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White matter hyperintensities partly mediate genetically predicted blood pressure effects on vascular dementia

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Research Article

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Abstract

Background

White matter hyperintensities (WMH) mark cerebral small vessel disease and sit on the path from hypertension to vascular dementia (VaD). Prior Mendelian randomization in European ancestry has linked blood pressure (BP) to WMH. We tested whether that association replicates in Japanese ancestry and whether WMH captures part of the genetically predicted BP effect on VaD after a priori *APOE* exclusion.

Methods

Two-sample Mendelian randomization used European genome-wide association studies of BP, WMH, and VaD, with Japanese replication of BP residual to WMH residual. The primary estimator was random-effects inverse-variance weighted analysis. Two-step Mendelian randomization multiplied each *APOE*-excluded BP to WMH estimate by the *APOE*-excluded WMH to VaD log-odds ratio.

Results

Genetically predicted diastolic and systolic BP associated with higher WMH in Europeans (β = 0.176 and 0.091 WMH SD per 10 mm Hg). The same direction replicated in Japanese ancestry on a residual-SD scale. Pulse pressure did not. Diastolic and systolic BP associated with VaD (odds ratios 1.36 and 1.12). Both had an indirect path through WMH (indirect odds ratios 1.10 and 1.05). The descriptive mediated proportion was 0.31 for diastolic BP. The systolic proportion interval included 0.

Conclusions

Genetically predicted BP raises WMH in European and Japanese ancestry. Diastolic and systolic BP have an indirect path through WMH to VaD. A descriptive mediated proportion whose interval excludes 0 is limited to diastolic BP.

Introduction

Cerebral small vessel disease (SVD) is a major cause of ischemic stroke, intracerebral hemorrhage, and vascular dementia (VaD). On brain imaging, SVD is marked by lacunes, white matter hyperintensities (WMH), perivascular spaces, cerebral microbleeds, and related lesions.[1,2] WMH are the most common of these markers in older adults and associate with stroke, dementia, and death.[1–3] They reflect damage to small penetrating arteries that supply deep white matter. VaD in clinic and in registries is often mixed

with Alzheimer pathology. WMH help keep a blood pressure path to dementia distinct from an Alzheimer path.

Hypertension is the leading modifiable driver of WMH.[4] High pressure is transmitted into long penetrating arteries with little collateral supply. Clinic blood pressure (BP) is recorded as systolic BP (SBP), diastolic BP (DBP), and pulse pressure (PP). SBP and DBP contribute to mean pressure. PP rises as large arteries stiffen. These loads need not injure white matter in the same way. SVD studies have described blood-brain barrier leakage, vessel stiffening, and white matter injury.[2] Higher BP and poorer BP control associate with WMH progression.[4] Observational studies still leave confounding and reverse causation open. Other diseases can induce a correlation that is not causal. Brain injury can also change later BP.

Trials of BP lowering and late-life cognition leave the same gap. In SPRINT-MIND, intensive SBP lowering reduced mild cognitive impairment but not probable dementia.[5] The trial tested a time-limited change in measured SBP. Dementia was not limited to VaD. WMH was not tested as a mediator. DBP and PP were not separate treatment targets. That result does not show whether WMH lies on a path from genetically predicted BP to VaD. It also cannot show whether BP lowering would remove WMH-related VaD risk.

Mendelian randomization (MR) uses genetic variants associated with BP as instruments for a lifelong difference in genetically predicted BP. If those variants affect the outcome only through BP, MR is less open to confounding and reverse causation than observational studies. European MR already supports an effect of genetically predicted BP on WMH and other SVD markers.[6] That work does not test whether WMH captures part of a BP effect on VaD. WMH genomics has reported overlap with BP and a residual SVD component not fully explained by BP loci.[7,8] The same work linked WMH to dementia and found an inverse genetic association of BP with Alzheimer disease (AD).[8] An inverse BP to AD association is the opposite of a vascular path, so VaD should be kept distinct from AD.

APOE is the strongest common dementia locus.[9] WMH genetic studies also detect this region. A variant that raises Alzheimer risk can look like a WMH instrument while still moving a VaD label through mixed Alzheimer pathology. The variant can then affect VaD without going through WMH, which MR does not allow. Alzheimer-outcome MR already drops this region.[10] We therefore excluded a prespecified *APOE* window a priori from BP and WMH instruments, rather than after seeing the VaD result.

