SUPPLEMENTAL MATERIAL

Supplemental Methods

Parameterization of Main Model
The parameterization of the main model, which is a random intercept model or multi-level model, is outlined below. Covariates are not listed for clarity. *BP* represents the predictor of interest.

The Level 1 equation represents the repeated measures level, which allows us to estimate the expected mean log-transformed white matter hyperintensity volume for the *i*th region for the *j*th participant. β_{0j} represents the expected mean log-transformed white matter hyperintensity for the *j*th participant. β_{1j} represents the effect of brain region on mean log-transformed white matter hyperintensity volume. e_{ij} represents the within-subject effect (deviation of an individual's log-transformed white matter hyperintensity volume from their individual-specific mean of overall log-transformed white matter hyperintensity volume).

The Level 2 equations allow us to estimate the expected mean log-transformed white matter hyperintensity for the *j*th participant, where γ_{00} is the expected overall mean log-transformed white matter hyperintensity, γ_{01} is the expected effect of *BP* measure of interest, and r_{0j} is the random subject effect (deviation of an individual's expected mean log-transformed white matter hyperintensity from the population mean). We also specify an equation for β_{1j}, which allows us to specify a two-way interaction term between *BP* and region of interest in the combined equation.

The combined equation represents the parameterization of the simplest model (i.e. no covariates). The two-way interaction term between *BP* and region of interest allows us to examine whether the effect of *BP* measure on log-transformed white matter hyperintensity volume is different across regions of interest.

$$Level\ 1\ equation\ (repeated\ measures)\colon\ Y_{ij} = \beta_{0j} + \beta_{1j}(region_{ij}) + e_{ij}$$
$$Level\ 2\ equations\ (person)\colon \beta_{0j} = \gamma_{00} + \gamma_{01}(BP_{ij}) + r_{0j}$$
$$\beta_{1j} = \gamma_{10} + \gamma_{11}(BP_{ij})$$

$$Combined\ equation\colon Y_{ij} = \gamma_{00} + \gamma_{01}(BP_{ij}) + \gamma_{10}(region_{ij}) + \gamma_{11}(BP_{ij})(region_{ij}) + r_{0j} + e_{ij}$$

Model Selection Procedure

Step	Model Covariates	Rationale	Decision
1	age, sex, race/ethnicity, TIV, BMI, brain region, BP predictor of interest, smoking status, anti-hypertensive medication use, any physical activity, moderate alcohol consumption, diabetes, hyperlipidemia, years	Chose these covariates based on previous literature and previously published NOMAS papers. These are known covariates between BP and WMHV.	We are primarily concerned with the two-way interaction term between brain region and BP predictor of interest.

	between baseline and MRI and two-way interaction term between brain region and BP predictor of interest		
2	age, sex, race/ethnicity, TIV, BMI, brain region, BP predictor of interest, smoking status, anti-hypertensive medication use, any physical activity, moderate alcohol consumption, diabetes, hyperlipidemia, years between baseline and MRI and two-way interaction terms between all of the above and brain region	We are concerned about whether the other covariates might have differential associations with WMHV by region, so we added two-way interaction terms between all of the above and brain region.	We kept two-way interaction terms that had a p-value<0.05. These covariates were: age, sex, race/ethnicity, TIV, anti-hypertensive medication use, smoking status, diabetes, and years between baseline and MRI.
3	age, sex, race/ethnicity, TIV, BMI, brain region, BP predictor of interest, smoking status, anti-hypertensive medication use, any physical activity, moderate alcohol consumption, diabetes, hyperlipidemia, years between baseline and MRI, two-way multiplicative interaction terms between brain region and age, sex, race/ethnicity, TIV, anti-hypertensive medication use, smoking status, diabetes, years between baseline and MRI, and BP predictor of interest	This model included our covariates of interest based on previous literature and work in NOMAS, as well as two-way interaction terms that were significant in a fully-adjusted model (Step 2 above).	This was our final model.

Covariate Measurement

We chose known confounders of the association of interest *a priori* as covariates, which were measured at study entry. Standardized questionnaires based on the CDC Behavioral Risk Factor Surveillance System were used to collect self-reported demographic, medical, and risk factor data. Participants self-reported their age, sex, and race/ethnicity in response to questions based on the US Census. Smoking status was self-reported as never (reference), current, or former. Physical activity was measured using a questionnaire adapted from the National Health Interview Survey of the National Center for Health Statistics[1]. Moderate alcohol consumption was measured using a modified Block National Cancer Institute Food Frequency questionnaire[2],

and defined as current drinking of >1 drink per month up to 2 drinks per day as previously described[3]. All medication use was self-reported. Anthropomorphic measurements, including height and weight, were obtained using standardized protocols as previously described[4]. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Diabetes was defined as fasting serum glucose level >126 mg/dL or self-reported history of diabetes[5]. Hypercholesterolemia was defined as total cholesterol of >200 mg/dL or self-reported lipid-lowering medication use. Years between the original NOMAS baseline and MRI visit were computed for each participant.

