JAMA Network Open

Original Investigation | Genetics and Genomics

Genetic Complexities of Cerebral Small Vessel Disease, Blood Pressure, and Dementia

Muralidharan Sargurupremraj, PhD; Aicha Soumaré, PhD; Joshua C. Bis, PhD; Ida Surakka, PhD; Tuuli Jürgenson, MSc; Pierre Joly, PhD; Maria J. Knol, MSc; Ruiqi Wang, MSc; Qiong Yang, PhD; Claudia L. Satizabal, PhD; Alexander Gudjonsson, MSc; Aniket Mishra, PhD; Vincent Bouteloup, PhD; Chia-Ling Phuah, MD, MMSc; Cornelia M. van Duijn, PhD; Carlos Cruchaga, PhD; Carole Dufouil, PhD; Geneviève Chêne, MD, PhD; Oscar L. Lopez, MD; Bruce M. Psaty, MD, PhD; Christophe Tzourio, MD, PhD; Philippe Amouyel, MD, PhD; Hieab H. Adams, MD, PhD; Hélène Jacqmin-Gadda, PhD; Mohammad Arfan Ikram, MD, PhD; Vilmundur Gudnason, MD, PhD; Lili Milani, PhD; Bendik S. Winsvold, MD; Kristian Hveem, MD, PhD; Paul M. Matthews, MD, DPhil; W. T. Longstreth, MD; Sudha Seshadri, MD; Lenore J. Launer, PhD; Stéphanie Debette, MD, PhD

Abstract

IMPORTANCE Vascular disease is a treatable contributor to dementia risk, but the role of specific markers remains unclear, making prevention strategies uncertain.

OBJECTIVE To investigate the causal association between white matter hyperintensity (WMH) burden, clinical stroke, blood pressure (BP), and dementia risk, while accounting for potential epidemiologic biases.

DESIGN, SETTING, AND PARTICIPANTS This study first examined the association of genetically determined WMH burden, stroke, and BP levels with Alzheimer disease (AD) in a 2-sample mendelian randomization (2SMR) framework. Second, using population-based studies (1979-2018) with prospective dementia surveillance, the genetic association of WMH, stroke, and BP with incident all-cause dementia was examined. Data analysis was performed from July 26, 2020, through July 24, 2022.

EXPOSURES Genetically determined WMH burden and BP levels, as well as genetic liability to stroke derived from genome-wide association studies (GWASs) in European ancestry populations.

MAIN OUTCOMES AND MEASURES The association of genetic instruments for WMH, stroke, and BP with dementia was studied using GWASs of AD (defined clinically and additionally meta-analyzed including both clinically diagnosed AD and AD defined based on parental history [AD-meta]) for 2SMR and incident all-cause dementia for longitudinal analyses.

RESULTS In 2SMR (summary statistics–based) analyses using AD GWASs with up to 75 024 AD cases (mean [SD] age at AD onset, 75.5 [4.4] years; 56.9% women), larger WMH burden showed evidence for a causal association with increased risk of AD (odds ratio [OR], 1.43; 95% CI, 1.10-1.86; P = .007, per unit increase in WMH risk alleles) and AD-meta (OR, 1.19; 95% CI, 1.06-1.34; P = .008), after accounting for pulse pressure for the former. Blood pressure traits showed evidence for a protective association with AD, with evidence for confounding by shared genetic instruments. In the longitudinal (individual-level data) analyses involving 10 699 incident all-cause dementia cases (mean [SD] age at dementia diagnosis, 74.4 [9.1] years; 55.4% women), no significant association was observed between larger WMH burden and incident all-cause dementia (hazard ratio [HR], 1.02; 95% CI, 1.00-1.04; P = .07). Although all exposures were associated with mortality, with the strongest association observed for systolic BP (HR, 1.04; 95% CI, 1.03-1.06; $P = 1.9 \times 10^{-14}$), there was no evidence for selective survival bias during follow-up using illness-death models. In secondary

(continued)

Key Points

Question Do genetic instrumental variable analyses provide evidence of causation between vascular traits and Alzheimer disease (AD)?

Findings Using mendelian randomization (MR), this study showed a putative causal association of larger white matter hyperintensity (WMH) burden with increased AD risk after accounting for pulse pressure effects, and association of lower BP with AD risk with possible confounding by shared genetic instruments. Longitudinal analyses on individual-level data supported the association of genetically determined larger WMH with incident all-cause dementia and AD, independently of interim stroke.

Meaning With the use of complementary genetic epidemiology approaches, these findings suggest that WMH is a primary vascular factor associated with dementia risk.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

analyses using polygenic scores, the association of genetic liability to stroke, but not genetically determined WMH, with dementia outcomes was attenuated after adjusting for interim stroke.

CONCLUSIONS These findings suggest that WMH is a primary vascular factor associated with dementia risk, emphasizing its significance in preventive strategies for dementia. Future studies are warranted to examine whether this finding can be generalized to non-European populations.

JAMA Network Open. 2024;7(5):e2412824. doi:10.1001/jamanetworkopen.2024.12824

Introduction

With increasing life expectancy, the prevalence of dementia is expected to reach 75 million by 2030.[1,2] Devising strategies to prevent or delay its occurrence is a major public health priority. It is now widely recognized by the scientific community that most dementia cases in the population, including Alzheimer disease (AD), are related to a combination of vascular and neurodegenerative lesions.[3-6] On postmortem examinations, 80% of patients with clinically diagnosed AD have cerebrovascular lesions.[7] Among patients with stroke, the risk of incident dementia is at least doubled.[8,9] At the population level, covert cerebral small vessel disease, detectable on brain imaging in the absence of clinical stroke, is thought to be the main pathologic substrate underlying the vascular contribution to cognitive decline and dementia,[10] with nearly half of dementia cases exhibiting both AD and cerebral small vessel disease neuropathologic characteristics.[11]

White matter hyperintensity (WMH) burden is the most common cerebral small vessel disease feature on brain magnetic resonance imaging. Evidence from observational studies has established strong associations of WMH with increased risk of stroke and dementia, including AD,[12] yet evidence for causality is limited. A putative causal association has been suggested in a preliminary mendelian randomization (MR) analysis that used genetic instruments as proxies for WMH volume, thus leveraging the natural randomization of genetic variation at conception to mitigate risks of confounding and reverse causation inherent to observational studies.[13,14] However, while high blood pressure (BP) is by far the strongest risk factor for WMH, with extensive shared genetic variation,[13] several MR studies have reported inverse associations of genetically determined BP levels[15] with AD. These associations were observed both in datasets using standard AD diagnostic criteria[16-18] and in studies additionally using self-reported parental history as a proxy for AD diagnosis.[19] Complex age-dependent effects, possibly associated with the disease process, may lead to methodological issues, such as selective survival,[20] and intrinsic structural changes, such as arterial stiffness[21] and neurodegenerative lesions in BP-regulated regions, resulting in reverse causation.[22,23] However, these inconsistencies remain poorly understood. A better understanding of the causal associations of vascular traits with AD risk is crucial to prioritize interventions and optimally target populations to prevent cognitive decline and dementia. Here, taking a multipronged genetic epidemiologic approach, we aim to systematically examine putative causal associations of genetically defined vascular traits with all-cause dementia and AD, while ruling out potential biases.

