Pulse Pressure and Risk of Alzheimer Disease in Persons Aged 75 Years and Older
A Community-Based, Longitudinal Study
Chengxuan Qiu, MD, MPH; Bengt Winblad, MD, PhD; Matti Viitanen, MD, PhD; Laura Fratiglioni, MD, PhD

Background and Purpose—Elevated blood pressure has been found to increase the risk of dementia, including Alzheimer disease. We sought to investigate whether pulse pressure was predictive of Alzheimer disease and dementia.

Methods—A community-based, dementia-free cohort (n=1270) aged ≥75 years was clinically examined twice over 6 years to detect incident dementia with the use of the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition. Cox proportional hazards models were used to analyze pulse pressure in association with incident Alzheimer disease and dementia after adjustment for several potential confounders, including systolic pressure and diastolic pressure.

Results—During the 5464.6 person-years (median, 4.7 years) of follow-up, 339 subjects developed dementia, including 256 Alzheimer disease cases. Pulse pressure as a continuous variable was not statistically related to the risk of Alzheimer disease and dementia. In the categorical analysis, however, in comparison with median tertile of pulse pressure (70 to 84 mm Hg), subjects with higher pulse pressure had adjusted relative risks (95% CI) of 1.4 (1.0 to 2.0; \( P=0.04 \)) for Alzheimer disease and 1.3 (0.9 to 1.7) for dementia. The corresponding figures related to lower pulse pressure were 1.7 (1.2 to 2.3) for Alzheimer disease and 1.4 (1.0 to 1.9; \( P=0.03 \)) for dementia. This association was particularly pronounced among women.

Conclusions—Higher pulse pressure is associated with increased risk for Alzheimer disease and dementia in old adults, which is probably due to artery stiffness and severe atherosclerosis. Poor cerebral perfusion related to decreased pulse pressure may explain the association between lower pulse pressure and increased dementia risk. (Stroke. 2003;34:594-599.)

Key Words: Alzheimer disease ■ blood pressure ■ dementia ■ longitudinal studies ■ risk factors

Evidence has indicated that elevated blood pressure, occurring in either middle age or late life, may be involved in the development of dementia, including Alzheimer disease (AD).\(^1\)\(^-\)\(^7\) Usually, the relationship between level of either systolic or diastolic pressure and risk of AD and dementia has been investigated in most previous studies addressing this issue. Few population-based studies, however, are currently available concerning the association between level of pulse pressure and occurrence of dementia. Recently, high pulse pressure has been linked to an increased risk of cardiac and cerebrovascular events.\(^8\)\(^-\)\(^12\) Both systolic pressure and diastolic pressure increase with age up to approximately the sixth decade of life, and thereafter systolic pressure continuously increases while diastolic pressure starts to decrease, resulting in a steep rise in pulse pressure.\(^13\)\(^,\)\(^14\) High pulse pressure in old people is recognized as a marker of increased artery stiffness and widespread atherosclerosis.\(^15\)\(^-\)\(^18\) In addition, dementia and AD have been found to be related to atherosclerosis, cardiac events, and cerebrovascular diseases in a number of studies.\(^19\)\(^-\)\(^22\) It is therefore biologically plausible to hypothesize that higher pulse pressure should be related to the development of AD and dementia in old people. However, a recent community-based study found no evidence for the association between higher pulse pressure and risk of subsequent AD.\(^23\) In the present study we examined whether pulse pressure was predictive of incident AD and dementia using the 6-year follow-up data from the Kungsholmen Project.
were diagnosed as being free of dementia. Among them, 172 subjects refused to participate in the first follow-up examination (1991–1993) or had moved out of Stockholm before the examination, and baseline blood pressure readings were missing for 31 subjects, leaving 1270 subjects for the current analysis. Of these individuals, 967 subjects received a full dementia workup during the first follow-up period, which included a structured interview by trained nurses, a comprehensive clinical examination by physicians, and psychological assessments by neuropsychologists. Among those who remained free of dementia at the first follow-up examination (n = 772), 43 persons refused to participate in the second follow-up examination (1994–1996). Medical records and death certificates were available for all individuals who died during the first (n = 303) or second (n = 170) follow-up period. All parts of the project received approval from the Ethics Committee of Karolinska Institutet.

