Blood Pressure and Heart Rate Measures Associated With Increased Risk of Covert Brain Infarction and Worsening Leukoaraiosis in Older Adults

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Objective—In people without previous stroke, covert findings on serial magnetic resonance imaging (MRI) of incident brain infarcts and worsening leukoaraiosis are associated with increased risk for ischemic stroke and dementia. We evaluated whether various measures of blood pressure (BP) and heart rate are associated with these MRI findings.

Approach and Results—In the CHS (Cardiovascular Health Study), a longitudinal cohort study of older adults, we used relative risk regression to assess the associations of mean, variability, and trend in systolic BP, diastolic BP, and heart rate measured at 4 annual clinic visits between 2 brain MRIs with incident covert brain infarction and worsening white matter grade (using a 10-point scale to characterize leukoaraiosis). We included participants who had both brain MRIs, no stroke before the follow-up MRI, and no change in antihypertensive medication status during follow-up. Among 878 eligible participants, incident covert brain infarction occurred in 15% and worsening white matter grade in 27%. Mean systolic BP was associated with increased risk for incident covert brain infarction (relative risk per 10 mm Hg, 1.28; 95% confidence interval, 1.12–1.47), and mean diastolic BP was associated with increased risk for worsening white matter grade (relative risk per 10 mm Hg, 1.45; 95% confidence interval, 1.24–1.69). These findings persisted in secondary and sensitivity analyses.

Conclusions—Elevated mean systolic BP is associated with increased risk for covert brain infarction, and elevated mean diastolic BP is associated with increased risk for worsening leukoaraiosis. These findings reinforce the importance of hypertension in the development of silent cerebrovascular diseases, but the pathophysiologic relationships to BP for each may differ.

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Key Words: blood pressure ■ heart rate ■ hypertension ■ leukoaraiosis ■ risk factors

In people without previous stroke, covert brain infarction (CBI) and leukoaraiosis are described as silent cerebrovascular diseases, but they have clinically important consequences. CBI is associated with a 2- to 4-fold increased risk of clinically defined ischemic stroke, independent of vascular risk factors, and a 2- to 3-fold increased risk of dementia.[1–4] They may also directly disrupt functional networks, leading to deficits affecting cognition, gait, and other functions.[5] Similarly, leukoaraiosis is associated with an increased risk for ischemic stroke, worse outcomes after stroke, dementia, and mortality.[6–10] Leukoaraiosis prevalence in older adults exceeds 95%, and CBI is also common: the estimated prevalence of CBI in adults over age 50 is ≈20% compared with 2% to 14% for overt ischemic stroke in the United States.[2,7] Although the American Heart Association/American Stroke Association recently published a scientific statement highlighting the importance of these conditions and the need for further studies to guide their management, optimal prevention strategies after detection of these conditions have not been established, in part because of uncertainties about their pathogenesis that may resemble or differ from ischemic stroke.[11] Furthermore, strategies for the prevention of incident CBI and worsening of leukoaraiosis have not been established. Given their high prevalence and clinical sequelae, improving the understanding of the pathogenesis of CBI and leukoaraiosis may help guide strategies for prevention of cerebrovascular diseases.

Hypertension is associated with CBI and leukoaraiosis and clinically defined ischemic stroke.[2,12–14] Both primary and secondary stroke prevention guidelines focus on absolute reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP), but some studies suggest that very aggressive BP reductions may lead to an increased risk of recurrent stroke.[15]

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Nonstandard Abbreviations and Acronyms	
BMI	body mass index
BP	blood pressure
CBI	covert brain infarction
CHS	Cardiovascular Health Study
CI	confidence interval
DBP	diastolic blood pressure
HR	heart rate
MAP	mean arterial pressure
MRI	magnetic resonance imaging
PP	pulse pressure
RR	relative risk
SBP	systolic blood pressure
WMG	white matter grade

Accordingly, investigators have sought to improve current understanding of the role of cardiovascular physiology in brain infarction by studying other measures, including variability in BP and heart rate (HR). Previous studies suggest associations of BP and HR variability with ischemic stroke, but these associations are inconsistent and depend on the time interval of measurement (beat to beat, daily, weekly, or visit to visit).[16–18] Despite these potential associations with ischemic stroke, it is not known if visit-to-visit BP and HR measures are associated with an increased risk of incident CBI or progression of leukoaraiosis.

In this study, we used data from 2 brain magnetic resonance imaging (MRIs) performed ≈5 years apart in the CHS (Cardiovascular Health Study) to assess associations of visit-to-visit cardiovascular measurements, including mean, variability, and trend in SBP, DBP, and HR, with incident CBI and progression of leukoaraiosis, building on findings from previous work based on these scans.[19,20]

Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

Results

Study Population

As detailed in Figure 1, 878 participants were eligible for the primary analysis and 1844 participants for the sensitivity analysis. Baseline characteristics and mean (SD) for the exposure variables in the primary and sensitivity analysis samples are presented in Table 1 (additional descriptive statistics for each individual analysis and a comparison to all CHS participants undergoing the first MRI are provided in the Table I in the online-only Data Supplement). Among 683 participants who completed both brain MRIs and demonstrated no infarcts on the initial MRI, 101 individuals (15%) had incident CBI. Among 793 participants with white matter grade (WMG) measurements (a 10-point scale characterizing the extent of leukoaraiosis) on both MRIs and a grade of ≤8 on the initial MRI, 215 (27%) demonstrated worsening WMG. The distributions of number of CBI, WMG, and changes in WMG are shown in Figure 2. Evaluation of the exposure variables indicated minimal correlation for most pairs and at most modest correlations for a few pairs (Table II in the online-only Data Supplement).

Primary, Secondary, and Exploratory Analyses: Association With Incident CBI and Worsening WMG

In primary analyses, mean SBP was associated with increased risk for incident CBI (relative risk [RR], 1.28; 95% confidence interval [CI], 1.12–1.47; $P<0.001$), and mean DBP was associated with increased risk for worsening WMG (RR, 1.45; 95% CI, 1.24–1.69; $P<0.001$; Table 2). An association between positive HR trend and increased risk for incident CBI was nominally significant (RR, 2.03; 95% CI, 1.11–3.72; $P=0.02$, using a conservative Bonferroni correction of $P=0.003$ to account for multiple comparisons). In exploratory analyses, mean pulse pressure (PP) was nominally associated with increased risk for incident CBI (RR, 1.22; 95% CI, 1.03–1.44; $P=0.02$), and mean arterial pressure (MAP) was nominally associated with increased risk for incident CBI (RR, 1.42; 95% CI, 1.12–1.79; $P=0.004$) and associated with worsening WMG (RR, 1.29; 95% CI, 1.12–1.48; $P<0.001$; Table 3). In secondary analyses, we observed associations between mean SBP and increased number of incident CBIs (β=0.06; 95% CI, 0.02–0.10; $P=0.002$) and between mean DBP and higher WMG (β=0.13; 95% CI, 0.07–0.19; $P<0.001$; Table III in the online-only Data Supplement). An association between positive HR trend and increased number of incident CBIs was again nominally significant (β=0.18; 95% CI, 0.01–0.34; $P=0.03$). The findings of models incorporating both SBP and DBP and both PP and MAP demonstrated similar findings except that the nominal associations between mean PP and incident CBI and between mean MAP and incident CBI were no longer significant (Tables IV and V in the online-only Data Supplement).

Sensitivity Analysis

An inclusive sensitivity analysis corroborated results of the primary analyses (Table 4). Similar to the primary and secondary analyses, associations between mean SBP and increased number of CBI (β=0.07; 95% CI, 0.04–0.09; $P<0.001$) and between mean DBP and worsening WMG (RR, 1.32; 95% CI, 1.20–1.45; $P<0.001$) remained significant. Mean DBP was also associated with increased number of CBI (β=0.13; 95% CI, 0.08–0.19; $P<0.001$). Several associations were nominally significant, including mean HR and increasing number of CBI, mean SBP and worsening WMG, DBP variability and worsening WMG, and mean HR and worsening WMG.