Methods

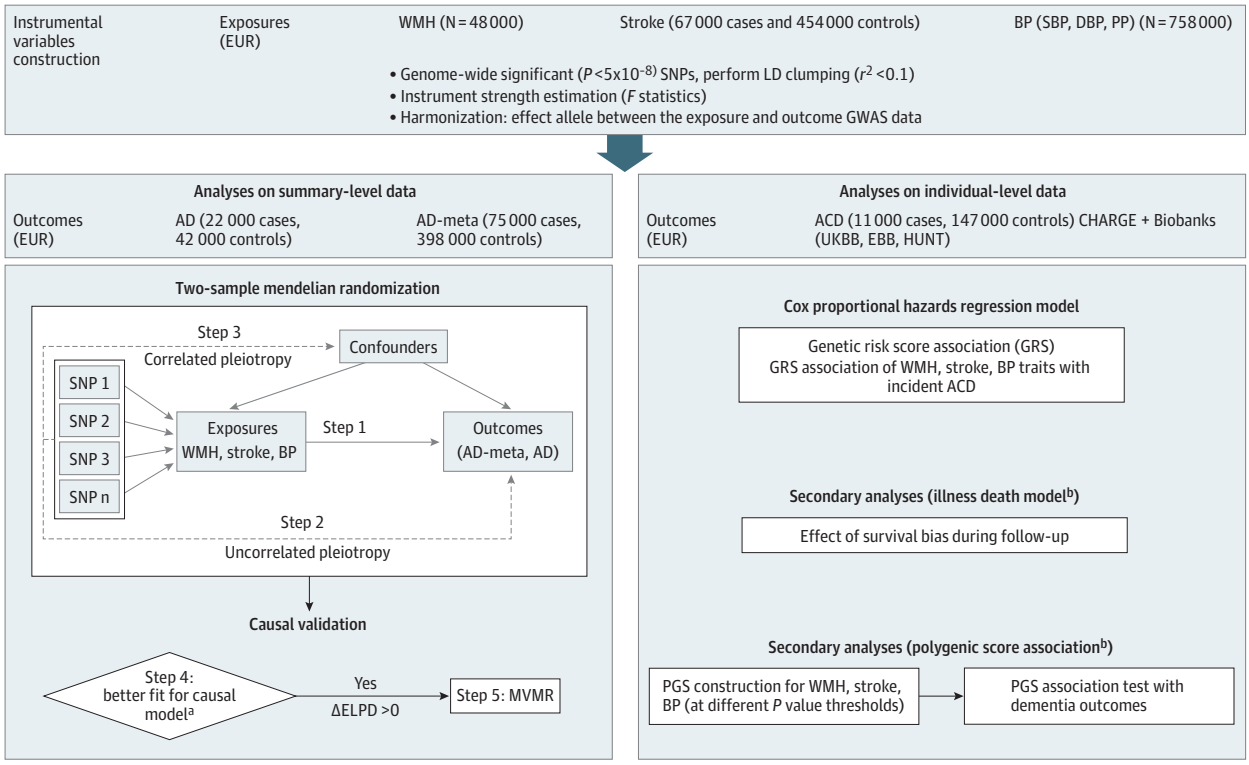
We used 2 complementary approaches to examine the association of vascular traits (WMH, stroke, and BP) with dementia risk (**Figure 1**). First, we used summary-level data from published genome-wide association study (GWAS) meta-analyses to examine putative causal associations in a 2-sample MR (2SMR) framework. These GWASs were based on cross-sectional studies with mostly clinic-based (stroke, dementia) or population-based (WMH, BP) recruitment.[13,15,24-26] Second, we leveraged individual-level data from 13 longitudinal cohorts and biobanks with prospective dementia

surveillance to examine the association of weighted genetic risk scores (wGRSs) for WMH, stroke, and BP with incident dementia using Cox proportional hazards regression models. Secondary analyses were conducted in 2 cohorts with participants aged 65 years or older (the Ages Gene/Environment Susceptibility [AGES] study[27] and the Three-City [3C] study[28]) using multistate models accounting for selective survival bias and polygenic scores. The MR study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline,[29] and the genetic association analyses followed the Strengthening the Reporting of Genetic Association Studies (STREGA) reporting guideline.[30] Cohorts included in individual-level analyses were approved by the relevant ethics committees and institutional review boards (eTable 3 in Supplement 1).

Analyses on Summary-Level Data

Two-sample MR uses single-nucleotide polymorphisms as genetic instruments for a given exposure (WMH, stroke, BP traits) to assess their putative causal association with the outcome (dementia). The validity of causal estimates relies on the assumption that these instruments are (1) strongly associated with the exposure (relevance) and (2) independent of the outcome given the exposure and confounders (independence) and (3) that the causal association is exclusively mediated by the exposure (exclusion restriction).

Figure 1. Study Design



Analyses on summary-level data: In step 1, we used the standard inverse variance weighting method to estimate causal effects between each exposure and Alzheimer disease (AD) or AD-meta with parental history of dementia. Steps 2 and 3 addressed potential pleiotropic effects confounding the initial causal estimates using MR-RAPS, weighted-median and mode-based methods. ACD indicates all-cause dementia; BP, blood pressure; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; DBP, diastolic blood pressure; EBB, Estonian Biobank; EUR, European population; GWAS, genome-wide association study; HUNT, Trøndelag Health Study; LD, linkage disequilibrium; PGS, polygenic profile score; PP, pulse pressure; SBP, systolic blood pressure; SNP, single-nucleotide polymorphism; UKBB, UK Biobank; and WMH, white matter hyperintensity.

[a] In step 4, we compared the causal model with the sharing model using MR-CAUSE. The risk factor–outcome associations favoring the causal model (change in expected log pointwise posterior density [ΔELPD] >0; see Methods) were validated in step 5 using multivariable mendelian randomization (MVMR).

[b] Association analyses in a subset of CHARGE cohorts (Three-City study, Ages Gene/Environment Susceptibility study).

Exposures

Genetic instruments for exposures were derived from European ancestry GWASs based on 48 454 population-based participants for WMH, 67 162 cases and 454 450 controls for stroke, and 757 601 population-based participants for systolic BP (SBP), diastolic BP (DBP), and pulse pressure (PP), of which the study design was described previously.[13,15,24] Cases in stroke GWASs were derived from both clinic-based and population-based studies and comprised patients with any stroke (ischemic stroke, intracerebral hemorrhage, or stroke of unknown or undetermined type), while controls were free of any stroke. In the BP GWASs, 15 mm Hg was added to SBP and 10 mm Hg was added to DBP for individuals taking BP-lowering medication. For each exposure, only independent genome-wide significant single-nucleotide polymorphisms ($P < 5 \times 10^{-8}$; $r^2 < 0.1$) were considered. Instrument strength was assessed using the Cragg-Donald *F* statistic to meet the relevance MR assumption (eMethods in Supplement 2).[31,32]

Outcomes

For dementia outcomes, we used European association statistics from GWASs of clinically diagnosed late-onset AD (21 982 cases and 41 944 controls)[25] and additionally meta-analyzed including both clinically diagnosed AD and broadly defined AD using self-reported parental history as a proxy for AD diagnosis (hereafter, *AD-meta*) that included both clinical AD cases (n = 21 982) and AD-meta cases based on parental history of dementia (n = 53 042) from the UK Biobank.[26] The AD-meta phenotype is a pseudolinear measure of AD risk incorporating the participant's dementia diagnosis weighted on parental dementia diagnoses and age, which was shown to have a near-unit correlation with clinical diagnosis.[33,34]

Causal Effect Estimation

In step 1, the inverse variance weighting method was used to estimate the putative causal association of WMH, stroke, SBP, DBP, and PP with AD (Figure 1). Step 2 aimed at testing the exclusion restriction MR assumption, using a suite of pleiotropy-robust methods (MR-RAPS, weighted median and mode) to account for potential effects of genetic instruments directly on the outcome that are uncorrelated with the exposure (uncorrelated pleiotropy).[35] Step 3 aimed at testing the independence MR assumption, using a bayesian approach that addresses correlated pleiotropy (MR-CAUSE), ensuring the independence of instruments from both exposure and outcome through confounders (Figure 1; eMethods in Supplement 2).[36] Two-sample MR analyses rely on published GWASs that are mostly adjusted for age and sex but not for other potential confounders. MR-CAUSE enables estimation of causal effects accounting for "unmeasured" confounding. When all instruments exhibit correlation for their effects on exposure and outcome, MR-CAUSE favors a causal model (γ) over the sharing model (*q*) in which pleiotropy due to confounders results in correlation only for a subset of instruments.[36] A positive difference in expected log pointwise posterior density ($\Delta ELPD = ELPD_{\gamma} - ELPD_{q}$) indicates the causal model's superiority (eMethods in Supplement 2). In step 4, for exposure-outcome pairs in which MR-CAUSE indicated a better fit for the causal model ($\Delta ELPD > 0$) but evidence for a significant sharing model ($P < .05$), we conducted multivariable MR (MVMR) to validate the putative causal association (Figure 1).[37] Multivariable MR simultaneously includes genetic instruments of all exposures in the same model, thus accounting for potential confounding of one exposure by the other (eg, potential confounding of the association between WMH and AD by SBP). Finally, for exposures with significant MVMR association, the following sensitivity analyses were conducted: (1) Qhet-MVMR to account for confounding due to weak instruments[38] and (2) bidirectional MR to confirm the causal direction (eMethods in Supplement 2). Causal estimates are scaled to represent a 1-SD change for continuous exposures and per 1-unit higher log odds for binary exposures. Analyses were performed using R, version 3.3.2 (R Project for Statistical Computing) and the TwoSampleMR, CAUSE-MR, and MVMR R packages. We used matSPDlite[39] to correct for multiple testing[40]; based on the correlation matrix between exposures, we identified 3 independent phenotypes leading to a *P* value threshold of $P < .02$ (.05/3).

Statistical Analysis

Analyses on Individual-Level Data

Statistical analysis was performed from July 26, 2020, through July 24, 2022. We conducted individual-level data analyses in longitudinal prospective cohort studies to examine the association of genetically determined WMH burden, stroke, and BP traits with incident dementia, while addressing potential selective survival bias.[41]

Primary Analyses | Analyses were conducted in 13 longitudinal cohorts participating in the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) consortium with cognitive assessment periods ranging from 1981 to 2016[42] and large biobanks (Trøndelag Health Study, Estonian Biobank, and UK Biobank) assessed between 1987 and 2018. Nearly all cohorts were population based, except MEMENTO (memory clinic patients without dementia and with cognitive symptoms), with an assessment period from 1979 to 2014. Dementia diagnosis was based on standard criteria (eMethods in Supplement 2).