With that window excluded, we performed a confirmatory European two-sample MR of genetically predicted SBP, DBP, and PP on WMH and VaD, and a two-step test of whether WMH captures part of the BP effect on VaD (Fig. 1). Japanese ancestry provided an independent residual-SD replication of the BP to WMH step. Japanese coefficients are not per mm Hg and are not pooled with the European estimates. Complete mediation was not hypothesized. A residual WMH to VaD association after BP-associated instruments are dropped is a secondary result and is not a locus.

Methods

European BP instruments came from Evangelou et al. (n = 757,601).[11] European WMH was GWAS Catalog GCST90472808 (n = 37,355, CHARGE and UK Biobank).[12] VaD used FinnGen R12 F5_VASCDEM (3,624 cases) for the two-step and FinnGen R13 F5_VASCDEM (4,254 cases) for the residual path.[13] Japanese replication used BioBank Japan BP residuals (SBP n = 136,597; DBP n = 136,615; pulse pressure [PP] n = 136,249)[14] and JPSC-AD WMH residual (n = 9,479).[15] Japanese units are WMH residual SD per 1-SD BP residual and are never labeled per mm Hg.

European instruments were selected at $P < 5\times10^{-8}$ and clumped in 1000 Genomes EUR at $r^2 < 0.001$ within 10 Mb.[16] Japanese instruments used the same P and r^2 rules in 1000 Genomes JPT. The primary Japanese traits were SBP, DBP, and PP (Bonferroni 0.05/3 = 0.0167). The primary estimator was multiplicative random-effects inverse-variance weighted (IVW) MR.[17,18] Weighted median and MR-Egger were used as sensitivity analyses when at least 3 instruments were available.[19,20] Steiger tested direction.[21] European effects are per 10 mm Hg for BP and per WMH SD for the mediator.

The *APOE* window (GRCh37 chr19:44,909,039–45,912,650) was excluded a priori from instruments. Dropped variants were WMH rs769449, DBP rs73036520, SBP rs7255933 and rs10420519, and PP rs7412 (**Table S1**). 17q21.31 (hg19 chr17:43–46 Mb) is a published WMH locus. A leave-out tested whether dropping that region changed the European BP to WMH estimate by more than 10%. It was not a locus scan.

The two-step multiplied each *APOE*-excluded BP to WMH estimate (a) by the *APOE*-excluded WMH to VaD log-odds (b).[22] The indirect odds ratio (OR) is exp(a×b). The standard error used a Sobel approximation with Cov(a,b) = 0.[23] The mediated proportion (indirect/total) is descriptive. Complete mediation was not hypothesized. The three indirect odds ratios are in Fig. 2D. Totals are in Fig. 2C. A DBP mediated proportion is reported because that interval excludes 0. The SBP proportion interval includes 0. No PP proportion is reported because the PP total log-OR is near 0.

The residual path started from *APOE*-excluded WMH instruments, dropped SBP or DBP associations at $P < 5\times10^{-8}$, and dropped 17q21.31, leaving 10 instruments. The prespecified FinnGen R12 residual IVW was null. FinnGen R13 used the same 16 unrestricted and 10 BP-independent instruments.

Analyses used R 4.4.2 and MendelianRandomization 0.10.0 on public GWAS summary statistics only. No individual-level data were accessed. Ethical approval and consent were obtained by the original studies. Japanese non-BP exposures, Steiger, and dataset sources are in **Tables S3-S5**.

Results

After *APOE* exclusion, genetically predicted DBP associated with higher European WMH (n = 454 instruments; β = 0.176 WMH SD per 10 mm Hg, 95% CI 0.115–0.236; $P = 1.40\times10^{-8}$; Fig. 2A, Table 1). SBP was smaller (n = 449; β = 0.091, 0.058–0.124; $P = 5.63\times10^{-8}$). PP included the null (n = 403; β = 0.048, − 0.004 to 0.100). Weighted median and MR-Egger agreed in direction for DBP and SBP. All-

instrument DBP and SBP estimates were essentially unchanged (**Table S6**). Heterogeneity was marked (all-instrument DBP Qp = 8.96×10^{-53}), which is why random-effects IVW was primary. Dropping 17q21.31 changed DBP by + 8.3% and SBP by + 5.1%. Neither change exceeded 10% (**Table S2**).

