Journal of the American Heart Association

ORIGINAL RESEARCH

Blood Pressure Partially Mediated the Association of Insulin Resistance and Cerebral Small Vessel Disease: A Community-Based Study

Mengyuan Zhou, MD, PhD*; Lerong Mei, MD*; Jing Jing, MD, PhD; Yingying Yang, MD, PhD; Xueli Cai, MD; Xia Meng, MD, PhD; Aoming Jin, PhD; Jinxi Lin, MD, PhD; Shan Li, MD; Hao Li, PhD; Tiemin Wei, MD; Yongjun Wang, MD; Yilong Wang, MD, PhD; Yuesong Pan, PhD

BACKGROUND: Insulin resistance as a significant vascular risk factor has been studied in relation to cerebral small vessel disease (SVD). Evidence suggests that insulin resistance might trigger high blood pressure (BP). Therefore, we aimed to investigate whether insulin resistance impacts SVD with a mediating effect of BP in nondiabetic subjects.

METHODS AND RESULTS: PRECISE (Polyvascular Evaluation for Cognitive Impairment and Vascular Events) study participants underwent brain and vascular imaging techniques and metabolomic risk factors measurements. Insulin resistance was evaluated by the insulin sensitivity index and the Homeostatic Model Assessment for Insulin Resistance based on the standard oral glucose tolerance test. On average, 2752 nondiabetic subjects (47.1% men) aged 60.9 years were included. The multivariable logistic regression model and linear regression model tested the association of insulin resistance with BP components (including systolic BP [SBP], diastolic BP (DBP), and pulse pressure [PP]) and SVD, and of BP components with SVD. In the mediation analysis, SBP, DBP, and PP were found to partially mediate the detrimental effect of insulin resistance (assessed by the insulin sensitivity index) on lacunes (mediation percentage: SBP, 31.15%; DBP, 34.21%; PP, 10.43%), white matter hyperintensity (mediation percentage: SBP, 37.34%; DBP, 44.15%; PP, 9.80%), and SVD total burden (mediation percentage: SBP, 42.07%; DBP, 49.29%; PP, 11.71%) (all $P<0.05$). The mediation analysis results were not significant when using the Homeostatic Model Assessment for Insulin Resistance to assess insulin resistance.

CONCLUSIONS: Higher insulin resistance was associated with SVD in this community-dwelling population. The association of insulin resistance with lacunes, white matter hyperintensity, and SVD total burden was explained in part by BP.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03178448.

Key Words: blood pressure ■ insulin resistance ■ mediation ■ small vessel disease

Cerebral small vessel disease (SVD), characterized by white matter hyperintensity (WMH), lacunes, perivascular space (PVS), and cerebral microbleeds, is associated with cognitive impairment, increased risk of stroke, and functional decline in the aged, imposing an increased socioeconomic burden on the health care system.[1,2] Emerging data from neuroimaging and genetic studies suggest that pathological processes such as microvascular endothelial dysfunction are likely to be inherited and subsequent

Correspondence to: Yilong Wang, MD, PhD and Yuesong Pan, PhD, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, No. 119 South 4th Ring West Road, Fengtai District, Beijing 100070, China. Email: yilong528@aliyun.com and yuesongpan@aliyun.com

*M. Zhou and L. Mei contributed equally.

This article was sent to Kolawole W. Wahab, MD, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.031723

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This cohort study, with 2752 nondiabetic community-dwelling participants, demonstrates an association between insulin resistance and cerebral small vessel disease.
- We used mediation analysis to find that the association between insulin resistance with lacunes, white matter hyperintensity, and total burden of small vessel disease was partially explained by blood pressure.

What Are the Clinical Implications?

- Early detection of insulin resistance and blood pressure monitoring in healthy individuals could help identify people at high risk of small vessel disease, and improving insulin sensitivity may help in the prevention and treatment of small vessel disease.

Nonstandard Abbreviations and Acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
DBP	diastolic blood pressure
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
ISI	insulin sensitivity index
PP	pulse pressure
PRECISE	Polyvascular Evaluation for Cognitive Impairment and Vascular Events
PVS	perivascular space
SBP	systolic blood pressure
SPRINT	Systolic Blood Pressure Intervention Trial
SVD	small vessel disease
WMH	white matter hyperintensity

to environmental and metabolic exposures.[3] Recently, a positive association between insulin resistance and SVD was indicated by cross-sectional studies and Mendelian randomization studies.[4–7] However, the mechanism by which insulin resistance affects SVD is still unclear.

Previous studies demonstrated that insulin sensitivity was independently associated with blood pressure (BP) levels, and elevated insulin values were predictive of the subsequent incidence of hypertension in the normotensive population.[8,9] Meanwhile, a large amount of evidence suggests that hypertension is independently associated with WMH, lacunes, and PVS.[10–13] Therefore, we hypothesized that elevated BP may mediate the relationship between insulin resistance and SVD in subjects without diabetes.

In this community-based population in China,[14] we investigated the mediation effect of elevated BP on the relationship between insulin resistance and SVD in nondiabetic subjects.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data were derived from the PRECISE (Polyvascular Evaluation for Cognitive Impairment and Vascular Events) study (NCT03178448).[14] The PRECISE study is a population-based prospective cohort study in Lishui City, Zhejiang Province, designed to investigate the prevalence and progression of clinical or subclinical polyvascular lesions in community-dwelling residents aged 50 to 75 years, as well as the association between polyvascular lesions and future risk of cognitive impairment, cardiovascular/cerebrovascular events, and death.[14] Subjects in the PRECISE study were recruited by subgroup sampling in 6 villages and 4 communities in Lishui City. Exclusion criteria were subjects with artificial teeth, implantable automatic defibrillator, or any implanted metal device that prevented them from undergoing magnetic resonance imaging (MRI). At the baseline survey, information on sociodemographic factors, medical history, medication history, diet, and vascular risk factors (eg, smoking, alcohol consumption, physical activity, hypertension, hyperlipidemia) was collected in person by trained interviewers. Fasting blood sample collection and structural brain MRI were also performed at baseline. The rational and detailed description of the PRECISE study has been previously presented.[14] The study was approved by the ethics committee at Beijing Tiantan Hospital (approval number: KY2017-010-01) and the ethics committee at Lishui Hospital (approval number: 2016-42). Informed consent was obtained from all participants or their legally authorized representatives.

The present analysis was based on data from the baseline survey. Subjects with available imaging data and plasma glucose and insulin concentration data based on the standard oral glucose tolerance test were included, whereas those with a history of diabetes were excluded.

Blood pressure was measured using an automated sphygmomanometer (Omron model HEM-7071; Omron) with the subject resting for 5 minutes in a seated position at the baseline survey. Three consecutive measurements were taken on the nondominant

arm with a 1-minute interval between measurements for each participant. The average of the second and third BP readings, including systolic BP (SBP) and diastolic BP (DBP), was recorded. Pulse pressure (PP) was calculated by subtracting DBP from SBP.

