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Hypertension

CEREBRAL BLOOD FLOW AND COGNITION

Contributions of Cerebral Blood Flow to Associations Between Blood Pressure Levels and Cognition

The Age, Gene/Environment Susceptibility-Reykjavik Study

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ABSTRACT: Cerebral hypoperfusion leads to adverse sequalae including dementia. Midlife higher blood pressure (BP) can lead to low cerebral blood flow (CBF), but older persons may need higher BP to maintain cerebral perfusion. We investigated the associations among late-life BP, CBF, and cognition. Data are from 2498 participants with a mean age of 79.8 (SD, 4.7) years of the second exam of the AGES (Age, Gene/Environment Susceptibility)–Reykjavik Study. BP was measured, and phase-contrast (PC) magnetic resonance imaging was acquired to estimate total brain CBF_{PC}. Cognitive outcomes included verbal and working memory, processing speed, mild cognitive impairment, and all-cause dementia. Relationships among late-life BP, CBF_{PC}, and cognition were assessed with regression models, controlling for socio-demographics, BP level at midlife (at a mean age of 49.6 [SD, 5.9] years), cardiovascular factors, and total brain volume. In fully adjusted models, each mm Hg increase in late-life diastolic BP was associated with a −0.082 mL/min per 100 mL (95% CI −0.123 to −0.041) lower CBF_{PC}. In contrast, each mm Hg increase in late-life systolic BP or pulse pressure was associated with a 0.027 mL/min per 100 mL (95% CI, 0.0065–0.048) and 0.061 mL/min per 100 mL (95% CI, 0.038–0.084) higher late-life CBF_{PC}, respectively. Higher CBF_{PC} was significantly related to higher cognitive scores for psychomotor speed, verbal, and working memory and to a lower odd of mild cognitive impairment or dementia, irrespective of late-life BP level. Higher late-life diastolic BP and systolic BP were differentially associated with CBF_{PC}. Our findings suggest CBF is an important correlate of late-life cognition, independent of BP level. **(*Hypertension*. 2021;77:2075–2083. DOI: 10.1161/HYPERTENSIONAHA.120.16894.)**

• **Data Supplement**

Key Words: aged blood pressure ■ cerebral blood flow cognition ■ dementia

Chronic hypoperfusion of the brain is one mechanism underlying the cerebral damage associated with high blood pressure (BP). Chronic hypertension and hemodynamic stress can lead to arterial stiffening, lumen narrowing, changes in neurovascular coupling, and cerebral autoregulation (CA)—thereby affecting cerebral blood flow (CBF) and delivery of nutrients and oxygen to the brain.[1,2] With age, these vascular changes tend to lead to an increase in systolic BP (SBP) and a decrease in diastolic BP (DBP)[3] and to cerebral vascular damage that may lead to cognitive decline or dementia.[4–6]

In older persons, an increased SBP and pulse pressure (PP), may be needed to overcome the increased resistance of a cerebral vascular bed that is affected by arteriolosclerosis.[7] This concern is raised in the context of adverse outcomes of a lower BP at old age such as falls, cognitive decline, and mortality.[8,9] However, there are few data on the relationship of late-life BP level to CBF in cohorts that better represent the range and distribution of CBF, BP, and health status typical in older populations. Further, few studies have compared the associations among BP, CBF, and cognitive function in the same population.

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Novelty and Significance

What Is New?

- We show that in late-life not blood pressure (BP) level, but a lower cerebral blood flow (CBF) is consistently related to worse cognitive outcomes.

What Is Relevant?

- To establish late-life BP values and treatment goals for optimizing brain function, it is crucial to consider CBF level.

Summary

This large population-based study in older persons shows that the effect of late-life BP on CBF is different for systolic BP and diastolic BP, with a higher systolic blood pressure but a lower diastolic BP relating to a higher CBF. Higher CBF was related to higher cognitive functioning and lower odd of mild cognitive impairment or dementia, irrespective of BP level.

Nonstandard Abbreviations and Acronyms

AGES-RS	Age Gene/Environment Susceptibility—Reykjavik Study
BMI	body mass index
BP	blood pressure
CA	cerebral autoregulation
CBF	cerebral blood flow
DBP	diastolic BP
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
PC	phase-contrast
PP	pulse pressure
SBP	systolic BP
TBV	total brain volume

Current studies indicate a negative, positive, or no association between late-life BP and cognitive function,[5] whereas CBF may be a more consistent marker.[10]

We examined the possible paradox between desirable BP levels, CBF, and cognitive function, in the AGES-RS (Age Gene/Environment Susceptibility—Reykjavik Study), a large population-based study with 30-year follow-up between middle and late age. We investigate whether a lower BP is related to a lower CBF at old age. Further, we hypothesize that in this older cohort there is an association between a higher CBF and better cognitive function.