We used Cox proportional hazards regression models to examine the association of genetic risk scores for WMH, stroke, and BP traits with incident all-cause dementia. For each exposure, we constructed wGRS based on the weighted sum of alleles of independent genome-wide significant risk variants for the corresponding exposure (the same variants as for genetic instruments in 2SMR analyses), using effect estimates from the GWAS that they were derived from as weights.[43] The wGRS were standardized (mean of 0, variance of 1), so that each unit change in the wGRS corresponds to 1-SD increase. Analyses were restricted to participants with no dementia at baseline and at least 1 follow-up visit. The Cox proportional hazards regression model used age as the time scale and was adjusted for sex, principal components of population stratification, and educational level (a strong determinant of cognitive function, associated with socioeconomic status and vascular risk factors; eTable 3 in Supplement 1). Data were censored at the age at dementia diagnosis or last follow-up. Cohort-specific estimates were combined using a fixed-effects inverse variance–weighted meta-analysis. Sensitivity analyses were conducted to rule out confounding by stroke, given the established association of WMH burden with stroke risk and of stroke with risk of dementia[13]: we excluded individuals with a stroke history at inclusion and adjusted for interim stroke (ie, occurring between blood draw and dementia diagnosis or end of follow-up), except in the Charles F. and Joanne Knight Alzheimer Disease Research Center biobank. As in the 2SMR, $P < .02$ was considered significant, accounting for 3 independent exposures.[40]

Secondary Analyses | Additional analyses were conducted in 3C and AGES, 2 large longitudinal population-based cohort studies with participants aged 65 years or older (eMethods in Supplement 2). We first examined whether survival bias during follow-up might affect our results using illness-death models,[44] accounting for interval censoring of time to onset of dementia and competing risk of death. Second, we examined associations of genetically determined vascular exposures (WMH, stroke, BP) with incident dementia subtypes (all-cause dementia, AD, vascular and/or mixed dementia; eMethods in Supplement 2) at more liberal instrument selection thresholds (P value between .50 and 5×10^{-8}) using polygenic scores (PGSs). A value of $P < .02$ correcting for 3 independent traits was considered statistically significant.

Results

Characteristics of Study Populations

For 2SMR analyses, the GWASs used to derive genetic instruments comprised up to 757 601 individuals of European ancestry: WMH GWASs included 48 454 individuals (mean [SD] age, 66.0 [7.5] years; 57.6% women); stroke GWASs included 67 162 cases and 454 450 controls (mean [SD] age, 63.7 [8.4] years; 44.8% women); and BP GWASs included 757 601 individuals (mean [SD] age, 56.8 [8.0] years; 54.2% women). The GWASs used for the dementia outcome comprised 75 024

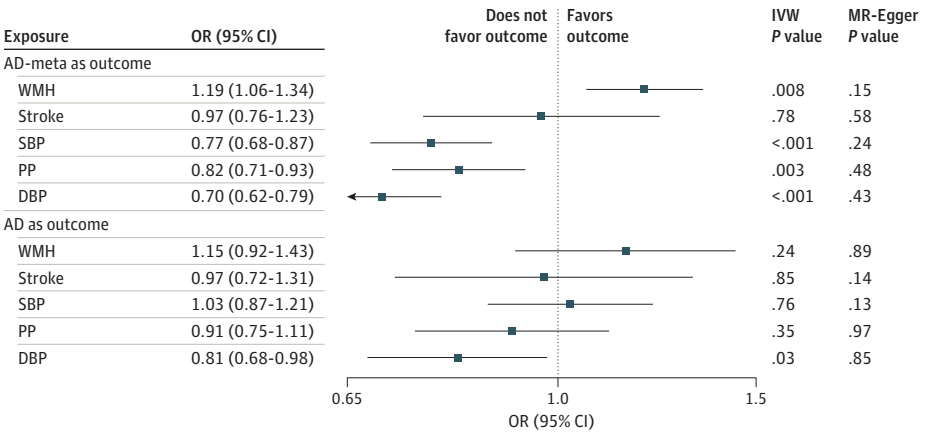
cases and 397 844 controls for AD-meta and 21 982 cases and 41 944 controls for clinically diagnosed AD (mean [SD] age at AD onset, 75.5 [4.4] years; 56.9% women).[13,15,24-26]

For individual-level analyses, the 13 longitudinal cohorts included 157 698 participants of European ancestry, of whom 10 699 developed incident all-cause dementia (mean [SD] age at baseline, 64.2 [11.3] years; mean [SD] age at dementia diagnosis, 74.4 [9.1] years; 55.4% women; follow-up ranged from 3 to 25 years). The AGES and 3C studies used for secondary analyses comprised 978 and 621 incident dementia cases, respectively; a mean (SD) age at baseline of 75.9 (5.3) years and 74.1 (5.4) years, respectively; a mean (SD) age at dementia diagnosis of 85.1 (4.7) years and 81.8 (5.4) years, respectively; and a follow-up of 10.2 and 7.7 years, respectively.

Associations of WMH, Stroke, and BP With AD Risk Using Summary-Level Data

The genetic instruments for WMH, stroke, and BP were strongly associated with the exposures (F = 22-65; eTables 1 and 2 in Supplement 1). Using the inverse variance weighting method, we found significant associations of genetically determined larger WMH burden (odds ratio [OR], 1.19 [95% CI, 1.06-1.34]; P = .008) and lower DBP (OR, 0.70 [95% CI, 0.62-0.79]; P < .001), SBP (OR, 0.77 [95% CI, 0.68-0.87]; P < .001), and PP (OR, 0.82 [95% CI, 0.71-0.93]; P = .003) with AD-meta risk and of lower DBP with clinically diagnosed AD risk (OR, 0.81 [95% CI, 0.68-0.98]; P = .03) (**Figure 2**; **Table**). The complementary MR tools MR-RAPS, weighted median and mode, robustly ruled out uncorrelated pleiotropy (eTables 4B and 5B in Supplement 1). The bayesian MR-CAUSE method that additionally accounts for correlated pleiotropy further supported a causal association of WMH with both AD and AD-meta, with a posterior distribution of the causal model distinctively different from the sharing model (ΔELPD = 0.91 for AD and 0.50 for AD-meta) (Table; eTable 6 in Supplement 1). On the contrary, stroke and BP traits suggested a better fit of the sharing model with potential unmeasured confounders for AD-meta (stroke, ΔELPD = −2.60; SPB, ΔELPD = −3.00; DBP, ΔELPD = −2.20) and AD (stroke, ΔELPD = 0.41; SPB, ΔELPD = 0.44; DBP, ΔELPD = −1.20) (Table). For associations of WMH with AD, although there was a better fit of the causal model (ΔELPD = 0.91), a significant proportion of genetic instruments appeared to be shared with unmeasured confounders (P < .001 for the sharing model) (Table; eFigure 1 in Supplement 2). We therefore performed a multivariable analysis, adjusting for the associations of closely related traits using MVMR. Greater genetically determined WMH burden was associated with a 43.4% increase in the probability of AD risk (OR, 1.43; 95% CI, 1.10-1.86; P = .007, per unit increase in WMH risk alleles) after accounting for PP associations (**Figure 3**; eTable 7 in Supplement 1), a 28.6% increase in disease risk compared with univariable estimates (OR, 1.15; 95% CI, 0.92-1.43; P = .24), with consistent direction of association. A bidirectional MR analysis between the WMH and PP suggested a causal path of higher PP with larger WMH burden (eTable 8 in Supplement 1).

Figure 2. Mendelian Randomization Results of Vascular Risk Factors With Alzheimer Disease (AD)



Point estimates and 95% CIs from the inverse variance weighted (IVW) method, along with the P value for the IVW and MR-Egger intercept, are shown. The causal estimates are scaled to represent a 1-SD change for the continuous exposures and per 1-unit higher log odds for binary exposures. DBP indicates diastolic blood pressure; OR, odds ratio; PP, pulse pressure; SBP, systolic blood pressure; and WMH, white matter hyperintensity.

Association of WMH, Stroke, and BP wGRS With Incident Dementia Using Individual-Level Data

In a meta-analysis of 13 longitudinal cohort studies, we observed a nonsignificant association of larger genetically determined WMH burden with increased risk of incident all-cause dementia (hazard ratio [HR], 1.02; 95% CI, 1.00-1.04; P = .07, per SD increase in WMH wGRS) (**Figure 4**; eTable 9 in Supplement 1). After adjustment for educational level and interim stroke, this association remained substantially unchanged (Figure 4). There was no significant heterogeneity across cohorts (I^2 = 7%; P = .38) (eFigure 2 in Supplement 2). Genetic liability to stroke and genetically determined BP traits failed to show significant associations with incident all-cause dementia, with negative point estimates for stroke and SBP. All exposures showed at least nominally significant associations with increased mortality, most significantly for SBP (HR, 1.04; 95% CI, 1.03-1.06; $P = 1.9 \times 10^{-14}$); the association of WMH with mortality was no longer significant after adjusting for educational level or interim stroke status (eTables 9 and 10 in Supplement 1).

