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Elevated blood pressure accelerates white matter brain aging among late middle-aged women: a Mendelian Randomization study in the UK Biobank

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Abstract

Background: Elevated blood pressure (BP) is a modifiable risk factor associated with cognitive impairment and cerebrovascular diseases. However, the causal effect of BP on white matter brain aging remains unclear.

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Conflicts of interest

There are no conflicts of interest.

Methods: In this study, we focused on $N = 228\,473$ individuals of European ancestry who had genotype data and clinical BP measurements available (103 929 men and 124 544 women, mean age = 56.49, including 16 901 participants with neuroimaging data available) collected from UK Biobank (UKB). We first established a machine learning model to compute the outcome variable brain age gap (BAG) based on white matter microstructure integrity measured by fractional anisotropy derived from diffusion tensor imaging data. We then performed a two-sample Mendelian randomization analysis to estimate the causal effect of BP on white matter BAG in the whole population and subgroups stratified by sex and age brackets using two nonoverlapping data sets.

Results: The hypertension group is on average 0.31 years (95% CI = 0.13–0.49; $P < 0.0001$) older in white matter brain age than the nonhypertension group. Women are on average 0.81 years (95% CI = 0.68–0.95; $P < 0.0001$) younger in white matter brain age than men. The Mendelian randomization analyses showed an overall significant positive causal effect of DBP on white matter BAG (0.37 years/10 mmHg, 95% CI 0.034–0.71, $P = 0.0311$). In stratified analysis, the causal effect was found most prominent among women aged 50–59 and aged 60–69.

Conclusion: High BP can accelerate white matter brain aging among late middle-aged women, providing insights on planning effective control of BP for women in this age group.

Keywords

blood pressure; brain aging; causal inference; Mendelian randomization; white matter fractional anisotropy

INTRODUCTION

Elevated blood pressure (BP) is a primary risk factor for cerebrovascular and cardiovascular diseases [1,2] and associated with a higher risk of cognitive impairment and dementia [3,4]. Studies have reported that high BP strongly correlates with alterations of both brain structure and neurobiological functions [5,6]. Previous study also showed a significant genetic correlation between BP and white matter integrity [7]. The microstructure of the human brain is constantly changing with normal aging, reflecting brain shrinkage, and cognitive and memory decline [8]. Thus, it is important to know how increased BP causes accelerated brain aging to reveal the underlying mechanism of BP on the brain and cognitive dysfunction. The prevalence of hypertension increases with age and differs among men and women in different age cycles [9,10], especially for older women after menopause. In this study, we will evaluate the causal effect of BP on white matter brain aging in the general population as well as sex-specific and age-specific groups to understand the benefits of controlling BP in reducing accelerated brain aging.

Brain age predicts chronological age from structural or functional neuroimaging features using machine learning algorithm [11,12]. In our study, we used multiple fractional anisotropy tract measures from diffusion tensor imaging (DTI) data to predict an age-adjusted white matter brain age metric, brain age gap (BAG), which represents the difference between individuals' brain age and their chronological age and regard it as the main outcome. Increases in BAG demonstrate evidence of accelerated aging and poorer brain

health. The scalar BAG measure has been widely used in the literature as an alternative to multivariate imaging models to yield more robust and interpretable results in brain aging studies [13,14].

BAG can be influenced by multiple genetic, biological, environmental, and lifestyle factors [15]. Previous studies on BAG associated with lifestyle risk factors have focused on smoking and alcohol consumption [14,16,17]. For high blood pressure and brain age, one study showed that elevated blood pressure was associated with brain aging but no direct causality was reported [18]. In traditional observational studies, it is challenging to identify the causal relationship solely between high blood pressure and BAG, as other health risk factors related to abnormal brain aging, such as smoking, alcohol use, and chronic diseases, often co-occur with high blood pressure [19,20]. The Mendelian randomization framework has provided an unprecedented chance to overcome this challenge by using the genetic variants as instrumental variables of the risk factor to estimate its causal effect on the outcome, which is less prone to reverse causation and confounding [21–23]. The genetic determinants of BP are increasingly characterized in large-scale genome-wide association study (GWAS) in the literature [24], which made it possible to identify better instruments for Mendelian randomization study. The Mendelian randomization methods have been successfully applied to investigate the causal effects of high blood pressure on myocardial infarction, atrial fibrillation, and other cardiovascular diseases as well as other chronic diseases [25–28], but no Mendelian randomization studies have looked at the causal effect of BP on white matter brain aging in a large-scale observational study.

To fill the gap, we used fractional anisotropy measures of DTI data from the UK Biobank (UKB) cohort to build an machine learning model to estimate white matter BAG and performed a two-sample Mendelian randomization analysis to investigate the causal effect of BP on BAG in the general population as well as stratified by sex and age groups. We hypothesized that elevated BP would accelerate brain aging; such causal effect is more prominent in more vulnerable age and sex groups. Our study highlights the age and sex disparities in the causal effects of modifiable cardiovascular disease-related risk factors on white matter microstructure change, which provides implications for understanding the contributions of the late-life cognitive impairment risk.