Measurement of Insulin Resistance

The oral glucose tolerance test was performed at baseline in subjects without previously diagnosed diabetes. A first venous blood sample was collected after an overnight fast, then participants were asked to take a calibrated dose (75 g) of glucose, and a second venipuncture was performed 2 hours later. The fasting and 2-hour postload glucose, insulin, and C-peptide levels were analyzed. Fasting and 2-hour postload glucose levels were analyzed with an enzymatic method. Fasting and 2-hour postload insulin levels were analyzed with a competitive radioimmunoassay (Diagnostic Products).[15] History of diabetes was defined according to self-reported medical history, previous diagnosis by a physician, or current use of antidiabetic medication.

Insulin resistance was measured by the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and Gutt insulin sensitivity index ($ISI_{0,120}$). The HOMA-IR was calculated as HOMA-IR=fasting insulin (microunits per milliliter)×fasting glucose (millimoles per liter)/22.5.[16] The $ISI_{0,120}$ was calculated as $ISI_{0,120}=m/[G\times\log10(I)]$, where m=[75 000 mg+(fasting glucose-2-hour glucose)×0.19×body weight kg]/120 minutes, G represents the average of fasting and 2-hour glucose concentrations from the oral glucose tolerance test, and I represents the average of fasting and 2-hour insulin concentrations. Units for the $ISI_{0,120}$ are $mg\times L^2/mmol\times mU\times min$.[17] Insulin resistance was defined by the highest HOMA-IR quartile (quartile 4) and the lowest quartile (quartile 1) of $ISI_{0,120}$.

Brain MRI Acquisition and Analysis

Subjects underwent brain MRI at baseline on a research-dedicated 3.0T magnetic resonance scanner (Ingenia 3.0T; Philips, Best, the Netherlands). Sequences included 3-dimensional T1-weighted magnetization-prepared rapid-acquisition gradient-echo, 2-dimensional T2-weighted, 2-dimensional fluid-attenuated inversion-recovery, diffusion-weighted imaging, susceptibility-weighted imaging, and 3-dimensional time-of-flight magnetic resonance angiography sequences. Subjects with artificial teeth, implantable automatic defibrillator, or any implanted metal device were excluded from the MRI scan. Imaging data were collected in digital imaging and communications in medicine format on discs and centrally interpreted by well-trained and experienced personnel (Y.Y., M.Z.) at the research center of Beijing Tiantan Hospital, who were blinded to clinical details.

Definitions of neuroimaging markers of SVD were based on the standards for reporting vascular changes on neuroimaging.[2] Lacunes were defined as rounded or ovoid lesions in the subcortical, basal ganglia, or brainstem, ranging from 3 to 20 mm in diameter, presenting with cerebral spinal fluid signal intensity on T2 and fluid-attenuated inversion recovery, generally featuring a hyperintense rim on fluid-attenuated inversion recovery and no increased signal on diffusion-weighted imaging.[2] White matter hyperintensities were defined as focal or confluent hyperintensities in the deep and periventricular white matter on fluid-attenuated inversion recovery images and coded according to the Fazekas scale.[18] Cerebral microbleedings were defined as rounded, hypodense foci within brain parenchyma on susceptibility-weighted imaging sequences, up to 10 mm in diameter, and were differentiated from microbleed mimics based on current guidelines.[19] PVS was defined as small punctate or linear hyperintensities on T2 images in the basal ganglia or centrum semiovale and were rated on a validated semiquantitative scale from 0 to 4.[20] Interrater agreement was tested and showed a good reliability with a Cohen κ of 0.80 for lacunes, 0.82 for WMHs, 0.90 for PVS, and 0.80 for cerebral microbleeds.

We calculated the total SVD score (0–4 points), by assigning 1 point to each feature for the presence of lacunae and microbleeds, moderate to severe PVS in basal ganglia (≥2), or severe periventricular (periventricular WMH Fazekas 3) or moderate to severe deep WMH (deep WMH Fazekas 2–3).[21] Additionally, we calculated the modified total SVD score (0–6 points), assigning 1 point for the presence of lacunes, 1 to 4 points for microbleeds, moderate to severe PVS in basal ganglia (≥2), moderate WMH (total periventricular+subcortical WMH grade 3–4), and 2 points for ≥5 microbleeds and severe WMH (total periventricular+-subcortical WMH grade 5–6).[22]

Statistical Analysis

Categorical variables were presented as frequencies and proportions. Continuous variables were tested for normality using the Shapiro-Wilk test and reported as mean (SD) for normally distributed data and median (interquartile range) for skewed distributed data. Logarithmic transformation of HOMA-IR, $ISI_{0,120}$, SBP, DBP, and PP was performed due to the skewed distribution. Linear regression models were applied to evaluate the associations of insulin resistance with BP, WMH burden, and total SVD burden, and of BP with WMH burden and total SVD burden, yielding β values and 95% CIs. For the dependent variable of lacunes, multivariable logistic regression models were applied to assess the associations between insulin resistance, BP, and lacunes, yielding odds ratios (ORs) and 95%

CIs. Age, sex, smoking, ideal physical activity, healthy diet, estimated creatinine-based glomerular filtration rate, alcohol intake, medical history, and medications were adjusted for in all models.

We conducted a mediation model, assuming that the independent variable influences the mediator variable and in turn influences the dependent variable, to test the present research hypothesis that BP (mediator) mediated the association between insulin resistance (independent variable) and SVD (dependent variable) (Figure 1). To demonstrate a reliable mediation relationship, there are 3 pathways necessary to test: step 1, the association of insulin resistance with SVD (pathway c); step 2, the association of insulin resistance with BP (pathway a); step 3, the association of BP with SVD, controlling for insulin resistance (pathway b). If all 3 associations are confirmed, mediation (indirect effect) can be established in a fourth step through the estimation of the direct causal relationship (pathway c'). The mediation of the relationship is full when c' is 0 and partial when c' is not equal to 0.[23] The associations of insulin resistance and BP with lacunes were tested using logistic regression models with adjustment for age and sex due to low prevalence (5.1%), and adjusted ORs with 95% CIs were reported. All other pathways were tested using a linear regression model with adjustment for age, sex, smoking, ideal physical activity, healthy diet, estimated creatinine-based glomerular filtration rate, alcohol intake, medical history, and medications, and reported as adjusted β with 95% CI. The proportion of the mediated effect of BP in the relationship between insulin resistance and lacunes was estimated by dividing the log ORs of the indirect effect (pathway ab) by the log ORs of the total effect (pathway c), whereas the proportions of the mediated effect of BP in the relationship of insulin resistance and other neuroimaging features were estimated as the product of the β values of pathway a and pathway b (Figure 1).[24,25]

A 2-sided *P* value <0.05 was considered statistically significant in all analyses conducted 2-sided. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

There were 3067 subjects in the PRECISE cohort. After excluding 307 subjects with diabetes, 4 subjects with missing data on glucose or insulin, and 4 subjects with uninterpretable MRI images for SVD, a total of 2752 subjects were finally included in this study. Subjects included were aged 60.9±6.6 years on average, of which 52.9% were women. Among all the included subjects, 1116 (40.6%) subjects had hypertension, 515 (18.7%) had dyslipidemia, 10 (0.4%) had coronary

