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DATE 12/1/2021
JOB NAME NEUROLOGY

ARTICLE 2021172399
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AU2) Per journal style, URLs in the text should be avoided. Thus, the URL for the UK Biobank was deleted.
AU3) Please confirm "Results identified as significant after IVW analysis have results from secondary methods…."
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RESEARCH ARTICLE

Cardiovascular Risk Factors and MRI Markers of Cerebral Small Vessel Disease

A Mendelian Randomization Study

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Neurology® 2022;98:1-9. doi:10.1212/WNL.0000000000013120

Abstract

Background and Objectives

Cardiovascular risk factors have been implicated in the etiology of cerebral small vessel disease (CSVD); however, whether the associations are causal remains unclear in part due to the susceptibility of observational studies to reverse causation and confounding. Here, we use mendelian randomization (MR) to determine which cardiovascular risk factors are likely to be involved in the etiology of CSVD.

Methods

We used data from large-scale genome-wide association studies of European ancestry to identify genetic proxies for blood pressure, blood lipids, body mass index (BMI), type 2 diabetes, smoking initiation, cigarettes per day, and alcohol consumption. MR was performed to assess their association with 3 neuroimaging features that are altered in CSVD (white matter hyperintensities [WMH], fractional anisotropy [FA], and mean diffusivity [MD]) using genetic summary data from the UK Biobank (N = 31,855). Our primary analysis used inverse-weighted median MR, with validation using weighted median, MR-Egger, and a pleiotropy-minimizing approach. Finally, multivariable MR was performed to study the effects of multiple risk factors jointly.

Results

MR analysis showed consistent associations across all methods for higher genetically proxied systolic and diastolic blood pressures with WMH, FA, and MD and for higher genetically proxied BMI with WMH. There was weaker evidence for associations between total cholesterol, low-density lipoprotein, smoking initiation, pulse pressure, and type 2 diabetes liability and at least 1 CSVD imaging feature, but these associations were not reproducible across all validation methods used. Multivariable MR analysis for blood pressure traits found that the effect was primarily through genetically proxied diastolic blood pressure across all CSVD traits.

Discussion

Genetic predisposition to higher blood pressure, primarily diastolic blood pressure, and to higher BMI is associated with a higher burden of CSVD, suggesting a causal role. Improved management and treatment of these risk factors could reduce the burden of CSVD.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

International Consortium of Blood Pressure (ICBP) coinvestigators are listed in appendix at the end of the article.

Glossary

BMI = body mass index; **CSVD** = cerebral small vessel disease; **DBP** = diastolic blood pressure; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **GWAS** = genome-wide association studies; **HbA1c** = hemoglobin A1c; **HDL** = high-density lipoprotein; **ICBP** = International Consortium of Blood Pressure; **IVW** = inverse variance–weighted; **LDL** = low-density lipoprotein; **MD** = mean diffusivity; **MR** = mendelian randomization; **SBP** = systolic blood pressure; **SNP** = single nucleotide polymorphism; **TC** = total cholesterol; **T2D** = type 2 diabetes; **MH** = white matter hyperintensities.

Cerebrovascular diseases are a leading cause of death and disability worldwide, and this is only predicted to increase with aging populations.[1] Cerebral small vessel disease (CSVD) is a disease of the small vessels in the brain that contributes to approximately a fifth of all strokes[2] and up to 45% of all dementia.[3,4] Radiologically, it is characterized by several features such as white matter hyperintensities (WMHs), lacunar infarcts, microbleeds, and brain atrophy[5] that can be identified on MRI. Diffusion tensor imaging (DTI) to characterize water-molecule diffusion within the brain can also be used to reveal microstructural changes that occur during CSVD and can be assessed with fractional anisotropy (FA) and mean diffusivity (MD) parameters.[6] Despite the substantial impact CSVD has on individuals and society, the factors contributing to disease are still not well understood, so no effective treatments have been developed.[7] Although uncovering the risk factors that contribute to CSVD could lead to new advances in understanding pathogenesis and treatments, identifying effective prevention strategies is the only way to reduce CSVD burden while no treatment is available.

Observational studies have suggested links between CSVD features and cardiovascular disease risk factors.[8,9] However, studies have produced conflicting results and are limited in their ability to infer causality due to confounding and reverse causation. Mendelian randomization (MR) can be used to overcome some of these biases. During conception, a random assortment of alleles are passed on to offspring, meaning the inheritance of 1 particular variant is not related to environmental factors. Consequently, single nucleotide polymorphisms (SNPs) associated with a risk factor in a population should be similar in all other characteristics, reducing any potential environmental confounding. Because having a disease does not alter the patient's underlying genetics, using MR also reduces any potential reverse causation bias.[10] Therefore, MR can have utility in identifying causal relationships between potential risk factors and disease.