In secondary analyses, using illness-death models for 2 older population-based cohorts (3C and AGES), genetically determined higher WMH burden, BP levels, and genetic liability to stroke were

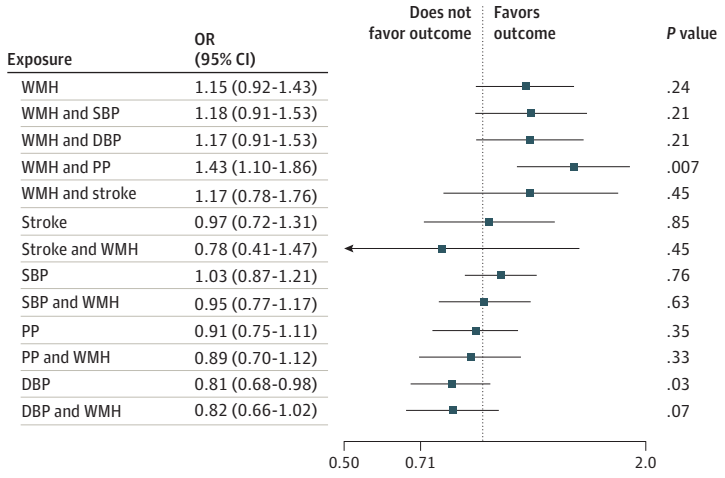
Table. Suite of 2-Sample MR Analyses With AD Outcomes

	MR-IVW method		MR-CAUSE			MVMR	
Exposure	Odds ratio	*P* value	ΔELPD[a]	*P* value for causal effect	*P* value for shared model	OR	*P* value
Vascular risk factors associated with AD-meta							
WMH	1.19 (1.06 to 1.34)	.008	0.50	.39	.62	NA	NA
Stroke	0.97 (0.76 to 1.23)	.78	−2.60	.005	.27	NA	NA
SBP	0.77 (0.68 to 0.87)	<.001	−3.00	<.001	<.001	NA	NA
PP	0.82 (0.71 to 0.93)	.003	−1.60	<.001	.001	NA	NA
DBP	0.70 (0.62 to 0.79)	<.001	−2.20	<.001	<.001	NA	NA
Vascular risk factors associated with clinically defined AD							
WMH	1.15 (0.92 to 1.43)	.24	0.91	.77	<.001	1.43 (1.10 to 1.86)	.007
Stroke	0.97 (0.72 to 1.31)	.85	0.41	.42	.52	NA	NA
SBP	1.03 (0.87 to 1.21)	.76	0.44	NA	.16	NA	NA
PP	0.91 (0.75 to 1.11)	.35	−0.97	NA	.42	NA	NA
DBP	0.81 (0.68 to 0.98)	.03	−1.20	.05	.09	NA	NA

Abbreviations: AD, Alzheimer disease; DBP, diastolic blood pressure; IVW, inverse variance weighting; MR, mendelian randomization; MVMR, multivariable MR; NA, not applicable; PP, pulse pressure; SBP, systolic blood pressure; WMH, white matter hyperintensity; ΔELPD, change in expected log pointwise posterior density, testing causal vs sharing model.

[a] ΔELPD > 0 indicates a better fit for the causal model.

Figure 3. Multivariable Mendelian Randomization (MVMR) Along With the Univariable Mendelian Randomization (MR) for Alzheimer Disease (AD) as the Outcome



Univariable MR and MVMR results are shown, and the association *P* values are shown on the far right. The causal estimates are scaled to represent a 1-SD change for the continuous exposures and per 1-unit higher log odds for binary exposures. DBP indicates diastolic blood pressure; OR, odds ratio; PP, pulse pressure; SBP, systolic blood pressure; and WMH, white matter hyperintensity.

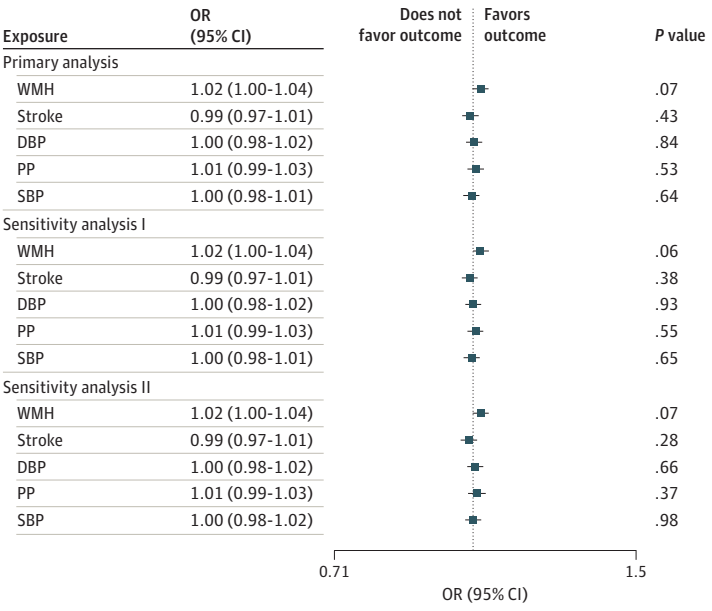
not associated with incident all-cause dementia, with effect estimates similar to those observed in Cox proportional hazards regression models (eTable 11 in Supplement 1), thus ruling out potential biases related to competing risk of death during follow-up in the context of interval censoring.

In further secondary analyses using PGSs, we found that PGSs for WMH and stroke with less stringent instrument-significance thresholds (eTable 12 in Supplement 1) were significantly associated with increased risk of all-cause dementia in both cohorts (eFigures 3 and 4 in Supplement 2 and eTables 13 and 14 in Supplement 1). In sensitivity analyses excluding prevalent stroke and adjusting for interim stroke, WMH PGS associations with dementia remained unchanged, while stroke PGS associations were markedly attenuated in both cohorts. Meta-analyses of effect estimates from 3C and AGES (for PGS bins at $P < .50$) showed significant associations of WMH and stroke PGS with increased risk of all-cause dementia, AD, and vascular or mixed dementia (eTable 15 in Supplement 1). Blood pressure PGSs were mostly not associated with dementia, except for protective associations of SBP and DBP PGSs with AD in AGES only, attenuated after excluding prevalent stroke and adjusting for interim stroke (eTable 16 in Supplement 1).

Discussion

Using comprehensive 2SMR workflow–leveraging summary statistics of large GWASs for vascular traits (WMH, stroke, and BP) and AD, we report a putative causal association of genetically determined larger WMH burden with increased risk of AD, both clinically diagnosed[25] and using parental history of dementia as a proxy.[26] The former association was strengthened after accounting for PP using multivariable MR. Blood pressure traits showed evidence for a protective association with AD, with evidence for confounding by shared genetic instruments. In longitudinal individual-level analyses across 13 cohorts and biobanks with 157 698 participants, we observed a nonsignificant trend toward an association of larger WMH burden with incident all-cause dementia. Although all vascular exposures were associated with mortality, there was no evidence for selective survival bias during follow-up in secondary analyses using illness-death models in AGES and 3C. In these cohorts, PGSs for WMH and stroke were associated with all-cause dementia, AD, and vascular or mixed dementia, and for WMH, these associations were independent of interim stroke.

Figure 4. Meta-Analysis Results of Risk Factor–Weighted Genetic Risk Scores (per SD Increase) With Incident All-Cause Dementia



Primary analysis: Cox proportional hazards regression model adjusted for sex, principal components of population stratification, study-specific criteria, and educational level. Sensitivity analysis I: Cox proportional hazards regression model adjusted for sex, principal components of population stratification, study-specific criteria. Sensitivity analysis II: prevalent stroke excluded and the Cox proportional hazards regression model adjusted for sex, principal components of population stratification, study-specific criteria, and interim stroke status. Association *P* values are shown on the far right. DBP indicates diastolic blood pressure; OR, odds ratio; PP, pulse pressure; SBP, systolic blood pressure; and WMH, white matter hyperintensity.