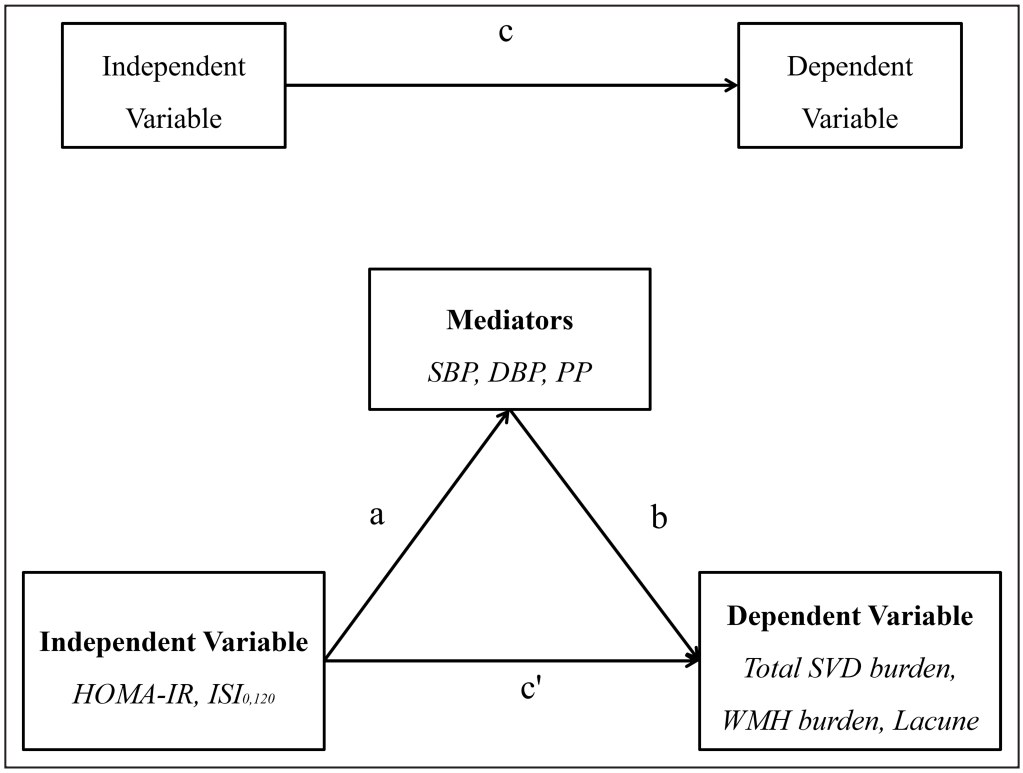

Figure 1. Mediation model of the hypothetical causal pathway.
Arrows indicate the causal direction or possible association. DBP indicates diastolic blood pressure; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; ISI, insulin sensitivity index; PP, pulse pressure; SBP, systolic blood pressure; SVD, small vessel disease; and WMH, white matter hyperintensity.

Table 1. Baseline Characteristics of the Subjects Included (N=2752)

Characteristic	Value
Age, y	60.9±6.6
Men, n (%)	1295 (47.1)
Blood pressure, mm Hg	
Systolic	128.5±16.1
Diastolic	75.0±9.1
Pulse pressure	53.5±11.8
BMI, kg/m^2	23.7±3.0
Ideal physical activity,* n (%)	2140 (77.8)
Healthy diet,† n (%)	678 (24.6)
Medical history, n (%)	
Hypertension	1116 (40.6)
Coronary artery disease	10 (0.4)
Atrial fibrillation	23 (0.8)
Dyslipidemia	515 (18.7)
Stroke/TIA	66 (2.4)
Current drinker, n (%)	526 (19.1)
Current smoker, n (%)	571 (20.7)
Fasting glucose, mmol/L	5.5 (5.2–5.9)
Total cholesterol, mmol/L	5.3 (4.6–5.9)
LDL-C, mmol/L	2.8 (2.3–3.3)
HDL-C, mmol/L	1.3 (1.1–1.6)
Estimated GFRcr, mL/min per 1.73 m^2	104.5 (96.5–110.3)
Medications, n (%)	
Antihypertensive	680 (24.7)
Lipid lowering	92 (3.3)
Antiplatelet	57 (2.1)
Anticoagulants	2 (0.1)
With WMH burden,‡ n (%)	428 (15.6)
With lacunes, n (%)	140 (5.1)
Total SVD burden score ≥1, n (%)	806 (29.3)
Modified total SVD burden score ≥1, n (%)	1101 (40.0)

Data are presented as mean±SD, median (interquartile range), or number (percent). BMI indicates body mass index; GFRcr, creatinine-based glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent; SVD, small vessel disease; TIA, transient ischemic attack; and WMH, white matter hyperintensity.

*Ideal physical activity was defined as ≥1500 MET-min/wk and ≥3 d/wk vigorous intensity or ≥3000 MET-min/wk and ≥7 d/wk moderate + vigorous intensity according to the International Physical Activity Questionnaire.

†Healthy diet score was based on 3 healthy diet components, each worth 1 point: (1) fruits and vegetables: >4.5 cups (1020 g) per d; (2) fish: ≥2 (3.5 oz) servings (200 g) per wk; and (3) sodium: <6 g per d. Those who scored 2 to 3 were defined as having a healthy diet.

‡WMH burden was defined as a severe periventricular (periventricular WMH Fazekas 3) or a moderate to severe deep WMH (deep WMH Fazekas 2–3).

artery disease, 526 (19.1%) were current drinkers, and 571 (20.7%) were current smokers. The average SBP and DBP were 128.5±16.1 mm Hg and 75.0±9.1 mm Hg, respectively. There were 428 (15.6%) subjects with WMH burden, and 140 (5.1%) reported the presence of lacunes. Details of clinical and demographic features of all subjects are presented in Table 1.

Associations Among Insulin Resistance, Blood Pressure Components, and Neuroimaging Features of SVD

Table S1 displays the associations of insulin resistance with SBP/DBP/PP and neuroimaging features of SVD, and associations of SBP/DBP/PP with neuroimaging features of SVD, which were consistent with the results of steps 1 to 3 in mediation analysis. Specifically, in step 1, log-transformed $ISI_{0,120}$ was independently associated with WMH burden (β=−0.13 [95% CI, −0.21 to −0.06]; *P*<0.001), lacunes (OR, 0.69 [95% CI, 0.48–0.99]; *P*=0.04), and modified total SVD score (β=−0.09 [95% CI, −0.16 to −0.03]; *P*=0.003), although marginally associated with total SVD score (β=−0.05 [95% CI, −0.11 to 0.00]; *P*=0.051). However, log-transformed HOMA-IR was only marginally associated with total SVD score (β=0.05 [95% CI, −0.001 to 0.09]; *P*=0.054). There was no significant association between HOMA-IR and WMH burden or lacunes. In step 2, insulin resistance, assessed by log-transformed HOMA-IR and log-transformed $ISI_{0,120}$, was positively associated with log-transformed SBP, log-transformed DBP, and log-transformed PP (all *P*<0.001) (Table S1). Log-transformed SBP, log-transformed DBP, and log-transformed PP were all strongly associated with WMH burden, lacunes, and SVD total burden (all *P*<0.05) (Table S1). In step 3, the associations between BP components and SVD remained significant after being additionally adjusted for insulin resistance (Figures 2 and 3).