Table 1
Primary inverse-variance weighted estimates after *APOE* exclusion

Contrast	Ancestry / scale	IVs	Estimate (95% CI)	P
DBP → WMH	EUR; WMH SD per 10 mm Hg	454	β = 0.176 (0.115–0.236)	1.40×10^{-8}
SBP → WMH	EUR; WMH SD per 10 mm Hg	449	β = 0.091 (0.058–0.124)	5.63×10^{-8}
PP → WMH	EUR; WMH SD per 10 mm Hg	403	β = 0.048 (− 0.004 to 0.100)	0.069
DBP residual → WMH residual	JP; residual SD per 1-SD BP residual	15	β = 0.808 (0.497–1.120)	3.75×10^{-7}
SBP residual → WMH residual	JP; residual SD per 1-SD BP residual	21	β = 0.667 (0.331–1.003)	9.95×10^{-5}
PP residual → WMH residual	JP; residual SD per 1-SD BP residual	17	β = 0.185 (− 0.314 to 0.683)	0.467
DBP → VaD	EUR; OR per 10 mm Hg; FinnGen R12	446	OR = 1.364 (1.171–1.588)	6.55×10^{-5}
SBP → VaD	EUR; OR per 10 mm Hg; FinnGen R12	441	OR = 1.117 (1.021–1.221)	0.0153
PP → VaD	EUR; OR per 10 mm Hg; FinnGen R12	397	OR = 1.005 (0.867–1.165)	0.943
DBP via WMH (a×b)	EUR; indirect OR	-	OR = 1.102 (1.033–1.176)	0.0031
SBP via WMH (a×b)	EUR; indirect OR	-	OR = 1.052 (1.017–1.088)	0.0035
PP via WMH (a×b)	EUR; indirect OR	-	OR = 1.027 (0.994–1.061)	0.107
DBP mediated proportion	EUR; descriptive	-	0.314 (0.055–0.573)	-
SBP mediated proportion	EUR; descriptive	-	0.458 (-0.023 to 0.939)	-

Japanese rows are not per mm Hg. Mediated proportions are indirect divided by total on the log-OR scale. No pulse-pressure proportion is reported because the total log-OR is near 0. Dataset sources, all-instrument contrasts, and two-step instrument F are in **Tables S5 and S6**.

In Japan, DBP residual (n = 15; β = 0.808, 0.497–1.120; P = 3.75×10^{-7}) and SBP residual (n = 21; β = 0.667, 0.331–1.003; P = 9.95×10^{-5}) associated with higher WMH residual (Fig. 2B). Both passed Bonferroni 0.0167. PP residual was null (n = 17; β = 0.185, − 0.314 to 0.683). These coefficients are not per mm Hg and cannot be pooled with the European estimates. They are an independent-ancestry, same-direction test of the a step.

APOE-excluded DBP associated with higher VaD odds (n = 446; OR 1.364 per 10 mm Hg, 1.171–1.588; P = 6.55×10^{-5}; Fig. 2C). SBP was weaker (n = 441; OR 1.117, 1.021–1.221). PP to VaD was null (OR 1.005, 0.867–1.165). The primary b step (16 WMH instruments, mean F = 59.1) gave OR 1.741 per WMH SD (1.273–2.382). The DBP product a×b was log-OR 0.0974 (0.0329–0.162), or indirect OR 1.102 (1.033–1.176; Fig. 2D). The descriptive mediated proportion was 0.314 (0.055–0.573). This is partial mediation. The SBP indirect OR was 1.052 (1.017–1.088), but that descriptive proportion interval included 0. The PP indirect OR included 1 (1.027, 0.994–1.061). With *APOE* left in, WMH to VaD was heterogeneous (Qp = 3.73×10^{-57}) and Steiger failed. After the prespecified window, Steiger was direction-consistent.

Alzheimer disease (AD) was an outcome-specificity check. Genetically predicted BP associated with lower, not higher, AD odds (DBP OR 0.871, 0.814–0.931; SBP OR 0.923, 0.889–0.958). WMH to AD was not significant (OR 1.104, 0.931–1.309).

After BP-associated instruments and 17q21.31 were dropped, 10 WMH instruments remained. In FinnGen R12 the residual IVW was null (OR 1.450, 0.970–2.167). In R13 it was 1.534 (1.012–2.324; P = 0.0437). The weighted median was not significant (OR 1.42, 0.902–2.23). This residual estimate is borderline and is not a locus (**Figure S1**).

Discussion

This confirmatory two-sample MR finds that genetically predicted DBP and SBP raise WMH in Europeans, that the same direction replicates in Japanese ancestry on a residual-SD scale, and that both have an indirect path through WMH to VaD after a priori *APOE* exclusion. A descriptive mediated proportion whose interval excludes 0 is limited to DBP. PP is not associated with WMH or VaD. The result agrees with observational BP–WMH cohorts[4] and with prior European BP–WMH MR,[6] while adding a Japanese a-step and a prespecified two-step to VaD.