Stratified Analysis: Antihypertensive Medications

Stratification by antihypertensive medication use status corroborated the association between mean DBP and worsening WMG in nonusers (RR, 1.49; 95% CI, 1.23–1.79; $P<0.001$; Table VI in the online-only Data Supplement). The association between mean SBP and increased risk for incident CBI in nonusers was still present but slightly less robust (RR, 1.24; 95% CI, 1.06–1.44; $P=0.007$). There were nominally significant associations between mean DBP and increased risk for incident CBI, DBP variability and CBI, HR trend and CBI, and mean SBP and worsening WMG. All associations were

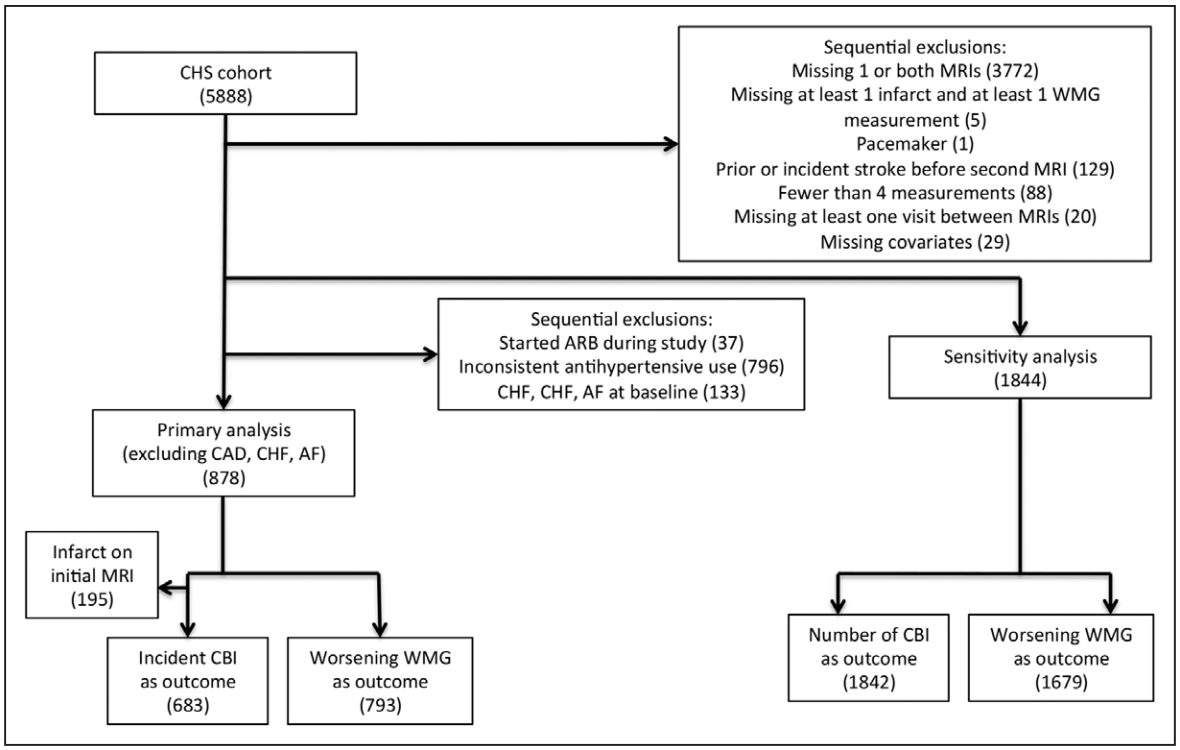

Figure 1. Flow chart of participants. AF indicates atrial fibrillation; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CHF, congestive heart failure; CHS, Cardiovascular Health Study; MRI, magnetic resonance imaging; and WMG, white matter grade.

attenuated in participants taking antihypertensive medications. When testing for interactions with antihypertensive medication use, the interactions were not statistically significant.

Discussion

Mean BP Is Associated With Incident CBI and Worsening Leukoaraiosis

In this prospective cohort study of older adults without previous stroke and cardiovascular disease, elevated mean SBP was associated with increased risk for incident CBI, and elevated mean DBP was associated with increased risk for worsening leukoaraiosis, extending previous findings from the CHS.[19,20] These associations remained robust across several secondary and sensitivity analyses incorporating adjustment for vascular risk factors and antihypertensive medication status, inclusion or exclusion of participants with previous imaging-defined infarcts (in the incident CBI analyses), and classification of the outcome as dichotomous or as counts. These findings are particularly important in the setting of potentially conflicting recommendations: the Joint National Committee advises less stringent control of hypertension in elderly adults, whereas a recent scientific statement from the American Heart Association/American Stroke Association highlights the clinical relevance of imaging-defined vascular brain injury and urges, at a minimum, initiation of stroke primary prevention measures in affected individuals.[11,21] In patients without a history of stroke, this study suggests that incident CBI and worsening leukoaraiosis could be treatment targets for control of systolic and diastolic hypertension.

Differential Associations Between Measures of Pulsatile and Steady Flow With CBI and Leukoaraiosis

Across several analyses, measures of steady blood flow (DBP and MAP) were associated with worsening leukoaraiosis. There was also a suggestion that measures of pulsatile blood flow (SBP and PP) were associated with incident CBI, although MAP was also associated with incident CBI in contrast to DBP and to a greater degree than PP. Although previous studies have reported variable associations of pulsatile and steady blood flow with different forms of imaging-defined vascular brain injury, this study provides evidence suggesting the roles of different types of hypertension in the pathogenesis of CBI and leukoaraiosis.[22–27] The more consistent finding is the relationship of measures of steady blood flow with leukoaraiosis: multiple pathophysiologic mechanisms for the development of leukoaraiosis have been postulated, but this study emphasizes that diastolic hypertension likely has a critical role. One theory is that increased peripheral arterial stiffness (represented by increased brachial DBP as a proxy for carotid DBP) in conjunction with increased aortic pulsatility may augment transmission of the effects of aortic pulsatility to the cerebral small vessels, resulting in increased endothelial shear stress and dysfunction.[23] Alternatively, diastolic hypertension may correspond with increased peripheral arterial stiffness and reduced carotid flow velocity, resulting in reduced blood flow to cerebral small vessels and local hypoperfusion, independent of atherosclerosis.[24] By contrast, on peripheral measures of pulsatile blood flow, it is hypothesized that the late-life development of atherosclerosis in intracranial arteries may

Table 1. Baseline Characteristics (Primary Analyses and Sensitivity Analyses)