METHODS

Study population and variables

The data used in the present study were from the UKB cohort, which is a large-scale population-based study recruiting around 500 000 individuals aged 40–69 years and collecting comprehensive physical, genomic, health, and brain imaging phenotypic data [29]. We focused on nonpregnant, family-unrelated individuals of European ancestry (i.e. primarily British and Irish) who had available genotypes, two nonnull clinical BP measurements from the initial assessment visits (2006–2010) and further excluded individuals with discordant self-reporting vs. genotype determined sex, those with extreme white matter hyperintensities, and those who took antihypertensive medicine (see Supplementary Material section 1.1, http://links.lww.com/HJH/C276). We also performed several sensitivity analyses to ensure there is no selection bias. The final pool for analysis

includes $N = 228\,473$ participants, including 16 901 participants with neuroimaging data available (Fig. 1).

Genotype data

The genotype data of participants provided by the UKB were assayed using two genotyping arrays, the UK BiLEVE Axiom Array and UK Biobank Axiom Array [30,31]. We further applied quality control to the genotype data (see Supplementary Material section 1.2, http://links.lww.com/HJH/C276).

Blood pressure data

As the exposures of interest, we analyzed the following two BP traits with complete data collected from the initial (2006–2010) assessment visit: SBP and DBP, both calculated as the mean of two nonnull BP measurements using phenotype codes 4079 and 4080 in UKB, respectively. Hypertension (HTN) was defined using International Classification of Diseases edition 10 (ICD-10) codes I10–I15 available in UKB. Hypertension status will be used to split the data for training and testing purposes.

Neuroimaging data

We used regional white matter fractional anisotropy measures collected from DTI data from UKB imaging assessment starting from 2014 to compute the outcome of the study, the BAG. According to ENIGMA protocol, the per-tract mean value of each brain white matter tract was calculated by using a Track-Based Spatial Statistics analysis from the DTI fractional anisotropy images [32]. Fractional anisotropy measure, ranging from 0 to 1, represents the degree of anisotropy of a diffusion process and the integrity of cortical white matter [33]. A lower value of fractional anisotropy indicates less probability of diffusion in one direction (isotropic). This study focuses on fractional anisotropy data for a total of 39 tracts that covered multiple brain regions (see the list of 39 regional white matter fractional anisotropy measures in Table S1, http://links.lww.com/HJH/C275).

Potential confounders

We treated sex, age, BMI, alcohol consumption, smoking status, fruit and vegetable consumption, and sedentary lifestyle as potential confounders for our association analysis and Mendelian randomization analysis based on a previous study [34] (see Supplementary Material section 1.3, http://links.lww.com/HJH/C276). We performed complete case analysis by excluding individuals with any missing covariates. Two-sample t tests were conducted comparing missingness vs. complete case group for each missing covariate to ensure the missing complete at random assumption is not violated (Table S5, http://links.lww.com/HJH/C275). The continuous age variable is categorized into 40–49, 50–59, 60–69 age groups. In this study, we conducted both overall analysis as well as stratified analysis within each sex and age group.

Existing large-scale blood pressure genome-wide association study summary data

To strengthen the instrumental variable selection step in two-sample Mendelian randomization analysis, in addition to UKB data alone, we also collected the largest existing

GWAS summary data on BP from a meta-analysis of over 750 000 participants of European ancestry that combined a total of 78 different cohorts [from International Consortium of Blood Pressure (ICBP) and part of UKB cohort] [24]. We used this existing meta-analyzed GWAS summary data to help select stronger and reproducible instrumental variables in our two-sample Mendelian randomization analysis.

Statistical analysis

Figure 1 shows a flowchart of the main statistical analysis performed and the number of participants included at each step of the analysis. For two-sample Mendelian randomization analysis, we split data into two nonoverlapping sets: Genetic-Exposure Association Set consisting of participants with only BP but no fractional anisotropy data (Mendelian randomization sample 1; $N = 203\,067$) and Genetic-Outcome Association Set consisting of participants with both BP and BAG outcome variables available (Mendelian randomization sample 2; $N = 8822$) (Fig. 1). The main analyses are in three parts. In the first part, we used machine learning model to estimate the outcome white matter BAG based on 39 regional fractional anisotropy measures and the chronological age, among those participants with both BP and fractional anisotropy data available. In the second part, we applied a multiple linear regression model to test for the association between BP and BAG in Mendelian randomization sample 2. In the last part, we performed a two-sample Mendelian randomization analysis to evaluate the causal effects of BP on BAG treating candidate genetic variants as Instrumental variables. Detailed steps of each part of the analysis can be found in the Supplementary Material section 1.4–1.7, http://links.lww.com/HJH/C276.

