Title

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Blood pressure from mid- to late life and risk of incident dementia

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ABSTRACT

Objective: To determine the association between blood pressure during midlife (40–64 years) to late life (≥65 years) and risk of incident dementia.

Methods: This study included 1,440 (758 women, mean age 69 ± 6 years) Framingham Offspring participants who were free of dementia and attended 5 consecutive examinations at 4-year intervals starting at midlife (1983–1987, mean age 55 years) until late life (1998–2001, mean 69 years) and subsequently were followed up for incident dementia (mean 8 years). We determined the effect of midlife hypertension (≥140/90 mm Hg), late life hypertension, lower late life blood pressure (<100/70 mm Hg), persistence of hypertension during mid- to late life, and steep decline in blood pressure from mid- to late life over an 18-year exposure period.

Results: During the follow-up period, 107 participants (71 women) developed dementia. Using multivariable Cox proportional hazards models, we found that midlife systolic hypertension (hazard ratio [HR] 1.57, 95% confidence interval [CI] 1.05–2.35) and persistence of systolic hypertension into late life (HR 1.96, 95% CI 1.25–3.09) were associated with an elevated risk of incident dementia. However, in individuals with low to normal blood pressure (≤140/90 mm Hg) at midlife, a steep decline in systolic blood pressure during mid- to late life was also associated with a >2-fold increase in dementia risk (HR 2.40, 95% CI 1.39–4.15).

Conclusions: Elevated blood pressure during midlife, persistence of elevated blood pressure into late life, and, among nonhypertensives, a steep decline in blood pressure during mid- to late life were associated with an increased dementia risk in a community-based cohort. Our data highlight the potential sustained cognitive benefits of lower blood pressures in midlife but also suggest that declining blood pressure in older adults with prehypertension or normotension, but not in those with hypertension, may be a risk marker for dementia. *Neurology*® 2017;89:2447–2454

GLOSSARY

AD = Alzheimer disease; **AUC** = area under the curve; **BP** = blood pressure; **CBI** = covert brain infarct; **CI** = confidence interval; **DBP** = diastolic blood pressure; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; **HR** = hazard ratio; **HV** = hippocampal volume; **JNC-7** = Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7; **PROGRESS** = Perindopril Protection Against Recurrent Stroke Study; **SBP** = systolic blood pressure; **Syst-Eur** = Systolic Hypertension in Europe; **TCBV** = total cerebral brain volume; **WMHV** = white matter hyperintensity volume.

Dementia is a significant health problem with an estimated prevalence of 35 million worldwide.[1] The number of dementia cases is expected to triple worldwide by 2050 as a result of an aging population and a lack of effective disease-modifying therapies.[1] Focusing on dementia prevention is therefore crucial to tackle this growing problem. Hypertension is a key modifiable risk factor for cerebrovascular pathology leading to stroke and dementia. Both midlife (40–64 years) hypertension and late life (≥65 years) hypertension have been associated with an increased risk of poor cognitive performance and cognitive decline.[2,3] However, the precise nature of the relationship between midlife and late life hypertension and clinically confirmed dementia is not well understood. Previous longitudinal studies have reported conflicting findings,[4–12] and

Supplemental data at Neurology.org

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some have been limited by the use of self-reported history of hypertension rather than objectively recorded blood pressure (BP) measurements, use of single rather than repeated BP measurements, small sample sizes with low outcome event rates, a short duration of follow-up, and use of medical record–based dementia outcomes that are less reliable than investigator-validated diagnoses.

Furthermore, the relationship between BP trajectories from mid- to late life and dementia risk is not well understood. Previous studies did not include BP measures across the mid- to late life period and excluded female patients.[13] A large decline in systolic BP (SBP) has been associated with increased risk of dementia and Alzheimer disease (AD) if it occurs within the 3 to 6 years preceding dementia diagnosis.[14] However, reverse causality may account for such an association. It is unknown if a large decline in BP over a longer period, e.g., from mid- to late life, is associated with increased dementia risk after adjustment for other risk factors. An improved understanding of the association between BP during mid- to late life and subsequent risk of dementia would help inform targeted interventions to mitigate the risk of late life dementia. In the present investigation, we evaluated the association of midlife BP, late life BP, and trends in BP from mid- to late life with the subsequent risk of all-cause dementia and AD in a large, community-based cohort.