Characteristic	Primary Analysis, Mean SD or n (%)	Sensitivity Analysis, Mean SD or n (%)
Total number of participants	878	1844
Age (y, at follow-up MRI)	73.5 (4.2)	74.0 (4.4)
Sex (male)	315 (36.0%)	734 (39.8%)
Race (black)	111 (12.6%)	274 (14.9%)
Body mass index	26.1 (4.1)	26.7 (4.3)
Smoking status		
Never smoker	429 (48.9%)	867 (47.0%)
Former smoker	365 (41.6%)	823 (44.6%)
Current smoker	84 (9.6%)	154 (8.4%)
Diabetes mellitus	69 (7.9%)	223 (12.1%)
CHS Clinic		
North Carolina	197 (22.4%)	435 (23.6%)
California	281 (32.0%)	547 (29.7%)
Maryland	165 (18.8%)	362 (19.6%)
Pennsylvania	235 (26.8%)	500 (27.1%)
Antihypertensive medications	236 (26.9%)	711 (38.6%)
Interval between MRI scans, d	1808.9±215	1827.2±217
MRI findings		
Incident covert brain infarct	101/683 (14.8%)	N/A
Worsening white matter grade	215/793 (27.1%)	472 (28.1%)
Systolic blood pressure		
Mean, mm Hg	129.8 (15.0)	133.1 (16.2)
Variability	7.4 (4.5)	8.3 (5.4)
Trend	0.6 (3.4)	−0.1 (4.2)
Diastolic blood pressure		
Mean, mm Hg	68.8 (7.9)	68.9 (8.7)
Variability	4.5 (3.2)	4.9 (3.5)
Trend	−0.39 (2.2)	−0.8 (2.5)
Heart rate		
Mean (bpm)	63.7 (8.2)	63.4 (8.7)
Variability	3.8 (2.6)	4.1 (3.2)
Trend	0.1 (2.5)	0.1 (2.6)

CHS indicates Cardiovascular Health Study; and MRI, magnetic resonance imaging.

arise in conjunction with increased peripheral PP.[28] This study may support that hypothesis and may implicate atherosclerotic pathologies in the development of CBI. In light of these differential associations and the clinical significance of these conditions, future studies in the treatment of hypertension in adults (such as those in the CHS) should include incident CBI and worsening leukoaraiosis as distinct outcomes from one another and from clinically defined ischemic stroke.

HR Trend and Increased Risk for CBI

We did find an association between positive HR trend and incident CBI, although its risk estimate has a moderately wide CI and its *P* value did not reach significance with a conservative Bonferroni correction. This association persisted through almost all analyses, including the stratified analyses. To our knowledge, an association between visit-to-visit HR trend and cerebrovascular outcomes has not been previously described. Although mechanisms of vascular injury because of hypertension have been rigorously studied, it is less certain how changes in HR would lead to vascular brain injury. It is possible that this association may reflect a downstream or compensatory response to other changes in vascular biology that more directly lead to increased risk for CBI.

Other BP and HR Measures Are not Consistently Associated With Incident CBI or Worsening Leukoaraiosis

In this study, variability and trend of SBP and DBP and mean and variability of HR were not consistently associated with CBI or worsening WMG: some demonstrated nominal statistical significance in the most inclusive sensitivity analysis, but these findings were unstable across analyses with exclusions aimed at reducing confounding. Although HR mean and visit-to-visit variability were associated with mortality in a previous CHS analysis, we did not find a consistent relationship between these measures and covert imaging-defined vascular brain injury.[29] The lack of association between SBP or DBP visit-to-visit variability and CBI is notable because it may suggest that CBI and clinically defined ischemic stroke have different relationships with BP variability.[16–18]

Role of Antihypertensive Medication Use

We assessed the potential for effect modification by antihypertensive medication use by stratifying study participants into users and nonusers of a stable medication regimen. Although the interactions in the full primary analysis sample were not statistically significant, we found that the associations between our primary exposure variables and incident CBI and worsening leukoaraiosis seemed to persist in the stratum of nonusers. Interpretation of the lack of association in the stratum of medication users is less certain because of a low sample size and an absence of medication dosage and administration timing data in this study, both of which would tend to increase the variability of exposure among medication users. Future clinical trials may be useful to determine whether there is a beneficial effect of antihypertensives on imaging-defined vascular brain injury.

Strengths and Limitations

Our study has several strengths, including standardized BP and HR measurements at structured annual study visits, central adjudication of clinical events, centralized analysis of MRI scans with characterization of infarcts and WMG, and high-quality data on vascular risk factors collected prospectively. In addition, this study population of healthy older adults offers an opportunity to establish these associations with relatively minimal confounding.

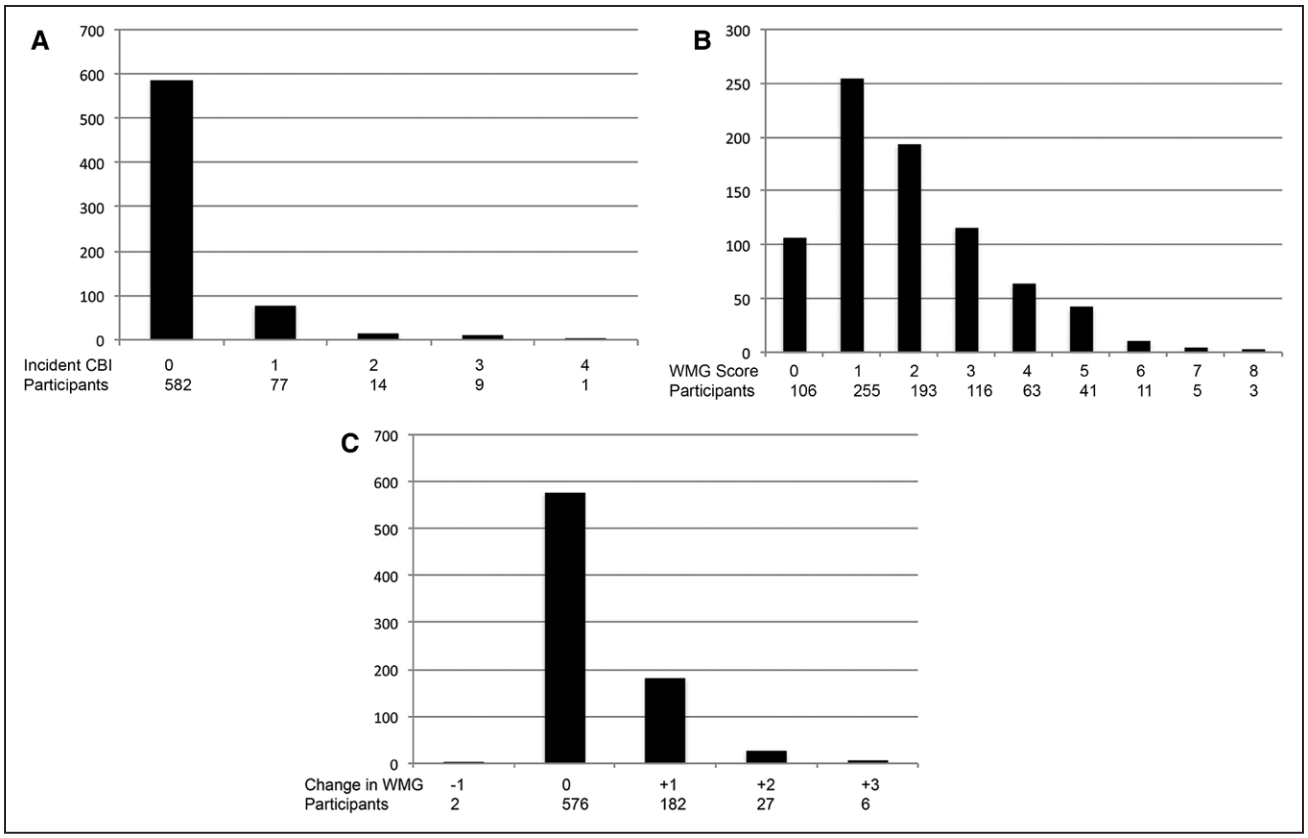

Figure 2. Incident covert brain infarcts (CBI) and white matter grade (WMG) on the follow-up magnetic resonance imaging (MRI). **A**, Distribution of number of incident CBI on the follow-up MRI. **B**, Distribution of WMG on the follow-up MRI. **C**, Distribution of changes in WMG on the follow-up MRI.