Baseline Data Collection

Measurement of Blood Pressure

Arterial blood pressure (ie, systolic Korotkoff phase I and diastolic phase V) was measured twice on the same occasion 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.26 Pulse pressure was defined as the difference between systolic pressure and diastolic pressure.

Assessment of Covariates

Data on age, sex, education, and cognitive functioning (assessed with the Mini-Mental State Examination [MMSE]) were collected according to standard protocols.24,25 Education was measured by total years of formal schooling and dichotomized into <8 years (elementary school and vocational training) and ≥8 years (high school and university).27 Pulse rate (beats per minute) was counted for 1 minute. Information on vascular disorders at baseline was derived from the computerized Stockholm Inpatient Register system, which encompassed the discharge diagnoses from all hospitals in the Stockholm area since 1969, and included heart disease (International Classification of Diseases, Eighth Revision [ICD-8] codes 410 to 414, 427, and 428), cerebrovascular disease (ICD-8 codes 430 to 438), and diabetes mellitus (ICD-8 code 250). Information on medical drug use was collected for the 2 weeks preceding the baseline survey. We inquired about use of both prescription and nonprescription drugs, and, if possible, the drug containers and prescriptions were inspected to verify this information. Medical drugs were coded and classified according to the Anatomical Therapeutic Chemical (ATC) classification system.26 Antihypertensive drugs were defined as all medicines potentially used for lowering blood pressure (ie, ATC codes C02, C03, and C07). The genomic DNA was prepared from peripheral blood samples that were taken at baseline, and a standard polymerase chain reaction was used for APOE genotyping.29 APOE genotypes were available for 76.1% (n = 966) of the study population (n = 1270).

Diagnosis of Incident Dementia and AD

The incident dementia cases were all individuals who developed dementia over the entire follow-up period. We used the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition criteria20 to define the incident dementia cases with a 3-step diagnostic procedure, as previously described.25,31,32 In brief, 2 examining physicians independently made a preliminary diagnosis, and a third opinion was sought in case of disagreement. The diagnosis of AD requires gradual onset, progressive deterioration, and lack of any other specific causes of dementia. Our criteria for AD were similar to those from the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association53 for probable AD. For deceased subjects, 2 physicians made dementia or AD diagnosis by reviewing the medical records and death certificates.

Statistical Analysis

The incidence rates were calculated as the number of events (AD or dementia) divided by person-years of follow-up. We examined the correlations between pulse pressure and other continuous variables using linear correlation analysis after adjustment for age and sex. Multiple Cox proportional hazards models were constructed to estimate the relative risk and 95% CI of AD and dementia related to baseline pulse pressure. Pulse pressure was first used as a continuous variable (per 10–mm Hg increment). Then all subjects were divided into 3 categories by reference to tertiles of pulse pressure, ie, <70 (lower), 70 to 84 (medium), and ≥84 (higher) mm Hg. We treated the medium category as a reference group because preliminary analyses showed a nonlinear relationship between tertile of pulse pressure and risk of dementia. Interaction was examined by including the independent variables and their cross-product term in the same model. Stratified analyses were further performed if a statistical interaction was suggested. We considered age (years), sex, education, vascular disease, baseline MMSE score, antihypertensive drug use, pulse rate, APOE genotype (indicator variable with 4 categories of ε2/ε2 or ε2/ε3, ε3/ε3, any ε4, and missing values), and systolic pressure (indicator variable with 3 categories of <140, 140 to 180, and ≥180 mm Hg) as covariates in multiple analyses. All types of dementia and AD were used as separate outcomes in all Cox regression analyses.

Results

Over the 5464.6 person-years of follow-up (median, 4.7; range, 0.1 to 8.3 years; the minimum follow-up period was due to death), 339 individuals were diagnosed with dementia, including 256 AD cases. Table 1 shows the baseline characteristics of the study population by pulse pressure levels. There was no statistically significant difference in the distributions of sex, vascular disease, and APOE genotype among pulse pressure groups. However, a higher proportion of antihypertensive drug users and less educated subjects was seen in subjects with higher pulse pressure than those with lower pulse pressure (P < 0.05). Linear correlation analysis suggested that pulse pressure (mm Hg) was strongly correlated with systolic pressure (mm Hg) (partial r = 0.87, P < 0.01), weakly correlated with baseline MMSE score (partial r = 0.08, P = 0.01) and age (years) (partial r = 0.05, P = 0.07, marginally significant), and not significantly related to diastolic pressure (mm Hg) (partial r = 0.05, P = 0.10) and pulse rate (bpm) (partial r = −0.01, P = 0.78).