METHODS

Study sample. The Framingham Offspring Study (recruited 1971–1975) is a large, middle-aged cohort based in the community that has been longitudinally followed up for cardiovascular risk factors and occurrence of stroke, cognitive decline, and dementia for >40 years.[15] Participants are examined approximately every 4 years from the date of entry into the cohort. Participants in the Offspring cohort who attended a minimum of 5 sequential examinations starting at midlife (examination 3 [1983–1987], mean age 55 years) and continuing into late life (examination 7 [1998–2001], mean age 69 years) who were ≥60 years and without a diagnosis of dementia (based on ongoing surveillance) at the time of examination 7 were included in this study. Baseline characteristics of excluded participants were broadly in line with those of included participants and are described in table e-1 at Neurology.org.

Standard protocol approvals, registrations, and patient consents. Written informed consent was provided by each participant. The institutional review board at the Boston University Medical Center approved all study protocols and consent forms.

Outcome measures. Our primary outcome measure was incident dementia developing at any time after the seventh Offspring examination visit and before December 2014. AD was a secondary outcome measure. Starting at examination 5, participants were systematically screened for the occurrence of dementia. In addition, at Offspring examinations 7 through 9, all participants were given the opportunity to complete a 45-minute neuropsychological test battery and brain MRI. If any concern for cognitive impairment was raised by the participant, a family member, or a Framingham study physician or the Mini-Mental State Examination score was below an education-based cutoff, 3 points lower than the preceding examination, or 5 points lower than the participant's highest recorded score, more in-depth cognitive testing was performed.[16] Participants with suspected cognitive impairment that did not meet diagnostic criteria for dementia underwent further yearly neuropsychological assessments between the scheduled Offspring examinations. Dementia was diagnosed according to the criteria of the DSM-IV, requiring impairment in memory and at least 1 other domain of cognitive function, along with documented functional disability.[17] The final diagnosis and date of diagnosis of dementia were established after a review of all available neurologic examination records; neuropsychological assessments; study records; hospital, nursing home, and outpatient clinic records; neuroimaging results; family interview information; and autopsy results (when available) by a committee that included at least 1 neurologist and 1 neuropsychologist. AD was diagnosed when participants met the criteria of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association for definite, probable, or possible AD.[18] See e-Methods for additional details.

Blood pressure. BP was recorded in a standardized fashion during each examination cycle and was calculated as the mean of 2 BP measurements recorded by a physician taken while the participant was seated for a minimum of 5 minutes with cuff size adjusted for arm circumference. We included measurements from examination cycles 3 through 7. Systolic hypertension was defined as SBP ≥140 mm Hg and diastolic hypertension as diastolic BP (DBP) ≥90 mm Hg, in line with Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7 (JNC-7) criteria.[19] Midlife hypertension was defined as hypertension present at examination 3, and late life hypertension was defined as hypertension present at examination 7. Persistent hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg during both examinations 3 and 7. Lower late life BP was defined as SBP <100 mm Hg and DBP <70 mm Hg.

Covariates. We adjusted for demographics and baseline covariates (measured at examination 7) associated with a greater risk of dementia, including age, sex, education, cardiovascular disease, and *APOE4* carrier status. Self-reported use of antihypertensive medication was recorded and verified with data from prescriptions and pill bottles when available. For participants with an available brain MRI completed within 2 years of examination 7 (median time from examination 7 to completion of MRI 0.5 years, range 0–2 years), we also adjusted for radiographic structural brain measures, including presence of covert brain infarcts (CBIs), total cerebral brain volume (TCBV), white matter hyperintensity volume (WMHV), and hippocampal volume (HV). See e-Methods for further details.

Statistical analysis. We estimated multivariable-adjusted Cox proportional hazards models to determine the association between BP status (midlife and late life hypertension [compared

to those without hypertension at the comparable time point], lower late life BP [compared to those without lower BP], and persistent hypertension during mid- to late life [compared to those without persistent hypertension]) and risk of dementia and AD. Participants were censored at the time of death. We hypothesized that a steep negative slope of SBP from mid- to late life would also be associated with an increased risk of dementia. We determined the slope of BP for each individual across all 5 examinations using a person-specific linear regression model and related this intraindividual slope to risk of subsequent dementia. A threshold effect was observed at the first quartile of SBP slope, slope of <-0.5 mm Hg/y, i.e., the steepest decline in SBP from mid- to late life. We generated multivariable-adjusted Cox proportional hazards models to determine the association between a steep decline in SBP from mid- to late life (slope <-0.5 mm Hg/y) compared to nonsteep decline (slope ≥ -0.5 mm Hg/y) and risk of dementia and AD.