Mediation Effect for Association of Insulin Resistance With Neuroimaging Features of SVD

Mediation analyses were performed to explore the mediating effect of BP (Table 2). Figure 2 shows the partial mediating role of BP components in the association between insulin resistance (assessed by $ISI_{0,120}$) and the total burden of SVD calculated by the modified total SVD score. The mediators SBP, DBP, and PP explained 42.07%, 49.29%, and 11.71% of the association of $ISI_{0,120}$ with modified total SVD score, respectively. However, the mediating effect of BP components was not significant with the application of the total SVD score to calculate the SVD total burden nor with the application of the HOMA-IR to evaluate insulin resistance (Figures S1 and S2). We also performed mediation analyses to explore the mediating role of BP components in the association between insulin resistance with lacunes and WMH, 2 core neuroimaging features of SVD. Figures 3A through 3C show that SBP, DBP, and PP partially explain 31.15%, 34.21%,

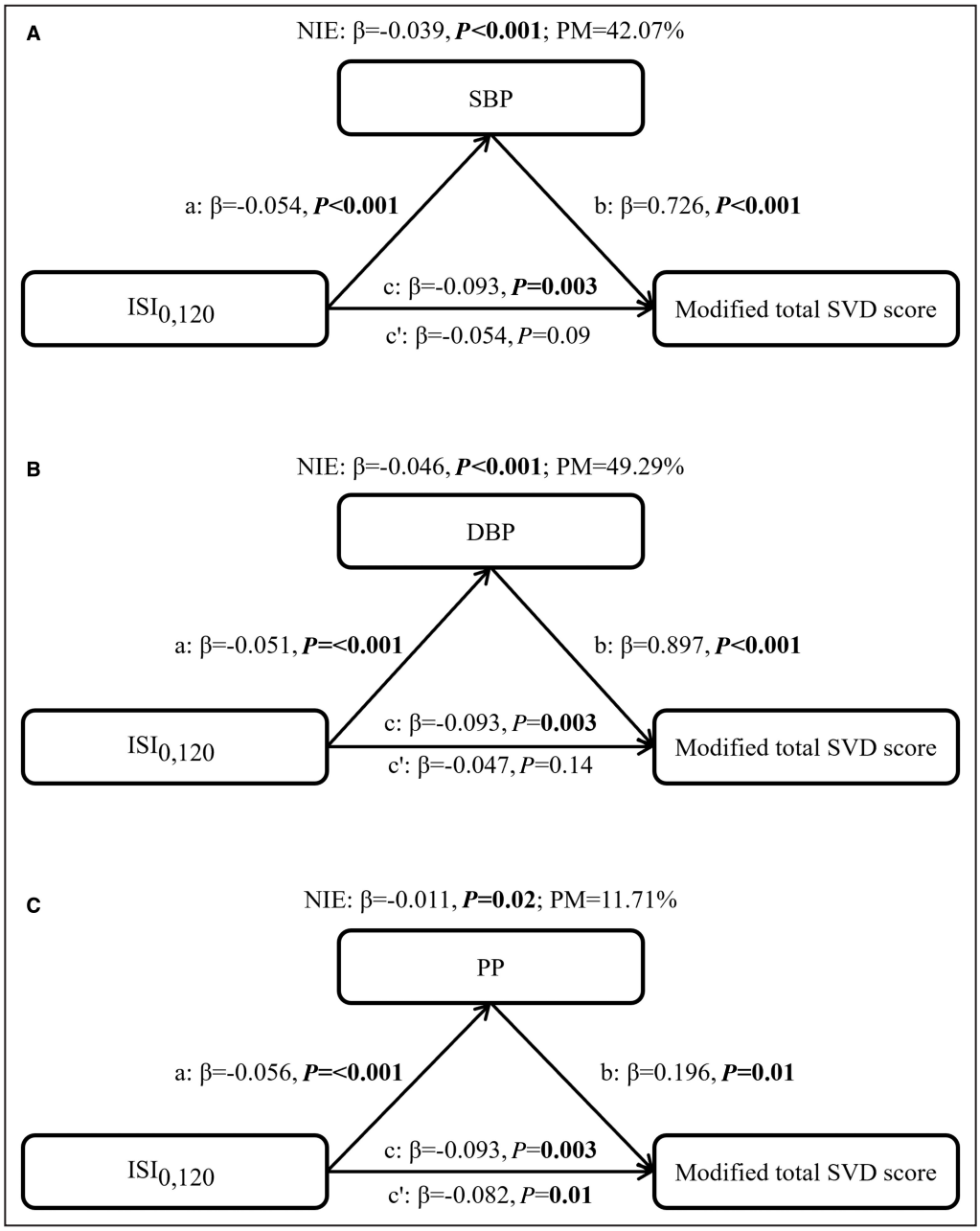

Figure 2. Mediation analysis of blood pressure components on the association between $ISI_{0,120}$ and SVD total burden calculated by modified total SVD score.
A, SBP. **B**, DBP. **C**, PP. DBP indicates diastolic blood pressure; ISI, insulin sensitivity index; NIE, natural indirect effect; PM, percentage of mediation; PP, pulse pressure; SBP, systolic blood pressure; and SVD, small vessel disease.

and 10.43%, respectively, of the association between insulin resistance (assessed by $ISI_{0,120}$) and lacunes. Figure 3D through 3F show that SBP, DBP, and PP partially explain 37.34%, 44.15%, and 9.80%, respectively, of the association between insulin resistance (assessed by $ISI_{0,120}$) and WMH burden. The results were negative when using HOMA-IR in the mediation analyses of insulin resistance and WMH burden or lacunes (Figure S2).

DISCUSSION

In the present analyses, we investigated the mediation effect of 3 BP components on the association between insulin resistance, measured by HOMA-IR and $ISI_{0,120}$, and SVD. The results indicated that SBP, DBP, and PP partially mediated the association of insulin resistance and SVD, especially lacunes, WMH burden, and SVD total burden. In addition, compared

