Low Blood Pressure and Risk of Dementia in the Kungsholmen Project

A 6-Year Follow-up Study

Chengxuan Qiu, MD, MPH; Eva von Strauss, MSc, PhD; Johan Fastbom, MD, PhD; Bengt Winblad, MD, PhD; Laura Fratiglioni, MD, PhD

Background: Previous studies have reported a higher prevalence of dementia in persons with low blood pressure.

Objective: To examine whether low blood pressure is prospectively associated with the occurrence of Alzheimer disease and dementia in elderly people.

Subjects and Methods: A community-based, dementia-free cohort (n=1270) aged 75 to 101 years was longitudinally examined twice within 6 years to detect incident dementia using the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition criteria. Cox proportional hazards models were used to analyze blood pressure in association with dementia after adjustment for several potential confounders.

Results: During the 6-year period, 339 subjects were diagnosed with dementia, including 256 persons with Alzheimer disease. Subjects with very high systolic pressure (>120 mm Hg) had an adjusted relative risk of 1.5 (95% confidence interval [CI], 1.0-2.3; P =.07) for Alzheimer disease, and 1.6 (95% CI, 1.1-2.2) for dementia. Low systolic pressure (≤140 mm Hg) was not related to incident dementia. In contrast, high diastolic pressure (>90 mm Hg) was not associated with dementia incidence, whereas extremely low diastolic pressure (≤65 vs 66-90 mm Hg) produced an adjusted relative risk of 1.7 (95% CI, 1.1-2.4) for Alzheimer disease and 1.5 (95% CI, 1.0-2.1; P =.03) for dementia. The latter association was pronounced particularly in persons who used antihypertensive drugs.

Conclusions: Both low diastolic and high systolic pressure are associated with an increased risk of Alzheimer disease and dementia in this elderly population. The atherosclerotic process may explain the observed associations. In addition, low diastolic pressure may increase dementia risk by affecting cerebral perfusion.

Arch Neurol. 2003;60:223-228

Several longitudinal studies have shown that hypertension or elevated blood pressure, occurring in either middle age or late-life, increases the risk of Alzheimer disease or other types of dementia. Conversely, an increased prevalence of Alzheimer disease and dementia has been reported in persons with low blood pressure. Two possible hypotheses may explain the observed cross-sectional association: (1) Low blood pressure is a consequence of dementia, as the dementia process itself may lower blood pressure; and (2) low blood pressure increases the risk of Alzheimer disease and dementia. Few population-based prospective studies have specifically explored the latter topic so far. In a cohort of Japanese American men, low blood pressure (especially low diastolic pressure) during middle age, as well as elevated blood pressure, has been found to be associated with an increased risk for developing Alzheimer disease and dementia in late life, particularly among those who were never treated with antihypertensive medication. The pooled data from 2 studies in Europe have also shown an inverse relationship between level of blood pressure and incidence of dementia, especially in persons who used antihypertensive drugs. A recent community study from East Boston found no evidence for the association between high blood pressure and increased risk of Alzheimer disease. In contrast, blood pressure level measured 4 years prior to dementia diagnosis was inversely associated with the risk of subsequent Alzheimer disease in this population. These studies indicate that low blood pressure may predispose the risk of Alzheimer disease and dementia.

In a 3-year follow-up study performed on a random sample from the Kungsholmen population in Stockholm, Sweden, we found that the association between low systolic pressure (≤140 mm Hg) and
increased incidence of dementia was very dependent on initial cognitive functioning, which supports the hypothesis that low blood pressure may be an early correlate of the dementia process. The present study aims to further explore whether low blood pressure is prospectively associated with occurrence of Alzheimer disease and dementia by using the 6-year follow-up data from the entire cohort of the Kungsholmen Project.

### METHODS

#### BASELINE DATA COLLECTION

Arterial blood pressure (ie, systolic Korotkoff phase I and diastolic phase V) was measured on the right arm by trained nurses using a standardized random-zero mercury sphygmomanometer, with the subject in a sitting position after at least a 5-minute rest. If the first reading was abnormal (ie, systolic pressure ≥ 160 mm Hg or diastolic pressure ≥ 95 mm Hg), 2 additional readings were then taken. The mean of the second and third readings was used for analysis. Pulse pressure was calculated as the difference between systolic and diastolic pressure.

