Low blood pressure and the risk of dementia in very old individuals

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Abstract—Background: The role of blood pressure (BP) as a risk factor for dementia is complex and may be age dependent. In very old individuals, low BP might increase risk for dementia, perhaps by reducing cerebral perfusion pressure. Methods: The association between BP and dementia was examined in the Bronx Aging Study, a prospective study of 488 community-dwelling elderly individuals over age 75, dementia-free at baseline (1980 to 1983) and followed at 12- to 18-month intervals. Subjects with baseline BP and with at least one follow-up visit were included (n = 406). Incident dementia was diagnosed using the criteria of the Diagnostic and Statistical Manual of Mental Disorders (3rd rev. ed.). Results: Over 21 years (median 6.7 years), 122 subjects developed dementia (65 Alzheimer’s disease [AD], 28 vascular dementia, 29 other dementias). Relative risk of dementia increased for each 10-mm Hg decrement in diastolic (hazard ratio [HR] 1.20, 95% CI 1.03 to 1.40) and mean arterial (HR 1.16, 95% CI 1.02 to 1.32) pressure, adjusted for age, sex, and education. Low diastolic BP significantly influenced risk of developing AD but not vascular dementia. Upon examination of groups defined by BP, mildly to moderately raised systolic BP (140 to 179 mm Hg) was associated with reduced risk for AD (HR vs normal systolic BP group 0.55, 95% CI 0.32 to 0.96), whereas low diastolic BP (<70 mm Hg) was associated with increased risk of AD (HR vs normal diastolic BP group 1.91, 95% CI 1.05 to 3.48). Subjects with persistent low BP over 2 years had higher risk of developing dementia (HR 2.19, 95% CI 1.27 to 3.77). Conclusions: Low diastolic pressure is associated with higher risk of dementia in elderly individuals over age 75. Dementia risk was higher in subjects with persistently low BP.

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The influence of blood pressure (BP) on the risk of developing dementia is complex and may be age dependent.1-13 Midlife hypertension is an important risk factor for developing coronary heart disease, stroke, and dementia.2,5 The relationship between BP and risk of dementia in older populations is less clear.6-12 Treatment of systolic hypertension in the elderly is associated with reduced incidence of dementia.14 Yet, hypotension may increase the risk of dementia in very old individuals, if higher cerebral perfusion pressures are required to maintain cerebral circulation.5-12,14 Whereas some studies have found an association between low BP and dementia in the elderly, it has been suggested that low BP may be the consequence rather than the cause of dementia.9-15 These studies have mainly examined individuals below age 80 (“young old”), without standardized BP protocols. Establishing the relationship between BP and dementia in old–old individuals has important public health implications. Optimal BP management in the very elderly may require identification of a therapeutic window to reduce incidence of dementia.

The Bronx Aging Study provides an opportunity to examine the role of BP as a risk factor for dementia in very old individuals.17-19 This community-based study followed an initially nondemented elderly cohort for up to 21 years with detailed clinical and neuropsychological evaluations.17,19 Herein, we examine the relationship between BP measured at baseline and risk of developing dementia in elderly individuals over age 75.

Methods. Study population. The Bronx Aging Study recruited 488 volunteer subjects between 1980 and 1983 from senior citizen centers, by local newspaper advertisements, and by word of mouth.17,19 Study design and methods have been previously described.17,19 In brief, entry criteria specified English-speaking subjects between the ages of 75 and 85 years; absence of previous diagnoses of idiopathic Parkinson’s disease, liver disease, alcoholism, or a known terminal illness; sufficient visual and hearing acuity to complete neuropsychological tests; and absence of dementia. Subjects were screened to rule out dementia and were included if they made 8 or fewer errors on the Blessed Information–Memory–Concentration Test (worst possible score, 32 errors).19 This test has high test–retest reliability (0.86) and correlates well with Alzheimer’s disease (AD) pathology.21 The inception cohort was middle class, mostly Caucasian (90%) and female (64.5%). Subjects received detailed clinical and neuropsychological evaluations at baseline and at follow-up visits every 12 to 18 months. Subjects were interviewed about their medical history with the use of structured questionnaires. Whenever possible, a close friend or family member was also interviewed by a study clinician to confirm the history and assess functional status. Written informed consent was obtained at enrollment, and subjects were asked to consider eventual participation in an autopsy program. The local institutional review board approved the study protocol.