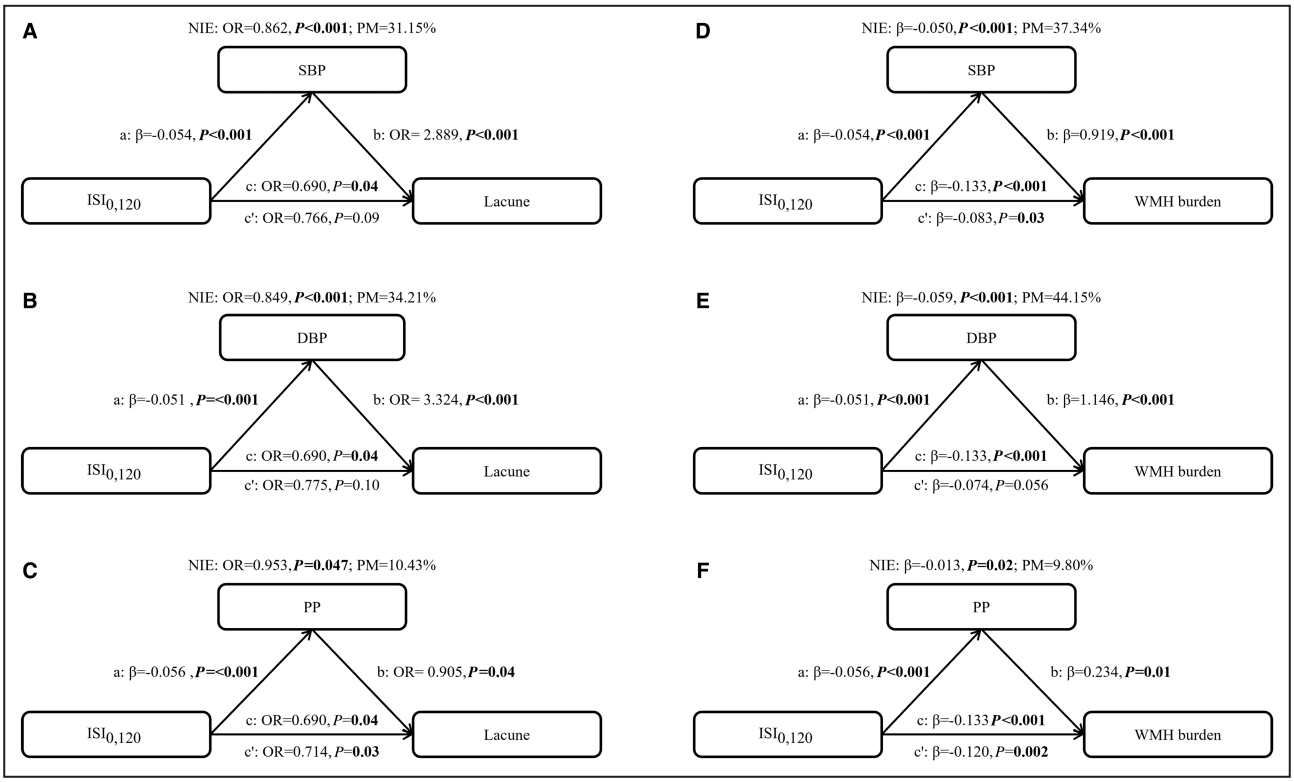

Figure 3. Mediation analysis of blood pressure components on the association between $ISI_{0,120}$ and neuroimaging features of SVD.

A through **C**, Mediating role of SBP, DBP, and PP in the association between $ISI_{0,120}$ and lacunes. **D** through **F**, mediating role of SBP, DBP, and PP in the association between $ISI_{0,120}$ and WMH burden. DBP indicates diastolic blood pressure; ISI, insulin sensitivity index; NIE, natural indirect effect; PM, percentage of mediation; PP, pulse pressure; SBP, systolic blood pressure; SVD, small vessel disease; and WMH, white matter hyperintensity.

with HOMA-IR, the mediating effect of SBP, DBP, and PP was more marked with the use of $ISI_{0,120}$ to assess insulin resistance.

Although the issue of the origin of hypertension and insulin resistance is controversial and complex, previous studies have also provided more evidence from epidemiological and experimental studies on the causality of insulin resistance on the development of hypertension,[8,9,26] supporting that the finding of pathway a in our study is reliable. Hypertension plays an important role in SVD, both in terms of elevated BP levels[12,13,27] and BP variability,[28] as well as components of BP such as SBP, DBP, mean arterial pressure, and PP,[29] all of which are closely related to SVD and support the reliability of pathway b. However, there is little evidence on the relationship among insulin resistance, BP, and SVD. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) BP study and the subanalyses of the SPRINT (Systolic Blood Pressure Intervention Trial) study both evaluated the effect of intensive blood pressure control in slowing the progression of white matter lesions with the same SBP targets in patients with and without diabetes, the former showing significantly less increase in white matter lesion volume in the intensive treatment group (–0.16 versus –0.13),[30,31] which might support the partial mediating role of SBP suggested by the present study. Our study demonstrated the partial mediating role of BP in the association of insulin resistance and SVD, implicating the importance of assessment for insulin resistance and BP to distinguish high-risk subjects for SVD. This may also indicate that preventing or alleviating hypertension may be a target for the prevention of SVD caused by insulin resistance; nevertheless, this requires further investigations.

Research has suggested several pathological processes arising from insulin resistance that lead to SVD.[4,32,33] Our study confirms the association between insulin resistance and SVD and suggests a possible role for mediation through hypertension. A recent Mendelian randomization analysis also demonstrated a mediating role of SBP on the effect of obesity on ischemic stroke.[34] These might indicate an intimate association of both insulin resistance and hypertension with brain vascular health. Previous literature has discussed the contribution

Table 2. Causal Mediation Analysis Predicting the Mediating Effect of Blood Pressure on Small Vessel Disease via Insulin Resistance

Effector	Mediator	Outcome	Total effect		Natural direct effect		Natural indirect effect	Percentage mediated	
			β/OR[§] (95% CI)	*P* value	β/OR (95% CI)	*P* value	β/OR (95% CI)	*P* value	β/OR (95% CI)
HOMA-IR*	SBP*	Lacunes	1.34 (1.00 to 1.79)	0.051	1.22 (0.86 to 1.58)	0.24	1.15 (1.06–1.23)	<0.001‖	45.18
		WMH burden	0.06 (–0.006 to 0.12)	0.08	0.01 (–0.06 to 0.08)	0.78	0.05 (0.03 to 0.07)	<0.001‖	83.85
		Total SVD score[†]	0.05 (–0.001 to 0.09)	0.054	0.01 (–0.03 to 0.06)	0.58	0.03 (0.02 to 0.04)	<0.001‖	71.10
		Modified total SVD score[‡]	0.04 (–0.01 to 0.09)	0.14	0.002 (–0.05 to 0.06)	0.95	0.04 (0.02 to 0.05)	<0.001‖	95.63
	DBP*	Lacunes	1.34 (1.00 to 1.79)	0.051	1.20 (0.84 to 1.56)	0.27	1.17 (1.08 to 1.25)	<0.001‖	49.97
		WMH burden	0.06 (–0.005 to 0.12)	0.08	0.001 (–0.06 to 0.07)	0.98	0.06 (0.04 to 0.08)	<0.001‖	98.29
		Total SVD score	0.05 (–0.001 to 0.09)	0.054	0.01 (–0.04 to 0.06)	0.73	0.04 (0.02 to 0.05)	<0.001‖	81.71
		Modified total SVD score	0.04 (–0.01 to 0.09)	0.14	–0.005 (–0.06 to 0.05)	0.84	0.05 (0.03 to 0.06)	<0.001‖	-
	PP*	Lacunes	1.34 (1.00 to 1.79)	0.051	1.30 (0.92 to 1.68)	0.13	1.04 (1.00 to 1.09)	0.057	16.02
		WMH burden	0.06 (–0.01 to 0.12)	0.08	0.05 (–0.02 to 0.11)	0.17	0.01 (0.003 to 0.02)	0.01‖	21.96
		Total SVD score	0.05 (–0.001 to 0.09)	0.054	0.04 (–0.01 to 0.08)	0.13	0.009 (0.002 to 0.02)	0.009‖	20.50
		Modified total SVD score	0.04 (–0.01 to 0.09)	0.14	0.03 (–0.02 to 0.08)	0.28	0.01 (0.003 to 0.02)	0.009‖	26.46
$ISI_{0,120}$*	SBP	Lacunes	0.69 (0.49 to 0.98)	0.04‖	0.77 (0.50 to 1.03)	0.09	0.86 (0.79 to 0.93)	<0.001‖	31.15
		WMH burden	–0.13 (–0.21 to –0.06)	<0.001‖	–0.08 (–0.16 to –0.01)	0.03‖	–0.05 (–0.07 to –0.03)	<0.001‖	37.34
		Total SVD score	–0.05 (–0.11 to 0.00)	0.050	–0.02 (–0.07 to 0.04)	0.49	–0.03 (–0.05 to –0.02)	<0.001‖	64.03
		Modified total SVD score	–0.09 (–0.16 to –0.03)	0.003‖	–0.05 (–0.12 to 0.01)	0.09	–0.04 (–0.05 to –0.02)	<0.001‖	42.07
	DBP	Lacunes	0.69 (0.49 to 0.98)	0.04‖	0.77 (0.50 to 1.05)	0.10	0.85 (0.78 to 0.92)	<0.001‖	34.21
		WMH burden	–0.13 (–0.21 to –0.06)	<0.001‖	–0.07 (–0.15 to 0.002)	0.056	–0.06 (–0.08 to –0.04)	<0.001‖	44.15
		Total SVD score	–0.05 (–0.11 to 0.00)	0.050	–0.02 (–0.07 to 0.04)	0.59	–0.04 (–0.05 to –0.03)	<0.001‖	72.20
		Modified total SVD score	–0.09 (–0.16 to –0.03)	0.003‖	–0.05 (–0.11 to 0.02)	0.14	–0.05 (–0.06 to –0.03)	<0.001‖	49.29
	PP	Lacunes	0.69 (0.49 to 0.98)	0.04‖	0.71 (0.46 to 0.97)	0.03‖	0.95 (0.91 to 1.00)	0.047‖	10.43
		WMH burden	–0.13 (–0.21 to –0.06)	<0.001‖	–0.12 (–0.20 to –0.04)	0.002‖	–0.01 (–0.02 to –0.002)	0.02‖	9.80
		Total SVD score	–0.05 (–0.11 to 0.00)	0.050	–0.04 (–0.10 to 0.01)	0.11	–0.01 (–0.02 to –0.002)	0.01‖	18.74
		Modified total SVD score	–0.09 (–0.16 to –0.03)	0.003‖	–0.08 (–0.14 to –0.02)	0.01‖	–0.01 (–0.02 to –0.002)	0.02‖	11.71