Pulse Pressure and Risk of Incident AD and Dementia

Each 10–mm Hg increment in pulse pressure was associated with adjusted (systolic pressure was not included in the model because of the possible colinearity with pulse pressure) relative risks of 1.06 (95% CI, 0.99 to 1.13) for AD and 1.05 (95% CI, 0.99 to 1.11) for dementia. Table 2 shows the incidence rates as well as relative risks for AD and dementia with basic and multiple adjustments by tertiles of pulse pressure. Compared with a pulse pressure of 70 to 84 mm Hg, subjects with either higher or lower pulse pressure were at an increased risk for developing AD and dementia, even when both systolic and diastolic pressures were taken into account (Table 2).

There was a statistical interaction between lower pulse pressure (<70 versus 70 to 84 mm Hg) and sex (women versus men) on dementia risk (adjusted relative risk for the interaction term, 2.1; 95% CI, 1.0 to 4.1; P = 0.04), but the
interactive effect on AD did not reach a statistically significant level (relative risk with multiple adjustments, 2.0; 95% CI, 0.8 to 4.8; \( P < 0.12 \)). The relationship between pulse pressure and incident AD and dementia was further examined by sex stratification. The U-shaped relationship between level of pulse pressure and risk of AD and dementia was evident in women but not in men (Figure). There was no statistical interaction of pulse pressure with age, vascular disease, and antihypertensive drug use on the development of AD and dementia.

Supplementary Analyses
Supplementary analyses were performed to further clarify the relationship between pulse pressure and risk of AD and dementia. First, to assess the effect of baseline cognitive impairment on the observed results, the analyses were repeated in the subgroup of subjects with baseline MMSE score \( \geq 24 \) (n=1183; 293 dementia cases, 219 AD cases), which yielded results similar to those shown in Table 2. Compared with pulse pressure of 70 to 84 mm Hg, for instance, persons with higher pulse pressure had relative risks with multiple adjustments of 1.6 (95% CI, 1.1 to 2.3) for AD and 1.3 (95% CI, 1.0 to 1.8; \( P = 0.07 \)) for dementia, whereas lower pulse pressure produced the adjusted relative risks of 1.8 (95% CI, 1.2 to 2.6) for AD and 1.4 (95% CI, 1.0 to 2.0; \( P = 0.03 \)) for dementia.

Second, for deceased subjects the dementia diagnoses were based on medical records and death certificates, which might result in an underestimation of dementia cases. To address this issue, we performed the same analyses in those who