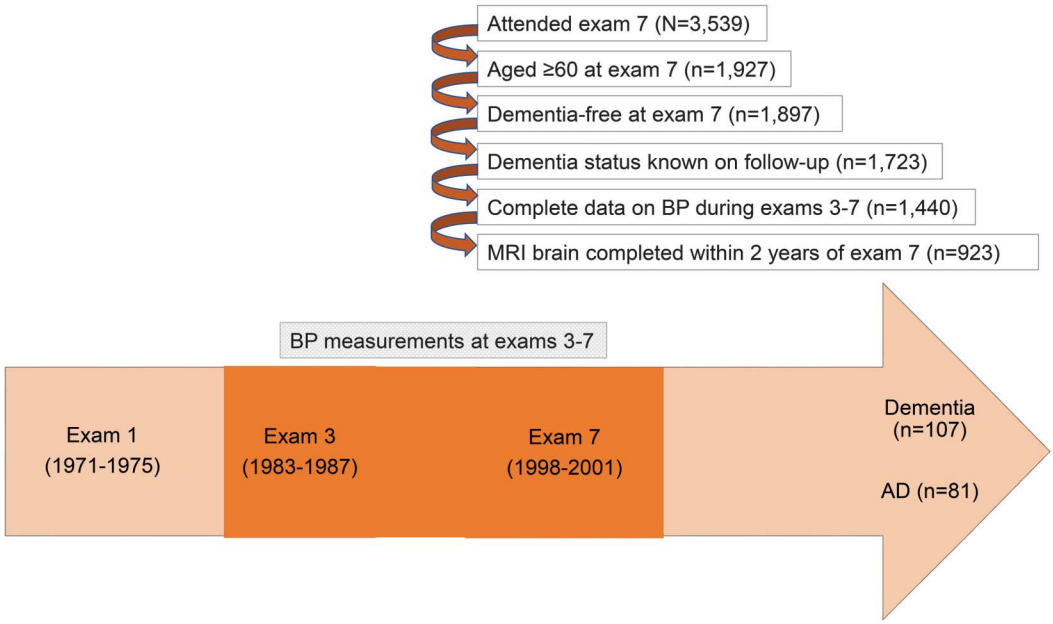
Model 1 adjusted for age and sex; model 2 additionally accounted for education, cardiovascular disease history, and *APOE4* carrier state; and model 3 additionally adjusted for midlife BP. We also assessed the effect of the cumulative burden of BP during mid- to late life (examinations 3–7) on the risk of dementia using the area under the curve (AUC). We estimated the mean curve for SBP using a linear model with a linear spline in age, with knots at 55, 65, and 75 years of age corresponding to the approximate mean age during follow-up examinations and to ensure sufficient numbers of BP measurements in each of the age ranges as defined by the knots. We calculated participant-specific SBP curves as best linear unbiased predictions based on the model and then calculated the AUC for the interval between examinations 3 and 7. We completed unadjusted and adjusted linear regression analyses to determine the association of the AUC with risk of all dementia and AD (per each SD unit increase in SBP AUC).

We performed subgroup analyses according to use/nonuse of antihypertensive medication at any time during the 18-year exposure period, as well as subgroup analyses to determine whether the effect of a steep decline in SBP from mid- to late life on incident dementia varied according to baseline midlife BP or use of antihypertensive therapy. We completed sensitivity analyses defining hypertension as SBP/DBP $\geq$140/90 mm Hg or use of antihypertensive agents at examination 3 (for midlife hypertension) or examination 7 (for late life hypertension) to account for individuals with treated hypertension. Finally, we completed additional analyses adjusting for radiographic structural brain measures, namely CBI, TCBV, HV, and WMHV, in those participants who had a brain MRI completed within 2 years of examination 7 (n = 923, 64% of the cohort) to determine whether adjusting for structural brain measures influenced the association between BP and incident dementia and AD. For all analyses, a value of $p < 0.05$ or a 95% confidence interval (CI) that did not include 1.0 was considered to be of statistical significance. The analyses were conducted with SAS statistical software, version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS The study cohort included 1,440 participants. During a mean follow-up period of 8 (SD 3) years, 107 (7.4%) participants were diagnosed with dementia, 81 of whom were diagnosed with AD (figure 1). The mean age of participants at examination 7 was 69 (SD 6) years, and 53% were female (table 1). Mean midlife BP was 127/80 (SD 17/9) mm Hg in the cohort; 27% of the cohort met JNC-7 criteria for a diagnosis of midlife hypertension.