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Study sample. Of the 488 subjects, 65 without a follow-up visit and 17 without baseline BP measurements were excluded. After exclusions, 406 subjects (83.2%) were eligible for this study. The potential study period was the 21-year period from 1980 to 2001. Over the study period, 330 subjects died. Seventy-six subjects (53 women), comprised of low diastolic and 3% with low systolic BP at enrollment, dropped out of the study.

Clinical evaluation. At enrollment, all participants underwent detailed medical history evaluation and were examined by study clinicians. Prescription and over-the-counter medication use was recorded. A significant other or close family member accompanied most subjects or was contacted to confirm details of history. Medical and medication history was reviewed at subsequent visits.

BP. Trained registered nurses measured BP at each visit. Four readings at 1-minute intervals were taken from the right forearm after 5 minutes of rest in a sitting position. The second and fourth readings were done with random zero mercury sphygmomanometer, and the mean of these two readings was used for analyses. Systolic Korotkoff phase I and the diastolic Korotkoff phase V were used as cutoff points. Mean arterial pressure was calculated as the sum of the diastolic BP and one-third pulse pressure (systolic – diastolic BP). Recent guidelines define hypertension as a systolic level of >140 mm Hg and diastolic level of >90 mm Hg.22,23 We selected values 110 mm Hg and a diastolic level of <80 mm Hg.22,23 We selected values 10 mm Hg below optimal values to define low BP (≤110 mm Hg systolic and ≤70 mm Hg diastolic).

Dementia diagnosis. At study visits, subjects with suspected dementia, based on study clinicians’ evaluations, neuropsychological tests, or worsening Blessed test scores (by 4 points or a total score over 7), received a workup, including a CT scan and blood tests (complete blood count, routine chemical screen, liver and thyroid function tests, vitamin B12 and folate levels, and syphilis serology).17-18 A diagnosis of dementia was assigned at consensus case conferences attended by the study neurologists, neuropsychologist, and a geriatric nurse clinician, using the criteria of the Diagnostic and Statistical Manual (3rd ed. and 3rd rev. ed. after 1986).24-25

As updated criteria for dementia and subtypes were introduced after the study launch, all cases were reconfirmed in 2001 to ensure uniformity of diagnosis by a neurologist and a neuropsychologist who did not participate in the original Bronx Aging Study conferences. Dementia diagnosis followed the criteria of the Diagnostic and Statistical Manual (3rd ed.26). The raters were not blinded to clinical evaluations, though BP measurements were not used to define dementia.17-19 Disagreements between raters were resolved by consensus after presenting the case to a second neurologist. Dementia was subtyped using established criteria for probable/possible AD,26 probable/possible/mixed vascular dementia,27 and probable/possible dementia with Lewy bodies.28 We have previously reported good validity for clinical diagnosis using pathologic diagnosis as the gold standard.10,19,20,21

Statistical analysis. Descriptive statistics was used to compare baseline characteristics. The relative risk of dementia and subtypes by baseline BP was calculated with Cox proportional hazards regression analysis to estimate hazard ratios (HR) with 95% CI adjusted for age at enrollment, sex, and education level (high school or less and college).21 In supplementary analyses, we adjusted for other potential confounders such as body mass index (BMI), history of chronic medical illness, smoking history, and antihypertensive medication use. BMI was calculated as self-reported weight in kilograms divided by the square of self-reported height in meters. The following chronic medical illnesses were each entered in the models: hypertension, diabetes, stroke, cardiac disease, chronic pulmonary disease, and hypothyroidism. Subjects were censored when they were diagnosed with dementia, at death, or at final study contact.