Rationale for and Calculation of Stabilized Inverse Probability of Selection Weights and Weighted Analysis

By selecting participants who had regional white matter lesion load data available, we are effectively conditioning on survival to the MRI sub-study and thus introducing selection bias into our estimates[6,7]. This selection process is illustrated by the directed acyclic graph above. By using inverse probability of selection weights[8], we can estimate the associations of interest in the pseudo-population of original NOMAS cohort participants, i.e. the entire original NOMAS cohort survived to the MRI sub-study.

Predicted probabilities of selection were computed using binary logistic regression models adjusted for the following covariates: age, sex, race/ethnicity, anti-hypertensive medication use, BMI, any physical activity, history of cardiac disease, education, marital status, diabetes mellitus, hypertension, hypercholesterolemia, diabetes medication use, and cholesterol medication use. Stabilized inverse probability of selection weights were calculated as the predicted probability of selection divided by the predicted probability of selection conditional on covariates[8] and truncated at 1% to further stabilize the weights. Weighted analyses were conducted using generalized estimating equations with an independent correlation structure that use robust variance estimators, accounting for the induced within-subject correlation due to the weights[9].

Supplemental Tables

Supplemental Table I. Comparison of Original NOMAS Cohort Members and Household Members

	Original Members (N=1025)	Household Members (N=180)	*P*
Sociodemographic variables			
Women, n (%)	619 (60)	120 (67)	0.111
Age (years), mean (SD)	64 (8)	63 (9)	0.131
Age categories, n (%)			
<65 years old	555 (54)	104 (58)	0.367
65+ years old	470 (46)	76 (42)	
Race/ethnicity, n (%)			
Non-Hispanic White	152 (15)	21 (12)	0.002
Non-Hispanic Black	191 (19)	18 (10)	
Hispanic/Latino	657 (64)	140 (78)	
Other	25 (2)	1 (1)	
Years between Baseline and MRI, mean (SD)	7 (2)	0 (0)	<.0001
Clinical variables			
Systolic blood pressure, mmHg, mean (SD)	141 (20)	132 (17)	<.0001
SBP categories			
<120 mmHg, n(%)	104 (10)	37 (21)	<.0001
120-129 mmHg, n(%)	173 (17)	39 (22)	
130-139 mmHg, n(%)	217 (21)	49 (27)	
140+ mmHg, n(%)	531 (52)	55 (31)	
Diastolic blood pressure, mmHg, mean (SD)	84 (11)	78 (9)	<.0001
DBP categories			
<80 mmHg, n(%)	290 (28)	100 (56)	<.0001
80-90 mmHg, n(%)	381 (37)	60 (33)	
90+ mmHg, n(%)	354 (35)	20 (11)	
Pulse pressure, mmHg, mean (SD)	57 (16)	54 (14)	0.015
Mean arterial pressure, mmHg, mean (SD)	103 (12)	96 (11)	<.0001
Body mass index, kg/m^2, mean (SD)	28 (5)	29 (5)	0.006
Anti-hypertensive medication use, n (%)	396 (39)	94 (53)	0.001
Diabetes mellitus, n (%)	188 (18)	42 (23)	0.116

Hypercholesterolemia, n (%)	650 (63)	131 (73)	0.015
Health behaviors			
Smoking status, n (%)			
Current	155 (15)	27 (15)	
Former	386 (38)	64 (36)	0.843
Never	484 (47)	89 (49)	
Any physical activity, n (%)	578 (56)	76 (46)	0.011
Moderate alcohol consumption, n (%)	398 (39)	91 (51)	0.003
Brain MRI variables			
Total intracranial volume, mL, mean (SD)	1152 (123)	1146 (117)	0.544
Total WMHV, mL, median (q1, q3)	4.39 (2.56, 9.04)	2.87 (1.74, 5.31)	<.0001
Regional WMHV, mL, median (q1, q3)			
Frontal	0.83 (0.59, 1.31)	0.83 (0.63, 1.13)	0.925
Temporal	0.31 (0.23, 0.42)	0.33 (0.26, 0.42)	0.054
Parietal	0.29 (0.19, 0.48)	0.25 (0.17, 0.37)	0.013
Occipital	0.08 (0.05, 0.14)	0.07 (0.05, 0.13)	0.377
Anterior periventricular	1.47 (0.72, 3.18)	0.97 (0.54, 1.81)	<.0001
Posterior periventricular	2.01 (1.13, 3.96)	1.48 (0.91, 2.58)	<.0001

P-values obtained from chi-squared tests for categorical variables, one-way ANOVAs for normally distributed variables, and Wilcoxon rank-sum test for non-normally distributed variables.