Midlife BP and dementia. On multivariable analysis, midlife systolic hypertension was associated with an elevated risk of incident dementia (hazard ratio [HR] 1.57, 95% CI 1.05–2.35), with increasing risk per each 10–mm Hg increment in midlife SBP (HR 1.17, 95% CI 1.05–1.31) (table 2 and figure 2). Tests for interactions according to use of antihypertensive medication were not significant (table e-2). On sensitivity analyses, the association between midlife BP

Figure 1 Flow of cohort participants



AD = Alzheimer disease; BP = blood pressure.

Table 1 Baseline characteristics and BP data

	Participants (n = 1,440)
Age, mean (SD), y	69 (6)
Male, n (%)	682/1,440 (47)
Education, n (%)	
No high school degree	101/1,420 (7)
High school degree	491/1,420 (35)
Some years of college	414/1,420 (29)
College degree	414/1,420 (29)
Prevalent CVD, n (%)	283/1,440 (20)
APOE ε4 allele, n (%)	306/1,428 (21)
Diabetes mellitus, n (%)	232/1,405 (17)
Atrial fibrillation, n (%)	91/1,440 (6)
Current smoking, n (%)	117/1,440 (8)
Antihypertensive medication, n (%)	723/1,440 (50)
Midlife blood pressure	
SBP, mean (SD), mm Hg	127 (17)
DBP, mean (SD), mm Hg	80 (9)
Systolic hypertension, n (%)	300 (21)
Diastolic hypertension, n (%)	232 (16)
Any hypertension, n (%)	390 (27)
Late life blood pressure	
SBP, mean (SD), mm Hg	132 (19)
DBP, mean (SD), mm Hg	72 (10)
Systolic hypertension, n (%)	462 (32)
Diastolic hypertension, n (%)	67 (5)
Any hypertension, n (%)	476 (33)
Lower systolic blood pressure, n (%)	27 (2)
Lower diastolic blood pressure, n (%)	555 (39)
mid- to late life trajectory in blood pressure, n (%)	
Persistent systolic hypertension	166 (12)
Persistent diastolic hypertension	31 (2)
Steep decline in SBP	317 (22)
Steep decline in DBP	748 (52)

Abbreviations: BP = blood pressure; CVD = cardiovascular disease; DBP = diastolic blood pressure; SBP = systolic blood pressure.
Baseline demographic and clinical characteristics were defined at examination 7 except for antihypertensive medication use, which included use of antihypertensives at any time during examinations 3 and 7.
Systolic hypertension was defined as SBP ≥140 mm Hg and diastolic hypertension as DBP ≥90 mm Hg, in line with Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7 criteria. A cutoff score of slope <−0.5 indicates a steep decline in blood pressure during mid- to late life. Examination 3 represented midlife (mean age 55 years); examination 7 represented late life (mean age 69 years).

and dementia was consistent in direction and magnitude, although it did not reach statistical significance (table e-3).

mid- to late life BP and dementia. Persistence of systolic hypertension from mid- to late life was associated with an elevated risk of dementia (HR 1.96, 95% CI 1.25–3.09) and AD (HR 1.73, 95% CI 1.02–2.94). A higher cumulative burden of SBP from mid- to late life was also associated with increased dementia risk (HR 1.27, 95% CI 1.05–1.53 for each SD unit increase in AUC) (table 3). On multivariable analysis, a steep decline in SBP from mid- to late life (slope <-0.5 vs ≥-0.5 mm Hg/y) was associated with an increased risk of overall dementia (HR 1.63, 95% CI 1.08–2.46) but not AD (HR 1.47, 95% CI 0.91–2.37). There was a significant interaction between midlife hypertension (presence/absence) and a steep decline in SBP from mid- to late life in their association with incident dementia ($p = 0.023$), with a significantly increased risk of dementia (HR 2.40, 95% CI 1.39–4.15) and AD (HR 2.12, 95% CI 1.12–4.00) noted in individuals without elevated BP at midlife (table 3 and figure e-1). Most individuals (61%) with low to normal midlife BP were not on antihypertensive medications at any of the 5 index examinations.