All statistical analyses were conducted using R (version 4.0.5) [35]. R packages, including '*MendelianRandomization*' (version 0.5.1) [36], '*MRPRESSO*' (version 0.1.0) [37], and '*MRMix*' (version 0.1.0) [38] were used to perform Mendelian randomization analyses. Except for GWAS analysis and instrumental variables selection, P less than 0.05 was regarded as statistically significant for all other analyses unless otherwise specified. For both association analysis and Mendelian randomization analysis, the Benjamini–Hochberg (BH) method was used to adjust for multiple comparisons [39]. We also performed several sensitivity analyses to ensure our analysis is robust and unbiased (see Supplementary Material section 1.8, http://links.lww.com/HJH/C276).

RESULTS

Descriptive statistics

The Genetic-Exposure Dataset consists of 91 771 men and 111 296 women, mean age of 56.71 (SD = 8.02) years. Non-HTN Training Dataset consists of 3513 men and 4215 women [mean age = 54.23 (SD = 7.35)], Non-HTN Testing Dataset with 4116 men and 3309 women [mean age = 54.31 (SD = 7.36)], and HTN Testing Dataset with 639 men and 758 women [mean age = 58.48 (SD = 6.53)] (Table 1). No systematic difference in the distribution of age, sex, BMI and BP was observed between the non-HTN training group and non-HTN testing group (Table S3, http://links.lww.com/HJH/C275).

Estimation of white matter brain age gap

The optimal RF regression model selected 25 fractional anisotropy measures for BAG estimation (Figures S1, http://links.lww.com/HJH/C276). After correcting age-bias on white matter BAG, the adjusted predicted BAG achieved $R^2 = 0.94$ in both HTN test dataset (MAE = 2.64 years, $P < 2.2 \times 10^{-16}$) and non-HTN test dataset (MAE = 2.48 years, $P < 2.2 \times 10^{-16}$) (Fig. 2b), greatly improving the prediction performance in testing data when the bias is not corrected (Fig. 2a). The hypertension group was on average 0.31 years (95%CI = 0.13–0.49; $P < 0.0001$) older in white matter brain age than the nonhypertension group, and such trend is consistent across age groups (Fig. 2c–d). Furthermore, our data showed that, women on average had 0.81 years (95% CI = 0.68–0.95; $P < 0.0001$) younger brain age than men and the difference is consistent across all age strata (all $P < 0.01$, Fig. 2e). The detailed difference between men and women by age strata and by each testing dataset can be found in Table S4, http://links.lww.com/HJH/C275. Our results validated a previous finding that the adult women's brains are on average a few years younger than the men's brains in terms of brain metabolism [40].

Linear association analysis

Both SBP and DBP were found positively associated with white matter BAG (Table 2: $\beta_{SBP} = 0.012$, 95% CI = 0.0083–0.011, $P = 4.30 \times 10^{-10}$; $\beta_{DBP} = 0.018$, 95% CI = 0.011–0.024, $P = 1.31 \times 10^{-7}$). With age and sex stratification, we found that both SBP and DBP were associated with white matter BAG specifically in 50–59 ($\beta_{SBP} = 0.016$, P= 3.74×10^{-7}; $\beta_{DBP} = 0.026$, $P = 5.54 \times 10^{-6}$) and 60–69 ($\beta_{SBP} = 0.0086$, $P = 4.25 \times 10^{-3}$; $\beta_{DBP} = 0.015$, $P = 7.11 \times 10^{-3}$) age groups, and more significant association was found among women ($\beta_{SBP} = 0.015$, $P = 7.38 \times 10^{-9}$; $\beta_{DBP} = 0.023$, $P = 3.59 \times 10^{-7}$). Further stratification by both sex and age groups showed that BP was most significantly associated with white matter BAG among older women, but no association was found between BP and white matter BAG in 40–49 age group for both sexes (Table 2 and Fig. 3). These results remained largely consistent in several sensitivity analyses (Table S8–S10, http://links.lww.com/HJH/C275).

Two-sample Mendelian randomization analysis

We identified 4813 and 5646 genetic variants with GWAS P value less than 5×10^{-8} for SBP and DBP, respectively. A majority of these single nucleotide polymorphisms (SNPs) were mapped to blood pressure-related genes (e.g. *CACNB2, ATP2B1*, and *ARHGAP42*) that have been reported in previous studies [41,42] (full gene annotations were summarized in Table S6, http://links.lww.com/HJH/C275). The final number of variants selected as valid instrumental variables are 153 for both SBP and DBP (the number of variants passing each instrumental variables selection step is summarized in Table S7, http://links.lww.com/HJH/C275). Using these instrumental variables, we found an overall significant causal effect of DBP ($\beta = 0.037$, 95% CI = 0.0034–0.071, $P = 0.0311$) on white matter BAG (Table 2), that is, increment of 10 mmHg of DBP increases brain age by an additional 0.37 years. In stratified analysis, DBP had most significant causal effect on white matter BAG in 60–69 age group ($\beta = 0.0991$, 95% CI = 0.041–0.16, $P = 7.68 \times 10^{-4}$) and among women ($\beta = 0.0484$, 95% CI = 0.0062–0.091, $P = 2.45 \times 10^{-2}$). Late middle-aged women are most vulnerable to blood pressure change: women in 50–59 age group ($\beta = 0.069$, 95% CI =