### TABLE 1. Baseline Characteristics of the Initial Dementia-Free Cohort of the Kungsholmen Project by Pulse Pressure Levels (n=1270)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pulse Pressure (mm Hg)</th>
<th>Lower (&lt;70)</th>
<th>Medium (70–84)</th>
<th>Higher (&gt;84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects, n (%)</td>
<td>464 (36.5)</td>
<td>397 (31.3)</td>
<td>409 (32.2)</td>
<td></td>
</tr>
<tr>
<td>Age (y), mean (SD)</td>
<td>81.1 (5.1)</td>
<td>81.4 (4.8)</td>
<td>82.0 (5.1)</td>
<td></td>
</tr>
<tr>
<td>Female sex, %</td>
<td>74.8</td>
<td>73.8</td>
<td>76.8</td>
<td></td>
</tr>
<tr>
<td>Education=8 years, %</td>
<td>43.3</td>
<td>43.1</td>
<td>35.5</td>
<td></td>
</tr>
<tr>
<td>Vascular disease*, %</td>
<td>22.4</td>
<td>19.4</td>
<td>22.5</td>
<td></td>
</tr>
<tr>
<td>Antihypertensive drug use, %</td>
<td>40.3</td>
<td>47.6</td>
<td>46.7</td>
<td></td>
</tr>
<tr>
<td>APOE genotype†, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ε2/ε2 or ε2/ε3</td>
<td>10.4</td>
<td>11.4</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>ε3/ε3</td>
<td>46.1</td>
<td>42.8</td>
<td>42.3</td>
<td></td>
</tr>
<tr>
<td>Any ε4</td>
<td>20.9</td>
<td>23.4</td>
<td>21.8</td>
<td></td>
</tr>
<tr>
<td>MMSE score‡, mean (SD)</td>
<td>26.5 (3.0)</td>
<td>26.7 (2.9)</td>
<td>26.8 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Pulse rate§ (bpm), mean (SD)</td>
<td>73.6 (10.3)</td>
<td>73.6 (9.4)</td>
<td>73.8 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Systolic pressure (mm Hg), mean (SD)</td>
<td>136.2 (13.5)</td>
<td>155.9 (12.4)</td>
<td>177.0 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg), mean (SD)</td>
<td>80.5 (10.4)</td>
<td>81.1 (11.2)</td>
<td>81.5 (10.9)</td>
<td></td>
</tr>
<tr>
<td>Pulse pressure (mm Hg), mean (SD)</td>
<td>55.7 (8.5)</td>
<td>74.8 (4.4)</td>
<td>95.4 (10.2)</td>
<td></td>
</tr>
</tbody>
</table>

*At least one of heart disease, cerebrovascular disease, or diabetes mellitus was present.
†Data on APOE genotypes were missing for 335 subjects, including 22.6%, 22.4%, and 26.9% of subjects with lower, medium, and higher pulse pressure, respectively.
‡MMSE indicates Mini-Mental State Examination. MMSE score was from 0 (worst) to 30 (best).
§Information on pulse rate was missing for 27 subjects, and the mean value of 74 bpm was used for these subjects in the analysis.

IR indicates incidence rates (per 1000 person-years).
*The relative risks (RRs) and 95% confidence intervals (CIs) were estimated after adjustment for age, sex, and education.
†The RRs and 95% CIs were estimated after adjustment for age, sex, education, baseline MMSE score, vascular disease, antihypertensive drug use, pulse rate, and APOE genotype as well as systolic pressure and diastolic pressure.
‡\( P < 0.05 \).
underwent the thorough clinical examination during the first follow-up (n=967; 316 dementia cases, 247 AD cases). Higher pulse pressure (>84 versus 70 to 84 mm Hg) led to relative risks with multiple adjustments of 1.9 (95% CI, 1.3 to 2.7) for AD and 1.6 (95% CI, 1.2 to 2.3) for dementia. The corresponding figures related to lower pulse pressure (<70 versus 70 to 84 mm Hg) were 2.0 (95% CI, 1.4 to 2.9) for AD and 1.7 (95% CI, 1.2 to 2.3) for dementia.

Finally, at baseline, only participants with a MMSE score <24 underwent the comprehensive clinical examination necessary for dementia diagnosis. As a result, some persons with a higher MMSE score but with very mild dementia might have been missed at baseline and included in our initial dementia-free cohort, which could affect the estimate of association between pulse pressure and dementia. To avoid this dilution, the analysis was repeated in the dementia-free cohort identified at the first follow-up examination (n=729; 121 dementia cases, 94 AD cases), which produced a pattern of association between level of pulse pressure and risk of AD and dementia similar to those from the entire follow-up period (data not shown).

**Discussion**

In this community-based, longitudinal study of persons aged ≥75 years, we found a U-shaped relationship between level of pulse pressure and incidence of AD and all dementias, as both higher and lower tertiles of pulse pressure were associated with an increased risk of the disease. This pulse pressure–dementia association was particularly pronounced in women. The observed associations were independent of systolic pressure, diastolic pressure, antihypertensive drug use, APOE genotype, and several other potential confounders.