Overall, of all vascular phenotypes considered, WMH appeared to show the most robust associations with dementia risk, including AD, AD-meta, and all-cause dementia, adding evidence of causal associations to findings from observational studies[12,45-48] and highlighting WMH as a key pathway to target for dementia prevention (eFigure 5 in Supplement 2). This finding reinforces earlier observations of a putative causal association of WMH with AD-meta,[13] expanding it to a larger AD-meta GWAS[26] and to clinically diagnosed AD.[25] The stronger association of WMH with the latter after accounting for PP, with a marked (28.6%) increase in AD risk, is intriguing. Pulse pressure is a marker of arterial stiffness,[49,50] which was shown to be associated with WMH burden and amyloid-β deposition and its progression in the brain.[51,52] Elevated PP may dysregulate brain endothelial cells and increase cellular production of oxidative and inflammatory molecules, possibly leading to amyloid-β secretion and blood-brain barrier breakdown.[53-55]

High BP is the strongest known risk factor for WMH, with MR studies suggesting a causal association, even among persons without clinically defined hypertension.[13] Moreover, BP-lowering treatments were shown to slow WMH progression in randomized trials,[56-60] especially with intensive BP lowering.[60] Given the aforementioned associations of WMH with AD, the association of high BP with lower risk of AD and AD-meta in the 2SMR analysis appears counterintuitive. However, it aligns with earlier MR studies using instruments from smaller BP GWASs or genetic proxies for BP-lowering effect.[16-19,61] Our sensitivity analyses using MR-CAUSE suggest that pleiotropic effects from unmeasured confounders might explain this unexpected directionality of association, highlighting the importance of such examinations rather than merely removing or downweighing pleiotropic variants (MR-RAPS, weighted median and mode). Moreover, while we did not observe selective survival bias during follow-up, given the late age of dementia onset (mean age, 85 years),[62] the strong association of genetically determined high BP with premature death, in line with observational studies,[63-66] raises the possibility of selective survival bias before study entry. The apparently protective effect of high BP on dementia risk might thus reflect underlying collider bias[67] rather than causality.[68-70] Although nonsignificant, the association of PP and DBP with incident all-cause dementia had point estimates above 1 in the longitudinal cohort studies, which are probably less exposed to selective survival than the AD case-control GWAS used for the 2SMR analyses.[25,26] Beyond these possible biases, our results highlight the complexity of the epidemiologic association between BP and dementia risk, with strong age effects. High BP in midlife but not late life was shown to be associated with dementia risk,[71-73] and in a meta-analysis of longitudinal cohorts, the reduction in AD risk associated with antihypertensive medication use was greater among younger compared with older participants with hypertension.[74] Meta-analyses of clinical trials have shown the effectiveness of antihypertensive medication in reducing the combined outcome of dementia and cognitive impairment, while evidence for dementia alone remains inconclusive.[74,75]

In contrast to BP measurements, which show high intraindividual variability,[76] WMH volume is a more stable marker, reflecting white matter damage secondary to changes in the structure and/or function of cerebral small vessels. Assuming that WMH at least partly mediates the association of BP with dementia in the population, WMH may better capture the brain damage caused by BP than BP itself. White matter hyperintensity likely also reflects the association of other parameters with white matter integrity, such as cerebral amyloid angiopathy or factors associated with the resilience of the brain white matter to vascular insults. Given the high prevalence of WMH in the general population among stroke-free individuals,[48] our results highlight WMH as a major causal pathway to consider for the prevention of dementia.

Limitations

This study has some limitations. First, despite the large samples used for 2SMR, we observed imprecise estimates for certain associations (stroke and BP traits). This finding could be attributed to comparatively weaker instruments (the stroke *F* statistic was lower than for other exposures)[77] or to limitations of certain MR methods for exposures comprising very large numbers of genetic instruments (eg, BP traits).[78,79] Second, the AD-meta phenotype that uses family history of dementia

as a proxy for AD enables the increase in sample size and also possibly includes more patients with mixed dementia, who are likely underrepresented in GWASs using clinically defined AD only, although they represent most dementia cases in the population. However, the imprecision of the AD-meta phenotype is a limitation; therefore, we have provided additional analyses focusing exclusively on clinically defined AD. Third, single-exposure MR analyses might oversimplify underlying causal associations, and therefore complementary approaches investigating more broadly the dementia exposome are warranted.[80] Fourth, in our longitudinal analyses, the number of incident dementia cases remained modest, with some differences in ascertainment methods, which may have limited power to detect associations. Although secondary exploratory analyses showed an association of PGS for genetically determined WMH with incident dementia subtypes, these require validation in independent datasets, especially as our multiple testing correction did not account for the dementia subtypes analyzed. Fifth, validation of our findings in populations of non-European ancestry, as larger datasets become available, will be crucial.

Conclusions

Our findings provide converging evidence that WMH is a major vascular factor associated with dementia risk, emphasizing that it should be prioritized in preventive efforts. They also support WMH as a surrogate marker for clinical trials to prevent dementia by controlling vascular risk.[60,81] Our results prompt caution when interpreting MR studies with late-onset diseases, particularly when survival is strongly associated with the exposure instruments, and highlight the importance of combining complementary analytical approaches and applying them to several independent studies to mitigate study-specific limitations and biases.

ARTICLE INFORMATION

Accepted for Publication: March 21, 2024.

Published: May 22, 2024. doi:10.1001/jamanetworkopen.2024.12824

Corresponding Authors: Stephanie Debette, MD, PhD (stephanie.debette@u-bordeaux.fr), and Muralidharan Sargurupremraj, PhD (sargurupremr@uthscsa.edu), Bordeaux Population Health Research Center, University of Bordeaux, Inserm, UMR 1219, 146 rue leo saignat, 33076 Bordeaux, France.

Author Affiliations: Bordeaux Population Health Research Center, University of Bordeaux, Inserm, UMR 1219, Bordeaux, France (Sargurupremraj, Soumaré, Joly, Mishra, Bouteloup, Dufouil, Chêne, Tzourio, Jacqmin-Gadda, Debette); Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases, University of Texas Health Sciences Center, San Antonio (Sargurupremraj, Satizabal, Seshadri); Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle (Bis, Psaty); Department of Internal Medicine, University of Michigan, Ann Arbor (Surakka); Estonian Genome Centre, Institute of Genomics, University of Tartu, Tartu, Estonia (Jürgenson, Milani); Department of Epidemiology, Erasmus MC University Medical Center, Rotterdam, the Netherlands (Knol, Ikram); School of Public Health, Boston University and the National Heart, Lung, and Blood Institute Framingham Heart Study, Boston, Massachusetts (Wang, Yang, Satizabal, Seshadri, Debette); Department of Neurology, Boston University School of Medicine, Boston, Massachusetts (Wang, Yang, Satizabal, Seshadri); Icelandic Heart Association, Kopavogur, Iceland (Gudjonsson, Gudnason); Department of Neurology, Washington University School of Medicine & Barnes-Jewish Hospital, St Louis, Missouri (Phuah); NeuroGenomics and Informatics Center, Washington University in St Louis, St Louis, Missouri (Phuah, Cruchaga); Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom (van Duijn); Department of Psychiatry, Washington University School of Medicine, St Louis, Missouri (Cruchaga); Charles F. and Joanne Knight Alzheimer Disease Research Center, Washington University School of Medicine, St Louis, Missouri (Cruchaga); Department of Public Health, CHU de Bordeaux, Bordeaux, France (Chêne, Tzourio); Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (Lopez); Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (Lopez); Department of Epidemiology, University of Washington, Seattle (Psaty, Longstreth); Department of Health Systems and Population Health,

University of Washington, Seattle (Psaty); INSERM U1167, University of Lille, Institut Pasteur de Lille, Lille, France (Amouyel); Department of Epidemiology and Public Health, CHRU de Lille, Lille, France (Amouyel); Department of Human Genetics, Radboud University Medical Center, Nijmegen, the Netherlands (Adams); Latin American Brain Health (BrainLat), Universidad Adolfo Ibáñez, Santiago, Chile (Adams); Faculty of Medicine, University of Iceland, Reykjavik, Iceland (Gudnason); Division of Clinical Neuroscience, Department of Research and Innovation, Oslo University Hospital, Oslo, Norway (Winsvold); K. G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Trondheim, Norway (Winsvold, Hveem); Department of Neurology, Oslo University Hospital, Oslo, Norway (Winsvold); HUNT Research Centre, Department of Public Health and Nursing, Norwegian University of Science and Technology, Levanger, Norway (Hveem); Department of Brain Sciences, Imperial College London, London, United Kingdom (Matthews); UK Dementia Research Institute, Imperial College London, London, United Kingdom (Matthews); Data Science Institute, Imperial College London, London, United Kingdom (Matthews); Department of Neurology, University of Washington, Seattle (Longstreth); Laboratory of Epidemiology and Population Sciences, Intramural Research Program, National Institute on Aging, Bethesda, Maryland (Launer); Institute for Neurodegenerative Diseases, Department of Neurology, Bordeaux University Hospital, Bordeaux, France (Debette).

Author Contributions: Drs Sargurupremraj and Debette had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Sargurupremraj and Soumaré are co-first authors and contributed equally to this work. Drs Launer and Debette contributed equally to supervision.

Concept and design: Sargurupremraj, Joly, Lopez, Ikram, Seshadri, Debette.

Acquisition, analysis, or interpretation of data: Sargurupremraj, Soumaré, Bis, Surakka, Jürgenson, Knol, Wang, Yang, Satizabal, Gudjonsson, Mishra, Bouteloup, Phuah, van Duijn, Cruchaga, Dufouil, Chêne, Psaty, Tzourio, Amouyel, Adams, Jacqmin-Gadda, Ikram, Gudnason, Milani, Winsvold, Hveem, Matthews, Longstreth, Seshadri, Launer, Debette.

Drafting of the manuscript: Sargurupremraj, Soumaré, Surakka, Launer, Debette.

Critical review of the manuscript for important intellectual content: Sargurupremraj, Soumaré, Bis, Surakka, Jürgenson, Joly, Knol, Wang, Yang, Satizabal, Gudjonsson, Mishra, Bouteloup, Phuah, van Duijn, Cruchaga, Dufouil, Chêne, Lopez, Psaty, Tzourio, Amouyel, Adams, Jacqmin-Gadda, Ikram, Gudnason, Milani, Winsvold, Hveem, Matthews, Longstreth, Seshadri, Debette.