METHODS

Study Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. This study included cohort members from the AGES-RS, which originated from the RS (Reykjavik Study).[11] Briefly, the RS was initiated by the Icelandic Heart Association to study cardiovascular disease in a population-based cohort of persons born between 1907 and 1935 and living in Reykjavik and surroundings in 1967. AGES-RS is based on a random sample of RS cohort survivors who were examined in 2002 to 2006 and then again 5 years later (2007–2011) to study genetic and environmental factors for disease and disability at old age. AGES–RS was approved by the National Bioethics Committee in Iceland (VSN 00-063) acting as the institutional review board for the Icelandic Heart Association, and by the institutional review board governing the National Institute on Aging. All participants gave written informed consent.

Blood Pressure

In both the AGES-RS and the RS, BP was measured twice after 5 minutes of rest in a sitting position with a standardized cuff (bladder width×length: 15×22 cm) according to the World Health Organization and European guidelines. The mean of 2 consecutive measurements, that were separated by 1 to 2 minutes, was used in analyses. PP was calculated as (SBP—DBP). Late-life BP levels were measured at the second visit, concurrently with the CBF magnetic resonance imaging (MRI) measure, when participants had a mean age of 79.8 (SD, 4.7) years. The measured midlife BP levels were taken from the RS exam conducted closest to when the participants were age 50 years (mean age [SD] in years: 49.6 [SD, 5.9]). Antihypertensive treatment and other medication were registered by using a questionnaire that participants were asked to fill out.

MRI Acquisition and Image Processing

All consenting participants without contraindications were eligible for brain MRI acquired on a study dedicated 1.5-Tesla Signa Twinspeed Excite system (General Electric Medical Systems, Waukesha, WI), using an 8 channel phased array head cap coil. Described in detail elsewhere[12] the image protocol included a 3-dimensional spoiled gradient-echo T1-weighted, fast spin-echo proton density/T2-weighted, and fluid-attenuated inversion recovery sequences for structural imaging. Different tissue volumes, including white matter lesion load a measure of vascular injury, were segmented automatically using a validated image analysis postprocessing pipeline. Total brain volume (TBV) was defined as the sum of volumes of gray matter, white matter, and white matter lesions. Intracranial volume was estimated as TBV plus cerebral spinal fluid volume. A measure of atrophy was defined as the volume of TBV/intracranial volume to give a percent (%TBV).

Total CBF (mL/min) was estimated with 2-dimensional phase-contrast (PC)-MRI. The PC-MR images were

processed using the software package FLOW (Division of Image Processing, Leiden University Medical Center, the Netherlands).[13] Total CBF was derived from the flow-through one standardized oblique axial slice perpendicular to the internal carotid arteries and the basal artery on a PC sagittal angiographic localizer image. Estimated total CBF_{PC} was defined as the sum of the flow in internal carotid arteries and basal artery and was expressed per 100 mL brain volume in mL/min per 100 mL. CBF_{pc} was normally distributed.

Confounding or Moderating Factors

In our analyses, we controlled for several factors that may confound the association or moderate the association of BP to CBF_{PC}. Questionnaires were used to assess level of education (dichotomized at primary education) and smoking status (current versus never or former). Measured weight and height were used to calculate body mass index (BMI; kg/m^2). Diabetes was defined as a self-reported history of diabetes, use of blood glucose-lowering medication, or fasting serum glucose of ≥7 mmol/L. Hospital records identified events of stroke and heart failure. Coronary calcium load (in mm^3), as a measure of atherosclerosis load, was acquired using computerized tomography, calculated as the sum score of the 4 coronary arteries, and scored in Agatston units.[14]

Cognitive Function

As described previously,[15] cognitive function was measured by 3 composite domain scores, verbal memory, working memory, and processing speed. The verbal memory compound score included the immediate- and delayed-recall portions of the original California Verbal Learning Test.[16] The working memory composite includes Digits Backward,[17] the Cambridge Neuropsychological Test Automated Battery spatial working memory test,[18] and the Stroop Test Part III.[19] The processing speed composite includes the Digit Symbol Substitution Test,[17] Figure Comparison,[20] and the Stroop Test Parts 1 and 2.[19] All tests had a normal distribution and inter-rater reliability was high (Spearman correlations for cognitive tests range from 0.96–0.99). Composite domain scores measures were computed by converting raw scores of each cognitive test to standardized *Z* scores and averaging them across the tests in each composite. Dementia and mild cognitive impairment (MCI) were assessed in a 3-step process, as previously described[21] including testing the total population with measures of general cognitive function; detailed assessment of cognitive function of those falling below a cut point; and among those falling again below a cut point, a third step that included a neurological examination and a proxy interview. A consensus diagnosis of dementia and subtypes, according to criteria of the Diagnostic and Statistical Manual of Mental Disorders IV[22] or of MCI[23] was made by a panel including a geriatrician, a neurologist, a neuropsychologist, and a neuroradiologist.