With the increasing availability of data from large-scale genome-wide association studies (GWAS) on CSVD, including imaging data from the UK Biobank, there is now sufficient statistical power to apply an MR framework. This study uses MR to evaluate whether well-established cardiovascular risk factors have a causal role in the etiology of CSVD MRI features (WMH and 2 parameters from DTI: FA and MD) using GWAS summary data from up to 31,855 individuals from the UK Biobank.

Methods

Study Design

MR analysis was performed to test the causal relationship between 12 cardiovascular risk factors and the CSVD neuroimaging features WMH, FA, and MD. Cardiovascular risk factors were selected on the basis of evidence of association with CSVD from previous studies, including those with conflicting evidence (eTable 1, links.lww.com/WNL/B671): diastolic blood pressure (DBP), systolic blood pressure (SBP), pulse pressure, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, total cholesterol (TC), body mass index (BMI), type 2 diabetes (T2D), smoking initiation, cigarettes smoked per day, and alcoholic drinks consumed per week. On identifying suggestive associations with T2D liability, we explored this further by investigating hemoglobin A1c (HbA1c), a marker of blood glucose.

Data Sources

For each cardiovascular trait, summary-level data (effect estimates, standard errors, and p values) were obtained from recent large European GWAS (Table 1). All summary data were in the public domain, and ethics approval for each study can be found in the original publications. To evaluate the impact of participant overlap between exposure and outcome when individuals from the UK Biobank were used in both datasets,[11] results were additionally obtained from alternative (although smaller) GWAS (eTable 2, links.lww.com/WNL/B671). Unfortunately, no comparable datasets were available for cigarettes smoked per day, smoking initiation, and alcoholic drinks consumed per week.

Data for CSVD neuroimaging features were derived from an analysis of up to 31,855 individuals from the UK Biobank, a long-term study of 500,000 UK participants 40 to 69 years of age at recruitment covering genetic, lifestyle, and health outcome data.[12] Three continuous variables representing CSVD imaging features were used to represent CSVD risk; WMH (field 25,781) and DTI measures FA (fields 25,056–25,103) and MD (fields 25,104–25,151). WMH is a radiologic marker commonly used to identify CSVD, while FA and MD are measures of white matter microstructural integrity that are abnormal in CSVD. We used imaging-derived phenotypes generated by an image-processing pipeline developed and run on behalf of UK Biobank. WMH was log-transformed in all analyses to approximate a normal distribution. For each biomarker, outliers outside the ±8 SD

range were removed. DTI measures were available as part of the UK Biobank central analysis for 48 individual white matter regions. To obtain a single global measure of global white matter FA and MD from the DTI images, we performed principal component analysis on the FA and MD measures of each of the 48 different brain regions analyzed. We excluded brain regions that did not contribute substantially to the first principal component. FA was reoriented so that increases in the FA value used reflected more disease. We assessed the association of genome-wide SNPs with WMH, FA, and MD using linear regression with age, age squared, sex, and 20 ancestry-informative principal components as covariates. For WMH, we included brain volume as an additional covariate. Before analysis, we excluded individuals who were not classified as White British (field 22,006), related individuals with a *Kinship*-Based Inference for Genome-Wide Association Studies kinship coefficient ≥0.088413 (to keep only 1 individual per group of up to second-degree relationships), those who had withdrawn from the study, and those who had history of stroke, multiple sclerosis, or other neurodegenerative disease (self-reported field 20,002 codes 1081, 1086, 1491, 1583, 1261, 1262, 1263, 1397; ICD10 fields 41202 and 41204 codes I60, I61, I63, I64, G35, G20, F00-F03, G30-G32, G36, G37). The distributions of these MRI features are shown in eFigure 1 (links.lww.com/WNL/B671).

Instrument Variant Selection

Using the summary-level data obtained for each cardiovascular risk factor, we selected independent SNPs (based on linkage disequilibrium clumping of $r^2 > 0.01$ within a 500-kb window and using 1,000 Genomes European ancestry data as a reference dataset[14]) reaching genome-wide significance ($p < 5 \times 10^{-8}$) using PLINK version 1.07,15 resulting in 64 to 1,492 SNPs per trait (full results and details of SNPs used are shown in the additional supplementary data, links.lww.com/WNL/B671). Multiallelic SNPs were removed before MR analysis. Before all MR analyses, SNP data were imported into R (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria), and effect alleles were aligned to harmonize the data across the different studies. Estimated variance explained and statistical power are shown in eTable 3.