mid- to late life BP and structural brain measures. On multivariable analysis, the association between significant mid- to late life BP measures (persistent systolic hypertension and steep decline in SBP) and incident all-cause dementia was not substantially altered (in direction or magnitude of association) after additional adjustment for structural brain measures, including CBI and WMHV. There was a small attenuation in the magnitude of association after adjustment for TCBV and HV, although results did not reach significance (tables e-4 and e-5). Compared to participants with a nonsteep decline in SBP from mid- to late life, those with a steep decline in SBP had significantly lower TCBV, but not HV, at examination 7, after accounting for age and sex (table e-6).

DISCUSSION We found that elevated BP in midlife was associated with increased risk of all-cause dementia, with a further increase in risk with persistence of hypertension into late life. Persistent hypertension from mid- to late life was also associated with an elevated risk of AD. In middle-aged adults without hypertension, a steep decline in BP from mid- to late life was associated with a >2-fold increased risk of developing dementia and AD.

We found an elevated risk of late life dementia in adults with midlife hypertension. The risk of dementia increased with increasing SBP, with an additional 20% increase in risk per each 10–mm Hg increment in midlife SBP. Furthermore, persistence of hypertension from midlife into late life resulted in a 25% increase in the risk of dementia above that attributable to midlife hypertension alone, while greater cumulative exposure to elevated SBP across mid- to late life was associated with an increased risk of dementia. These data together provide evidence to

Table 2 BP from mid- to late life and dementia

	Dementia, HR (95% CI)			AD, HR (95% CI)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Midlife						
Systolic hypertension	1.70 (1.14–2.53)	1.57 (1.05–2.35)	—	1.52 (0.95–2.42)	1.35 (0.84–2.17)	—
Diastolic hypertension	1.08 (0.64–1.81)	1.14 (0.67–1.91)	—	1.11 (0.61–2.00)	1.21 (0.66–2.19)	—
SBP (per 10-mm Hg increment)	1.19 (1.07–1.21)	1.17 (1.05–1.31)	—	1.13 (1.00–1.28)	1.11 (0.97–1.26)	—
DBP (per 10-mm Hg increment)	1.27 (1.04–1.56)	1.24 (1.01–1.52)	—	1.28 (1.02–1.62)	1.24 (0.98–1.57)	—
Late life						
Systolic hypertension	1.48 (1.01–2.19)	1.42 (0.96–2.10)	1.22 (0.81–1.84)	1.43 (0.92–2.23)	1.31 (0.84–2.07)	1.20 (0.75–1.93)
Diastolic hypertension	1.53 (0.67–3.49)	1.61 (0.70–3.68)	1.39 (0.60–3.23)	2.06 (0.90–4.74)	2.27 (0.98–5.26)	1.99 (0.84–4.69)
Lower SBP	1.47 (0.36–5.97)	1.43 (0.35–5.83)	—	1.92 (0.47–7.85)	1.87 (0.45–7.73)	—
Lower DBP	0.97 (0.66–1.44)	0.97 (0.65–1.43)	—	0.97 (0.62–1.52)	0.98 (0.62–1.54)	—
mid- to late life trajectory						
Persistent systolic hypertension	2.15 (1.37–3.35)	1.96 (1.25–3.09)	—	2.02 (1.20–3.39)	1.73 (1.02–2.94)	—
Persistent diastolic hypertension	2.34 (0.86–6.39)	2.11 (0.77–5.79)	—	3.21 (1.17–8.82)	2.94 (1.06–8.18)	—
Steep decline in SBP	1.62 (1.08–2.44)	1.63 (1.08–2.46)	1.32 (0.84–2.10)	1.47 (0.91–2.37)	1.47 (0.91–2.37)	1.32 (0.78–2.24)
Steep decline in DBP	1.48 (0.99–2.21)	1.44 (0.97–2.16)	1.30 (0.85–1.99)	1.55 (0.97–2.46)	1.48 (0.93–2.35)	1.34 (0.82–2.18)
mid- to late life burden						
SBP burden (SD units)	1.29 (1.07–1.54)	1.27 (1.05–1.53)	—	1.14 (0.92–1.42)	1.10 (0.88–1.38)	—

Abbreviations: AD = Alzheimer disease; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; HR = hazard ratio; SBP = systolic blood pressure.
Systolic hypertension was defined as SBP ≥140 mm Hg and diastolic hypertension as DBP ≥90 mm Hg, in line with Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7 criteria. A cutoff score of slope <−0.5 indicates a steep decline in blood pressure during mid- to late life. Examination 3 represented midlife (mean age 55 years); examination 7 represented late life (mean age 69 years).
Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, education, *APOE4*, and prevalent cardiovascular disease (CVD). Model 3 adjusted for age, sex, education, *APOE4*, prevalent CVD, and midlife BP (as a continuous variable).