Few population-based studies have thus far specifically examined the relation between pulse pressure and dementia. In the community study of East Boston, pulse pressure (as a continuous variable) measured 4 years before dementia assessment showed a marginally significant inverse association with AD risk. When similar analyses were performed in our study, we found that each 10-mm Hg increment in pulse pressure was related to a slightly increased risk of AD and dementia (approximately 5%), although the association was not statistically significant. In the categorical analysis, the East Boston study found an increased AD risk in subjects with a lower pulse pressure (50 to 59 versus 60 to 69 mm Hg) but not in those with a higher pulse pressure (≥70 mm Hg). Differences in age distribution of the 2 study populations may explain the discrepancies. Because our cohort is considerably older than that of the East Boston study and pulse pressure increases with age, low pulse pressure may be defined at different levels. We could not completely replicate the findings from the East Boston study by using the same cutoffs of pulse pressure because, as expected, the distribution patterns of pulse pressure were much different.

Several studies have shown that dementia is associated with atherosclerosis, cardiac events, and cerebrovascular disorders. Increased pulse pressure in old people, which results from an increase in systolic pressure and a decrease in diastolic pressure, is believed to be primarily due to increased arterial stiffness or widespread atherosclerosis. Differences in age distribution of the 2 study populations may explain the discrepancies. Because our cohort is considerably older than that of the East Boston study and pulse pressure increases with age, low pulse pressure may be defined at different levels. We could not completely replicate the findings from the East Boston study by using the same cutoffs of pulse pressure because, as expected, the distribution patterns of pulse pressure were much different.

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estimated after adjustment for several potential confounders, including baseline cognitive functioning.

A major problem concerns the association between higher pulse pressure and risk of the degenerative dementing disorders such as AD. Previous studies have shown an association between hypertension and neuropathological markers of AD, suggesting that elevated blood pressure may play a direct role in the pathogenesis or clinical progression of AD by affecting the development of neuropathological lesions of AD or by causing brain atrophy.  

Alternatively, clinically silent cerebrovascular lesions caused by chronic hypertension could act in an additive way with the degenerative lesions of AD to produce dementia in individuals otherwise not having sufficient neurodegenerative damage to develop AD. These mechanisms may emphasize the association between higher pulse pressure and increased AD risk. Similarly, lower pulse pressure may contribute to the development of AD through cerebral hyperfusion.

The strengths of this study are the community-based design, the relatively long-term follow-up, and the adjustment for multiple potential confounders. However, several methodological issues deserve mention. First, the study population consisted of individuals with a minimum age of 75 years at entry. Dynamic changes in blood pressure and pulse pressure as well as pathophysiological implications of these changes are largely age dependent. Therefore, our findings may not totally apply to younger persons. Second, the blood pressure measurement being made on a single occasion may diminish the data accuracy, which might attenuate the association between pulse pressure and dementia. Third, information on vascular diseases was taken from the inpatient register system, which would identify more severe cases and miss mild cases. However, controlling for vascular disease in the present study had a slight effect on the association between pulse pressure and dementia. Given this slight effect due to severe cases of vascular disease, it is likely that mild cases of the disease may have even less effect. Moreover, our previous study showed similar results concerning blood pressure in relation to cognitive performance by controlling for either the self-reported data or the register data of cardiovascular disease. Nevertheless, although several major confounders were taken into account in the analyses, some unknown confounding effects might still be present. Finally, the diagnosis of AD and dementia was made on a clinical basis, and neuroimaging was not a part of the diagnostic procedure. However, the clinical assessment for dementia diagnosis was comprehensive and precise in this project. Moreover, the cerebral vascular lesions detected with neuroimaging are difficult to determine as causes of dementia since coexistence of AD and vascular changes in the brain is fairly common in very old people. The findings from this community-based prospective study, if replicated, have several implications for clinical practice and dementia prevention. First, pulse pressure can be used to identify the high-risk population for AD and dementia. Second, the therapeutic options for high blood pressure aimed at reducing pulse pressure and severity of artery stiffness are relevant for dementia prevention. Third, the potential confounding effect of pulse pressure should be controlled for in studies investigating the role of vascular risk factors or disorders in AD and dementia.

We conclude that an increased pulse pressure, which is a clinical indicator of large-artery stiffness and severe atherosclerosis, can be predictive of AD and dementia. In addition, lower pulse pressure may increase the risk of AD and dementia through a deleterious effect on cerebral perfusion. These findings, as well as the suggested underlying mechanisms, need confirmation.

Acknowledgments

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