DBP indicates diastolic blood pressure; GFRcr, creatinine-based glomerular filtration rate; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; ISI, insulin sensitivity index; OR, odds ratio; PP, pulse pressure; PVS, perivascular spaces; SBP, systolic blood pressure; and WMH, white matter hyperintensity.

*Logarithmic transformation was performed for HOMA-IR, $ISI_{0,120}$, SBP, DBP, and PP.

[†]One point was allocated to each of the following: (1) presence of lacunes, (2) presence of microbleeds, (3) moderate-to-severe basal ganglia PVS, and (4) severe periventricular or moderate-to-severe deep WMH.

[‡]One point was allocated to presence of lacunes, 1 to 4 microbleeds, frequent to severe (>20) PVS in basal ganglia, moderate WMH (total periventricular 1 subcortical WMH grade 3–4), and 2 points were allocated for ≥5 microbleeds and severe WMH (total periventricular + subcortical WMH grade 5–6).

[§]Logistic regression model was applied for lacunes (binary) and reported as OR with 95% CI after adjustment for age and sex due to the low prevalence (5.1%), and a linear regression model was performed for others and reported as β with 95% CI after adjustment for age, sex, smoking, ideal physical activity, healthy diet, estimated GFRcr, alcohol intake, medical history, and medications.

‖$P<0.05$.

of insulin resistance to elevated BP[35–37] and the underlying mechanisms by which abnormal BP may affect SVD.[38,39] Further investigations are needed to clarify the underlying mechanisms and to try to develop strategies to target insulin resistance to defend against SVD.

In addition, our study indicated a slightly higher proportion mediated by DBP than SBP. To date, the contribution of SBP and DBP to SVD has reported controversial results,[12,40–42] which is probably due to the diversity of the age group and ethnic group of the study population, also to the different physiological roles of SBP and DBP. It was suggested that elevated DBP is mainly an indicator of peripheral resistance reflecting small vascular dysfunction, whereas elevated SBP as well as PP is mainly an indicator of large artery atherosclerosis and stiffness.[29] However, elevated SBP could also increase peripheral vascular resistance subsequent to arteriolar changes. It still needs further investigation.

We observed that $ISI_{0,120}$ showed a more significant association with SVD, as compared with HOMA-IR. A possible explanation is that $ISI_{0,120}$ incorporates both peripheral and hepatic insulin sensitivity and takes the effect of body weight on the glucose uptake rates in peripheral tissues into account, achieving a better agreement with the hyperinsulinemic-glycated clamp (the gold standard for measuring insulin resistance), whereas HOMA-IR reflects only hepatic insulin sensitivity based on fasting glucose and insulin levels.[17,43] Studies indicated that the use of HOMA-IR may lead to misclassification of a proportion of patients.[44,45] Thus, $ISI_{0,120}$ may be a preferable indicator for the detection and evaluation of early insulin resistance.

Several limitations need to be acknowledged when interpreting the results. First, BP was measured during study visits that might not reflect ambulatory values. However, a previous study showed that in a random subsample of 10% of those who came to the in-person evaluation annually, blood pressure was stable over time.[41] Moreover, the office blood pressure is assessed in most large prospective cohorts and randomized clinical trials.[46,47] Second, the interpretation of WMH severity in the present study was based on visual scaling, which is less precise than the measurements of white matter volume or white matter integrity. Third, because our findings are based on a cross-sectional study, caution is needed in drawing definitive conclusions about causal effect. Therefore, further validation of the causality in a large-scale longitudinal study and experimental study is still needed.

In conclusion, we added evidence for the association between insulin resistance and SVD in nondiabetic subjects and suggested a proportion of this effect extended beyond BP, especially lacunes, WMH burden, and total burden of SVD. In addition, the results were more marked when using the index of $ISI_{0,120}$ to assess insulin resistance compared with HOMA-IR. Our results suggest the importance of insulin resistance and BP as critical contributors to SVD and support the pursuit of potential therapeutics targeting insulin resistance for SVD.

ARTICLE INFORMATION

Received July 14, 2023; accepted January 26, 2024.

Affiliations

Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China (M.Z., J.J., Y.Y., X.M., A.J., J.L., H.L., Y.W., Y.W., Y.P.); China National Clinical Research Center for Neurological Diseases, Beijing, China (M.Z., J.J., Y.Y., X.M., A.J., J.L., H.L., Y.W., Y.W., Y.P.); Cerebrovascular Research Lab, Lishui Hospital, Zhejiang University School of Medicine, Lishui, China (L.M., S.L.); Department of Neurology, Lishui Hospital, Zhejiang University School of Medicine, Lishui, China (X.C.); Department of Cardiology, Lishui Hospital, Zhejiang University School of Medicine, Lishui, China (T.W.); Chinese Institute for Brain Research, Beijing, China (Y.W.); National Center for Neurological Diseases, Beijing, China (Y.W., Y.W.); Advanced Innovation Center for Human Brain Protection (Y.W., Y.W.) and Beijing Laboratory of Oral Health (Y.W.), Capital Medical University, Beijing, China.