Analytical Sample

Of the 2643 participants who had MRI, 138 participants had incomplete data on CBF_{PC}, 2 had incomplete data on brain volume, and 12 had missing BP measures at mid- or late-life, and 2 extreme outliers for CBF were excluded, leaving 2489 participants available for analysis.

Statistical Analysis

Late-life characteristics of participants are reported as mean (SD), median (interquartile range), or number (%) where appropriate. Population characteristics are compared among late-life SBP and DBP groups with χ^2 for categorical variables, with ANOVA for normally distributed continuous variables, and with Kruskal-Wallis for non-normally distributed continuous variables. Late-life BP group was categorized according to BP Joint National Committee-8 hypertension guideline[7] cut-offs, late-life SBP; <120, 120 to <140, 140 to <150, 150+, late-life DBP; ≤70, 70 to <80, 80 to <90, 90+, and PP; <25th percentile, 25th to <75th percentiles, and 75th+ percentiles. The association between late-life BP and CBF_{PC} was estimated with linear regression analysis. Nonlinearity of associations was tested by entering quadratic terms into an age and sex-adjusted model, but terms were not significant. Model 1 included age, sex, education, and %TBV; model 2 additionally included coronary calcium load, diabetes, BMI, heart failure, smoking status, stroke, use of antihypertensive medication (never, both mid- and late-life, only mid- or only late-life), and midlife BP level of the same late-life measure (ie, late-life DBP was adjusted for midlife DBP). The relationships among BP level, CBF, and cognitive function (psychomotor speed, verbal and working memory, and MCI or dementia status) were examined with linear (or logistic) regression adjusting for age, sex, education, and %TBV.

In secondary analyses, we assessed if the relationship between a higher SBP and higher CBF may be more pronounced in subgroups of frailer older persons. We assessed whether the following indicators of health status modified the association of late-life BP to CBF_{PC}, including age (median split at 80 years), sex; groups for midlife SBP and DBP,[7] use of antihypertensive treatment, late-life BMI (≤18.5, 18.5–24.9, 25–29.9, ≥30 kg/m^2), late-life smoking (yes/no), prevalent diabetes, heart failure, stroke, coronary calcium Agatston score (absent: 0, mild: 1–100, moderate: 101–400, severe >400),[24] and upper quartile of abnormal white matter volume (≥29.9 cc). Effect modification by these factors was tested by adding an interaction term in the linear regression model (late-life BP×covariate). Stratified and interaction analyses were adjusted for age and sex (model 1). *P* values for significant interaction-terms will be corrected for multiple testing using the Bonferroni adjustment. We also examined the association of CBF to cognition in strata of BP, and we tested if there was significant interaction between late-life BP and CBF on cognitive function. SAS v. 9 was used for all analyses.

RESULTS

Population Characteristics

The cohort included 40.9% male; 59.9% used antihypertensive medications in late life (Table 1); descriptive statistics by late-life SBP and DBP categories are found in Tables S1A and S1B in the Data Supplement. In this cohort, 4.3% of the study population had high DBP (>90 mm Hg) and 37.8% had high SBP (>150 mm Hg).

Table 1. Characteristics of the AGES-RS Cohort in Mid and Late Life

Characteristics	Sample, n=2489
Late-life age in years, y, mean (SD)	79.8 (4.7)
≥80 y, n (%)	1207 (48.49)
Male, n (%)	1017 (40.9)
Education, ≤primary school (%)	504 (20.2)
Blood pressure in mm Hg, mean (SD)	
Midlife SBP	129.4 (15.2)
Midlife DBP	82.3 (9.1)
Late-life SBP	145.0 (21.05)
Late-life DBP	70.3 (10.7)
Use of antihypertensive medication in late-life, n (%)	1491 (59.9)
Late-life characteristics	
Body mass index, mean (SD)	26.8 (4.3)
Coronary calcium (Agatston units), median (IQR)	461.07 (92.68–1302.21)
Heart failure, n (%)	138 (5.5)
Type 2 diabetes, n (%)	317 (12.7)
Stroke, n (%)	208 (8.4)
Smoking status, n (%)*	
Never	1308 (52.6%)
Former	977 (39.3%)
Current smoker	158 (6.3%)
Cognition*	
Normal cognitive function	2110 (84.8%)
Mild cognitive Impairment	216 (8.7%)
Dementia	134 (5.4%)
Late-life brain MRI measures	
Total brain volume in % ICV, mean (SD)	0.69 (0.042)
Abnormal white matter volume, median (IQR)	15.66 (8.27–29.69)
Cerebral blood flow in mL/(100 mL·min), mean (SD)	56.7 (10.5)