Statistical Analysis

The primary analysis was conducted using 2-sample MR on summary statistics with a random-effects inverse variance–weighted (IVW) analysis approach. Results were corrected for multiple comparisons (12 cardiovascular risk factors) using Bonferroni correction with a resulting p value threshold for significance of $p < 0.0042$.

MR analysis is based on a series of assumptions: that the genetic variants forming the instrument variables for the risk factors are associated with those traits, that the genetic variants are not associated with any confounders, and that the genetic variants are associated with CSVD through the cardiovascular risk factor and not an alternative pathway. To evaluate whether these MR model assumptions were valid for

Table 1 GWAS Summary Data Sourced for Cardiovascular Risk Factors

Trait	Cohorts	Participants, n	Reference
T2D GWAS	DANISH-UCPH, EGCUT, FHS, FUSION, GCKD, GENOA, GERA, GoDARTS, GoMAP and TEENAGE, InterAct, KORA, MESA, METSIM, MGI, Mount Sinai BioMe Biobank, PIVUS and ULSAM, PROSPER, the Rotterdam Study, WTCCC, UK Biobank	898,130	Mahajan et al.,[43] 2018
SmkIn GWAS CigDay GWAS DrinkWk GWAS	23andMe, ALSPAC, ARIC, BEAGESS, BLS, CADD, COGEND, COPDGene, deCODE, EGCUT, eMERGE, FHS, FinnTwin, GERA, GFG, Harvard, HRS, HUNT, MCTFR, MESA, METSIM, NESCOG, NAG-FIN, NTR, QIMR, SardiNIA, STROKE, UK Biobank, WHI	SmkIn 1,232,091 CigDay 337,334 DrinkWk 941,280	Lui et al.,[44] 2019
BMI GWAS	GIANT, UK Biobank	681,275	Yengo et al.,[45] 2018
HDL GWAS LDL GWAS Triglycerides GWAS TC GWAS	ADVANCE, AGES, AMC-PAS, AMISH, ARIC, B58C, BLSA, BRIGHT, CHS, COLAUS, deCODE, DIAGEN, DILGOM, DPS, DR'S EXTRA, EAS, EGCUT, ELY, EPIC, ERF and Rotterdam Study, ESS, FHS, FINCAVAS, Framingham, FUSION2, FENLAND, GLACIER, GenomEUTWIN, Go-DARTs, HUNT2, IMPROVE, KORA, LifeLines, LOLIPOP, LURIC, MDC, MICROS, METSIM, MRC, NFBC1986, NSPHS and FRISCII, ORCADES, PIVUS, SardiNIA, SCARFSHEEP, Swedish Twin Reg., SUVIMAX, THISEAS, TROMSO, TWINGENE, ULSAM, WGHS, WHII	188,578	Willer et al.,[46] 2013
DBP GWAS SBP GWAS Pulse pressure GWAS	UK BioBank, ICBP-GWAS, MVP, EGCUT	1,006,863	Evangelou et al.,[47] 2018

Abbreviations: BMI = body mass index; CigDay = cigarettes smoked per day; DBP = diastolic blood pressure; DrinkWk = alcoholic drinks consumed per week; GWAS = genome-wide association studies; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure; SmkIn = smoking initiation; TC = total cholesterol; T2D = type 2 diabetes.
In preparation for mendelian randomization analysis, summary-level data were sourced from recently published European GWAS. This table identifies the data source for all cardiovascular risk factor single nucleotide polymorphism data.

all SNPs and to assess the robustness of the results, a number of secondary analyses were performed:

1. Weighted median analysis, which is less sensitive to a subset of invalid instruments;
2. MR-Egger analysis[16] to identify pleiotropy within the data by assessing whether the intercepts were significantly different from zero on a plot of the genetic associations of the SNPs with exposure and outcome;
3. Pleiotropy-minimizing analysis, removing SNPs that are genome-wide significant for other risk factor traits in the analysis (excluding removing traits for which interrelatedness is expected in the blood lipid group, blood pressure, and smoking);
4. Multivariable MR to investigate the joint effects of blood lipids (LDL, HDL and triglycerides) and between DBP and SBP (SNPs used in the initial MR analysis for each trait were combined to generate a list for multivariable MR analysis; SNPs for which summary statistics required for analysis were not available for all traits tested in the multivariable MR were excluded); and
5. Sample overlap analysis, an MR analysis on cardiovascular risk factor datasets that do not contain UK Biobank data/participants (eTable 2, links.lww.com/WNL/B671), removing any bias from a potential overlap between data sets.