Statistical analysis: Sargurupremraj, Soumaré, Bis, Surakka, Jürgenson, Joly, Knol, Wang, Yang, Gudjonsson, Mishra, Bouteloup, Phuah, van Duijn, Jacqmin-Gadda, Winsvold.

Obtained funding: van Duijn, Dufouil, Psaty, Tzourio, Amouyel, Gudnason, Milani, Matthews, Seshadri, Debette.

Administrative, technical, or material support: Mishra, Bouteloup, Chêne, Lopez, Tzourio, Milani, Winsvold, Hveem, Matthews.

Supervision: van Duijn, Cruchaga, Dufouil, Ikram, Milani, Matthews, Seshadri, Debette.

Conflict of Interest Disclosures: Dr Soumaré reported receiving grants from the University of Bordeaux during the conduct of the study. Dr Phuah reported receiving the Charleston Conference on Alzheimer's Disease New Vision Award during the conduct of the study. Dr Psaty reported receiving grants from the National Institutes of Health (NIH) during the conduct of the study and serving on the steering committee of the Yale Open Data Access Project funded by Johnson & Johnson. Dr Amouyel reported receiving personal fees from Fondation Alzheimer, Genoscreen Biotech, and Qalis outside the submitted work. Dr Winsvold reported serving as a local principal investigator in a clinical trial and delivering lectures for Lundbeck outside the submitted work. Dr Matthews reported receiving grants from Biogen, Merck, and Bristol Myers Squibb and personal fees from Novartis, Sudo Bioseciences, and UK Research and Renovation Medical Research Council outside the submitted work. No other disclosures were reported.

Funding/Support: The Cardiovascular Health Study (CHS) research was supported by National Heart, Lung, and Blood Institute (NHLBI) contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and 75N92021D00006; and NHLBI grants R01AG15928, R01AG20098, R01AG033193, U01HL080295, R01HL087652, R01HL105756, R01HL103612, R01HL120393, and U01HL130114 with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided through grant R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org. The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, Clinical and Translational Science Institute grant UL1TR001881, and the National Institute of Diabetes and Digestive and Kidney Disease Diabetes Research Center grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

The Age/Gene-Environment Susceptibility study was funded by the NIA (grants N01-AG-12100 and HHSN27120120022C), Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament), with contributions from the Intramural Research Programs at the NIA.

The MEMENTO cohort is sponsored by Bordeaux University Hospital (coordination: CIC1401-EC, Bordeaux) and was funded through research grants from the Foundation Plan Alzheimer (Alzheimer Plan 2008–2012) and the French Ministry of Research and Higher Education (Plan Maladies Neurodégénératives [2016–2019]).

The Trøndelag Health Study (HUNT) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, NTNU [Norwegian University of Science and Technology]), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. The genotyping in HUNT was financed by the NIH; University of Michigan; the Research Council of Norway; the Liaison Committee for Education, Research and Innovation in Central Norway; and the Joint Research Committee between St Olavs Hospital and the Faculty of Medicine and Health Sciences, NTNU. The genetic investigations of the HUNT Study is a collaboration between researchers from the K.G. Jebsen Center for Genetic Epidemiology, NTNU, and the University of Michigan Medical School and the University of Michigan School of Public Health. The K.G. Jebsen Center for Genetic Epidemiology is financed by Stiftelsen Kristian Gerhard Jebsen; Faculty of Medicine and Health Sciences, NTNU, Norway.

The Framingham Heart Study (FHS) was supported by the National Heart, Lung, and Blood Institute's FHS Contract (N01-HC-25195, HHSN268201500001I, and 75N92019D00031). This study was also supported by grants from the NIA (R01AG031287, R01AG054076, R01AG049607, and R01AG059421). In addition, Drs Seshadri, Satizabal, and Sargurupremraj are partially supported by the South Texas Alzheimer's Disease Research Center (P30AG066546). The computational work reported in this article was performed on the Shared Computing Cluster that is administered by Boston University's Research Computing Services. We thank the staff and participants of the Framingham Study.

Estonian Biobank (EstBB) thanks all participants and staff of the EstBB for their contribution to this research, and the analytical work of EstBB was carried out in part in the High Performance Computing Center of the University of Tartu. We acknowledge the work of the EstBB Research Team: Andres Metspalu, Mari Nelis, Reedik Mägi, and Tõnu Esko. This research at EstBB was supported by the Estonian Research Council grant PUT (PRG184) and the European Union through the European Regional Development Fund (Project No. 2014-2020.4.01.15-0012); the PRECISE4Q project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under Grant agreement 777107.

Rotterdam study: the generation and management of genome-wide association study genotype data for the Rotterdam Study is supported by the Netherlands Organisation of Scientific Research (NOW) Investments (nr. 175.010.2005.011, 911-03-012). This study is funded by the Research Institute for Diseases in the Elderly (014-93-015; RIDE2), the Netherlands Genomics Initiative (NGI)/NWO project 050-060-810. The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organisation for the Health Research and Development, the Research Institute for Diseases in the Elderly, the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam.

Charles F. and Joanne Knight Alzheimer Disease Research Center: the Knight Washington University Alzheimer Disease Research Center is supported by the following grants: NIH P30AG066444, P01AG003991, and P01AG026276.

This project is supported by a grant overseen by the French National Research Agency (ANR) as part of the "Investment for the Future Programme" ANR-18-RHUS-0002. It is also supported by a European Union (EU) Joint Programme-Neurodegenerative Disease Research (JPND) project through the following funding organizations under the aegis of JPND (www.jpnd.eu): Australia, National Health and Medical Research Council; Austria, Federal Ministry of Science, Research and Economy; Canada, Canadian Institutes of Health Research; France, French National Research Agency; Germany, Federal Ministry of Education and Research; Netherlands, the Netherlands Organisation for Health Research and Development; and United Kingdom, Medical Research Council. This project has received funding from the EU Horizon 2020 research and innovation program under grant agreements 643417, 640643, 667375, and 754517. The project also received funding from the ANR through the VASCOGENE and SHIVA projects, the France 2030 IHU Precision and Global Vascular Brain Health Institute (ANR-23-IAHU-0001). Computations were performed on the Bordeaux Bioinformatics Center computer resources, University of Bordeaux. Funding support for additional computer resources has been provided to Dr Debette by the Fondation Claude Pompidou.

The Three-City (3C) Study is conducted under a partnership agreement among the Institut National de la Santé et de la Recherche Médicale (INSERM), the University of Bordeaux, and Sanofi-Aventis. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The 3C Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, Mutuelle Générale de l'Education

Nationale (MGEN), Institut de la Longévité, Conseils Régionaux of Aquitaine and Bourgogne, Fondation de France, and Ministry of Research–INSERM Programme "Cohortes et collections de données biologiques."

This work was supported by the National Foundation for Alzheimer's Disease and Related Disorders, the Institut Pasteur de Lille, the Labex DISTALZ, and the Centre National de Génotypage.

This research has been conducted using the UK Biobank Resource under applications 94113 and 18545.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank the FHS participants, as well as the study team (especially the investigators and staff of the neurology team) for their contributions and dedication to the study. The computational work reported in this article was performed on the Shared Computing Cluster, which is administered by Boston University Research Computing Services. We thank the Age/Gene-Environment Susceptibility study participants for their participation. We thank all study participants for their contributions.

REFERENCES

1. Prince M, Ali GC, Guerchet M, Prina AM, Albanese E, Wu YT. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. *Alzheimers Res Ther*. 2016;8(1):23. doi:10.1186/s13195-016-0188-8

2. Wang H, Naghavi M, Allen C, et al; GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1459-1544. doi:10.1016/S0140-6736(16)31012-1

3. Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia: how to move forward? *Neurology*. 2009;72(4):368-374. doi:10.1212/01.wnl.0000341271.90478.8e

4. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci*. 2011;12(12):723-738. doi:10.1038/nrn3114

5. Skoog I, Lernfelt B, Landahl S, et al. 15-Year longitudinal study of blood pressure and dementia. *Lancet*. 1996; 347(9009):1141-1145. doi:10.1016/S0140-6736(96)90608-X

6. Nichols E, Merrick R, Hay SI, et al. The prevalence, correlation, and co-occurrence of neuropathology in old age: harmonisation of 12 measures across six community-based autopsy studies of dementia. *Lancet Healthy Longev*. 2023;4(3):e115-e125. doi:10.1016/S2666-7568(23)00019-3

7. Toledo JB, Arnold SE, Raible K, et al. Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain*. 2013;136(Pt 9): 2697-2706. doi:10.1093/brain/awt188

8. Savva GM, Stephan BCM; Alzheimer's Society Vascular Dementia Systematic Review Group. Epidemiological studies of the effect of stroke on incident dementia: a systematic review. *Stroke*. 2010;41(1):e41-e46. doi:10.1161/STROKEAHA.109.559880