First, we examined BP and risk of developing dementia and subtypes as a continuous variable. The results are reported using 10-mm Hg decrements in BP. Second, we studied the effect of BP on dementia risk by treating it as a categorical variable with four systolic BP categories of ≥180 mm Hg (severe hypertension), 140 to 179 mm Hg (mild to moderate hypertension), 110 to 139 mm Hg (normal reference), and ≤110 mm Hg (low).17-18 Similarly we defined categories for diastolic BP: ≥110 mm Hg (severe), 91 to 110 mm Hg (mild to moderate), 71 to 89 mm Hg (normal reference), and ≤70 mm Hg (low).17-21

Results. Demographics. Baseline demographic and medical characteristics are presented in table 1 as a function of dementia outcome status. Except for years of education and self-reported history of hypertension, there were no significant differences in these variables at baseline between subjects who did and did not develop dementia over the study period. Baseline Blessed scores20 were in the normal range but higher in subjects who developed dementia (3.53 ± 2.41 vs 1.96 ± 1.78; p = 0.001).

BP, dementia, and subtypes. Subjects who developed dementia had lower systolic (149.8 ± 23.4 vs 155 ± 24.8 mm Hg; p = 0.047) and diastolic (82.8 ± 12.3 vs 86.8 ± 12.4 mm Hg; p = 0.003) pressure at enrollment than dementia-free subjects (table 2). Low systolic pressure (≤110 mm Hg) was seen in 3% and low diastolic pressure (≤70 mm Hg) in 14% of subjects. Antihypertensive medications, mainly diuretics or β blockers, were used by 54% of subjects. Although more subjects who took these medications at baseline remained dementia-free, there were no significant differences compared with subjects who developed dementia.

Over a median follow-up of 6.7 years (range 1 to 21 years), dementia developed in 122 subjects (30%; 82 men and 40 women); 65 were diagnosed as AD, 28 vascular dementia, 21 mixed AD–vascular dementia, and 8 other dementias. The overall results relating BP to the development of dementia are presented in tables 3 and 4. The adjusted HR of dementia for each 10-mm Hg decrement in systolic pressure was 1.07 (95% CI 0.99 to 1.15), for diastolic pressure 1.20 (95% CI 1.03 to 1.40), and for mean arterial pressure 1.16 (95% CI 1.02 to 1.32). The influence

| Table 1 Baseline demographic and self-reported medical history variables as function of dementia outcome |
|--------------------------------------------------|------------------|------------------|
| Variables                                       | Dementia, n = 122| No dementia, n = 284 |
| Mean (SD) age, y                                 | 79.8 (3.07)      | 78.9 (3.08)      |
| Men, n (%)                                       | 40 (32.8)        | 105 (37.1)       |
| Education high school, n (%)                    | 48 (39.3)        | 144 (50.8)       |
| Caucasian, n (%)                                 | 111 (90.9)       | 257 (90.8)       |
| Hypertension, n (%)                              | 54 (44.3)        | 150 (52.8)       |
| Cardiac disease, n (%)                           | 31 (25.4)        | 68 (23.9)        |
| Myocardial infarctions, n (%)                    | 20 (16.4)        | 33 (11.6)        |
| Strokes, n (%)                                   | 9 (7.4)          | 17 (5.9)         |
| Head injuries, n (%)                             | 15 (12.3)        | 26 (9.2)         |
| Diabetes mellitus, n (%)                         | 16 (13.1)        | 28 (9.9)         |
| Lung disease, n (%)                              | 36 (29.5)        | 85 (29.9)        |
| Thyroid disease, n (%)                           | 10 (8.2)         | 38 (13.4)        |
| Smoker                                          | 4 (3.3)          | 12 (4.2)         |
| Ever, n (%)                                      | 35 (28.7)        | 59 (20.8)        |

*p < 0.05.
of BP on risk of developing dementia was significant for AD but not vascular dementia (see table 3). For instance, the adjusted HR of developing AD is 1.23 (95% CI 1.00 to 1.52) and 1.15 (95% CI 0.84 to 1.58) for vascular dementia with every 10-mm Hg decrement in diastolic pressure. Effect of potential confounding variables. Demographic and vascular risk factors may modify the association between BP and dementia. However, the association between BP and dementia was not significantly altered by adjusting for demographic variables (age, sex, education), medical illnesses (hypertension, cardiac disease, diabetes, strokes), antihypertensive medication use, and smoking status. BP is correlated with BMI, and BMI in the elderly may be low as a result of aging or dementia. The relative risk of dementia, adjusted for BMI, for each 10-mm Hg decrement in diastolic BP remains significant (HR 1.22, 95% CI 1.08 to 1.33).