All MR analyses were performed with RStudio (version 1.2.5001) and the MendelianRandomization package,[17] multivariable MR *F* statistics were calculated with the MVMR R Package.[18]

Standard Protocol Approvals, Registrations, and Patient Consents

Ethics approval for UK Biobank was received from the research ethics committee (REC reference 11/NW/0382). All participants gave informed written consent.

Data Availability

Data required to duplicate analysis are included in the supplementary materials or are available from the associated GWAS publications. Access to the original UK Biobank data can be applied for at the UK Biobank website. Requests for International Consortium of Blood Pressure (ICBP) data can be made to the consortium.

Results

Results obtained from IVW MR for the effect of cardiovascular risk factors on neuroimaging features of CSVD are shown in Figure 1, with more detailed information provided in eTable 4 (links.lww.com/WNL/B671). Results identified as significant after IVW analysis have results from secondary methods shown in Table 2 Full results of the multivariable MR analysis for lipid and blood pressure traits can be found in eTables 5 and 6. MR-Egger analysis results can be found in eTable 7. MR results for cardiovascular traits repeated with non–UK Biobank data are shown in eTable 8. Graphs of genetic association of SNPs for outcome and exposure for the initial IVW and MR-Egger analysis are shown in eFigures 2 through 13. To maximize the inclusivity of ancestral backgrounds, a further IVW analysis was performed on the basis of data from all the ethnic groups available in UK Biobank (eTable 9).

Blood Pressure Traits

Genetic predisposition to SBP and DBP was associated with all 3 CSVD features (Figure 1) Similar estimates were obtained after a weighted median MR analysis (Table 2), and the association persisted in the secondary analyses. Pulse pressure did not reach the *p* value threshold for any CSVD feature in the initial analysis but was below $p < 0.05$ for WMH and MD, as well as reaching significance in some of the secondary analysis, indicating that it could still be a contributing factor. We performed multivariable MR including DBP and SBP to assess whether a specific measure was driving the association with CSVD. Our results indicated that DBP was the main contributing factor, with no significant effect from SBP when additionally included in the model (eTable 5, links.lww.com/WNL/B671). For DBP and SBP multivariate MR, WMH = DBP (estimate = 0.022, p = 1.32E-07) and SBP (estimate = 0.000, p = 0.859), FA = DBP (estimate = 0.082, p = 6.47E-06) and SBP (estimate = −0.009, p = 0.401), and MD = DBP (estimate = 0.093, p = 4.59E-07) and SBP (estimate = 0.001, p = 0.912).