Data on age, sex, education, and cognitive functioning (assessed with the Mini-Mental State Examination [MMSE]) were collected at baseline interview according to standardized protocols. Educational level was measured by the maximum years of formal schooling and was categorized as less than 8 years (elementary or vocational training) or 8 years or more (high school or university). Information on vascular disorders at baseline was derived from the computerized Stockholm Inpatient Register system that encompassed all hospitals in the Stockholm area since 1969. Vascular diseases were diagnosed based on the International Classification of Diseases, Eighth Revision (ICD-8), including heart disease (ICD-8 codes 410-414, 427, and 428), cerebrovascular disease (ICD-8 codes 430-438), and diabetes mellitus (ICD-8 code 250). Information on medical drug use (both prescription and nonprescription) in the 2 weeks prior to the baseline interview was collected, and the drug containers and prescriptions were inspected to verify this information. Drug use was coded and classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Antihypertensive drugs were defined as all medicines potentially used for lowering blood pressure (ie, ATC codes C02, C03, and C07).

### STATISTICAL ANALYSIS

The incidence rates were calculated as the number of events (Alzheimer disease or dementia) divided by the follow-up time (person-years at risk). We considered the different types of dementia as competing causes of dementia, which meant that a subject who developed any type of dementia was no longer at risk of developing other types of dementia. Cox proportional hazards models were used to estimate the relative risk of developing Alzheimer disease or dementia in relation to baseline blood pressure. Blood pressure levels were first grouped into 5 categories following the criteria used in a previous study, with a minor modification (ie, instead of > 95 mm Hg, a cutoff of > 90 mm Hg was used due to limited numbers in the original category). Preliminary analysis showed that some adjacent groups had a similar incidence of dementia; for instance, subjects with systolic pressure between 141 and 160 mm Hg, and those with 161 to 180 mm Hg had a dementia incidence of 58.4 and 55.3 per 1000 person-years, respectively. These groups were then merged, leading to a final model with 3 categories of blood pressure (ie, systolic pressure: ≤ 140, 141-180 [reference], and > 180 mm Hg; diastolic pressure: ≤ 65, 66-90 [reference], and > 90 mm Hg). Age, sex, education, vascular disease, baseline MMSE score, antihypertensive drug use, and systolic pressure or diastolic pressure were included as covariates in all multiple regression models. As further adjustment for squared age and pulse pressure (as an indicator variable with 3 categories of ≤ 70, 70-84, > 84 mm Hg based on the tertiles) did not substantially affect the estimate of the association between blood pressure and risk of dementia, we only reported the results determined without controlling for squared age, and pulse pressure.
In addition, the results of the preliminary analysis indicated that "questionable dementia" and "clinically definite dementia" were related to blood pressure in a very similar way (ie, similar results were obtained when the category of "questionable dementia" was excluded from the analysis). Thus, in this study, both groups were considered to have dementia. All types of dementia and Alzheimer disease were used as separate outcomes in all Cox regression analyses.

**RESULTS**

Across a total of 5465 person-years (median, 5 years) of follow-up, 339 subjects were diagnosed with dementia, including 256 individuals with Alzheimer disease. Subjects who developed dementia during the follow-up period were older, more likely to be female, less educated, and with lower MMSE scores, and there were fewer persons with antihypertensive therapy at baseline than those who remained nondemented. However, the 2 groups did not differ significantly in terms of the frequency of vascular disease and means of systolic pressure, diastolic pressure, and pulse pressure (Table 1).

Table 2 presents the crude incidence rates and the adjusted relative risks of Alzheimer disease and all dementias by baseline blood pressure levels. For systolic pressure, very high systolic pressure (>180 vs 141-180 mm Hg) was significantly related to an increased incidence of dementia, while the relative risk for Alzheimer disease was marginally statistically significant. Subjects with low systolic pressure (≤140 vs 141-180 mm Hg) had the age-, sex-, and education-adjusted relative risks of 1.3 (95% confidence interval [CI], 1.0–1.7; *P* = .09) for Alzheimer disease and 1.2 (95% CI, 1.0–1.6; *P* = .09) for dementia. However, these relative risks considerably decreased after further adjustment for other potential confounders, especially baseline MMSE score and diastolic pressure (Table 2). High diastolic pressure (>90 vs 66-90 mm Hg) was not related to the risk of Alzheimer disease and dementia, but extremely low diastolic pressure (≤65 vs 66-90 mm Hg) was significantly associated with an increased incidence of Alzheimer disease and dementia, even when several potential confounders were taken into account (Table 2). These analyses were repeated using less extreme cut-offs for blood pressure, which produced results similar to those presented in Table 2. Compared with less than 130 mm Hg, for instance, systolic pressure between 130 and 159 mm Hg, and 160 mm Hg or greater was related to adjusted relative risks of 1.4 (95% CI, 0.9–2.2) and 1.4 (95% CI, 0.9–2.4) for Alzheimer disease, and 1.3 (95% CI, 0.9–2.0) and 1.3 (95% CI, 0.9–2.0) for dementia.
Use of Antihypertensive Drugs