AGES-RS indicates Age Gene/Environment Susceptibility—Reykjavik Study; DBP, diastolic blood pressure; ICV, intracranial volume; IQR, interquartile range; MRI, magnetic resonance imaging; and SBP, systolic blood pressure.

*Smoking status is missing for n=46, and cognitive status is missing for n=29.

Late-Life BP and CBF

Each mm Hg increase in DBP was associated with −0.082 mL/min per 100 mL (95% CI, −0.123 to −0.041) lower CBF_{PC} (Table 2, Model 2). Each mm Hg increase in SBP and in PP was associated with a 0.027 mL/min per 100 mL (95% CI, 0.0065–0.048) and 0.061 mL/min per 100 mL (95% CI, 0.038–0.084) higher late-life CBF_{PC}, respectively. Mean CBF per BP group is visualized in Figure 1. The positive (for SBP) and negative (for DBP) direction of these associations with CBF were similar across several demographic characteristics, cardiovascular risk factors, and sub-clinical vascular disease markers (Figure 2). There was no positive association for SBP and CBF_{PC}, in persons with dementia, but the interaction term for (dementia status×SBP) was not significant (*P* interaction=0.15; Figure 2).

Table 2. Relationship Between Late-Life BP and CBF (n=2489): AGES-RS

BP	β value	95% CI		*P* value
		Lower	Upper	
DBP				
Model 1	−0.081	−0.121	−0.042	<0.0001
Model 2	−0.082	−0.123	−0.041	<0.0001
SBP				
Model 1	0.027	0.0066	0.047	0.009
Model 2	0.027	0.0065	0.048	0.010
PP				
Model 1	0.060	0.037	0.082	<0.0001
Model 2	0.061	0.038	0.084	<0.0001

Model 1: adjusted for age, sex, education, brain volume. Model 2: adjusted for sex, education, brain volume, coronary calcium, BMI, diabetes mellitus, heart failure, smoking, stroke, midlife BP, use of antihypertensive medication. β indicates change in CBF per 1 mm Hg increase in BP, that is, a positive β indicates that a higher BP is related to a higher CBF. AGES-RS indicates Age Gene/Environment Susceptibility—Reykjavik Study; BMI, body mass index; BP, blood pressure; CBF, cerebral blood flow; DBP, diastolic blood pressure; PP, pulse pressure; and SBP, systolic blood pressure.

Late-Life BP, CBF, and Cognition

Both CBF_{PC} and late-life BP (either DBP, SBP, or PP) were entered into the models to examine their association with cognition. Higher CBF_{PC} was significantly related to higher cognitive scores for verbal, working memory, and psychomotor speed (Table 3) and to a lower odd of MCI or dementia (Table 4) while controlling for age, sex, education, BP level, and %TBV. In this model with both BP level and CBF, except for higher PP being related to lower working memory scores (Table 3), levels of DBP, SBP, and PP were not associated with any cognitive domain or with MCI or dementia status. Table S2 shows the relationship between CBF and cognitive domains by BP level. Estimates were higher in those with a lower DBP or in the range of SBP between 120 and 140 mm Hg, whereas no clear pattern was observed by PP level. There was no significant interaction between late-life BP and CBF on cognitive function (Table S2). There was no significant relationship between midlife DBP, SBP, or PP and late-life CBF (Table S3A) or cognitive function (Table S3B). To evaluate the use of a single standardized cuff size, which could potentially lead to faulty BP measurements in those with extremes of BMI, we have rerun BP analyses excluding those in either the lower or the upper quartile of BMI, which provided similar results (data not shown).