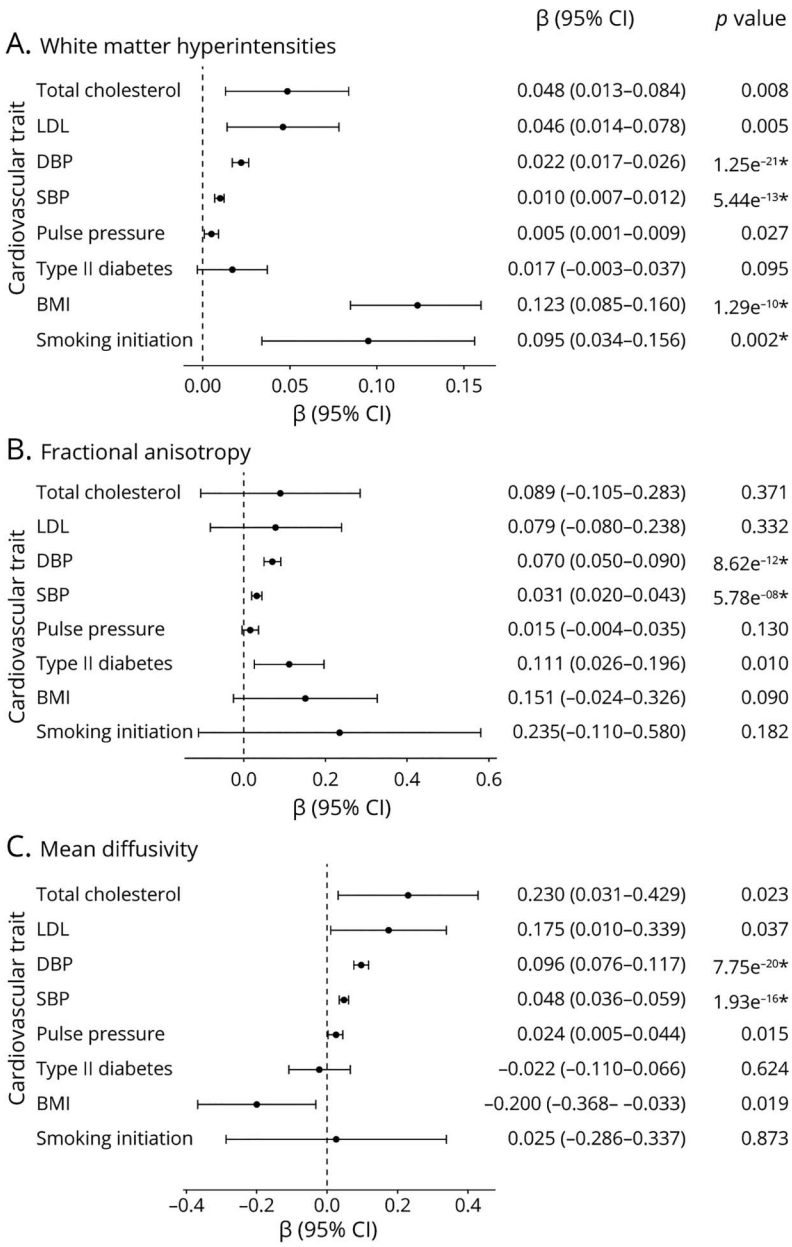
Lipid Traits

MR identified potential for a causal relationship for TC and LDL with WMH. The IVW MR analysis (Figure 1) showed values of $p = 0.023$ (TC) and $p = 0.037$ (LDL) for MD and p = 0.008 (TC) and p = 0.005 (LDL) for WMH. However, we note that these associations would not reach the significance threshold when the Bonferroni correction is applied. Similar estimates were obtained from weighted median analysis in which TC reached significance for WMH ($p = 0.003$; Table 2) but not for MD. These results were not significant in the pleiotropy-minimizing analysis. There were no significant associations with HDL or triglycerides (eTable 4, links.lww.com/WNL/B671). We performed multivariable MR of LDL, HDL, and triglycerides in combination. In this analysis, LDL maintained a suggestive association with WMH (estimate = 0.037, p = 0.009), while neither triglycerides nor HDL was significant (full results, eTable 6).

T2D Liability

MR IVW analysis showed a suggestive association with FA (Figure 1). However, MR-Egger analysis showed evidence of pleiotropy in the WMH analysis (eTable 7, links.lww.com/WNL/B671). The effect of pleiotropy within the data did not persist after the pleiotropy-minimizing analysis, in which we removed SNPs associated with multiple traits (eTable 10). However, no significant effect was identified in this analysis. The association between FA and T2D was unaffected by pleiotropy (eTables 7 and 10–13) and remained suggestively

Figure 1 Causal Estimates for the Association Between CSVD Features and Known Cardiovascular Risk Factors



Analysis of associations between cerebral small vessel disease (CSVD) features and known cardiovascular risk factors using mendelian randomization. The 3 CSVD MRI features used were (A) white matter hyperintensities (WMH), (B) fractional anisotropy (FA), and (C) mean diffusivity (MD). Causal estimates were obtained with the inverse variance–weighted method. β Values are presented for genetically proxied increase in the risk factor on its original scale. Outcomes are on their original scale. *Results with a significant p value ($p < 0.0042$) after multiple-testing correction.

associated across IVW (estimate = 0.111, p = 0.010) and weighted median (estimate = 0.156, p = 0.023) but not in the pleiotropy-minimizing analysis (IVW: estimate = 0.078, p = 0.141; and weighted median: estimate = 0.064, p = 0.352). We further investigated this potential association by evaluating the association with HbA1c, a marker of blood glucose, using the largest available GWAS data.[19] In this analysis, we found no significant evidence of an association (eTable 14).

Body Mass Index

We found strong evidence for a causal link between BMI and WMH, with a consistent association across all methods (Table 2; initial IVW: estimate = 0.123, p = 1.29E-10, 95% CI 0.085–0.160). IVW analysis also indicated a suggestive negative association with MD (estimate = −0.200, p = 0.019); however, this did not reach significance in any secondary analysis or remain below $p < 0.05$ in weighted median analysis.

Smoking and Drinking

Genetically proxied smoking initiation was associated with WMH in the main IVW analysis (estimate = 0.095, p = 0.002, 95% CI 0.034–0.156) and remained at a suggestive level ($p <$ 0.05) but was not significant in further supporting analysis. No evidence for causal relationships was found for alcohol intake (IVW analysis: WMH p = 0.244, FA p = 0.551, MD p = 0.140) and daily cigarette use (IVW analysis: WMH p = 0.102, FA p = 0.774, MD p = 0.931) with any CSVD imaging features.