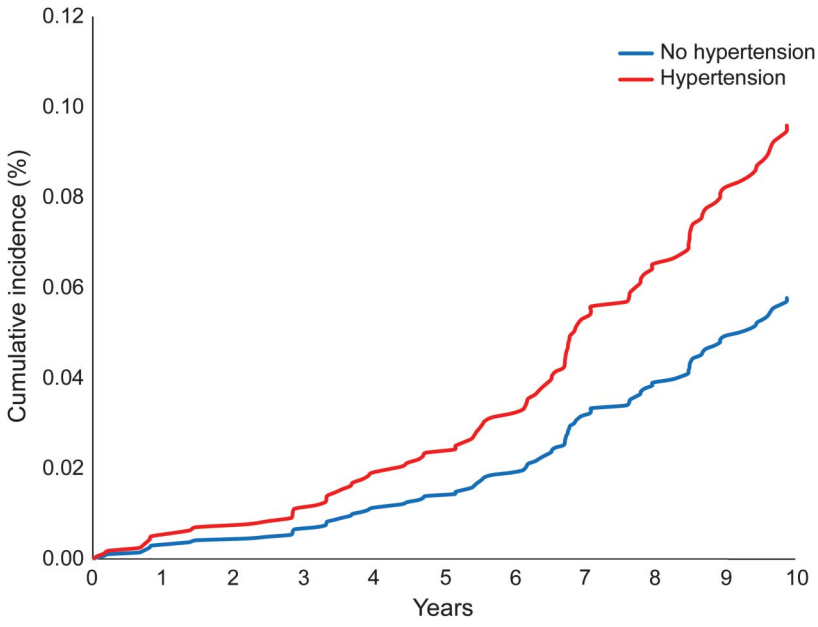
support a dose-response relationship between degree and duration of elevated BP and dementia risk.

Hypertension can predispose to stroke and dementia through a multitude of effects on the cerebral vasculature, including small vessel disease (arteriosclerosis, lipohyalinosis, fibrinoid necrosis, and microbleeds), large artery atherosclerosis, and hypertension-related cardiac dysfunction, predisposing to cerebral hypoperfusion (hypothesized to result in reduced clearance of β-amyloid).

Our results highlight the potential cognitive benefits of effective BP modification in middle-aged adults. Previous trials investigating the effects of BP control for dementia prevention have reported mainly negative results, except for Perindopril Protection Against Recurrent Stroke Study (PROGRESS) and Systolic Hypertension in Europe (Syst-Eur), and have focused largely on an elderly population, have measured cognitive performance rather than clinically confirmed dementia, and have been further limited by insufficient power to detect a treatment effect or a short follow-up period (range 0.5–5 years).[20–27]

In individuals without midlife hypertension, a steep decline in SBP from mid- to late life was associated with a >2-fold increase in the risk of developing incident dementia and AD. Previous studies have reported greater cortical atrophy and WMHV in association with steep BP decline over 20 to 25 years,[28,29] as well as impaired cognitive performance noted in association with lower later life BP compared to stable BPs from mid- to late life,[30,31] supporting our observation. The relationship between BP decline from mid- to late life and increased dementia risk is likely multifactorial. With advancing age, arterial elasticity and compliance decline, leading to impaired cerebral autoregulation and the ability to maintain adequate cerebral perfusion in the setting of BP fluctuations.[32] This predisposes to cerebral ischemia from episodes of hypotension,[33] as well as a reduction in β-amyloid clearance. Reverse causality may also explain the association. A decline in BP has been observed in the early stages of dementia, proposed to be due to neurodegenerative effects on brainstem and hypothalamic nuclei controlling BP,[34,35] as well as the coexistent development of weight loss and cardiovascular disease (including myocardial infarction and heart failure) in this age group, reducing recorded BP and systemic and cerebral perfusion.