Our study had several limitations. First, it was limited to participants who underwent 2 brain MRIs according to the CHS protocol, an exclusion that reduced our study sample size and likely introduced a selection bias. Having no MRI or only a single MRI was the most frequent reason for exclusion from this analysis, which resulted from loss to follow-up, death, and various other reasons. Previous studies of the CHS demonstrated that participants who underwent brain MRI scans were healthier than those who did not, and those who underwent both brain MRIs were healthier than those that only underwent a single scan.[19,20,30] Accordingly, our study may underestimate the frequency of incident CBI and worsening WMG.

Second, the sample size for the primary analyses was also limited because of the exclusions of participants with

Table 2. Relationships of SBP, DBP, and HR to Dichotomous Outcomes: Incident CBI and Worsening WMG

	SBP (10 Points mm Hg)		DBP (10 Points mm Hg)		HR (10 bpm)	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
Incident CBI (n=683)						
Mean	1.28 (1.12, 1.47)	<0.001	1.30 (0.99, 1.71)	0.06	1.17 (0.93, 1.47)	0.19
Variability	0.89 (0.60, 1.31)	0.54	1.56 (0.95, 2.56)	0.08	0.81 (0.42, 1.56)	0.54
Trend	0.65 (0.39, 1.07)	0.09	0.94 (0.34, 2.62)	0.90	2.03 (1.11, 3.72)	0.02
Worsening WMG (n=793)						
Mean	1.09 (1.00, 1.20)	0.06	1.45 (1.24, 1.69)	<0.001	1.10 (0.95, 1.28)	0.19
Variability	0.97 (0.72, 1.31)	0.83	1.26 (0.85, 1.86)	0.25	1.19 (0.78, 1.82)	0.43
Trend	1.10 (0.77, 1.57)	0.62	0.98 (0.56, 1.72)	0.95	1.13 (0.73, 1.74)	0.58

Visit-to-visit mean was calculated from 4 annual measurements. Visit-to-visit trend was calculated using linear regression (slope). Visit-to-visit variability was calculated from the SD of the residuals of the linear regression. Relative risks (RRs) and 95% confidence intervals (CIs) estimated from RR regression model adjusted for age, sex, race, clinic location, smoking status, BMI, diabetes mellitus, time between magnetic resonance imaging scans, and antihypertensive medication status. RRs are presented for mean, variability, and trend per 10 points of mm Hg for systolic blood pressure (SBP) and diastolic blood pressure (DBP) and 10 bpm of heart rate (HR). The Bonferroni corrected *P* value is 0.003. CBI indicates covert brain infarction; and WMG, white matter grade.

Table 3. Relationships of PP and MAP to Dichotomous Outcomes: Incident CBI and Worsening WMG

	PP (10 Points mm Hg)		MAP (10 Points mm Hg)	
	RR (95% CI)	*P* Value	RR (95% CI)	*P* Value
Incident CBI (n=683)				
Mean	1.22 (1.03, 1.44)	0.02	1.42 (1.12, 1.79)	0.004
Variability	1.13 (0.75, 1.71)	0.55	1.15 (0.67, 1.97)	0.61
Trend	0.63 (0.34, 1.14)	0.13	0.63 (0.26, 1.53)	0.31
Worsening WMG (n=793)				
Mean	0.98 (0.88, 1.10)	0.74	1.29 (1.12, 1.48)	<0.001
Variability	1.04 (0.77, 1.41)	0.81	1.12 (0.74, 1.69)	0.60
Trend	1.15 (0.77, 1.71)	0.51	1.07 (0.62, 1.86)	0.80

Visit-to-visit mean was calculated from 4 annual measurements. Visit-to-visit trend was calculated using linear regression (slope). Visit-to-visit variability was calculated from the SD of the residuals of the linear regression. Relative risks (RRs) and 95% confidence intervals (CIs) estimated from RR regression model adjusted for age, sex, race, clinic location, smoking status, BMI, diabetes mellitus, time between magnetic resonance imaging scans, and antihypertensive medication status. RRs are presented for mean, variability, and trend per 10 points of mm Hg for pulse pressure and mean arterial pressure. The Bonferroni corrected *P* value is 0.003. CBI indicates covert brain infarction; MAP, mean arterial pressure; PP, pulse pressure; and WMG, white matter grade.

baseline coronary artery disease, congestive heart failure, and atrial fibrillation. We were concerned about the relationships between these cardiovascular conditions and our primary exposures of interest: all could be confounders or mediators of the association of these exposures on incident CBI and worsening WMG. We chose to exclude these individuals from the primary analyses and include them in a sensitivity analysis. The β coefficients and risk estimates in the sensitivity analysis did not change substantially, suggesting that these conditions may be minor confounders or mediators. Nonetheless, the main findings of this study, the associations between mean SBP and incident CBI and between mean DBP and worsening leukoaraiosis, were not affected substantially by these conditions.

Third, our study focused on annual measurements and cannot detect potential associations between shorter intervals of BP and HR measurements and the outcomes.

Finally, our analysis involved multiple comparisons with potentially nonindependent exposure variables and outcomes; if these were all independent, we would expect 1 significant finding by chance alone among 18 tests of interest. Because a Bonferroni correction may inadvertently obscure meaningful associations if the exposures or outcomes are not independent, we elected to present both

Table 4. Sensitivity Analysis: Relationships of SBP, DBP, and HR to Number of CBI and Worsening WMG Without Exclusions for Previous CBI, Changing Antihypertensive Status, or Cardiovascular Comorbidities

	SBP (10 Points mm Hg)		DBP (10 Points mm Hg)		HR (10 bpm)	
	β	*P* Value	β	*P* Value	β	*P* Value
No. of CBI (n=1842)						
Mean	0.07 (0.04, 0.09)	<0.001	0.13 (0.08, 0.19)	<0.001	0.06 (0.009, 0.10)	0.02
Variability	0.05 (–0.04, 0.13)	0.28	0.12 (0.001, 0.24)	0.05	–0.04 (–0.16, 0.07)	0.47
Trend	–0.001 (–0.10, 0.10)	0.98	0.03 (–0.13, 0.20)	0.69	0.13 (–0.02, 0.27)	0.09
Worsening WMG (n=1679)						
Mean	1.06 (1.00, 1.12)	0.04	1.32 (1.20, 1.45)	<0.001	1.10 (1.00, 1.20)	0.04
Variability	1.03 (0.88, 1.20)	0.72	1.30 (1.05, 1.62)	0.02	1.09 (0.89, 1.32)	0.41
Trend	1.07 (0.88, 1.32)	0.49	1.06 (0.76, 1.47)	0.66	1.01 (0.76, 1.34)	0.96

Visit-to-visit mean was calculated from 4 annual measurements. Visit-to-visit trend was calculated using linear regression (slope). Visit-to-visit variability was calculated from the SD of the residuals of the linear regression. Covert brain infarction (CBI) analysis: β coefficients and 95% confidence intervals (CIs) estimated from linear regression model adjusted for age, sex, race, clinic location, smoking status, BMI, diabetes mellitus, time between magnetic resonance imaging (MRI) scans, and antihypertensive medication status (always, never, variable). White matter grade (WMG) analysis: relative risks (RRs) and 95% confidence intervals (CIs) estimated from RR regression model adjusted for age, sex, race, clinic location, smoking status, BMI, diabetes mellitus, time between MRI scans, and antihypertensive medication status (always, never, variable). RRs are presented for mean, variability, and trend per 10 points of mm Hg for systolic blood pressure (SBP) and diastolic blood pressure (DBP) and 10 bpm of heart rate (HR). The Bonferroni corrected *P* value is 0.003.

uncorrected *P* values and a formal Bonferroni threshold for comparison.