All Dementias

All Dementias

Table 3. Relative Risks and 95% Confidence Intervals (CIs) of Alzheimer Disease and All Types of Dementia Associated With Baseline Blood Pressure Levels by Antihypertensive Drug Use

<table>
<thead>
<tr>
<th>Blood Pressure, mm Hg</th>
<th>No Use of Antihypertensive Drugs</th>
<th>Use of Antihypertensive Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alzheimer Disease RR (95% CI)</td>
<td>Alzheimer Disease RR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>All Dementias RR (95% CI)</td>
<td>All Dementias RR (95% CI)</td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>No. of Subjects</td>
<td>No. of Subjects</td>
</tr>
<tr>
<td>≤140</td>
<td>230</td>
<td>52</td>
</tr>
<tr>
<td>141-180</td>
<td>415</td>
<td>92</td>
</tr>
<tr>
<td>&gt;180</td>
<td>58</td>
<td>19</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>No. of Subjects</td>
<td>No. of Subjects</td>
</tr>
<tr>
<td>≤65</td>
<td>69</td>
<td>17</td>
</tr>
<tr>
<td>66-90</td>
<td>534</td>
<td>122</td>
</tr>
<tr>
<td>&gt;90</td>
<td>100</td>
<td>24</td>
</tr>
</tbody>
</table>

Abbreviation: RR, relative risk.

*Both RR and 95% CI were estimated after adjustment for age, sex, education, vascular disease, baseline Mini-Mental State Examination score, and if applicable, diastolic or systolic pressure.

†P = .06.

In this elderly Swedish population, aged 75 years and older, we found that not only high systolic pressure, but also low diastolic pressure, was associated with an increased incidence of Alzheimer disease and dementia. The risk effect of low diastolic pressure on dementia was pronounced particularly among antihypertensive drug users. These results could be confirmed even when blood pressure was measured at least 6 years before diagnosis.

Numerous population-based studies have examined the longitudinal relationship between blood pressure and risk of dementia. Although the findings from these studies have been inconsistent, an association between elevated blood pressure and increased incidence of Alzheimer disease or other dementias is reported in most previous studies, suggesting that high blood pressure (especially high systolic pressure) may be a risk factor for Alzheimer disease and dementia. These findings from observational studies are supported by a randomized placebo-controlled clinical trial (Syst-Eur), which showed that active treatment of isolated systolic hypertension in elderly persons decreased the dementia incidence by 50% throughout 2 years. Our population-based study provides further evidence for the association between high systolic pressure and elevated dementia incidence. In addition, we could confirm our previous report of a protective effect of antihypertensive therapy against Alzheimer disease and dementia in the general elderly population. However, we found that antihypertensive medication could not substantially modify the increased dementia risk in subjects with high systolic pressure. This suggests that very elderly people with hypertension (especially systolic hypertension) whose high blood pressure is treated, but not well controlled, remain at an increased risk for developing dementing disorders. The etiological role of hypertension in vascular...
dementia has been well documented. Elevated blood pressure may be also connected with Alzheimer disease in different ways. First, the neuropathological studies have linked elevated blood pressure to the density of neuritic plaques and neurofibrillary tangles,21,22 which are the histopathological hallmarks of Alzheimer disease. Second, long-standing hypertension may be linked to Alzheimer disease by contributing to atherosclerosis,23 white matter lesions,24 blood-brain barrier disturbance,25 and brain atrophy.26 Third, cerebrovascular disease secondary to hypertension may accelerate the clinical expression of Alzheimer disease in the presence of coexisting Alzheimer pathological changes in the brain.27,28