What this study adds is the path through WMH to VaD, not a first BP to WMH estimate. Ma et al. already linked Evangelou BP to WMH and lacunar stroke.[6] Sargurupremraj et al. linked WMH to dementia and reported an inverse genetic BP–AD association,[8] matching our AD outcome-specificity check.

Mediation is incomplete. A descriptive 31% does not mean that one-third of VaD is caused by WMH. The proportion interval is descriptive because Sobel sets Cov(a,b) = 0 and because the a and b estimates are not independent. The SBP indirect OR excludes 1, but that proportion interval includes 0, so a systolic

mediated fraction is not claimed. The residual R13 path is the most tentative result. Its lower CI bound is 1.012. The weighted median does not exclude 1. The prespecified FinnGen R12 residual IVW was null.

This analysis does not show that lowering BP accounts for all WMH-related VaD genetic risk. MR estimates a lifelong, modest difference in genetically predicted BP, not the time-limited treatment effect on measured SBP that SPRINT-MIND tested.[5] The two designs answer related questions rather than the same one.

These estimates should be read with the following limitations. Evangelou et al. include UK Biobank, and GCST90472808 is annotated CHARGE and UK Biobank, so overlap and winner's curse can pull the European BP to WMH estimate toward the observational association. FinnGen VaD is an ICD registry endpoint rather than research-adjudicated VaD, and Japanese coefficients are residual SD rather than mm Hg, so the Japanese a-step cannot be pooled with Europe. Japanese instruments were clumped in 1000 Genomes JPT (n = 104). The DBP to VaD MR-Egger interval includes 1.

In conclusion, genetically predicted BP raises WMH in European and Japanese ancestry. After a priori *APOE* exclusion, DBP and SBP have an indirect path through WMH to VaD. A descriptive mediated proportion whose interval excludes 0 is limited to DBP. A residual WMH to VaD association after BP-associated instruments are dropped is borderline and is not a locus.

Declarations

Acknowledgments

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Data Availability

Analyses used publicly available GWAS summary statistics only (**Table S5**). No individual-level data were accessed. Analysis code and variant-level association results are available at https://github.com/sw4rsw4r/BP-WMH-VaD.

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Unsectioned Paragraphs

Supplemental Material

Tables S1-S6

Figure S1

Japanese rows are not per mm Hg. Mediated proportions are indirect divided by total on the log-OR scale. No pulse-pressure proportion is reported because the total log-OR is near 0. Dataset sources, all-instrument contrasts, and two-step instrument F are in **Tables S5 and S6**.

Figures

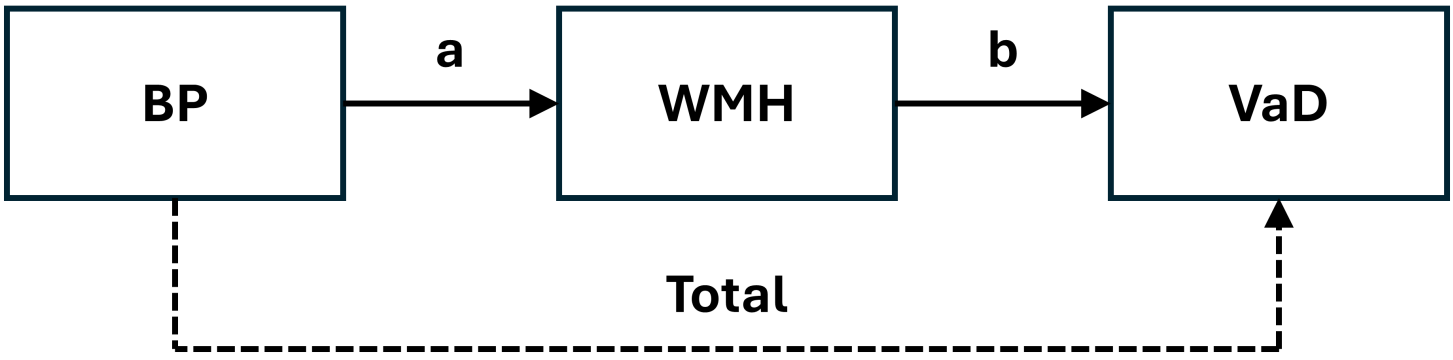

Figure 1

Study design. Solid arrows *a* and *b* are the two-step path. The dashed path is the total BP to VaD effect. Arrow *a* is estimated in Europe and in Japan (Japanese units are residual SD). Arrow *b* and the total effect are Europe only. European instruments exclude the *APOE* window a priori.