Conclusions

In summary, this study provides evidence that systolic hypertension is associated with increased risk for CBI, and diastolic hypertension is associated with increased risk for leukoaraiosis. Combining these findings with previous studies, these differential associations could suggest differences in pathophysiologic mechanisms underlying CBI, leukoaraiosis, and clinically defined ischemic stroke.[16–18] Given the clinical significance of silent cerebrovascular diseases, these findings suggest a need to reevaluate the balance of benefits and risks of controlling systolic and diastolic hypertension in elderly adults. These findings need to be confirmed in other populations, including younger adults, and clinical trials may better establish the potential effect of antihypertensive medications on the risk of incident CBI and worsening leukoaraiosis.

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Disclosures

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References

1. Fanning JP, Wesley AJ, Wong AA, Fraser JF. Emerging spectra of silent brain infarction. *Stroke*. 2014;45:3461–3471. doi: 10.1161/STROKEAHA.114.005919.
2. Fanning JP, Wong AA, Fraser JF. The epidemiology of silent brain infarction: a systematic review of population-based cohorts. *BMC Med*. 2014;12:119. doi: 10.1186/s12916-014-0119-0.
3. Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol*. 2007;6:611–619. doi: 10.1016/S1474-4422(07)70170-9.
4. Gupta A, Giambrone AE, Gialdini G, Finn C, Delgado D, Gutierrez J, Wright C, Beiser AS, Seshadri S, Pandya A, Kamel H. Silent brain infarction and risk of future stroke: a systematic review and meta-analysis. *Stroke*. 2016;47:719–725. doi: 10.1161/STROKEAHA.115.011889.
5. Price TR, Manolio TA, Kronmal RA, Kittner SJ, Yue NC, Robbins J, Anton-Culver H, O'Leary DH. Silent brain infarction on magnetic resonance imaging and neurological abnormalities in community-dwelling older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. *Stroke*. 1997;28:1158–1164.
6. Arba F, Palumbo V, Boulanger JM, Pracucci G, Inzitari D, Buchan AM, Hill MD; CASES Investigators. Leukoaraiosis and lacunes are associated with poor clinical outcomes in ischemic stroke patients treated with intravenous thrombolysis. *Int J Stroke*. 2016;11:62–67. doi: 10.1177/1747493015607517.
7. Kuller LH, Longstreth WT Jr, Arnold AM, Bernick C, Bryan RN, Beauchamp NJ Jr; Cardiovascular Health Study Collaborative Research Group. White matter hyperintensity on cranial magnetic resonance imaging: a predictor of stroke. *Stroke*. 2004;35:1821–1825. doi: 10.1161/01.STR.0000132193.35955.69.
8. Moghekar A, Kraut M, Elkins W, Troncoso J, Zonderman AB, Resnick SM, O'Brien RJ. Cerebral white matter disease is associated with Alzheimer pathology in a prospective cohort. *Alzheimers Dement*. 2012;8(suppl 5):S71–S77. doi: 10.1016/j.jalz.2012.04.006.
9. Carmichael O, Schwarz C, Drucker D, Fletcher E, Harvey D, Beckett L, Jack CR Jr, Weiner M, DeCarli C; Alzheimer's Disease Neuroimaging Initiative. Longitudinal changes in white matter disease and cognition in the first year of the Alzheimer disease neuroimaging initiative. *Arch Neurol*. 2010;67:1370–1378. doi: 10.1001/archneurol.2010.284.
10. Kuller LH, Arnold AM, Longstreth WT Jr, Manolio TA, O'Leary DH, Burke GL, Fried LP, Newman AB. White matter grade and ventricular volume on brain MRI as markers of longevity in the cardiovascular health study. *Neurobiol Aging*. 2007;28:1307–1315. doi: 10.1016/j.neurobiolaging.2006.06.010.
11. Smith EE, Saposnik G, Biessels GJ, Doubal FN, Fornage M, Gorelick PB, Greenberg SM, Higashida RT, Kasner SE, Seshadri S; American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Functional Genomics and Translational Biology; and Council on Hypertension. Prevention of stroke in patients with silent cerebrovascular disease: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2017;48:e44–e71. doi: 10.1161/STR.0000000000000116.
12. Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. *Stroke*. 2002;33:21–25.
13. Gottesman RF, Coresh J, Catellier DJ, Sharrett AR, Rose KM, Coker LH, Shibata DK, Knopman DS, Jack CR, Mosley TH Jr. Blood pressure and white-matter disease progression in a biethnic cohort: Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2010;41:3–8. doi: 10.1161/STROKEAHA.109.566992.
14. Bernick C, Kuller L, Dulberg C, Longstreth WT Jr, Manolio T, Beauchamp N, Price T; Cardiovascular Health Study Collaborative Research Group. Silent MRI infarcts and the risk of future stroke: the cardiovascular health study. *Neurology*. 2001;57:1222–1229. doi: 10.1212/WNL.57.7.1222.
15. Ovbiagele B, Diener HC, Yusuf S, Martin RH, Cotton D, Vinisko R, Donnan GA, Bath PM; PROFESS Investigators. Level of systolic blood pressure within the normal range and risk of recurrent stroke. *JAMA*. 2011;306:2137–2144. doi: 10.1001/jama.2011.1650.
16. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010;375:895–905. doi: 10.1016/S0140-6736(10)60308-X.
17. Shimbo D, Newman JD, Aragaki AK, LaMonte MJ, Bavry AA, Allison M, Manson JE, Wassertheil-Smoller S. Association between annual visit-to-visit blood pressure variability and stroke in postmenopausal women: data from the Women's Health Initiative. *Hypertension*. 2012;60:625–630. doi: 10.1161/HYPERTENSIONAHA.112.193094.
18. Muntner P, Whittle J, Lynch AI, Colantonio LD, Simpson LM, Einhorn PT, Levitan EB, Whelton PK, Cushman WC, Louis GT, Davis BR, Oparil S. Visit-to-visit variability of blood pressure and coronary heart disease, stroke, heart failure, and mortality: a cohort study. *Ann Intern Med*. 2015;163:329–338. doi: 10.7326/M14-2803.
19. Longstreth WT Jr, Dulberg C, Manolio TA, Lewis MR, Beauchamp NJ Jr, O'Leary D, Carr J, Furberg CD. Incidence, manifestations, and predictors of brain infarcts defined by serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke*. 2002;33:2376–2382.
20. Longstreth WT Jr, Arnold AM, Beauchamp NJ Jr, Manolio TA, Lefkowitz D, Jungreis C, Hirsch CH, O'Leary DH, Furberg CD. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke*. 2005;36:56–61. doi: 10.1161/01.STR.0000149625.99732.69.
21. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507–520. doi: 10.1001/jama.2013.284427.
22. Gutierrez J, Elkind MS, Cheung K, Rundek T, Sacco RL, Wright CB. Pulsatile and steady components of blood pressure and subclinical cerebrovascular disease: the Northern Manhattan Study. *J Hypertens*. 2015;33:2115–2122. doi: 10.1097/HJH.0000000000000686.
23. Webb AJ, Simoni M, Mazzucco S, Kuker W, Schulz U, Rothwell PM. Increased cerebral arterial pulsatility in patients with leukoaraiosis: arterial