An association between low blood pressure and high risk of subsequent Alzheimer disease or other dementias has been previously suggested.29-31 Our follow-up data further indicate that low, rather than high, diastolic pressure is prospectively associated with an increased incidence of Alzheimer disease and dementia. These findings are in good line with the East Boston study,3 in which low, but not high, diastolic pressure (<70 mm Hg) tended to increase the risk of subsequent Alzheimer disease. Furthermore, we found that the association between low diastolic pressure and increased risk of Alzheimer disease and dementia was evident particularly among the users of antihypertensive drugs. Different mechanisms may underlie this association. First, evidence has shown that cerebral hypoperfusion seems to precede the neurodegenerative pathological changes29; therefore, it is likely that in advanced ages, a reduction in cerebral blood flow associated with hypotension, particularly when treated with antihypertensive drugs, may play a critical role in the pathogenesis of Alzheimer disease and dementia.30,31 An alternative explanation relies on the fact that low diastolic pressure, as well as high systolic pressure, is an indicator of increased large arterial stiffness and widespread atherosclerosis in elderly people.32-34 These pathological changes have already been linked to dementia and Alzheimer disease.23,35 As expected, heart disease, cerebrovascular disease, and diabetes mellitus were more common among antihypertensive drug users than nonusers in this population (32.1% vs 12.9%, P < .001). It is therefore biologically plausible that the association between low diastolic pressure and increased risk of Alzheimer disease and dementia may be stronger in individuals affected by these vascular disorders.

The finding of low diastolic pressure in association with Alzheimer disease and dementia in elderly people may have relevant implications for clinical practice and dementia prevention. First, diastolic pressure needs to be closely monitored when high systolic pressure is targeted with clinical treatment. The protective effect of appropriate antihypertensive treatment on cardiovascular disease and stroke has been well established.30 In terms of dementia prevention, however, our findings may call into question the presumption that for antihypertensive treatment in the very elderly, “the lower the better.” Second, as low diastolic pressure may predispose a subpopulation to Alzheimer disease and dementia, low diastolic pressure can be used to identify high-risk individuals.

Several potential limitations of this study deserve mentioning. First, the defined population of the current study consisted of subjects with a minimum age of 75 years at entry. The pathophysiological implications of blood pressure levels are largely age-dependent.33,37 Our findings may therefore not totally apply to younger age groups. Second, the diagnosis of Alzheimer disease and dementia was made on a clinical basis, as the use of imaging techniques was unfeasible in a large-scale population study started in the 1980s. However, the cerebral vascular lesions detected with neuroimaging are difficult to determine as causes of dementia since the coexistence of Alzheimer disease or dementia and vascular changes in the brain are quite common in the very elderly.30,38 Third, dementia cases might have been under-diagnosed among the deceased subjects, which could only have resulted in an underestimation of the association between both low and high blood pressure and incidence of dementia due to the selective survival related to blood pressure levels.39 Finally, the blood pressure measurement made on a single occasion might diminish the data accuracy, which could attenuate the association between blood pressure and dementia.

In summary, our data indicate that both high systolic and low diastolic pressure are possible risk factors for Alzheimer disease and dementia in elderly people. In view of the clinical implications, further investigations are imperative to elucidate whether the antihypertensive treatment could strengthen the association between low diastolic blood pressure and risk of dementia.

Accepted for publication September 17, 2002.

Author contributions: Study concept and design (Drs Qiu, von Strauss, Winblad, and Fratiglioni); acquisition of data (Drs von Strauss, Fastbom, Winblad, and Fratiglioni); analysis and interpretation of data (Drs Qiu, Winblad, and Fratiglioni); drafting of the manuscript (Drs Qiu and Fratiglioni); critical revision of the manuscript for important intellectual content (Drs von Strauss, Fastbom, Winblad, and Fratiglioni); statistical expertise (Drs Qiu, von Strauss, and Fratiglioni); obtained funding (Drs Qiu, von Strauss, Winblad, and Fratiglioni); administrative, technical, and material support (Drs von Strauss, Winblad, and Fratiglioni); study supervision (Drs Winblad and Fratiglioni).

This study received research grants from the Swedish Research Council (Stockholm), the Swedish Municipal Pension Institute (Stockholm), the Gamla Tjänarinnor Foundation (Stockholm), the Swedish Alzheimer Foundation (Lund), and the Gun and Bertil Stohne Foundation (Stockholm).

We thank all the members of the Kungsholmen Project study group for their cooperation in data collection and management.

Corresponding author and reprints: Chengxuan Qiu, MD, MPH, Stockholm Gerontology Research Center, Box 6401 (Olivecronas väg 4), S-113 82 Stockholm, Sweden (e-mail: chengxuan.qiu@neurotec.ki.se).

REFERENCES