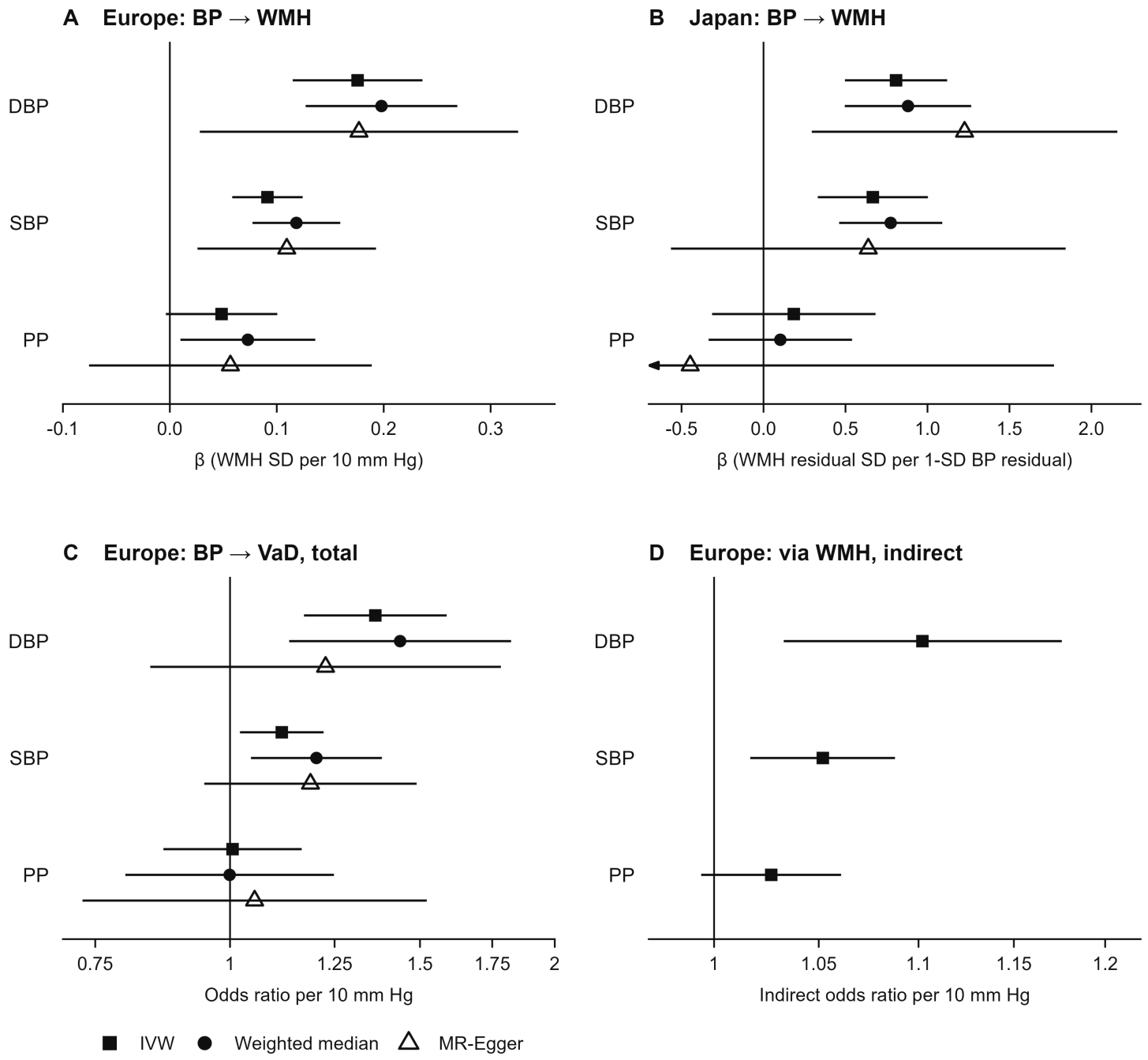

Figure 2

Primary Mendelian randomization estimates after *APOE* exclusion. Filled square, inverse-variance weighted (primary). Filled circle, weighted median. Open triangle, MR-Egger. A, Europe, BP to WMH (WMH SD per 10 mm Hg). B, Japan, BP residual to WMH residual (not per mm Hg). C, Europe, total BP to VaD (odds ratio per 10 mm Hg). D, Two-step indirect odds ratios through WMH (IVW a×b only). Horizontal bars are 95% CIs. Arrowheads mark truncated intervals. European and Japanese coefficients are not on a common mm Hg scale.

Supplementary Files

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