9. Levine DA, Galecki AT, Langa KM, et al. Trajectory of cognitive decline after incident stroke. *JAMA*. 2015;314 (1):41-51. doi:10.1001/jama.2015.6968

10. Wardlaw JM, Smith EE, Biessels GJ, et al; STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12(8):822-838. doi:10.1016/S1474-4422(13)70124-8

11. Iadecola C. The pathobiology of vascular dementia. *Neuron*. 2013;80(4):844-866. doi:10.1016/j.neuron.2013.10.008

12. Debette S, Schilling S, Duperron MG, Larsson SC, Markus HS. Clinical significance of magnetic resonance imaging markers of vascular brain injury: a systematic review and meta-analysis. *JAMA Neurol*. 2019;76(1):81-94. doi:10.1001/jamaneurol.2018.3122

13. Sargurupremraj M, Suzuki H, Jian X, et al; International Network against Thrombosis (INVENT) Consortium; International Headache Genomics Consortium (IHGC). Cerebral small vessel disease genomics and its implications across the lifespan. *Nat Commun*. 2020;11(1):6285. doi:10.1038/s41467-020-19111-2

14. Burgess S, Swanson SA, Labrecque JA. Are mendelian randomization investigations immune from bias due to reverse causation? *Eur J Epidemiol*. 2021;36(3):253-257. doi:10.1007/s10654-021-00726-8

15. Evangelou E, Warren HR, Mosen-Ansorena D, et al; Million Veteran Program. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nat Genet*. 2018;50(10):1412-1425. doi:10.1038/s41588-018-0205-x

16. Østergaard SD, Mukherjee S, Sharp SJ, et al; Alzheimer's Disease Genetics Consortium; GERAD1 Consortium; EPIC-InterAct Consortium. Associations between potentially modifiable risk factors and Alzheimer disease: a mendelian randomization study. *PLoS Med*. 2015;12(6):e1001841. doi:10.1371/journal.pmed.1001841

17. Larsson SC, Traylor M, Malik R, Dichgans M, Burgess S, Markus HS; CoSTREAM Consortium, on behalf of the International Genomics of Alzheimer's Project. Modifiable pathways in Alzheimer's disease: mendelian randomisation analysis. *BMJ*. 2017;359:j5375. doi:10.1136/bmj.j5375

18. Andrews SJ, Fulton-Howard B, O'Reilly P, Marcora E, Goate AM; Collaborators of the Alzheimer's Disease Genetics Consortium. Causal associations between modifiable risk factors and the Alzheimer's phenome. *Ann Neurol*. 2021;89(1):54-65. doi:10.1002/ana.25918

19. Sproviero W, Winchester L, Newby D, et al. High blood pressure and risk of dementia: a two-sample mendelian randomization study in the UK Biobank. *Biol Psychiatry*. 2021;89(8):817-824. doi:10.1016/j.biopsych.2020.12.015

20. Smit RAJ, Trompet S, Dekkers OM, Jukema JW, le Cessie S. Survival bias in mendelian randomization studies: a threat to causal inference. *Epidemiology*. 2019;30(6):813-816. doi:10.1097/EDE.0000000000001072

21. Franklin SS, Gustin W IV, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure: the Framingham Heart Study. *Circulation*. 1997;96(1):308-315. doi:10.1161/01.CIR.96.1.308

22. Qiu C, von Strauss E, Winblad B, Fratiglioni L. Decline in blood pressure over time and risk of dementia: a longitudinal study from the Kungsholmen project. *Stroke*. 2004;35(8):1810-1815. doi:10.1161/01.STR.0000133128.42462.ef

23. Gregson J, Qizilbash N, Iwagami M, et al. Blood pressure and risk of dementia and its subtypes: a historical cohort study with long-term follow-up in 2.6 million people. *Eur J Neurol*. 2019;26(12):1479-1486. doi:10.1111/ene.14030

24. Malik R, Chauhan G, Traylor M, et al; AFGen Consortium; Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium; International Genomics of Blood Pressure (iGEN-BP) Consortium; INVENT Consortium; STARNET; BioBank Japan Cooperative Hospital Group; COMPASS Consortium; EPIC-CVD Consortium; EPIC-InterAct Consortium; International Stroke Genetics Consortium (ISGC); METASTROKE Consortium; Neurology Working Group of the CHARGE Consortium; NINDS Stroke Genetics Network (SiGN); UK Young Lacunar DNA Study; MEGASTROKE Consortium. Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. *Nat Genet*. 2018;50(4):524-537. doi:10.1038/s41588-018-0058-3

25. Kunkle BW, Grenier-Boley B, Sims R, et al; Alzheimer Disease Genetics Consortium (ADGC); European Alzheimer's Disease Initiative (EADI); Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium (CHARGE); Genetic and Environmental Risk in AD/Defining Genetic, Polygenic and Environmental Risk for Alzheimer's Disease Consortium (GERAD/PERADES). Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. *Nat Genet*. 2019;51(3):414-430. doi:10.1038/s41588-019-0358-2

26. Schwartzentruber J, Cooper S, Liu JZ, et al. Genome-wide meta-analysis, fine-mapping and integrative prioritization implicate new Alzheimer's disease risk genes. *Nat Genet*. 2021;53(3):392-402. doi:10.1038/s41588-020-00776-w

27. Chang M, Jonsson PV, Snaedal J, et al. The effect of midlife physical activity on cognitive function among older adults: AGES–Reykjavik Study. *J Gerontol A Biol Sci Med Sci*. 2010;65(12):1369-1374. doi:10.1093/gerona/glq152

28. 3C Study Group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. *Neuroepidemiology*. 2003;22(6):316-325. doi:10.1159/000072920

29. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: the STROBE-MR Statement. *JAMA*. 2021;326(16):1614-1621. doi:10.1001/jama.2021.18236

30. Little J, Higgins JPT, Ioannidis JPA, et al. STrengthening the REporting of Genetic Association Studies (STREGA)—an extension of the STROBE statement. *Genet Epidemiol*. 2009;33(7):581-598. doi:10.1002/gepi.20410

31. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44(2):512-525. doi:10.1093/ije/dyv080

32. Swerdlow DI, Kuchenbaecker KB, Shah S, et al. Selecting instruments for mendelian randomization in the wake of genome-wide association studies. *Int J Epidemiol*. 2016;45(5):1600-1616. doi:10.1093/ije/dyw088

33. Marioni RE, Harris SE, Zhang Q, et al. GWAS on family history of Alzheimer's disease. *Transl Psychiatry*. 2018; 8(1):99. doi:10.1038/s41398-018-0150-6

34. Jansen IE, Savage JE, Watanabe K, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nat Genet*. 2019;51(3):404-413. doi:10.1038/s41588-018-0311-9

35. Smith GD, Ebrahim S. "Mendelian randomization": can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003;32(1):1-22. doi:10.1093/ije/dyg070

36. Morrison J, Knoblauch N, Marcus JH, Stephens M, He X. Mendelian randomization accounting for correlated and uncorrelated pleiotropic effects using genome-wide summary statistics. *Nat Genet*. 2020;52(7):740-747. doi: 10.1038/s41588-020-0631-4

37. Sanderson E, Davey Smith G, Windmeijer F, Bowden J. An examination of multivariable mendelian randomization in the single-sample and two-sample summary data settings. *Int J Epidemiol*. 2019;48(3):713-727. doi:10.1093/ije/dyy262

38. Sanderson E, Spiller W, Bowden J. *Testing and Correcting for Weak and Pleiotropic Instruments in Two-Sample Multivariable Mendelian Randomisation*. Cold Spring Harbor Laboratory; 2020. doi:10.1101/2020.04.02.021980

39. Statistical and Genomic Epidemiology Laboratory. Welcome to the Statistical and Genomic Epidemiology Laboratory SGEL). Accessed April 17, 2024. https://neurogenetics.qimrberghofer.edu.au/matSpDlite/

40. Li J, Ji L. Adjusting multiple testing in multilocus analyses using the eigenvalues of a correlation matrix. *Heredity (Edinb)*. 2005;95(3):221-227. doi:10.1038/sj.hdy.6800717

41. Swanson SA. *A Practical Guide to Selection Bias in Instrumental Variable Analyses*. Lippincott Williams & Wilkins; 2019:345-349.