DISCUSSION

In this large population-based study of 2489 persons followed for 30 years, we found that the effect of BP on CBF is different for SBP and DBP. A higher late-life DBP was related to a lower CBF_{PC}, whereas a higher

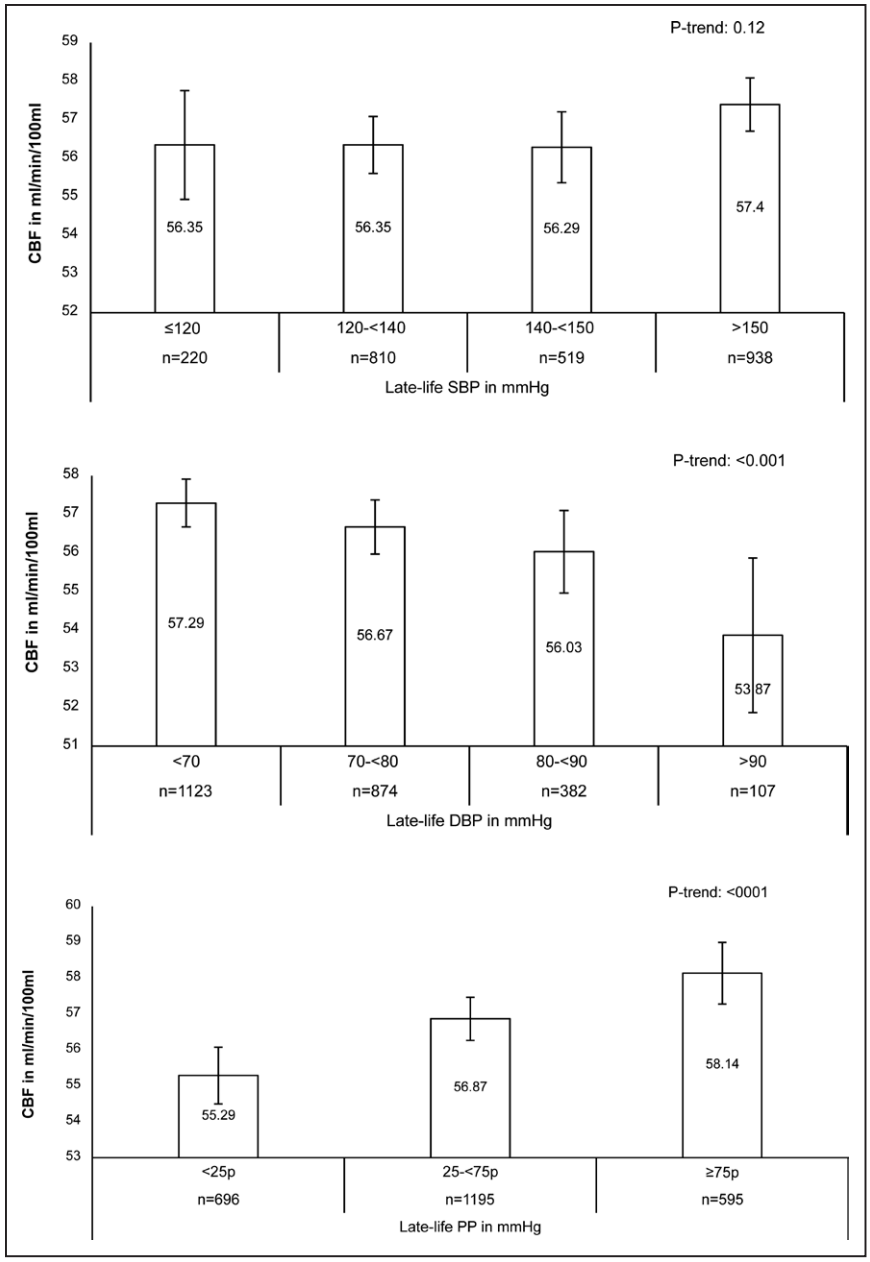

Figure 1. Mean cerebral blood flow (95% CI) per blood pressure group. Adjusted for age, sex, brain volume, and education. CBF indicates cerebral blood flow; and SBP, systolic blood pressure.

late-life, SBP was associated with higher CBF_{PC}. Extensive stratified and interaction analyses suggested these relationships were robust to level of midlife BP, cardiovascular risk factors, and use of antihypertensive treatment. Our findings also indicate that CBF is an important correlate of late-life cognition, while accounting for atrophy and for level of BP. There were no systematic differences in CBF modulation of cognition by level of BP (ie, no significant interaction), but the data suggest that particularly people with lower DBP, or with SBP between 120 and 140 mm Hg may have a cognitive benefit of having a higher CBF.