stiffness enhances transmission of aortic pulsatility. *Stroke*. 2012;43:2631–2636. doi: 10.1161/STROKEAHA.112.655837.
24. Turk M, Zaletel M, Pretnar-Oblak J. Ratio between carotid artery stiffness and blood flow - a new ultrasound index of ischemic leukoaraiosis. *Clin Interv Aging*. 2016;11:65–71. doi: 10.2147/CIA.S94163.
25. 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.
26. Zhang C, Wang Y, Zhao X, Wang C, Liu L, Pu Y, Zou X, Pan Y, Du W, Li Z, Jing J, Wang D, Luo Y, Wong KS, Wang Y; Chinese IntraCranial AtheroSclerosis Study Group. Factors associated with severity of leukoaraiosis in first-ever lacunar stroke and atherosclerotic ischemic stroke patients. *J Stroke Cerebrovasc Dis*. 2014;23:2862–2868. doi: 10.1016/j.jstrokecerebrovasdis.2014.07.021.
27. Yamaguchi Y, Wada M, Sato H, Nagasawa H, Koyama S, Takahashi Y, Kawanami T, Kato T. Impact of ambulatory blood pressure variability on cerebral small vessel disease progression and cognitive decline in community-based elderly Japanese. *Am J Hypertens*. 2014;27:1257–1267. doi: 10.1093/ajh/hpu045.
28. Ritz K, Denswil NP, Stam OC, van Lieshout JJ, Daemen MJ. Cause and mechanisms of intracranial atherosclerosis. *Circulation*. 2014;130:1407–1414. doi: 10.1161/CIRCULATIONAHA.114.011147.
29. Floyd JS, Sitlani CM, Wiggins KL, Wallace E, Suchy-Dicey A, Abbasi SA, Carnethon MR, Siscovick DS, Sotoodehnia N, Heckbert SR, McKnight B, Rice KM, Psaty BM. Variation in resting heart rate over 4 years and the risks of myocardial infarction and death among older adults. *Heart*. 2015;101:132–138. doi: 10.1136/heartjnl-2014-306046.
30. Longstreth WT Jr, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, Enright PL, O'Leary D, Fried L. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke*. 1996;27:1274–1282.

Highlights

- Persistently elevated systolic blood pressure is associated with incident covert brain infarction.
- Persistently elevated diastolic blood pressure is associated with worsening leukoaraiosis.
- This suggests that hypertension is a major risk factor in the development of both forms of silent cerebrovascular diseases.
- The exact relationship of blood pressure levels and variability to cerebrovascular diseases may differ between covert brain infarction, white matter disease, and stroke, suggesting potential differences in pathophysiology.

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Blood Pressure and Heart Rate Measures Associated With Increased Risk of Covert Brain Infarction and Worsening Leukoaraiosis in Older Adults

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MATERIALS AND METHODS

Study population

We conducted a longitudinal analysis in the CHS, a prospective cohort of men and women ages 65 and older who were monitored for the development of cardiovascular disease.[1] An initial cohort of 5,201 participants was recruited from Medicare eligibility lists at four centers in California, Maryland, North Carolina, and Pennsylvania beginning in 1989-1990. A supplemental cohort of predominantly African-American participants was recruited in 1992-1993, bringing the total number of participants to 5,888.

As part of the study protocol, participants were evaluated at annual clinic visits with measurements of resting HR and blood pressure (BP) through 1998-1999, as detailed previously.[2] BP measurements were not collected at the clinic visit in 1995-1996. In all participants, SBP and DBP were obtained as the average of two seated BP measurements taken at each annual clinic visit. HR was obtained from electrocardiograms performed annually. The protocol included two brain MRI scans that occurred approximately in conjunction with the 1992-1993 and 1998-1999 visits. CHS participants were included in this analysis if they underwent both scheduled brain MRIs, had BP and HR measurements from at least four annual visits between the scans, and had no history of stroke or incident stroke prior to the follow-up MRI. For the primary analysis, to ensure that brain infarction detected on the follow-up MRI represented incident CBI, we excluded participants with CBI on the initial MRI for CBI outcomes. To

address potential confounding effects on the cardiovascular measures of interest, we excluded participants with any changes to antihypertensive medication status between the two scans, such as changing status between user and non-user or changing antihypertensive medication class. We also excluded participants with coronary artery disease (CAD), congestive heart failure (CHF), and atrial fibrillation (AF) assessed at the time of the initial MRI.

Blood pressure and heart rate measures

For our primary analyses, we evaluated three measures of BP and HR that correspond to mean, variability, and trend in SBP, DBP, and HR over time. We also calculated these measures for pulse pressure (PP) and mean arterial pressure (MAP) for an exploratory (post hoc) analysis. If participants had more than 4 measurements over time, we randomly selected 4 of their measurements. First, we calculated each participant's mean across the four visits between MRI scans. Second, we estimated each participant's trend using linear regression to determine the visit-to-visit slope within participants. Lastly, we calculated each participant's visit-to-visit variability as the standard deviation of the residuals from the linear regression. This approach is similar to the model used in a prior analysis of the CHS.[2]

Covariates

Covariate data were collected from the last clinic visit prior to the initial MRI. These variables included age, sex, race, body mass index (BMI), CHS clinic site, smoking status, diabetes, CAD, CHF, AF, time between MRI scans, and antihypertensive medication status.

Imaging outcomes

Two readers at a central coordinating center trained in the CHS protocol reviewed all brain MRIs to identify brain infarcts (size, number up to 5) and severity of leukoaraiosis graded on a scale of 0 to 9, the most severe.[3-5] Imaging definitions for infarcts were previously described: small infarcts were 3 to 20 millimeters in diameter in any direction, large infarcts were greater than 20 millimeters, infarcts were described as subcortical or cortical, and they had to have specific characteristics on T1-weighted, T2-weighted, and spin density sequences depending on lesion location to distinguish them from perivascular spaces.[6] MRIs were re-read side by side to assess change in white matter grade (WMG), with readers being unaware of which was the initial and follow-up scan; reproducibility measures have been reported previously.[4] The primary outcomes were any incident CBI or any worsening WMG on the follow-up MRI, using criteria similar to prior analyses of the serial MRIs.[3-4] The secondary outcomes were the number of incident CBI and the WMG on the follow-up MRI. In the sensitivity analysis, the primary outcomes were number of incident CBI (as participants with infarcts on the initial MRI were included) and any worsening WMG on the follow-up MRI.

Statistical analysis

Baseline characteristics were described using means and standard deviations (SD) for continuous variables and counts and percentages for categorical variables. Pairwise correlation coefficients were calculated to examine the relationship between mean, variability, and trend for intra-individual SBP, DBP, and HR.[2] To minimize collinearity, SBP, DBP, HR, PP, and MAP were modeled separately in relation to incident CBI and worsening WMG, but the mean, variability, and trend for each physiological measure were included in the same model. To help with clinical interpretability in models, SBP, DBP, PP, and MAP were standardized to units of 10 mm Hg, and HR to units of 10 beats per minute (bpm). In primary analyses, we used relative risk regression using Poisson regression with robust standard errors to assess the relationship between SBP, DBP, and HR exposure variables and the binary outcomes. In secondary analyses, we used linear regression to assess the relationship between the exposure variables and the number of incident CBIs and WMG on the follow-up MRI.[7] Each analysis included adjustment for demographic factors (age, sex, race, clinic site), smoking (never, former, current), diabetes, BMI, time between MRI scans, and antihypertensive medication status (always, variable, never), with additional adjustment for the WMG on the initial MRI for the WMG on follow-up MRI outcome. We also tested these associations with a minimally adjusted model adjusted only for age, sex, race, and clinic site. We used stratification to assess effect modification by antihypertensive medication status (users of a stable medication regimen versus non-users). The significance of the interaction of antihypertensive medication status and the exposures of interest was tested in the full

primary analysis sample with a likelihood ratio test. In order to address potential selection bias related to our exclusions, we performed a sensitivity analysis that included participants with inconsistent antihypertensive use, CAD, CHF, AF, or infarcts on the initial MRI (for the CBI analysis) and assessed associations with number of CBIs and worsening WMG on the follow-up MRI. To assess the robustness of our findings in the primary analyses, we also conducted an exploratory analysis evaluating mean, variability, and trend of pulse pressure (PP) and mean arterial pressure (MAP) to reflect measures of pulsatile and steady flow, similar to SBP and DBP, respectively. Additional analyses included SBP and DBP in the same model and PP and MAP in the same model. Acknowledging that the outcomes of CBI and WMG are likely not independent and that the exposure variables may not be independent, we present uncorrected p-values together with a conservative Bonferroni corrected p-value threshold of 0.003, assuming a total of 18 hypotheses, to account for multiple comparisons. Stata (version 12.1, College Station, Texas) was used for statistical analyses.