0.0054–0.13, $P = 0.0335$) and 60–69 age group ($\beta = 0.096$, 95% CI = 0.021–0.17, $P = 0.0122$) had a significant causal effect of DBP on white matter BAG, that is, increasing 10 mmHg DBP increases brain age by additional 0.69–0.96 years in women aged 50–69. Those significant results were confirmed by implementing several sensitivity analyses using different Mendelian randomization methods and leave-one-out approach (see Table S11, http://links.lww.com/HJH/C275). On the other hand, a weak positive causal effect of DBP in age 60–69 ($P = 0.0571$) was presented in the men's group, and a weak causal effect for SBP in the 50–59 aged women's group ($P = 0.0718$). No consensus results for the causal effects of DBP on white matter BAG were found among the men's groups by reviewing all the Mendelian randomization analyses, thus we could not draw any statistically valid causal conclusion for the men's group (Table 2 and Tables S7, and S8, http://links.lww.com/HJH/C275). We also performed another Mendelian randomization analysis by switching the outcome and the exposure, no significant causal relationship was observed thus no reverse causality existed (Table S12, http://links.lww.com/HJH/C275).

DISCUSSION

In this study, we used the fractional anisotropy data and chronological age to train an optimal RF model in a healthy reference population without a diagnosis of hypertension to calculate white matter BAG with age-related bias corrected. We found significant increases in white matter BAG in HTN individuals and men compared with non-HTN individuals and women, respectively. Our linear association analysis between BP and BAG confirmed that high blood pressure is highly related to elevated brain aging. Furthermore, the two-sample Mendelian randomization analysis identified age-dependent and sex-dependent causal effect of BP on white matter BAG. Specifically, we found positive causal effects of DBP on white matter BAG among 50–69 age-group women.

In our investigation, we found that women have younger brains (neoteny) than men, consistent with the findings by Goyal *et al.* [40] that the adult women's brains are a few years younger than men's over the entire adult life span. Interestingly, even though women exhibited younger brains, we observed a more robust causal relationship between DBP and brain aging in women starting at the age of 50 years, compared with men. This causal effect became even more pronounced among women aged 60–69, compared with those aged 50–59. On the other hand, studies have revealed that the prevalence of HTN and brain aging increases with age and differs among men and women in different age cycles [9,10], especially for older adults and women after menopause. This may be because of the sex difference in sex hormones and the vascular functions at molecular, cellular, and tissue levels [43]. Sex hormones produced among women of reproductive age may protect them from hypertension and related organ function (cardio vasculature, kidneys, and brain) [44–46]. We provided novel insights on how BP causes increasing brain aging in humans, especially in late middle-aged women, and affects differently in an age-dependent and sex-dependent manner, but the causal effects warrant further investigations. Our study focused on the causal effect of BP measure at baseline on white matter brain aging measured at the imaging visit and its age-specific and sex-specific pattern comparison. Since the imaging visit (instance 2) is 4–12 years apart from baseline, we can regard the baseline BP as past BP measurement. As the prior history of elevated BP before baseline is not available in UKB, we do not

further distinguish the past elevated BP based on years of exposure of elevated BP without medications. Several longitudinal studies found that both concurrent and past elevated blood pressure were associated with white matter hyperintensities, but concurrent BP had weaker effect than past BP measurements taken several years ago WMH [47–51]. However, the evidence is still limited, and we will leave it to future studies.

Our study identified that DBP, not SBP, had a causal impact on white matter BAG in the entire population aged between 40 and 69. As individuals age, SBP typically increases, while DBP may decrease because of changes in the cardiovascular system or other factors [52,53]. Our findings are consistent with previous research, which suggests that a history of high blood pressure in midlife may contribute to brain changes that can lead to white matter lesions [54]. However, there have been more debates and uncertainties surrounding the effect of DBP on brain structures and cognitive function compared with SBP [55,56]. Nevertheless, both genetically proxied and regular measurements of SBP and DBP have shown diverse causal effects or significant associations with various targets and regional effects related to white matter fractional anisotropy tracks, brain structures, white matter lesions, cortical volume, and cerebral blood flow [56–59]. The relationship between blood pressure and brain aging is complex, multifactorial [60], time-dependent, or even nonlinear [61]. Other factors, such as genetics, lifestyle, and comorbidities, may also contribute to brain changes and cognitive decline in advanced age. Further research is required to fully understand the complexities of how these blood pressure measures influence the brain and its functions.