There are few data on the association of BP to CBF in community-based cohorts. A previous study in nondemented older adults[25] also showed that higher DBP, but not SBP was significantly associated with lower CBF. To better understand the difference in directionality of late-life DBP and SBP with CBF additional studies are needed. We did not observe a relationship between midlife BP and late-life CBF, while in a middle-aged cohort with manifest atherosclerotic disease (SMART-MR [Secondary Manifestations of Arterial disease-Magnetic Resonance] Study) both higher SBP and DBP were associated with a decline in CBF.[26] Differences in study findings may be attributable to differences in population characteristics such as the prevalence of cardiovascular comorbidities.

Whereas the evidence on the association of BP levels to CBF is mixed, there is robust and consistent evidence of an adverse impact of midlife hypertension on late-life cognitive function.[4] A higher BP in late-life, however, has demonstrated no[27], a negative,[28]or a positive relationship

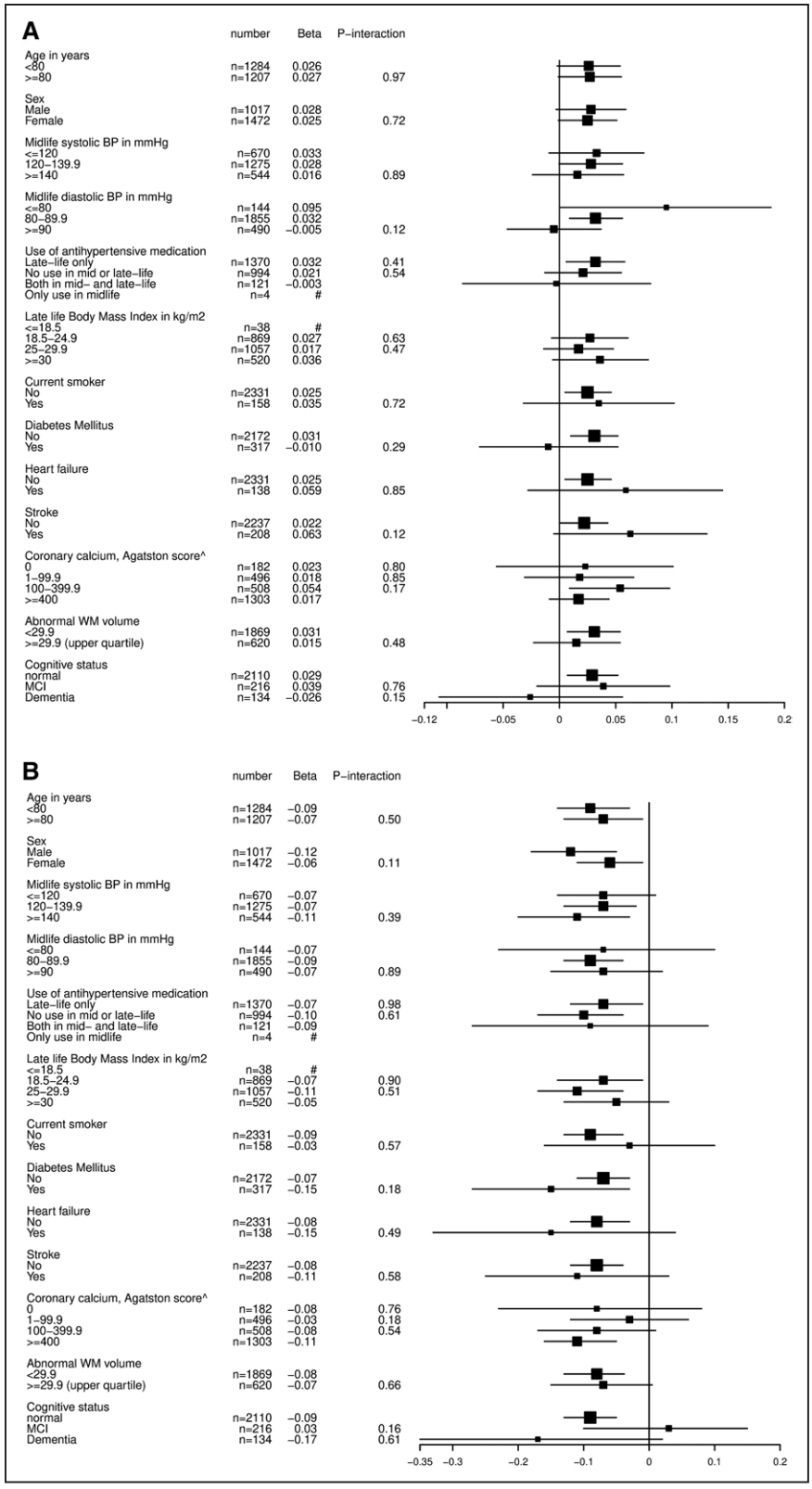

Figure 2. A, Stratified analyses for the association between late-life systolic blood pressure (BP) and cerebral blood flow (CBF).
B, Stratified analyses for the association between late-life diastolic blood pressure and CBF. MCI indicates mild cognitive impairment. #indicates subgroup too small; data not shown. Analyses are adjusted for age, sex, and total brain volume. ^Grading of coronary calcium, 0: none, mild: 1–99.9, moderate: 100–399.9, and severe: ≥400.

