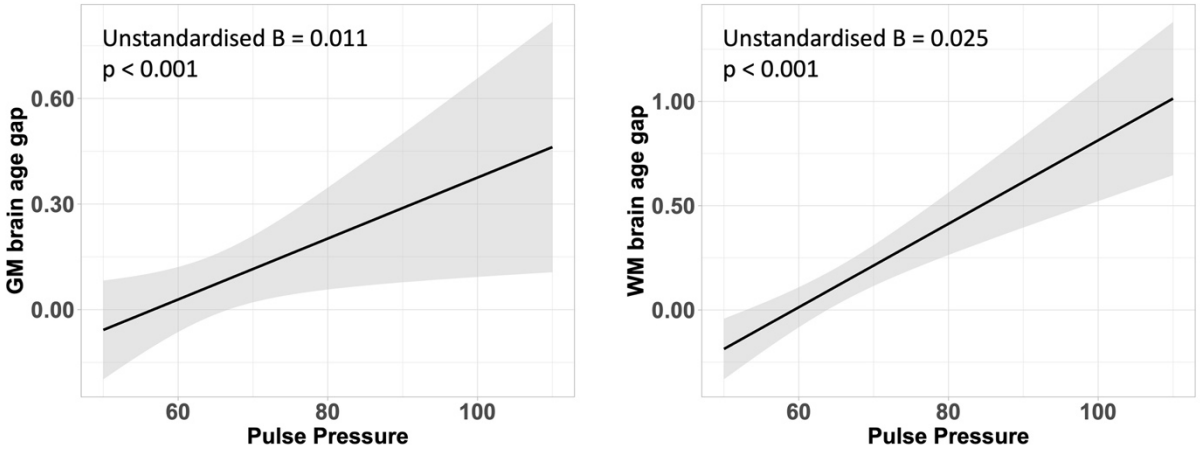
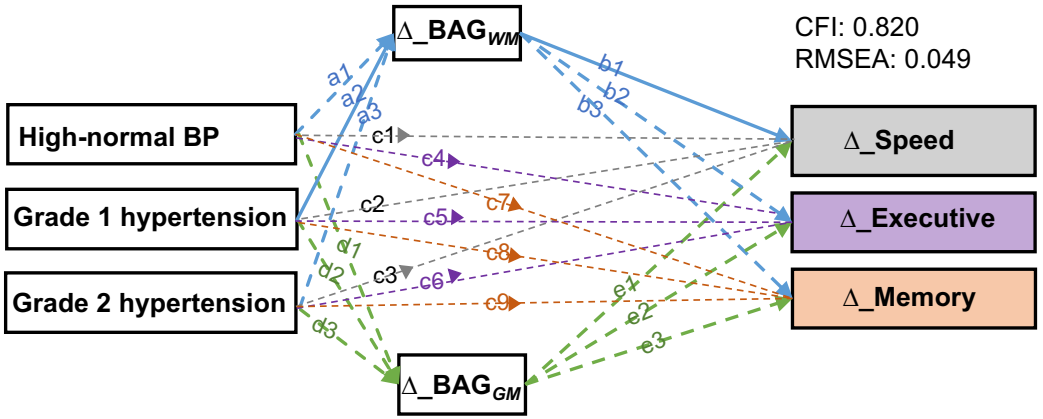


Figure S3 Association between pulse pressure and WM and GM brain age gaps. WM = white matter; GM = grey matter



	Processing speed		Executive		Memory	
Indirect (WM)	(a1*b1):	0.003	(a1*b2):	0.001	(a1*b3):	-0.002
	(a2*b1):	0.007	(a2*b2):	0.002	(a2*b3):	-0.004
	(a3*b1):	0.003	(a3*b2):	0.001	(a3*b3):	-0.002
Indirect (GM)	(d1*e1)	-0.002	(d1*e2)	0.002	(d1*e3)	-0.002
	(d2*e1)	-0.003	(d2*e2)	0.002	(d2*e3)	-0.003
	(d3*e1)	-0.002	(d3*e2)	0.002	(d3*e3)	-0.002
Direct	c1	-0.071	c4	-0.015	c7	-0.121
	c2	-0.030	c5	-0.023	c8	-0.058
	c3	-0.018	c6	0.073	c9	-0.135

Figure S4 Longitudinal mediation analyses for baseline BP, changes of BAGs and changes of cognition. a*b indicate the indirect effect mediated by Δ_BAG$_{WM}$; d*e indicate the indirect effect mediated by Δ_BAG$_{GM}$; c1-9 indicate the average direct effect between BP levels and cognition; solid lines indicate significant paths while dash lines indicate the insignificant paths. Abbreviations: BP = blood pressure; Δ_BAG$_{GM}$ = change of grey matter brain age gap; Δ_BAG$_{WM}$ = change of white matter brain age gap; Δ_Speed = change of processing speed; Δ_Executive = change of executive function; Δ_Memory = change of memory; RMSEA = Root mean square error of approximation; CFI = comparative fit index. * indicates the $p < 0.05$, ** indicates the $p < 0.001$.