Table 2 Results From Multiple Secondary MR Analysis for All Initially Suggestive IVW MR Results

	IVW		Weighted median MR		IVW pleiotropy-minimizing analysis		WM pleiotropy-minimizing analysis	
	β (95% CI)	*p* Value	β (95% CI)	*p* Value	β (95% CI)	*p* Value	β (95% CI)	*p* Value
WMH								
TC	0.048 (0.013 to 0.084)	0.008	0.073 (0.025 to 0.122)	0.003[a]	0.012 (−0.031 to 0.054)	0.596	0.028 (−0.030 to 0.087)	0.347
LDL	0.046 (0.014 to 0.078)	0.005	0.048 (0.009 to 0.087)	0.015	0.025 (−0.021 to 0.071)	0.286	0.034 (−0.023 to 0.092)	0.244
DBP	0.022 (0.017 to 0.026)	1.25E-21[a]	0.022 (0.017 to 0.028)	1.93E-15[a]	0.022 (0.017 to 0.026)	1.15E-20[a]	0.022 (0.017 to 0.028)	1.10E-14[a]
SBP	0.010 (0.007 to 0.012)	5.44E-13[a]	0.011 (0.008 to 0.014)	1.87E-11[a]	0.009 (0.007 to 0.012)	1.21E-12[a]	0.011 (0.008 to 0.015)	3.16E-11[a]
Pulse pressure	0.005 (0.001 to 0.009)	0.027	0.006 (0.001 to 0.012)	0.014	0.004 (0.000 to 0.008)	0.078	0.008 (0.003 to 0.013)	0.004[a]
BMI	0.123 (0.085 to 0.160)	1.29E-10[a]	0.109 (0.053 to 0.165)	1.41E-04[a]	0.114 (0.073 to 0.154)	3.85E-08[a]	0.116 (0.061 to 0.170)	3.40E-05[a]
Smoking initiation	0.095 (0.034 to 0.156)	0.002[a]	0.100 (0.019 to 0.181)	0.015	0.079 (0.011 to 0.148)	0.024	0.101 (0.009 to 0.192)	0.031
FA								
DBP	0.070 (0.050 to 0.090)	8.62E-12[a]	0.073 (0.048 to 0.097)	7.24E-09[a]	0.073 (0.053 to 0.094)	3.34E-12[a]	0.080 (0.054 to 0.106)	1.20E-09[a]
SBP	0.031 (0.020 to 0.043)	5.78E-08[a]	0.036 (0.021 to 0.050)	1.50E-06[a]	0.036 (0.024 to 0.047)	1.44E-09[a]	0.046 (0.030 to 0.061)	5.91E-09[a]
T2D	0.111 (0.026 to 0.196)	0.010	0.156 (0.022 to 0.291)	0.023	0.078 (−0.026 to 0.183)	0.141	0.064 (−0.071 to 0.199)	0.352
MD								
TC	0.230 (0.031 to 0.429)	0.023	0.161 (−0.076 to 0.397)	0.182	0.113 (−0.127 to 0.353)	0.355	0.226 (−0.067 to 0.519)	0.130
LDL	0.175 (0.010 to 0.339)	0.037	0.113 (−0.066 to 0.293)	0.216	0.124 (−0.123 to 0.371)	0.326	0.280 (−0.013 to 0.573)	0.061
DBP	0.096 (0.076 to 0.117)	7.75E-20[a]	0.100 (0.075 to 0.124)	1.13E-15[a]	0.101 (0.080 to 0.122)	2.00E-21[a]	0.109 (0.083 to 0.134)	6.30E-17[a]
SBP	0.048 (0.036 to 0.059)	1.93E-16[a]	0.056 (0.042 to 0.071)	1.66E-14[a]	0.055 (0.043 to 0.066)	6.10E-21[a]	0.066 (0.051 to 0.081)	9.58E-18[a]
Pulse pressure	0.024 (0.005 to 0.044)	0.015	0.035 (0.011 to 0.059)	0.004[a]	0.031 (0.010 to 0.051)	0.003[a]	0.037 (0.012 to 0.062)	0.003[a]
BMI	−0.200 (−0.368 to −0.033)	0.019	0.013 (−0.264 to 0.289)	0.928	−0.203 (−0.387 to −0.019)	0.030	−0.100 (−0.351 to 0.151)	0.435