with cognitive function.[5,29] Several studies indicate that it is essential to consider history of midlife hypertension to understand how late-life BP affects cognitive function. Walker et al[30] showed that those participants with hypertension in both mid and late-life and participants with midlife hypertension, and late-life hypotension had significantly increased risk of subsequent dementia compared with those who remained normotensive. Considering midlife BP only, we did not observe a relationship with late-life cognition. However, Muller et al[31] has previously

Table 3. Relationship Between BP, CBF, and Cognition: AGES-RS

	Verbal memory				Working memory				Speed			
	95% CI				95% CI				95% CI			
BP	β value	Lower	Upper	*P* value	β value	Lower	Upper	*P* value	β value	Lower	Upper	*P* value
DBP	0.0028	−0.00060	0.0062	0.11	0.002	−0.001	0.005	0.210	0.0015	−0.0019	0.0048	0.393
CBF	0.0060	0.0026	0.0095	0.0006	0.004	0.001	0.007	0.001	0.0059	0.0025	0.0093	0.001
SBP	−0.00071	−0.0024	0.0010	0.42	−0.0011	−0.003	0.0005	0.169	−0.00071	−0.0024	0.0010	0.409
CBF	0.0059	0.0024	0.0093	0.0009	0.0039	0.001	0.007	0.018	0.0058	0.0024	0.0092	0.001
PP	−0.0018	−0.0037	0.00012	0.066	−0.002	−0.004	−0.00028	0.023	−0.0014	−0.0033	0.0005	0.151
CBF	0.0062	0.0027	0.0096	0.001	0.004	0.001	0.007	0.012	0.0060	0.0026	0.0094	0.0005

Model includes age, sex, education, BP, CBF, and brain volume (% ICV). The β's indicate change in standardized cognitive domain score per 1 mm Hg increase in BP, or per 1 mL/(min·100 mL) CBF. The significant positive β's for CBF, indicate that a higher CBF is related to a higher cognitive function. AGES-RS indicates Age Gene/Environment Susceptibility—Reykjavik Study; BP, blood pressure; CBF, cerebral blood flow; DBP, diastolic blood pressure; ICV, intracranial volume; PP, pulse pressure; and SBP, systolic blood pressure.

demonstrated in the AGES-RS that those participants with midlife hypertension and late-life lower DBP had the worst memory performance. BP is known to decline 3 to 6 years before dementia diagnosis.[32]

Low CBF has been shown to be a consistent marker of dementia,[10] although results are mixed in the MCI stage.[33] The Rotterdam study showed that dementia risk estimates for low cerebral perfusion were higher in those with higher BP levels at baseline (with significant interaction for mean arterial pressure).[10] de Heus et al[34] also showed that the BP to CBF ratio is higher in dementia and MCI compared with controls. In line with these findings, we showed that effect estimates for the relationship between CBF and cognitive function were highest in those with a lower level of DBP or normal range of SBP, although the interaction term for BP and CBF did not reach significance.

Our findings on the complex interplay between BP, CBF, and cognitive function may be attributable to several factors, which fall broadly into 3 categories: physiological changes accumulating with age and disease; co-occurrence of BP changes, low CBF, and increased mortality; or selective survival.

First, with aging there is an increase in central arterial stiffness, leading to an increase in SBP and decline in DBP, resulting in a higher PP at old age.[35] A higher PP transmitted into smaller cerebral arterioles and capillary beds can lead to cerebral vascular remodeling, including narrowing of lumen and increased vascular resistance.[1,2] These structural changes may be accompanied by dysfunction of CA and neurovascular coupling, which renders the brain vulnerable for hypoperfusion with lower SBP. Cerebral hypoperfusion leads to an imbalance of neuronal metabolic supply and demand, thereby precipitating cognitive dysfunction.[10] Nevertheless, de Heus et al[34] showed that in MCI or dementia CA remains functional (as measured by transcranial Doppler ultrasound in the middle cerebral artery). Possibly, larger cerebral arteries may still be able to compensate to maintain and stabilize CBF with varying BP through CA, while there is localized increased cerebral vascular resistance and impaired CA in smaller arteries.