Supplemental Table II. Re-Analysis of the Association between Systolic and Diastolic Blood Pressure Levels with Regional White Matter Lesion Load, Weighted by Stabilized Inverse Probability of Selection Weights, In Subsample of Participants Recruited from the Original NOMAS Cohort (N=1022*)

Systolic Blood Pressure Levels				
	beta	LCL	UCL	*P*
Frontal				
<120 mmHg	-17.276	-31.423	-0.210	0.047
120-129 mmHg	-5.178	-16.960	8.275	0.432
130-139 mmHg	-8.114	-19.406	4.762	0.206
Parietal				
<120 mmHg	-14.057	-26.858	0.985	0.066
120-129 mmHg	1.522	-10.779	15.519	0.819
130-139 mmHg	2.403	-9.278	15.587	0.701
Temporal				
<120 mmHg	-8.540	-22.315	7.677	0.284
120-129 mmHg	-1.068	-10.609	9.490	0.836
130-139 mmHg	-5.813	-14.371	3.601	0.218
Anterior PV				
<120 mmHg	-12.212	-29.438	9.220	0.243
120-129 mmHg	-10.652	-25.281	6.841	0.217
130-139 mmHg	-0.371	-13.930	15.325	0.960
Posterior PV				
<120 mmHg	-12.785	-26.705	3.779	0.123
120-129 mmHg	3.061	-10.164	18.231	0.667
130-139 mmHg	10.553	-3.524	26.684	0.149
Occipital				
<120 mmHg	9.434	-5.429	26.633	0.226
120-129 mmHg	-4.549	-12.113	3.666	0.269
130-139 mmHg	-1.497	-8.765	6.349	0.700

Diastolic Blood Pressure Levels				
	beta	LCL	UCL	*P*
Frontal				
<80 mmHg	-19.865	-30.768	-7.245	0.003
80-90 mmHg	-11.040	-21.542	0.868	0.068
Parietal				
<80 mmHg	-18.820	-29.162	-6.968	0.003
80-90 mmHg	-6.767	-16.708	4.360	0.223
Temporal				
<80 mmHg	-4.252	-13.884	6.456	0.422
80-90 mmHg	2.480	-6.490	12.312	0.600
Anterior PV				
<80 mmHg	-25.149	-36.171	-12.222	<0.001
80-90 mmHg	-14.257	-25.290	-1.595	0.029
Posterior PV				
<80 mmHg	-19.608	-30.068	-7.583	0.002
80-90 mmHg	-15.239	-24.965	-4.253	0.008
Occipital				
<80 mmHg	-2.145	-9.897	6.274	0.607
80-90 mmHg	-6.784	-12.561	-0.626	0.031

Pulse Pressure (z-score)				
	beta	LCL	UCL	*P*
Frontal	-1.188	-6.659	4.603	0.681
Parietal	-2.474	-7.026	2.300	0.304
Temporal	2.185	-2.267	6.840	0.342

Mean Arterial Pressure (z-score)				
	beta	LCL	UCL	*P*
Frontal	10.864	4.586	17.520	0.001
Parietal	8.697	3.362	14.307	0.001
Temporal	3.535	-1.011	8.291	0.129

Anterior PV	0.119	-5.940	6.569	0.970	***Anterior PV***	13.992	6.439	22.081	<0.001
Posterior PV	-0.972	-5.948	4.268	0.711	***Posterior PV***	11.022	5.157	17.214	<0.001
Occipital	-0.564	-3.586	2.553	0.719	***Occipital***	1.160	-2.378	4.825	0.526

*3 missing weights due to missing covariates. Generalized estimating equations used to generate estimates and robust standard errors. Beta coefficients and 95% confidence are transformed such that they represent the expected percent change in WMHV for each category, compared to SBP 140+ mmHg or DBP 90+ mmHg. Model adjusted for age at study entry, sex, race/ethnicity, total intracranial volume (TIV), region (ref=occipital), anti-hypertensive medication use, baseline BMI, baseline smoking status, baseline physical activity, baseline moderate alcohol consumption, years between baseline and MRI, region*age, region*sex, region*race/ethnicity, region*TIV, region* anti-hypertensive medication use, region*smoking status, and region*years between baseline and MRI.