Abbreviations: BMI = body mass index; CI = confidence interval; DBP = diastolic blood pressure; FA = fractional anisotropy; GWAS = genome-wide association studies; HDL = high-density lipoprotein; IVW = inverse variance–weighted; LDL = low-density lipoprotein; MD = mean diffusivity; MR = mendelian randomization; SBP = systolic blood pressure; TC = total cholesterol; T2D = type 2 diabetes; WM = weighted median; WMH = white matter hyperintensities.
Secondary analysis of associations between cerebral small vessel disease features and cardiovascular risk factors found be suggestive for a causal relationship ($p < 0.05$) in the initial IVW MR. Causal estimates were obtained with the IVW method and WM MR method. Pleiotropy-minimizing analysis removed single nucleotide polymorphisms associated with multiple traits in the analysis.
[a] Results with a significant *p* value ($p < 0.0042$) after multiple-testing correction.

Discussion

We performed an MR analysis of MRI markers of CSVD in up to 31,855 individuals from UK Biobank to assess whether cardiovascular risk factors play a causal role in the etiology of CSVD. We found strong evidence of a causal association of blood pressure traits with all 3 CSVD imaging features tested. The association between hypertension and CSVD is well established and is supported by a large number of population-based studies.[8,9,20] While this study supports the importance of blood pressure control in reducing CSVD risk, the multivariable MR results provide an interesting insight that the causal effect appears to come from DBP rather than SBP, which is the primary focus of BP reduction.[21] The effect of age could be a factor, with SBP continuing to rise with age, while DBP stabilizes and reduces in those >60 years of age.22,23 With some debate already existing concerning the importance of DBP in cardiovascular risk,[23-25] this result highlights the importance of further understanding how age and differing aspects of blood pressure interact in their contributions to CSVD. According to these results, it is possible that better management of DBP might be more effective in reducing risk of CSVD.

While obesity has long been associated with cardiovascular disease, mixed results have been reported on the association between BMI and CSVD.[26,27] Despite the lack of clear prior evidence between BMI and CSVD, this study found strong evidence for a causal link with WMH, which was consistent across all MR analyses. Results for FA and MD could have been affected by reduced power compared to the WMH analysis (Table e-3, links.lww.com/WNL/B671). Recent recommendations have suggested obesity as a potential dementia risk factor,[28] and here we provide strong causal evidence for a link, with CSVD as a potential mechanism for the effect. This highlights why BMI should be a key area for concern in dementia given the upward BMI trend in the world population.[29]

While blood lipids have a well-established role in the pathogenesis of cardiovascular disease and stroke, whether there is a causal association with CSVD is less clear.[9,26,30] Our results

showed possible evidence for a causal relationship between LDL, TC, and CSVD features (WMH and MD) with values of $p < 0.05$ but not meeting the significance threshold set in this study. Multivariate MR analysis provided suggestive evidence for an association with LDL after considering the effect of HDL and triglycerides again with a value of $p < 0.05$ but above the significance threshold. This possible relationship could indicate the potential for statins to have a preventive role in CSVD, which currently has mixed support.[31,32] A previous MR study looking for associations between blood lipids and CSVD (small vessel stroke, WMH, and intracerebral hemorrhage) found that HDL cholesterol has the strongest relationship with CSVD features when compared across the lipid subtypes with multivariable MR.[33] While this differs from the results found in this study, which may be due to our larger sample size and the different aspects of CSVD studied, both studies point to a potential causal role for lipids in CSVD, indicating that further research is necessary.

Despite a lack of power compared to other cardiovascular traits tested, this study found suggestive evidence of a significant causal relationship between T2D liability and FA, and attempts to establish causality with WMH were affected by pleiotropy. The literature commonly recognizes T2D as a CSVD risk factor,[9,20] including associations with CSVD imaging features. A prior MR study looking at T2D liability and CSVD in a smaller UK Biobank sample found causal links between FA and lacunar stroke and not MD or WMH. Together, these MR studies provide some evidence for a role for T2D in FA, although further work is needed to establish whether this extends to other CSVD features. We explored whether a marker of hyperglycemia (HbA1c) was associated with CSVD features but found no evidence of a significant association.

Several studies have reported an association between history of smoking and CSVD risk,[9,20,34] whereas others have found no significant association.[35,36] This could be due partly to the lack of standardization of smoking definitions, so for this study, we looked at both smoking initiation and cigarettes per day. While smoking initiation showed some evidence of a causal relationship to WMH, it was not conclusive. This could be related to the relatively small sample size of the underlying GWAS, being a third of the other cardiovascular traits in this study, as well as the limited power of the analysis. Alcohol consumption is also a potential risk factor, having been associated with decreased CSVD risk in some studies.[37,38] However, no causal links were able to be established definitively in this analysis. Due to the lower power of this analysis compared to other cardiovascular traits studied, further research is required.