42. Psaty BM, O'Donnell CJ, Gudnason V, et al; CHARGE Consortium. Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium: design of prospective meta-analyses of genome-wide association studies from 5 cohorts. *Circ Cardiovasc Genet*. 2009;2(1):73-80. doi:10.1161/CIRCGENETICS.108.829747

43. Chouraki V, Reitz C, Maury F, et al; International Genomics of Alzheimer's Project. Evaluation of a genetic risk score to improve risk prediction for Alzheimer's disease. *J Alzheimers Dis*. 2016;53(3):921-932. doi:10.3233/JAD-150749

44. Touraine C, Gerds TA, Joly P. SmoothHazard: an R package for fitting regression models to interval-censored observations of illness-death models. *J Stat Software*. 2017;79(7):1-22. doi:10.18637/jss.v079.i07

45. Guo W, Shi J. White matter hyperintensities volume and cognition: a meta-analysis. *Front Aging Neurosci*. 2022;14:949763. doi:10.3389/fnagi.2022.949763

46. Roseborough AD, Saad L, Goodman M, Cipriano LE, Hachinski VC, Whitehead SN. White matter hyperintensities and longitudinal cognitive decline in cognitively normal populations and across diagnostic categories: a meta-analysis, systematic review, and recommendations for future study harmonization. *Alzheimers Dement*. 2023;19(1):194-207. doi:10.1002/alz.12642

47. Hu HY, Ou YN, Shen XN, et al. White matter hyperintensities and risks of cognitive impairment and dementia: a systematic review and meta-analysis of 36 prospective studies. *Neurosci Biobehav Rev*. 2021;120:16-27. doi:10.1016/j.neubiorev.2020.11.007

48. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ*. 2010;341:c3666. doi:10.1136/bmj.c3666

49. Niiranen TJ, Kalesan B, Mitchell GF, Vasan RS. Relative contributions of pulse pressure and arterial stiffness to cardiovascular disease. *Hypertension*. 2019;73(3):712-717. doi:10.1161/HYPERTENSIONAHA.118.12289

50. Safar ME, Blacher J, Jankowski P. Arterial stiffness, pulse pressure, and cardiovascular disease—is it possible to break the vicious circle? *Atherosclerosis*. 2011;218(2):263-271. doi:10.1016/j.atherosclerosis.2011.04.039

51. Hughes TM, Kuller LH, Barinas-Mitchell EJ, et al. Pulse wave velocity is associated with β-amyloid deposition in the brains of very elderly adults. *Neurology*. 2013;81(19):1711-1718. doi:10.1212/01.wnl.0000435301.64776.37

52. Hughes TM, Kuller LH, Barinas-Mitchell EJ, et al. Arterial stiffness and β-amyloid progression in nondemented elderly adults. *JAMA Neurol*. 2014;71(5):562-568. doi:10.1001/jamaneurol.2014.186

53. Tong Y, Zhou W, Fung V, et al. Oxidative stress potentiates *BACE1* gene expression and Aβ generation. *J Neural Transm (Vienna)*. 2005;112(3):455-469. doi:10.1007/s00702-004-0255-3

54. Levin RA, Carnegie MH, Celermajer DS. Pulse pressure: an emerging therapeutic target for dementia. *Front Neurosci*. 2020;14:669. doi:10.3389/fnins.2020.00669

55. McEniery CM, Wallace S, Mackenzie IS, et al. Endothelial function is associated with pulse pressure, pulse wave velocity, and augmentation index in healthy humans. *Hypertension*. 2006;48(4):602-608. doi:10.1161/01.HYP.0000239206.64270.5f

56. Kjeldsen SE, Narkiewicz K, Burnier M, Oparil S. Intensive blood pressure lowering prevents mild cognitive impairment and possible dementia and slows development of white matter lesions in brain: the SPRINT Memory and Cognition in Decreased Hypertension (SPRINT MIND) study. *Blood Press*. 2018;27(5):247-248. doi:10.1080/08037051.2018.1507621

57. Dufouil C, Chalmers J, Coskun O, et al; PROGRESS MRI Substudy Investigators. Effects of blood pressure lowering on cerebral white matter hyperintensities in patients with stroke: the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) magnetic resonance imaging substudy. *Circulation*. 2005;112(11):1644-1650. doi:10.1161/CIRCULATIONAHA.104.501163

58. de Havenon A, Majersik JJ, Tirschwell DL, McNally JS, Stoddard G, Rost NS. Blood pressure, glycemic control, and white matter hyperintensity progression in type 2 diabetics. *Neurology*. 2019;92(11):e1168-e1175. doi:10.1212/WNL.0000000000007093

59. White WB, Wakefield DB, Moscufo N, et al. Effects of Intensive Versus Standard Ambulatory Blood Pressure Control on Cerebrovascular Outcomes in Older People (INFINITY). *Circulation*. 2019;140(20):1626-1635. doi:10.1161/CIRCULATIONAHA.119.041603

60. Wardlaw JM, Debette S, Jokinen H, et al. ESO guideline on covert cerebral small vessel disease. *Eur Stroke J*. 2021;6(2):CXI-CLXII. doi:10.1177/23969873211012132

61. Walker VM, Kehoe PG, Martin RM, Davies NM. Repurposing antihypertensive drugs for the prevention of Alzheimer's disease: a mendelian randomization study. *Int J Epidemiol*. 2020;49(4):1132-1140. doi:10.1093/ije/dyz155

62. Satizabal C, Beiser AS, Seshadri S. Incidence of dementia over three decades in the Framingham Heart Study. *N Engl J Med*. 2016;375(1):93-94. doi:10.1056/NEJMoa1504327

63. Perkovic V, Huxley R, Wu Y, Prabhakaran D, MacMahon S. The burden of blood pressure-related disease: a neglected priority for global health. *Hypertension*. 2007;50(6):991-997. doi:10.1161/HYPERTENSIONAHA.107.095497

64. Miura K, Daviglus ML, Dyer AR, et al. Relationship of blood pressure to 25-year mortality due to coronary heart disease, cardiovascular diseases, and all causes in young adult men: the Chicago Heart Association Detection Project in Industry. *Arch Intern Med*. 2001;161(12):1501-1508. doi:10.1001/archinte.161.12.1501

65. Forouzanfar MH, Liu P, Roth GA, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. *JAMA*. 2017;317(2):165-182. doi:10.1001/jama.2016.19043

66. Seshadri S, Wolf PA. Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study. *Lancet Neurol*. 2007;6(12):1106-1114. doi:10.1016/S1474-4422(07)70291-0

67. Dudbridge F, Allen RJ, Sheehan NA, et al. Adjustment for index event bias in genome-wide association studies of subsequent events. *Nat Commun*. 2019;10(1):1561. doi:10.1038/s41467-019-09381-w

68. Boef AG, le Cessie S, Dekkers OM. Mendelian randomization studies in the elderly. *Epidemiology*. 2015;26(2):e15-e16. doi:10.1097/EDE.0000000000000243

69. Munafò MR, Tilling K, Taylor AE, Evans DM, Davey Smith G. Collider scope: when selection bias can substantially influence observed associations. *Int J Epidemiol*. 2018;47(1):226-235. doi:10.1093/ije/dyx206

70. Cole SR, Platt RW, Schisterman EF, et al. Illustrating bias due to conditioning on a collider. *Int J Epidemiol*. 2010;39(2):417-420. doi:10.1093/ije/dyp334

71. Launer LJ, Ross GW, Petrovitch H, et al. Midlife blood pressure and dementia: the Honolulu-Asia Aging Study. *Neurobiol Aging*. 2000;21(1):49-55. doi:10.1016/S0197-4580(00)00096-8

72. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol*. 2005;4(8):487-499. doi:10.1016/S1474-4422(05)70141-1

73. Tzourio C, Laurent S, Debette S. Is hypertension associated with an accelerated aging of the brain? *Hypertension*. 2014;63(5):894-903. doi:10.1161/HYPERTENSIONAHA.113.00147

74. Ding J, Davis-Plourde KL, Sedaghat S, et al. Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies. *Lancet Neurol*. 2020;19(1):61-70. doi:10.1016/S1474-4422(19)30393-X

75. Hughes D, Judge C, Murphy R, et al. Association of blood pressure lowering with incident dementia or cognitive impairment: a systematic review and meta-analysis. *JAMA*. 2020;323(19):1934-1944. doi:10.1001/jama.2020.4249

76. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. *Nat Rev Cardiol*. 2013;10(3):143-155. doi:10.1038/nrcardio.2013.1

77. Burgess S, Thompson SG; CRP CHD Genetics Collaboration. Avoiding bias from weak instruments in mendelian randomization studies. *Int J Epidemiol*. 2011;40(3):755-764. doi:10.1093/ije/dyr036

78. Burgess S, Foley CN, Allara E, Staley JR, Howson JMM. A robust and efficient method for mendelian randomization with hundreds of genetic variants. *Nat Commun*. 2020;11(1):376. doi:10.1038/s41467-019-14156-4

79. Smith GD, Ebrahim S. Mendelian randomization: prospects, potentials, and limitations. *Int J Epidemiol*. 2004; 33(1):30-42. doi:10.1093/ije/dyh132

80. Finch CE, Kulminski AM. The Alzheimer's disease exposome. *Alzheimers Dement*. 2019;15(9):1123-1132. doi: 10.1016/j.jalz.2019.06.3914

81. Brown R, Low A, Markus HS. Rate of, and risk factors for, white matter hyperintensity growth: a systematic review and meta-analysis with implications for clinical trial design. *J Neurol Neurosurg Psychiatry*. 2021;92(12): 1271-1277. doi:10.1136/jnnp-2021-326569

SUPPLEMENT 1.

SUPPLEMENT 2.

SUPPLEMENT 3.