To account for the influence of preclinical dementia, we adjusted for baseline Blessed scores. Subjects with low diastolic BP had worse Blessed test scores at enrollment than subjects with high diastolic pressure (mean ± SD 2.9 ± 2.5 vs 2.2 ± 1.9; p = 0.06). Adjusting for baseline Blessed test scores affected the association of diastolic (HR 1.12, 95% CI 0.96 to 1.32) but not mean arterial (HR 1.15, 95% CI 1.02 to 1.32) pressure with dementia. We also did a secondary analysis using a lag function and excluding subjects who developed dementia in the first 2 years of our study in whom low BP at entry might be the consequence of preclinical dementia. Diastolic BP was associated with increased risk of developing dementia in this analysis (HR 1.05, 95% CI 1.00 to 1.16).

BP categories. Table 4 and the figure show that low diastolic BP (≤70 mm Hg) increased the risk of developing dementia (HR 1.64, 95% CI 1.04 to 2.61), especially AD (HR 1.91, 95% CI 1.05 to 3.48). Subjects with mild to moderate systolic hypertension (140 to 179 mm Hg) had a reduced risk of developing AD (HR 0.55, 95% CI 0.32 to 0.96) compared with subjects with normal systolic pressure (111 to 139 mm Hg). A significant association was not seen with severe systolic hypertension (≥180 mm Hg). Systolic and diastolic BP was not associated with increased risk of developing vascular dementia.

Effect of persistent low BP. The effect of BP on risk of developing dementia was stronger in 30 subjects with persistently low BP (systolic BP ≤110 mm Hg or diastolic ≤70 mm Hg) at the first two study visits (HR 2.19, 95% CI 1.27 to 3.77).

Discussion. The findings of our prospective study show that low BP is significantly associated with higher risk of dementia in an initially nondemented elderly cohort. Our finding builds upon previous studies, which have generally examined the relationship between BP and dementia in younger populations over shorter follow-up periods. The association was significant when BP was examined both as a continuous variable and in categories. Decrements of 10 mm Hg in diastolic BP increased the risk for dementia by 20%. A similar result was seen when mean arterial pressure was examined (16%). The association of systolic BP with dementia was not significant.

The association between low BP and dementia may represent a true causal effect or the influence of measured or unmeasured confounders. If causal, the direction of the association is uncertain. That is, preclinical dementia may be associated with pathologic changes that cause BP dysregulation. Alternatively, low BP may be a risk factor for dementia, perhaps by decreasing cerebral perfusion. The association between hypotension and future risk of AD in elderly individuals has been reported to be dependent on cognitive status at the time of BP measurement, supporting the role of preclinical dementia.
Subjects in our study who developed dementia had higher baseline Blessed scores, which may reflect early pathology. However, adjusting for Blessed test scores reduces the HR for diastolic BP but not for the mean arterial pressure. Low BP has been correlated with brain atrophy in 85-year-old subjects with dementia, and the authors suggested that structural changes in various brain regions might lead to BP dysregulation. Neurotransmitter deficits seen in AD may also contribute to low BP. Alternatively, low BP may initiate or accelerate disease processes leading to dementia. The prospective nature of our study and the association with incident dementia suggest that in at least some very old individuals, hypotension precedes dementia. This explanation is favored by the strong effect of persistent hypotension on the risk of developing dementia. A direct relationship between low BP and dementia is suggested by experimental cerebral hypoperfusion studies in rodents that were associated with reversible deficits on cognitive task performance. Experimental cerebral hypoperfusion is also associated with overexpression of β-amyloid precursor protein. Amyloid deposits in cerebral vessels may compromise vasoactivity, result in vascular endothelial damage, and further increase the risk for dementia. Cerebral hypoperfusion deficits in functional imaging studies have been reported in nondemented individuals who later developed AD.