The study has several strengths. First, the two-sample Mendelian randomization approach represents a robust method for inferring causality between a modifiable exposure and an outcome in observational studies using genetic variants as instrumental variables. Mendelian randomization methods reduced the influence from confounding factors and reverse causation, thus enhancing the validity of the causal inference. Secondly, we used large-sample high-quality genotype and phenotype data from UKB and conducted both linear association and a two-sample Mendelian randomization analysis in overall and age-stratified and sex-stratified groups facilitating a more comprehensive understanding of the causal relationship between blood pressure and white matter BAG. Thirdly, we calculated white matter BAG by training an optimal machine learning model and adjusted for age bias, which resulted in an excellent predictive performance of the chronological age. Lastly, we conducted several sensitivity analyses in both association tests and two-sample Mendelian randomization to provide a more valid and robust estimation.

Our study also has some limitations. First, our study only included the participants not taking antihypertensive medicine, which aims to include a better genetically predicted BP data, and hence the ascertainment bias may have been introduced. Reassuringly, our sensitivity analysis by including the participants who took antihypertensive medicine had consistent findings, so the bias is unlikely. Second, because of the lack of data for younger individuals (i.e. age < 40), the potential impact of BP on white matter brain aging over a lifetime is not investigated in our current study. Third, although we demonstrated significant causal effects of BP on white matter BAG, the molecular mechanisms of selected valid instrumental variables remain unclear. It is critical to integrate other advanced methods (i.e.

transcriptome-wide association analysis) and/or to use multiple omics data (i.e. proteins and RNA) that would allow us to obtain a better understanding of the biological system underlying the causal pathway between BP and white matter BAG.

Perspectives

Our study has shown that the nonhypertension group and women had younger brains (white matter BAG) across all the mid-to-older year cycles. Hypertension and genetic predisposition to higher BP (i.e. SBP/DBP) can accelerate brain white matter aging in an age-dependent and sex-dependent manner. These findings shed insight on understanding the abnormal white matter brain changes because of high blood pressure and further provide evidence to reduce the incidence of late-life cognitive impairment and dementia, reflecting the effective control of BP in age and sex awareness would be essential for rational planning of health services.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement:

the raw genetic and phenotypic data used for this study can be found in the UK Biobank (http://www.ukbiobank.ac.uk/).

Abbreviations:

BAG	brain age gap
BH	Benjamini–Hochberg
BP	blood pressure
DTI	diffusion tensor imaging
GWAS	genome-wide association study
HTN	hypertension
ICBP	International Consortium of Blood Pressure

ICD-10	International Classification of Diseases edition 10
MR	Mendelian randomization
UKB	UK Biobank

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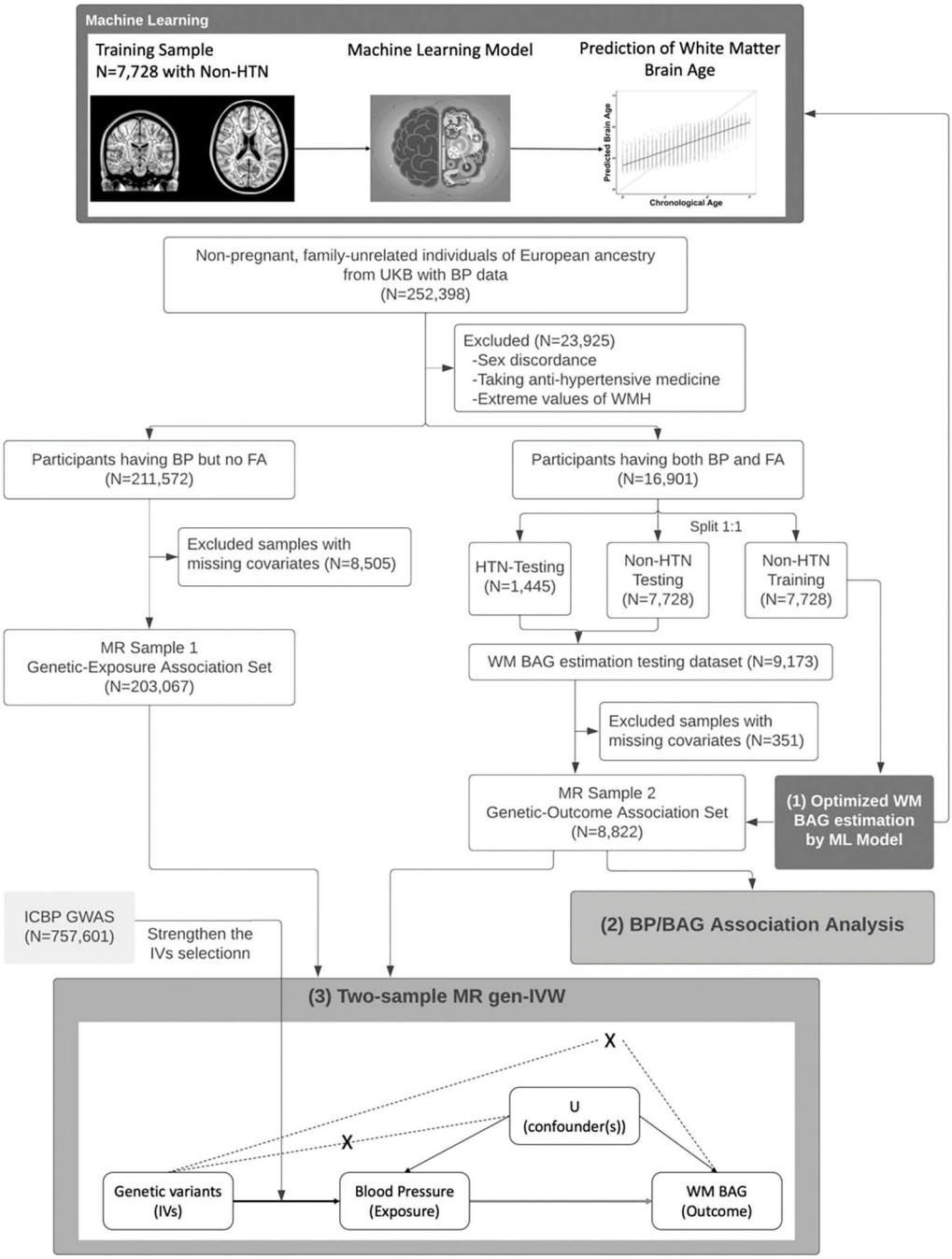