Supplemental Table III. Re-Analysis of the Association between Systolic and Diastolic Blood Pressure Levels with Regional White Matter Lesion Load, Among Original NOMAS Members (N=1025)

Systolic Blood Pressure Levels				
	beta	LCL	UCL	*P*
Frontal				
<120 mmHg	-11.675	-24.204	2.925	0.112
120-129 mmHg	-5.657	-16.726	6.885	0.360
130-139 mmHg	-6.008	-15.843	4.977	0.272
Parietal				
<120 mmHg	-9.157	-22.043	5.858	0.218
120-129 mmHg	0.157	-11.595	13.471	0.980
130-139 mmHg	2.876	-7.889	14.899	0.615
Temporal				
<120 mmHg	-5.797	-19.160	9.774	0.444
120-129 mmHg	-2.318	-13.780	10.667	0.713
130-139 mmHg	-4.632	-14.611	6.513	0.400
Anterior PV				
<120 mmHg	-7.758	-20.843	7.489	0.301
120-129 mmHg	-9.339	-19.977	2.712	0.124
130-139 mmHg	-3.182	-13.313	8.133	0.566
Posterior PV				
<120 mmHg	-9.227	-22.103	5.777	0.215
120-129 mmHg	0.264	-11.501	13.592	0.967
130-139 mmHg	4.178	-6.723	16.353	0.468
Occipital				
<120 mmHg	4.111	-9.601	19.902	0.576
120-129 mmHg	-2.864	-13.409	8.965	0.620
130-139 mmHg	-1.101	-10.649	9.467	0.831

Diastolic Blood Pressure Levels				
	beta	LCL	UCL	*P*
Frontal				
<80 mmHg	-11.998	-21.337	-1.550	0.026
80-90 mmHg	-3.255	-12.495	6.960	0.518
Parietal				
<80 mmHg	-10.581	-20.070	0.035	0.051
80-90 mmHg	-0.528	-10.028	9.975	0.918
Temporal				
<80 mmHg	-1.112	-11.606	10.628	0.845
80-90 mmHg	5.030	-5.001	16.120	0.338
Anterior PV				
<80 mmHg	-22.971	-31.146	-13.827	0.000
80-90 mmHg	-12.561	-20.912	-3.328	0.009
Posterior PV				
<80 mmHg	-15.207	-24.205	-5.140	0.004
80-90 mmHg	-9.773	-18.390	-0.245	0.045
Occipital				
<80 mmHg	-1.245	-10.979	9.553	0.813
80-90 mmHg	-6.124	-14.381	2.931	0.179

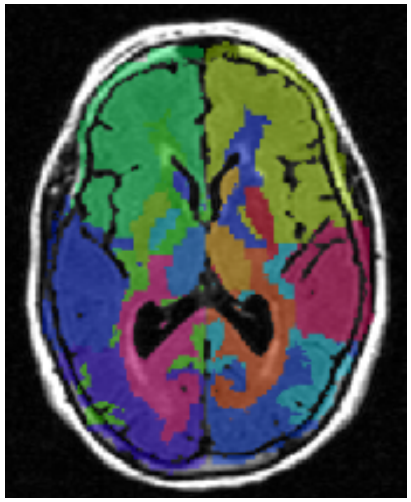
Pulse Pressure (z-score)				
	beta	LCL	UCL	*P*
Frontal	1.097	-3.407	5.811	0.639
Parietal	-0.900	-5.315	3.721	0.697
Temporal	2.320	-2.239	7.091	0.324
Anterior PV	0.627	-3.856	5.319	0.788

Mean Arterial Pressure (z-score)				
	beta	LCL	UCL	*P*
Frontal	6.857	2.110	11.823	0.004
Parietal	5.034	0.368	9.916	0.034
Temporal	1.741	-2.778	6.471	0.456
Anterior PV	11.952	6.979	17.156	0.000

Posterior PV	0.271	-4.196	4.947	0.907	***Posterior PV***	8.213	3.407	13.243	0.001
Occipital	-0.310	-4.397	3.952	0.885	***Occipital***	1.453	-2.703	5.787	0.499

Beta coefficients and 95% confidence are transformed such that they represent the expected percent change in WMHV for each category, compared to SBP 140+ mmHg or DBP 90+ mmHg. Model adjusted for age at study entry, sex, race/ethnicity, total intracranial volume (TIV), region (ref=occipital), anti-hypertensive medication use, baseline BMI, baseline smoking status, baseline physical activity, baseline moderate alcohol consumption, years between baseline and MRI, region*age, region*sex, region*race/ethnicity, region*TIV, region* anti-hypertensive medication use, region*smoking status, and region*years between baseline and MRI.

Supplemental Figure I. Segmentation of Regional Lobar WMHV by FSL. Credit: Noam Alperin, PhD.



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