Second, the positive slope between SBP and CBF_{PC} may be driven by factors at the lower end of the BP distribution, where a lower late-life SBP and lower CBF may be an epiphenomenon of incipient death. Lower late-life

Table 4. Relationship Between BP, CBF, and Cognitive Status: AGES—RS

	Dementia*				MCI†			
		95% CI				95% CI		
BP	OR	Lower	Upper	*P* value	OR	Lower	Upper	*P* value
SBP	1.00	0.99	1.01	0.68	1.00	0.99	1.007	0.92
CBF	0.97	0.95	0.99	0.003	0.98	0.97	0.999	0.03
DBP	1.00	0.98	1.02	0.80	0.99	0.98	1.006	0.23
CBF	0.97	0.95	0.99	0.003	0.98	0.97	0.998	0.03
PP	1.00	0.99	1.01	0.54	1.00	1.00	1.011	0.41
CBF	0.97	0.95	0.99	0.002	0.98	0.97	0.998	0.03

Model includes age, sex, education, BP, CBF, and brain volume (% ICV). OR <1 indicates a decreased odd for dementia or MCI with a higher CBF. OR <1 indicates a decreased odd for dementia or MCI with a higher CBF. AGES-RS indicates Age Gene/Environment Susceptibility—Reykjavik Study; BP, blood pressure; CBF, cerebral blood flow; DBP, diastolic blood pressure; ICV, intracranial volume; MCI, mild cognitive impairment; OR, odds ratio; PP, pulse pressure; and SBP, systolic blood pressure.

*0: normal cognitive status (n=2011) vs 1: dementia (n=134).

†0: normal cognitive status (n=2011) vs 1: MCI (n=216).

CBF has been strongly associated with increased mortality risk,[36] and SBP is known to decrease progressively for more than a decade before death and most steeply in the last 2 life years.[37]

Finally, selective survival may explain the relationship between a higher SBP and higher CBF as there may have been proportionately more loss from the cohort of those with higher SBP and lower CBF (potential high-risk group for cardiovascular mortality).

Strengths of our study include the population-based setting, the large sample size that is extensively phenotyped for cardiovascular risk and cognitive function, the availability of both midlife and late-life BP data over 30-year follow-up, and comprehensive analyses to explore the association of both level of BP and CBF with cognition. Our extensive stratified analyses provide insight into how markers of biological age influence the complex relationship between BP and CBF.

However, several characteristics of our study need to be considered when interpreting the results. We used phase-contrast MRI to estimate total brain CBF, which may be influenced by accuracy of the segmentation of the arteries, assumptions in the acquisition and processing protocols, changes in vascular morphology such as tortuosity and hemoglobin levels.[38,39] Further research is needed to identify factors that contribute to error in CBF measurement. Nevertheless, PC-MRI has proven to be a reliable measure for CBF in the AGES population; the intraclass correlation coefficient for whole brain CBF values obtained with PC-MRI against pCASL was 0.80.[40] Our estimates of CBF are also consistent with another, on average younger population-based cohort, that also used PC-MRI to measure CBF.[10] Second, CBF_{pc} was only measured once so we do not know the start of, how rapid, or to what extent there was a decline from middle to late age in CBF in total or regional brain areas. Also, we cannot determine the directionality of the relationship between a lower CBF and dementia risk, either a lower CBF precedes dementia, or vice versa. Future studies are needed with multiple time points and combined technologies, such as the MRI sequence arterial spin labeling and transcranial doppler to give temporal and regional measures of cerebral perfusion and autoregulation.[41] The AGES-RS included a white community-dwelling sample, with a prevalence of antihypertensive treatment use of 60%, stroke of 8%, and diabetes of 13%, which should be considered when generalizing our results. Future studies should examine whether BP, CBF, and cognition show similar associations in multi-racial samples or in samples with a different cardiovascular burden. Finally, a standardized cuff was used to measure BP that was not adjusted for arm circumference, which may have affected BP measurements of those participants with a particularly small or large arm circumference.

Higher late-life DBP and SBP were differentially associated with CBF_{PC}. Our findings suggest that late-life CBF is an important correlate of cognition.

PERSPECTIVES

In this large population-based study, the effect of late-life BP on CBF is different for SBP and DBP. A higher late-life DBP was related to a lower CBF whereas a higher late-life, SBP was associated with higher CBF. Not BP level, but a higher CBF was consistently related to better cognitive outcomes. To better understand BP-lowering strategies for optimal cognition, future trials on BP and cognition should include CBF measurements.

ARTICLE INFORMATION

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Disclosures

None.

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