FIGURE 1.

Flowchart of our main analysis procedures and the number of participants included at each step of the analysis. The main analyses are in three parts: estimation of age bias-corrected WM BAG using machine learning model; linear association analysis between BP and BAG; two-sample MR analysis to evaluate causal effect of BP on BAG. In the directed acyclic graph of MR analysis, the solid arrows correspond to the causal relationship, the dashed arrows with cross correspond to the instrumental variables assumptions (ii) and (iii) in MR (see Supplementary Materials section 1.7, http://links.lww.com/HJH/C276), the arrow is the

causal relationship of interest in MR model. BAG, brain age gap; BP, blood pressure; MR, Mendelian randomization; WM, white matter.

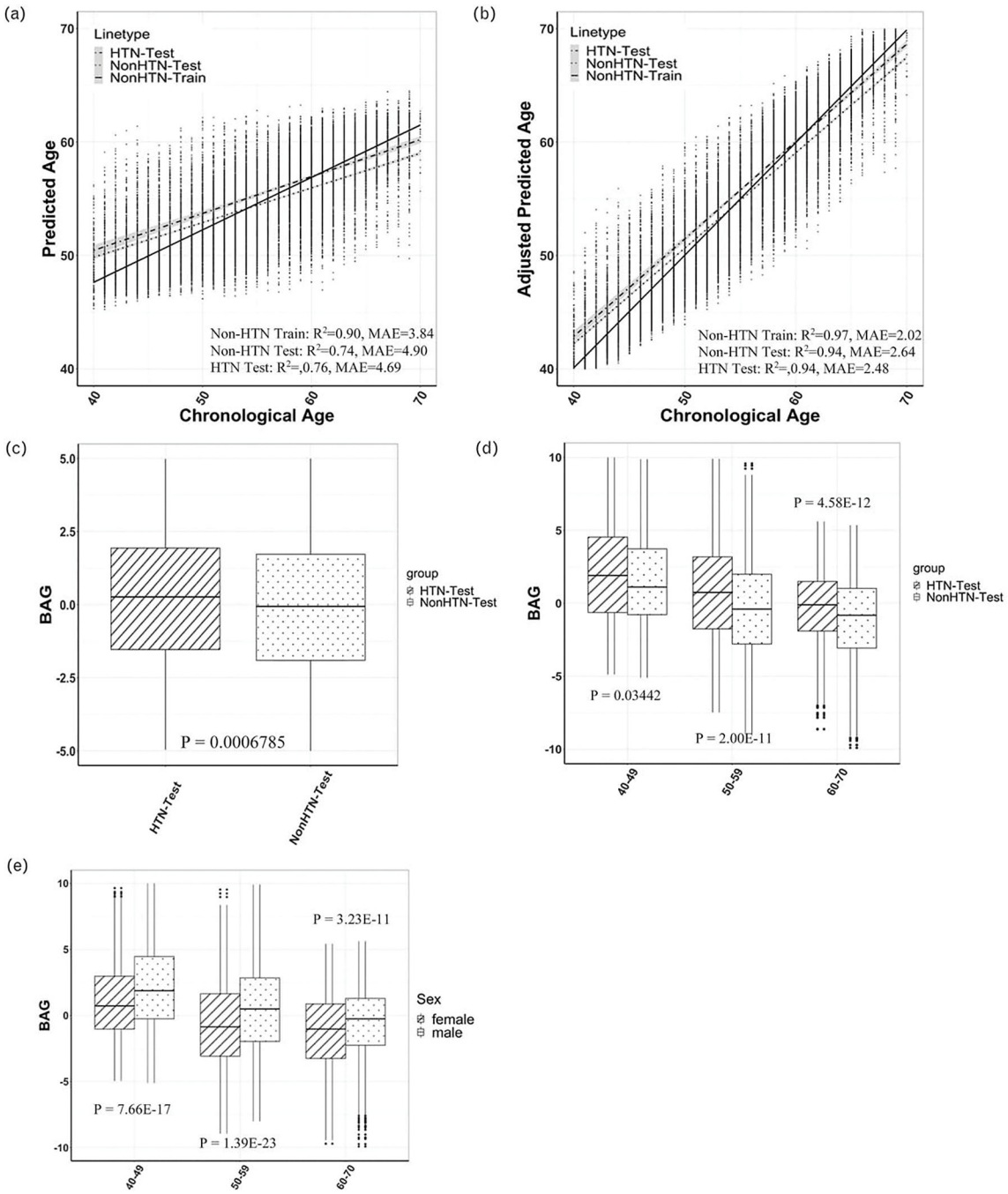

FIGURE 2.

(a) Predicted brain age vs. chronological without age bias correction. (b) Predicted brain age vs. chronological with age bias correction. (c) Box plots of estimated WM BAG in HTN vs. non-HTN test datasets. (d) Box plots of estimated WM BAG in HTN vs. non-HTN test datasets in different age groups. (e) Box plots of estimated WM BAG between women and men in different age groups. BAG, brain age gap; HTN, hypertension; WM, white matter.

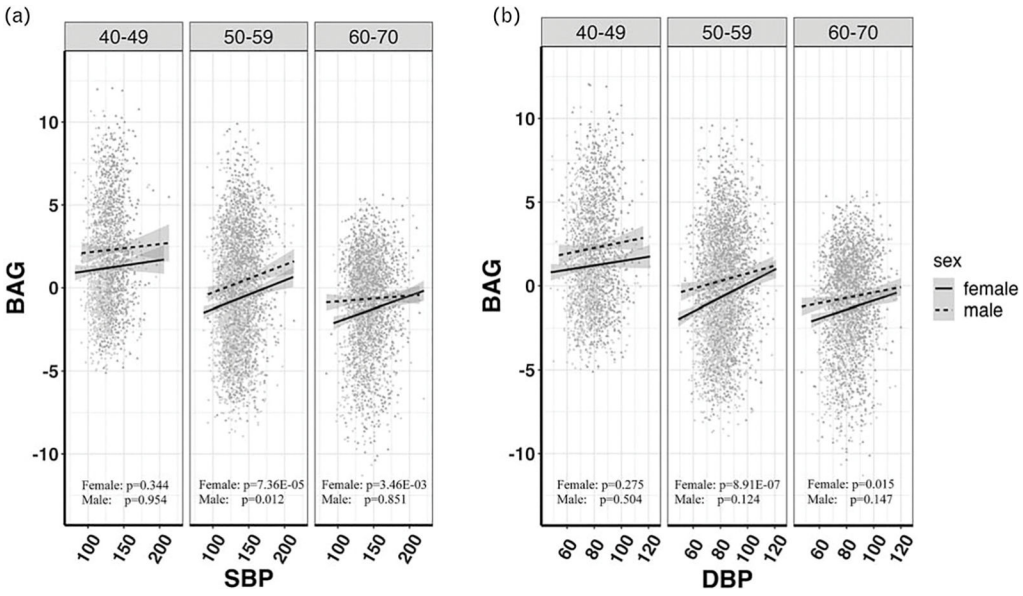

FIGURE 3.

Scatterplots and linear relationships between brain age gap and blood pressure [(a) SBP and (b) DBP] in different sex and age subgroups.

TABLE 1.