Some differences were observed in associations with cardiovascular risk factors between MRI markers of CSVD. WMH and MD were more closely aligned in the results than with FA. Both MD and FA reflect white matter integrity based on diffusion measures from MRI, so results would be expected to be similar. Prior studies have found MD to best distinguish WMH from normal tissue when compared with FA,[39] with the suggestion that this may be related to blood-brain barrier leakage occurring earlier in WMH pathogenesis compared with axonal loss, while FA appears to be sensitive to myelin alterations.[40]

Strengths of this study include using MR to study multiple AU4
cardiovascular risk factors and CSVD, providing key advantages in terms of establishing causality while reducing risk of reverse causation bias and the effect of environmental confounding factors. This was made possible by the substantial sample size of the neuroimaging dataset, which is the largest currently available on UK Biobank, enabling the use of MR. However, some limitations should also be considered. First, the genetic instruments used in this study reflect lifetime exposure to cardiovascular risk factors, whereas in observational studies, it may be midlife risk that has been associated. Second, this study focuses on only 3 aspects of CSVD neuroimaging and does not include aspects such as lacunar infarcts or cerebral microbleeds because unfortunately these parameters are not easily available in the UK Biobank. In addition, all GWAS were based on European populations, and while an additional analysis was performed including non-White British UK Biobank participants, the additional ethnic groups were still in the minority. Therefore, these findings may not translate to other population groups, and differences in risk due to ethnicity are yet to be determined, which is an area for future research. In addition, this study was based on published GWAS data on cardiovascular risk factors from multiple different studies. There is potential that subtle differences in ascertainment and study population could influence these results. Despite efforts to use the largest GWAS available for cardiovascular traits, some analyses were still limited by low power when calculated taking into account the epidemiologic relationship between the exposure and outcome[41] and therefore should be interpreted with this limitation in mind. The use of multiple large European GWAS also resulted in some overlap in populations with the CSVD UK Biobank data, which we have attempted to mitigate by repeating the analysis on smaller studies without this overlap. MR also has limitations, including the potential for pleiotropy within the data, which, as the results for T2D show, can be difficult to thoroughly eliminate. Some differences between the results from different MR methods were found that could be due to the reduced statistical power of these methods[42] and could be mitigated by the use of a larger neuroimaging dataset in future analyses.

This study found a potential causal association between blood pressure and CSVD features (WMH, FA, and MD), with DBP appearing to be a key factor, as well as new evidence supporting a causal link between BMI and WMH. In addition, suggestive evidence for links between lipids, smoking, and T2D was found that warrants further investigation. Our findings indicate that optimal management of cardiovascular

risk factors, particularly blood pressure and BMI, could reduce the burden of stroke and dementia, the primary consequences of CSVD.

Acknowledgment

Patricia B. Munroe acknowledges support from the National Institute of Health Research Barts Biomedical Research Centre. The authors thank the ICBP consortium for providing summary statistics for the non–UK Biobank blood pressure data. A full list of ICBP authors is provided at links.lww.com/WNL/B672.

Study Funding

Matthew Traylor and Victoria Taylor-Bateman were supported by The Barts Charity and the National Institute of Health Research Barts Biomedical Research Centre.

Disclosure

V. Taylor-Bateman reports no disclosures relevant to the manuscript. D. Gill is employed part-time by Novo Nordisk. M. Georgakis, R. Malik, P. Munroe, and M. Traylor report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* March 16, 2021. Accepted in final form November 19, 2021.

Appendix 1 Authors

Name	Location	Contribution
Victoria Taylor-Bateman, MRes	Queen Mary University of London, UK	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Dipender Gill, MD, PhD	Imperial College London, UK	Revised the manuscript for intellectual content
Marios Georgakis, MD, PhD	University Hospital of Ludwig-Maximilians-University, Munich, Germany	Revised the manuscript for intellectual content
Rainer Malik, PhD	University Hospital of Ludwig-Maximilians-University, Munich, Germany	Revised the manuscript for intellectual content
Patricia Munroe, PhD	Queen Mary University of London, UK	Revised the manuscript for intellectual content; provided study oversight
Matthew Traylor, PhD	Queen Mary University of London, UK	Acquisition of data; designed and conceptualized study; revised the manuscript for intellectual content; provided study oversight

Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/B672

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