REFERENCES

1. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A, O'Leary DH, Psaty B, Rautaharju P, Tracy RP, Weiler PG. The Cardiovascular Health Study: design and rationale. Ann Epidemiol. 1991;1:263-276.
2. Suchy-Dicey AM, Wallace ER, Mitchell SV, Aguilar M, Gottesman RF, Rice K, Kronmal R, Psaty BM, Longstreth WT Jr. Blood pressure variability and the risk

of all-cause mortality, incident myocardial infarction, and incident stroke in the Cardiovascular Health Study. Am J Hypertens. 2013;26:1210–1217.

3. Longstreth WT Jr, Dulberg C, Manolio TA, Lewis MR, Beauchamp NJ Jr, O'Leary D, Carr J, Furberg CD. Incidence, manifestations, and predictors of brain infarcts defined by serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. Stroke. 2002;33:2376-2382.
4. Longstreth WT Jr, Arnold AM, Beauchamp NJ Jr, Manolio TA, Lefkowitz D, Jungreis C, Hirsch CH, O'Leary DH, Furberg CD. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. Stroke. 2005;36:56-61.
5. Longstreth WT Jr, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, Enright PL, O'Leary D, Fried L. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people: the Cardiovascular Health Study. Stroke. 1996;27:1274–1282.
6. Longstreth WT Jr, Bernick C, Manolio TA, Bryan N, Jungreis CA, Price TR. Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study. Arch Neurol. 1998;55:1217-1225.
7. Lumley T, Diehr P, Emerson S, Chen L. The importance of the normality assumption in large public health data sets. Annu Rev Public Health. 2002;23:151-169.

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Table I. Baseline characteristics by analysis and outcome.

Characteristic	All CHS participants who underwent the first MRI, mean SD or n (%)	Primary analysis, any CBI as outcome, mean SD or n (%)	Primary analysis, any worsening of WMG as outcome, mean SD or n (%)	Sensitivity analysis, any CBI as outcome, mean SD or n (%)	Sensitivity analysis, any worsening of WMG as outcome, mean SD or n (%)
Total number of participants	3660	683	793	1842	1679
Age (years, at follow-up MRI)	75.1 (5.2)	73.3 (4.1)	73.5 (4.2)	74.0 (4.4)	74.0 (4.4)
Sex (male)	1527 (41.7%)	247 (36.2%)	281 (35.4%)	732 (39.7%)	671 (40.0%)
Race (black)	571 (15.6%)	92 (13.5%)	104 (13.1%)	274 (14.9%)	256 (15.2%)

Body mass index	26.6 (4.5)	26.3 (4.1)	26.1 (4.0)	26.7 (4.3)	26.7 (4.2)
Smoking status					
Never smoker	1621 (44.3%)	336 (49.2%)	386 (48.7%)	867 (47.0%)	784 (46.7%)
Former smoker	1690 (46.2%)	287 (42.0%)	330 (41.6%)	822 (44.6%)	752 (44.8%)
Current smoker	348 (9.5%)	60 (8.8%)	77 (9.7%)	154 (8.4%)	143 (8.5%)
Diabetes (baseline)	560 (15.5%)	57 (8.3%)	61 (7.7%)	222 (12.1%)	202 (12.0%)
CAD (baseline)	655 (17.9%)	0	0	237 (12.9%)	211 (12.6%)
CHF (baseline)	183 (5.0%)	0	0	49 (2.7%)	43 (2.6%)
AF (baseline)	194 (5.3%)	0	0	63 (3.4%)	56 (3.3%)
CHS Clinic					
North Carolina	938 (25.6%)	154 (22.5%)	183 (23.1%)	434 (23.6%)	405 (24.1%)
California	972 (26.6%)	219 (32.1%)	255 (32.2%)	547 (29.7%)	499 (29.7%)

Maryland	819 (22.4%)	131 (19.2%)	146 (18.4%)	361 (19.6%)	328 (19.5%)
Pennsylvania	931 (25.4%)	179 (26.2%)	209 (26.4%)	500 (27.1%)	447 (26.6%)
Antihypertensive medications	1783 (48.7%)	176 (25.8%)	210 (26.5%)	710 (38.5%)	648 (38.6%)
Interval between MRI scans (days)	N/A	1814.6 ± 218	1809.8 ± 213	1827.1 ± 217	1828.7 ± 217
MRI findings					
Incident covert brain infarcts	N/A	101 (14.8%)		N/A	
Worsening white matter grade	N/A		215 (27.1%)		472 (28.1%)
Systolic blood pressure					
Mean (mm Hg)	N/A	129.2 (14.1)	129.8 (15.0)	133.2 (16.2)	133.3 (16.3)
Variability	N/A	7.5 (4.5)	7.4 (4.4)	8.3 (5.4)	8.3 (5.5)
Trend	N/A	0.7 (3.3)	0.6 (3.4)	-0.1 (4.2)	-0.1 (4.2)

Diastolic blood pressure					
Mean (mm Hg)	N/A	68.9 (7.8)	68.9 (7.9)	68.9 (8.7)	69.0 (8.7)
Variability	N/A	4.4 (3.0)	4.4 (3.)	4.9 (3.5)	4.9 (3.4)
Trend	N/A	-0.4 (2.2)	-0.4 (2.2)	-0.8 (2.5)	-0.8 (2.5)
Heart rate					
Mean (beat per minute)	N/A	63.5 (8.0)	63.8 (8.0)	63.4 (8.7)	63.5 (8.6)
Variability	N/A	3.9 (2.6)	3.8 (2.6)	4.1 (3.2)	4.1 (3.3)
Trend	N/A	0.2 (2.5)	0.1 (2.5)	0.1 (2.6)	0.1 (2.6)
Baseline number of infarcts					
0	2529 (69.1%)	683 (100%)	616 (77.7%)	1370 (74.4%)	1249 (74.4%)
1	682 (18.6%)	0	114 (14.4%)	299 (16.2%)	271 (16.1%)
2	261 (7.1%)	0	35 (4.4%)	103 (5.6%)	96 (5.7%)
>2	188 (5.2%)	0	28 (3.5%)	70 (3.8)	63 (3.8%)

Baseline WMG (mean, SD)	1.8 (1.5)	1.5 (1.3)	1.7 (1.4)	1.8 (1.4)	1.8 (1.4)

MRI = magnetic resonance imaging, CAD = coronary artery disease, CHF = congestive heart failure, AF = atrial fibrillation, WMG = white matter grade.

Table II. Pairwise correlation coefficients for SBP, DBP, HR, PP, and MAP.

	SBP	DBP	HR	PP	MAP
Trend-variability	0.06	-0.14	0.25	0.07	-0.09
Trend-mean	0.06	0.13	0.05	0.11	0.08
Variability-mean	0.32	-0.13	0.29	0.37	0.10

SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, PP = pulse pressure, MAP = mean arterial pressure.

Table III. Relationships of SBP, DBP, and HR to count outcomes: number of covert brain infarcts (CBI) and white matter grade (WMG) on follow-up MRI.