Characteristics of Participants in Genetic-Exposure Association Set (MR sample 1), Genetic-Outcome Association set (MR sample 2 including non-HTN and HTN testing dataset) and the non-HTN training dataset[a] from UK Biobank

			Genetic-Outcome dataset		
Characteristics	**Level**	**Non-HTN training dataset**	**Non-HTN testing dataset**	**Non-HTN testing dataset**	**Genetic-Exposure dataset**
N		7728	7425	1397	203 067
Age [mean (SD)]		54.23 (7.35)	54.31 (7.36)	58.48 (6.53)	56.71 (8.02)
Sex (%)	Female	4215 (54.5)	4116 (55.4)	639 (45.7)	111 296 (54.81)
	Male	3513 (45.5)	3309 (44.6)	758 (54.3)	91 771 (45.19)
BMI [mean (SD)]		26.06 (3.96)	26.07 (3.93)	28.54 (4.64)	27.23 (4.65)
SBP [mean (SD)]		132.49 (16.48)	132.38 (16.51)	145.33 (17.95)	137.97 (18.58)
DBP [mean (SD)]		80.26 (9.38)	80.01 (9.32)	86.32 (10.64)	82.25 (10.08)
Smoking status (%)	Never	4916 (63.71)	4665 (62.83)	797 (57.05)	111 814 (55.06)
	Previous	2351 (30.47)	2332 (31.41)	536 (38.37)	70 756 (34.84)
	Current	449 (5.82)	428 (5.76)	64 (4.58)	20 497 (10.09)
Alcohol drinker status (%)	Never	159 (2.06)	143 (1.93)	28 (2.00)	6036 (2.97)
	Previous	153 (1.98)	122 (1.64)	38 (2.72)	6826 (3.36)
	Current	7414 (95.96)	7160 (96.43)	1331 (95.28)	190205 (93.67)
Fruit consumption [mean (SD)]		3.07 (2.40)	3.07 (2.28)	3.13 (2.47)	2.99 (2.48)
Vegetable consumption [mean (SD)]		4.72 (2.91)	4.71 (2.71)	4.94 (3.17)	4.81 (3.08)
Sedentary lifestyle [mean (SD)]		4.16 (2.39)	4.20 (2.33)	4.80 (2.45)	4.53 (2.48)