Acknowledgments

The authors thank Y. Chen, J. Pi, and M. Zhao for their contributions to imaging interpretation. Author contributions: Yilong W. and Y.P. conceived and designed the research. M.Z., L.M., and A.J. analyzed the data. J.J., Y.Y., J.L., X.M., H.L., T.W., and Y.P. directly accessed and verified the underlying data reported in the article. Yongjun W. supervised the whole project. M.Z. and L.M. wrote the original draft of the article. Y.P. reviewed and polished the article. All authors read and approved the final version of the article.

Sources of Funding

This work was supported by grants from the National Natural Science Foundation of China (number 81825007), Beijing Outstanding Young Scientist Program (number BJJWZYJH01201910025030), Beijing Hospitals Authority Youth Program (number QML20190501), Capital's Funds for Health Improvement and Research (number 2022-2-2045), National Key Research and Development Program of China (numbers 2022YFF1501500, 2022YFF1501501, 2022YFF1501502, 2022YFF1501503, 2022YFF1501504, 2022YFF1501505), Youth Beijing Scholar Program (number 010), Beijing Laboratory of Oral Health (number PXM2021-014226-000041), Beijing Talent Project - Class A: Innovation and Development (number 2018A12), National Ten-Thousand Talent Plan–Leadership of Scientific and Technological Innovation, National Key Research and Development Program of China (numbers 2017YFC1307900, 2017YFC1307905), Key Science and Technologies R&D Program of Lishui City (number 2019ZDYF18), Zhejiang Provincial Program for the Cultivation of High-Level Innovative Health Talents, Stroke Diagnosis, and Treatment Technology Research Center of Zhejiang (number JBZX-202002), and AstraZeneca Investment (China) Co., Ltd.

Disclosures

None.

Supplemental Material

Table S1
Figures S1–S2

REFERENCES

1. Ter Telgte A, van Leijsen EMC, Wiegertjes K, Klijn CJM, Tuladhar AM, de Leeuw FE. Cerebral small vessel disease: from a focal to a global perspective. *Nat Rev Neurol*. 2018;14:387–398. doi: 10.1038/s41582-018-0014-y
2. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, et al. Neuroimaging standards for research into small vessel disease and its contribution to

ageing and neurodegeneration. *Lancet Neurol*. 2013;12:822–838. doi: 10.1016/S1474-4422(13)70124-8
3. Sargurupremraj M, Suzuki H, Jian X, Sarnowski C, Evans TE, Bis JC, Eiriksdottir G, Sakaue S, Terzikhan N, Habes M, et al. Cerebral small vessel disease genomics and its implications across the lifespan. *Nat Commun*. 2020;11:6285. doi: 10.1038/s41467-020-19111-2
4. Nam KW, Kwon HM, Jeong HY, Park JH, Kwon H, Jeong SM. High triglyceride-glucose index is associated with subclinical cerebral small vessel disease in a healthy population: a cross-sectional study. *Cardiovasc Diabetol*. 2020;19:53. doi: 10.1186/s12933-020-01031-6
5. Ryu SY, Coutu JP, Rosas HD, Salat DH. Effects of insulin resistance on white matter microstructure in middle-aged and older adults. *Neurology*. 2014;82:1862–1870. doi: 10.1212/WNL.0000000000000452
6. Lee JE, Shin DW, Yun JM, Kim SH, Nam YS, Cho B, Lim JS, Jeong HY, Kwon HM, Park JH. Insulin resistance is a risk factor for silent lacunar infarction. *Stroke*. 2016;47:2938–2944. doi: 10.1161/STROKEAHA.116.014097
7. Georgakis MK, Harshfield EL, Malik R, Franceschini N, Langenberg C, Wareham NJ, Markus HS, Dichgans M. Diabetes mellitus, glycemic traits, and cerebrovascular disease: a mendelian randomization study. *Neurology*. 2021;96:e1732–e1742. doi: 10.1212/WNL.0000000000011555
8. Lissner L, Bengtsson C, Lapidus L, Kristjansson K, Wedel H. Fasting insulin in relation to subsequent blood pressure changes and hypertension in women. *Hypertension*. 1992;20:797–801. doi: 10.1161/01.hyp.20.6.797
9. Ferrannini E, Natali A, Capaldo B, Lehtovirta M, Jacob S, Yki-Jarvinen H. Insulin resistance, hyperinsulinemia, and blood pressure: role of age and obesity. European Group for the Study of Insulin Resistance (EGIR). *Hypertension*. 1997;30:1144–1149. doi: 10.1161/01.hyp.30.5.1144
10. Bezerra DC, Sharrett AR, Matsushita K, Gottesman RF, Shibata D, Mosley TH Jr, Coresh J, Szklo M, Carvalho MS, Selvin E. Risk factors for lacune subtypes in the atherosclerosis risk in communities (ARIC) study. *Neurology*. 2012;78:102–108. doi: 10.1212/WNL.0b013e31823efc42
11. Francis F, Ballerini L, Wardlaw JM. Perivascular spaces and their associations with risk factors, clinical disorders and neuroimaging features: a systematic review and meta-analysis. *Int J Stroke*. 2019;14:359–371. doi: 10.1177/1747493019830321
12. Wartolowska KA, Webb AJS. Midlife blood pressure is associated with the severity of white matter hyperintensities: analysis of the UK biobank cohort study. *Eur Heart J*. 2021;42:750–757. doi: 10.1093/eurheartj/ehaa756
13. Taylor-Bateman V, Gill D, Georgakis M, Malik R, Munroe P, Traylor M; International Consortium of Blood P. Cardiovascular risk factors and MRI markers of cerebral small vessel disease: a mendelian randomization study. *Neurology*. 2022;98:e343–e351. doi: 10.1212/WNL.0000000000013120
14. Pan Y, Jing J, Cai X, Wang Y, Wang S, Meng X, Zeng C, Shi J, Ji J, Lin J, et al. PolyvasculaR evaluation for cognitive impairment and vaScular events (PRECISE)-a population-based prospective cohort study: rationale, design and baseline participant characteristics. *Stroke Vasc Neurol*. 2021;6:145–151. doi: 10.1136/svn-2020-000411
15. Thacker EL, Psaty BM, McKnight B, Heckbert SR, Longstreth WT Jr, Mukamal KJ, Meigs JB, de Boer IH, Boyko EJ, Carnethon MR, et al. Fasting and post-glucose load measures of insulin resistance and risk of ischemic stroke in older adults. *Stroke*. 2011;42:3347–3351. doi: 10.1161/STROKEAHA.111.620773
16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412–419. doi: 10.1007/BF00280883
17. Gutt M, Davis CL, Spitzer SB, Llabre MM, Kumar M, Czarnecki EM, Schneiderman N, Skyler JS, Marks JB. Validation of the insulin sensitivity index (ISI(0,120)): comparison with other measures. *Diabetes Res Clin Pract*. 2000;47:177–184. doi: 10.1016/s0168-8227(99)00116-3
18. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *Am J Roentgenol*. 1987;149:351–356. doi: 10.2214/ajr.149.2.351
19. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, Launer LJ, Van Buchem MA, Breteler MM; Microbleed Study G. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol*. 2009;8:165–174. doi: 10.1016/S1474-4422(09)70013-4
20. Doubal FN, MacLullich AM, Ferguson KJ, Dennis MS, Wardlaw JM. Enlarged perivascular spaces on MRI are a feature of cerebral small vessel disease. *Stroke*. 2010;41:450–454. doi: 10.1161/STROKEAHA.109.564914
21. Staals J, Makin SD, Doubal FN, Dennis MS, Wardlaw JM. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology*. 2014;83:1228–1234. doi: 10.1212/WNL.0000000000000837
22. Lau KK, Li L, Schulz U, Simoni M, Chan KH, Ho SL, Cheung RTF, Kuker W, Mak HKF, Rothwell PM. Total small vessel disease score and risk of recurrent stroke: validation in 2 large cohorts. *Neurology*. 2017;88:2260–2267. doi: 10.1212/WNL.0000000000004042
23. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. 1986;51:1173–1182. doi: 10.1037//0022-3514.51.6.1173
24. Vanderweele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. *Am J Epidemiol*. 2010;172:1339–1348. doi: 10.1093/aje/kwq332
25. Freedman LS, Graubard BI, Schatzkin A. Statistical validation of intermediate endpoints for chronic diseases. *Stat Med*. 1992;11:167–178. doi: 10.1002/sim.4780110204
26. Reaven GM. Relationship between insulin resistance and hypertension. *Diabetes Care*. 1991;14(Suppl 4):33–38. doi: 10.2337/diacare.14.4.33
27. Lane CA, Barnes J, Nicholas JM, Sudre CH, Cash DM, Parker TD, Malone IB, Lu K, James SN, Keshavan A, et al. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (insight 46): an epidemiological study. *Lancet Neurol*. 2019;18:942–952. doi: 10.1016/S1474-4422(19)30228-5
28. Tully PJ, Yano Y, Launer LJ, Kario K, Nagai M, Mooijaart SP, Claassen J, Lattanzi S, Vincent AD, Tzourio C, et al. Association between blood pressure variability and cerebral small-vessel disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 2020;9:e013841. doi: 10.1161/JAHA.119.013841
29. Guo X, Pantoni L, Simoni M, Bengtsson C, Bjorkelund C, Lissner L, Gustafson D, Skoog I. Blood pressure components and changes in relation to white matter lesions: a 32-year prospective population study. *Hypertension*. 2009;54:57–62. doi: 10.1161/HYPERTENSIONAHA.109.129700
30. Murray AM, Hsu FC, Williamson JD, Bryan RN, Gerstein HC, Sullivan MD, Miller ME, Leng I, Lovato LL, Launer LJ, et al. ACCORDION MIND: results of the observational extension of the ACCORD MIND randomised trial. *Diabetologia*. 2017;60:69–80. doi: 10.1007/s00125-016-4118-x
31. Group SMIftSR, Nasrallah IM, Pajewski NM, Auchus AP, Chelune G, Cheung AK, Cleveland ML, Coker LH, Crowe MG, Cushman WC, et al. Association of intensive vs standard blood pressure control with cerebral white matter lesions. *JAMA*. 2019;322:524–534. doi: 10.1001/jama.2019.10551
32. Yang X, Zhang S, Dong Z, Zi Y, Luo Y, Jin Z, Shi L, Li C, Ren C, Wu D. Insulin resistance is a risk factor for overall cerebral small vessel disease burden in old nondiabetic healthy adult population. *Front Aging Neurosci*. 2019;11:127. doi: 10.3389/fnagi.2019.00127
33. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365:1415–1428. doi: 10.1016/S0140-6736(05)66378-7
34. Marini S, Merino J, Montgomery BE, Malik R, Sudlow CL, Dichgans M, Florez JC, Rosand J, Gill D, Anderson CD, et al. Mendelian randomization study of obesity and cerebrovascular disease. *Ann Neurol*. 2020;87:516–524. doi: 10.1002/ana.25686
35. Sowers JR, Khoury S, Standley P, Zemel P, Zemel M. Mechanisms of hypertension in diabetes. *Am J Hypertens*. 1991;4:177–182. doi: 10.1093/ajh/4.2.177
36. Soleimani M. Insulin resistance and hypertension: new insights. *Kidney Int*. 2015;87:497–499. doi: 10.1038/ki.2014.392
37. Ohishi M. Hypertension with diabetes mellitus: physiology and pathology. *Hypertens Res*. 2018;41:389–393. doi: 10.1038/s41440-018-0034-4
38. Ihara M, Yamamoto Y. Emerging evidence for pathogenesis of sporadic cerebral small vessel disease. *Stroke*. 2016;47:554–560. doi: 10.1161/STROKEAHA.115.009627
39. Ma Y, Song A, Viswanathan A, Blacker D, Vernooij MW, Hofman A, Papatheodorou S. Blood pressure variability and cerebral small vessel