Number of CBI (n=683)	**SBP (10 points mm Hg)**		**DBP (10 points mm Hg)**		**HR (10 bpm)**	
	Beta	P value	Beta	P value	Beta	P value
Mean	0.06 (0.02, 0.10)	0.002	0.09 (-0.001, 0.18)	0.05	0.02 (-0.03, 0.07)	0.36
Variability	0.005 (-0.10, 0.11)	0.93	0.14 (-0.004, 0.29)	0.06	-0.07 (-0.25, 0.11)	0.45
Trend	-0.10 (-0.24, 0.03)	0.12	0.009 (-0.20, 0.22)	0.94	0.18 (0.01, 0.34)	0.03

WMG (n=793)	**SBP (10 points mm Hg)**		**DBP (10 points mm Hg)**		**HR (10 bpm)**	
	Beta	P value	Beta	P value	Beta	P value
Mean	0.02 (-0.01, 0.06)	0.23	0.13 (0.07, 0.19)	<0.001	0.03 (-0.02, 0.08)	0.20
Variability	0.04 (-0.08, 0.16)	0.52	0.07 (-0.09, 0.22)	0.38	0.16 (-0.04, 0.36)	0.12

Trend	-0.01	0.84	-0.05	0.59	-0.002	0.99
	(-0.14, 0.12)		(-0.24, 0.13)		(-0.21, 0.20)	

Visit-to-visit mean was calculated from four annual measurements. Visit-to-visit trend was calculated using linear regression (slope). Visit-to-visit variability was calculated from the standard deviation of the residuals of the linear regression. Beta and 95% confidence intervals (CI) estimated from linear regression model adjusted for age, sex, race, clinic location, smoking status, BMI, diabetes, time between MRI scans, and antihypertensive medication status. WMG additionally adjusted for WMG on the initial scan. The Bonferroni corrected p-value is 0.003.

SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, bpm = beats per minute.

Table IV. Relationships of SBP and DBP to dichotomous outcomes in models incorporating both variables: incident covert brain infarcts (CBI) and worsening white matter grade (WMG).

Incident CBI (n=683)	**SBP (10 points mm Hg)**		**DBP (10 points mm Hg)**	
	RR (95% CI)	P value	RR (95% CI)	P value
Mean	1.25 (1.06, 1.47)	0.007	1.05 (0.78, 1.43)	0.74
Variability	0.85 (0.56, 1.29)	0.43	1.32 (0.78, 2.25)	0.30
Trend	0.63 (0.35, 1.12)	0.11	1.21 (0.44, 3.34)	0.71

Worsening WMG (n=793)	**SBP (10 points mm Hg)**		**DBP (10 points mm Hg)**	
	RR (95% CI)	P value	RR (95% CI)	P value

Mean	0.98 (0.88, 1.08)	0.66	1.50 (1.24, 1.80)	<0.001
Variability	0.92 (0.68, 1.24)	0.59	1.31 (0.88, 1.97)	0.19
Trend	1.21 (0.80, 1.82)	0.37	0.83 (0.44, 1.55)	0.56

Visit-to-visit mean was calculated from four annual measurements. Visit-to-visit trend was calculated using linear regression (slope). Visit-to-visit variability was calculated from the standard deviation of the residuals of the linear regression. Relative risks (RR) and 95% confidence intervals (CI) estimated from RR regression model adjusted for age, sex, race, clinic location, smoking status, BMI, diabetes, time between MRI scans, and antihypertensive medication status. RRs are presented for mean, variability, and trend per 10 points of mm Hg for systolic and diastolic blood pressure. The Bonferroni corrected p-value is 0.003.

SBP = systolic blood pressure, DBP = diastolic blood pressure.

Table V. Relationships of PP and MAP to dichotomous outcomes in models incorporating both variables: incident covert brain infarcts (CBI) and worsening white matter grade (WMG).

Incident CBI (n=683)	**PP (10 points mm Hg)**		**MAP (10 points mm Hg)**	
	RR (95% CI)	P value	RR (95% CI)	P value
Mean	1.13 (0.94, 1.37)	0.19	1.27 (0.99, 1.64)	0.06
Variability	1.11 (0.73, 1.67)	0.64	1.04 (0.59, 1.85)	0.89
Trend	0.69 (0.35, 1.33)	0.27	0.72 (0.27, 1.91)	0.51
Worsening WMG (n=793)	**PP (10 points mm Hg)**		**MAP (10 points mm Hg)**	
	RR (95% CI)	P value	RR (95% CI)	P value
Mean	0.86 (0.77, 0.97)	0.01	1.45 (1.23, 1.70)	<0.001
Variability	0.97 (0.68, 1.39)	0.88	1.19 (0.76, 1.87)	0.45
Trend	1.19 (0.78, 1.82)	0.42	1.00 (0.56, 1.81)	0.99

Visit-to-visit mean was calculated from four annual measurements. Visit-to-visit trend was calculated using linear regression (slope). Visit-to-visit variability was calculated from the standard deviation of the residuals of the linear regression. Relative risks (RR) and 95% confidence intervals (CI) estimated from RR regression model adjusted for age, sex, race, clinic location, smoking status, BMI, diabetes, time between MRI scans, and antihypertensive medication status. RRs are presented for mean, variability, and trend per 10 points of mm Hg for pulse pressure and mean arterial pressure. The Bonferroni corrected p-value is 0.003.

PP = pulse pressure, MAP = mean arterial pressure.

Table VI. Relationships of SBP, DBP, and HR to incident covert brain infarcts (CBI) and worsening white matter grade (WMG) stratified by antihypertensive medication status

	Users			**Non-Users**		
	SBP (10 points mm Hg)	DBP (10 points mm Hg)	HR (10 bpm)	SBP (10 points mm Hg)	DBP (10 points mm Hg)	HR (10 bpm)
Incident CBI	n=21/176 (11.9%)			n=80/507 (15.8%)		
Mean	1.43 (1.00, 2.05)	1.14 (0.59, 2.20)	0.90 (0.51, 1.59)	1.24 (1.06, 1.44)†	1.40 (1.04, 1.89)†	1.24 (0.97, 1.58)
Variability	0.56 (0.19, 1.66)	1.18 (0.32, 4.37)	3.31 (0.84, 12.99)	1.10 (0.71, 1.70)	1.74 (1.01, 2.97)†	0.72 (0.33, 1.54)
Trend	0.41 (0.07, 2.40)	0.79 (0.19, 3.25)	1.09 (0.28, 4.25)	0.67 (0.39, 1.16)	1.24 (0.51, 3.02)	2.75 (1.34, 5.65)†
Worsening WMG	n=59/210 (28.1%)			n=156/583 (26.8%)		
Mean	0.99	1.29	1.22	1.13	1.49	1.07

	(0.85, 1.14)	(0.96, 1.74)	(0.93, 1.60)	(1.01, 1.26)†	(1.23, 1.79)*	(0.90, 1.28)
Variability	0.80 (0.45, 1.42)	1.46 (0.59, 3.63)	0.78 (0.36, 1.69)	1.03 (0.72, 1.48)	1.06 (0.65, 1.74)	1.44 (0.89, 2.33)
Trend	1.57 (0.82, 3.03)	1.12 (0.47, 2.65)	1.42 (0.62, 3.28)	0.91 (0.61, 1.36)	0.94 (0.48, 1.84)	1.20 (0.73, 1.97)

Relative risks (RR) and 95% confidence intervals (CI) estimated from RR regression model adjusted for age, sex, race, clinic location, smoking status, BMI, time between MRI scans, and diabetes. *Significance with Bonferroni corrected p-value = 0.003. †Significance with p-value = 0.05. Interaction p-values: SBP covariates and CBI = 0.67, DBP covariates and CBI = 0.48, HR covariates and CBI = 0.5, SBP covariates and WMG = 0.27, DBP covariates and WMG = 0.6, HR covariates and WMG = 0.54.

SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, bpm = beats per minute.