SD, standard deviation.

[a]See Fig. 1.

TABLE 2.

Linear association (left) and two-sample MR analysis (right) results

		Linear association				MR analysis			
BP	**Group**	**Beta estimate**	**Lower 95% CI**	**Upper 95% CI**	**BH-adjusted *P* value**	**Standardized estimate**	**Lower 95% CI**	**Upper 95% CI**	***P* value**
Without stratification									
SBP	Whole	0.0120	0.0083	0.0156	4.30E-10 ***	−0.0048	−0.0234	0.0137	6.09E-01
DBP		0.0175	0.0111	0.0239	1.31E-07 ***	0.0371	0.0034	0.0709	3.11E-2 *
With age stratification									
SBP	40–49	0.0070	−0.0016	0.0156	1.64E-01	−0.0460	−0.0860	−0.0060	2.44E-2 *
DBP		0.0117	−0.0013	0.0246	1.18E-01	0.0069	−0.0539	0.0676	8.25E-01
SBP	50–59	0.0163	0.0103	0.0223	3.74E-07 ***	−0.0002	−0.0290	0.0287	9.91E-01
DBP		0.0259	0.0154	0.0364	5.54E-06 ***	0.0151	−0.0357	0.0659	5.60E-01
SBP	60–69	0.0086	0.0032	0.0140	4.25E-03 **	0.0230	−0.0099	0.0559	1.70E-01
DBP		0.0147	0.0048	0.0246	7.11E-03 **	0.0991	0.0414	0.1568	7.68E-04 ***
With sex stratification									
SBP	Female	0.0149	0.0100	0.0197	7.38E-09 ***	0.0112	−0.0130	0.0355	3.64E-01
DBP		0.0233	0.0146	0.0319	3.59E-07 ***	0.0484	0.0062	0.0905	2.45E-02 *
SBP	Male	0.0074	0.0017	0.0131	2.05E-02 *	−0.0281	−0.0635	0.0073	1.20E-01
DBP		0.0094	−0.0001	0.0189	9.54E-02 ~.	0.0297	−0.0293	0.0887	3.24E-01
With age by sex stratification									
SBP	40–49 female	0.0053	−0.0056	0.0161	3.44E-01	−0.0529	−0.0983	−0.0075	2.23E-02 *
DBP		0.0095	−0.0075	0.0265	2.75E-01	−0.0139	−0.0893	0.0615	7.17E-01
SBP	40–49 male	−0.0004	−0.0150	0.0141	9.54E-01	−0.0495	−0.1222	0.0231	1.81E-01
DBP		0.0072	−0.0139	0.0283	5.04E-01	0.0201	−0.0781	0.1184	6.88E-01
SBP	50–59 female	0.0153	0.0077	0.0228	7.36E-05 ***	0.0329	−0.0029	0.0688	7.18E-02 ~.
DBP		0.0352	0.0212	0.0492	8.91E-07 ***	0.0686	0.0054	0.1318	3.35E-02 *
SBP	50–59 male	0.0125	0.0027	0.0223	1.24E-02 *	−0.0438	−0.0986	0.0109	1.17E-01
DBP		0.0127	−0.0035	0.0288	1.24E-01	−0.0441	−0.1245	0.0363	2.83E-01

		Linear association				MR analysis			
BP	**Group**	**Beta estimate**	**Lower 95% CI**	**Upper 95% CI**	**BH-adjusted *P* value**	**Standardized estimate**	**Lower 95% CI**	**Upper 95% CI**	***P* value**
SBP	60–69 female	0.0114	0.0038	0.0190	3.46E-03 **	0.0137	−0.0263	0.0537	5.01E-01
DBP		0.0177	0.0034	0.0319	1.50E-02 *	0.0962	0.0209	0.1714	1.22E-02 *
SBP	60–69 male	0.0007	−0.0070	0.0085	8.51E-01	0.0289	−0.0214	0.0793	0.2602
DBP		0.0104	−0.0037	0.0246	1.47E-01	0.0949	−0.0029	0.1926	5.71E-02 ~.

Multiple potential confounders are adjusted in both models. Results for both overall analysis (i.e. without stratification) and stratified analysis by age and sex are shown.

~. $P < 0.1$.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.