disease: a systematic review and meta-analysis of population-based cohorts. *Stroke*. 2020;51:82–89. doi: 10.1161/STROKEAHA.119.026739
40. Jimenez-Balado J, Riba-Llena I, Maisterra O, Pizarro J, Palasi A, Pujadas F, Mundet X, Vinyoles E, Delgado P. Ambulatory blood pressure levels in the prediction of progression of cerebral small vessel disease. *J Am Geriatr Soc*. 2020;68:2232–2239. doi: 10.1111/jgs.16568
41. Marcus J, Gardener H, Rundek T, Elkind MS, Sacco RL, Decarli C, Wright CB. Baseline and longitudinal increases in diastolic blood pressure are associated with greater white matter hyperintensity volume: the northern Manhattan study. *Stroke*. 2011;42:2639–2641. doi: 10.1161/STROKEAHA.111.617571
42. Caunca MR, Simonetto M, Cheung YK, Alperin N, Lee SH, Elkind MSV, Sacco RL, Rundek T, Wright CB. Diastolic blood pressure is associated with regional white matter lesion load: the northern Manhattan study. *Stroke*. 2020;51:372–378. doi: 10.1161/STROKEAHA.119.025139
43. Otten J, Ahren B, Olsson T. Surrogate measures of insulin sensitivity vs the hyperinsulinaemic-euglycaemic clamp: a meta-analysis. *Diabetologia*. 2014;57:1781–1788. doi: 10.1007/s00125-014-3285-x
44. Lorenzo C, Haffner SM, Stancakova A, Kuusisto J, Laakso M. Fasting and OGTT-derived measures of insulin resistance as compared with the euglycemic-hyperinsulinemic clamp in nondiabetic Finnish offspring of type 2 diabetic individuals. *J Clin Endocrinol Metab*. 2015;100:544–550. doi: 10.1210/jc.2014-2299
45. Martinez-Hervas S, Argente C, Garcia-Jodar J, Priego A, Real JT, Carratala A, Carmena R, Ascaso JF. Misclassification of subjects with insulin resistance and associated cardiovascular risk factors by homeostasis model assessment index. utility of a postprandial method based on oral glucose tolerance test. *Metabolism*. 2011;60:740–746. doi: 10.1016/j.metabol.2010.07.024
46. Group SR, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116. doi: 10.1056/NEJMoa1511939
47. Group PC. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001;358:1033–1041. doi: 10.1016/S0140-6736(01)06178-5