Like other observational studies, the possibility of residual confounding remains. Although we adjusted for phenotype (BMI) in our analysis, we did not measure other potential confounders such as genotype. Other possible explanations for our findings include preferential survival of subjects with low BP to 75 years or increasing chronic disease burden resulting in hypotension. Our results cannot be explained by preferential survival after enrollment, as subjects with high diastolic BP had longer follow-up (median 7.3 years) than subjects with low diastolic BP (median 5.2 years). Adjusting for the presence of chronic medical illnesses in our models did not alter the association of BP and dementia. The association of low BP with dementia is significant for AD. There were limited cases with vascular dementia to make conclusions. The role of vascular mechanisms in the pathogenesis of AD is under investigation. Vascular risk factors such as diabetes mellitus and hypertension may influence the risk of developing AD. In contrast, hypertension did not increase the risk of developing AD in an elderly cohort followed over 7 years.

The direction of the relationship in our older subjects is opposite to that seen in middle-aged populations where hypertension increases the risk of developing dementia.
dementia. The seemingly discrepant results among previous studies may in part be due to a significant age effect. The association between BP and dementia depends on the age at exposure measurement. Studies that have examined midlife hypertension have reported that it is a risk factor for dementia, reflecting its association with late-life atherosclerosis and vascular mechanisms of dementia. Studies that have done exposure ascertainment in older populations, especially over age 75, generally report that low BP is a risk factor for developing dementia. Aging is accompanied by significant structural and functional cardiovascular modifications. Diastolic BP plateaus at age 50, resulting in raised pulse pressure in the elderly. The raised systolic and pulse pressure with aging is a consequence of arterial stiffness. Hence, higher systemic perfusion pressures may be required to maintain adequate cerebral perfusion. Whereas treating hypertension is associated with reduced risk of dementia, our and other studies suggest that overtreatment may be associated with adverse cerebral outcomes in elderly individuals. Few studies have adequately represented very old subjects or incident cases of dementia after age 80, which may also contribute to the discrepant results.

Strengths of this study include the prospective design, long follow-up with low attrition, systematic BP ascertainment reducing measurement and observer bias, serial evaluations, standardized diagnostic procedures, and inclusion of the very old. Limitations include a relatively small sample size and the nature of our community-dwelling volunteer cohort, which was overwhelmingly Caucasian, potentially limiting generalizability of our results. Categorical examination of systolic and diastolic BP was based on small samples. For instance, there were only 57 subjects in the low diastolic category, of whom 24 developed dementia (HR 1.6). Interestingly, the Kungsholmen Study recently reported similar relative risk (1.5) for the association of low diastolic BP and dementia. A major difference compared with our study was that raised systolic BP was a risk factor for dementia. However, subjects with mildly to moderately elevated systolic BP (140 to 180 mm Hg) were used as the reference group in contrast to our normal systolic BP reference group (111 to 139 mm Hg). The median follow-up was 5 years compared with 6.7 years in our study.

Treatment guidelines of hypertension in the elderly are not established, with concerns raised about aggressive treatment in very old individuals. Previous studies have reported an inverse relationship between BP and the risk of strokes in elderly persons on antihypertensive medications. It was recently reported that the APOE-ε4 allele combined with low diastolic pressure greatly increased the risk of AD in older persons. Furthermore, antihypertensive therapy decreased the combined risk exerted by the APOE-ε4 allele with high systolic pressure on AD, but not with low diastolic pressure. Lowering systemic BP below a critical threshold may result in cerebral hypoperfusion, increasing the risk of dementia. The nature of hypotension and risk of dementia need to be examined in other cohorts with adequate representation of very old individuals. Our results suggest that low BP may be both the cause and the consequence of dementia. If our results are replicated, intervention studies are required to study whether maintaining BP at optimal levels reduces the risk of dementia in elderly individuals.

References