Figure 2 Cumulative incidence of dementia according to midlife BP



(A) Cumulative incidence of dementia according to midlife BP. (B) Cumulative incidence of dementia in individuals without midlife hypertension. BP = blood pressure.

In our study, participants with a steep decline in SBP from mid- to late life had lower TCBV compared to those without a steep decline, and the magnitude of the association between steep decline in SBP and dementia risk was partially attenuated after adjustment for TCBV. Regression toward the mean is unlikely to account for the observation, given that we observed the association in individuals who were normotensive to prehypertensive at midlife, so a further steep reduction in BP is likely to be pathologic, not due to regression to the mean.

Our findings suggest that a more aggressive approach to BP modification in middle-aged adults with hypertension could lower the risk of late life dementia and provide reassurance that lowering BP in persons with hypertension up to 70 years of age is beneficial rather than harmful for the risk of dementia. Our findings raise the possibility that a reduction in BP in older adults with prehypertension (e.g., 130–140/80–90 mm Hg) may be harmful to cognition, despite a beneficial effect on risk of adverse cardiovascular outcomes. However, most adults with prehypertension were not on antihypertensive medications, so the steep decline might be a marker of dementia risk, possibly secondary to preclinical neurodegenerative changes, even if it could also potentiate vascular brain injury. Further research is required to determine the optimal BP range in older adults associated with the lowest risk of late life dementia.

Strengths of our study include the completeness of data on risk factors and outcomes, inclusion of a population free of clinical dementia at baseline, an 18-year surveillance period with multiple BP measurements enabling a more accurate assessment of lifetime BP and careful evaluation of BP trajectories across mid- to late life, stringent procedures for dementia surveillance, and a long duration of follow-up. Limitations include the predominantly white Framingham cohort, which may affect the generalizability of our findings to nonwhite patients. In addition, we were unable to adjust for more sensitive MRI measures of vascular brain injury, including regional fractional anisotropy and mean diffusivity,[36] which likely would have further attenuated the association between BP and dementia.

Elevated BP in midlife, persistence of hypertension into late life, and, among nonhypertensives, a steep decline in BP from mid- to late life were independently associated with an increased risk of

Table 3 Subgroup analysis: Steep decline in SBP

	Dementia		AD	
	HR (95% CI)	*p* Value for interaction	HR (95% CI)	*p* Value for interaction
Midlife BP ≥140/90 mm Hg	0.89 (0.47–1.67)	0.02	0.88 (0.41–1.88)	0.09
Midlife BP <140/90 mm Hg	2.40 (1.39–4.15)		2.12 (1.12–4.00)	
Midlife BP <140/90 mm Hg and receiving antihypertensive therapy at midlife	2.46 (0.67–9.00)	0.50	—	—
Midlife BP <140/90 mm Hg and not receiving antihypertensive therapy at midlife	2.11 (1.14–3.93)		1.86 (0.93–3.70)	

Abbreviations: AD = Alzheimer disease; BP = blood pressure; CI = confidence interval; HR = hazard ratio; SBP = systolic blood pressure.
Systolic hypertension was defined as SBP ≥140 mm Hg and diastolic hypertension as diastolic BP ≥90 mm Hg, in line with Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7 criteria. A cutoff score of slope <−0.5 indicates a steep decline in blood pressure during mid- to late life. Examination 3 represented midlife (mean age 55 years); examination 7 represented late life (mean age 69 years).
Models are adjusted for age, sex, education, *APOE4*, and prevalent cardiovascular disease.
Blank cells indicate insufficient sample size to complete the analysis.

dementia in a community-based cohort. Our data highlight the potential sustained cognitive benefits of lower BP in midlife, provide reassurance that lowering BP in hypertensive older adults diminishes rather than increases dementia risk, but raise the possibility that lowering of BP in older individuals with prehypertension may be harmful to cognition despite a beneficial effect on risk of adverse cardiovascular events. Further research is required to determine the optimal BP range in older adults associated with the lowest risk of late life dementia.

AUTHOR CONTRIBUTIONS

Drs. McGrath and Seshadri had full access to all of the data in the study and had final responsibility for the decision to submit for publication. Study concept and design: McGrath, Seshadri, Beiser, Vasan. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: McGrath. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Beiser, Plourde. Obtained funding: Seshadri. Administrative, technical, or material support: Beiser, Plourde. Study supervision: Seshadri.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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