Decline in Blood Pressure Over Time and Risk of Dementia
A Longitudinal Study From the Kungsholmen Project

Chengxuan Qiu, MD, PhD; Eva von Strauss, PhD; Bengt Winblad, MD, PhD; Laura Fratiglioni, MD, PhD

Background and Purpose—Low blood pressure has been related to an increased risk of dementia. We sought to verify blood pressure variations before and after a dementia diagnosis and to relate blood pressure decline to subsequent Alzheimer disease and dementia.

Methods—A community dementia-free cohort aged ≥75 years (n=947) underwent follow-up examinations twice over a period of 6 years to detect dementia cases (Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised [DSM-III-R] criteria, n=304). Blood pressure variation before and after dementia diagnosis was verified with linear mixed-effects models. Using the dementia-free cohort identified at first follow-up (n=719), the association between blood pressure decline from baseline to first follow-up and subsequent risk of dementia was examined.

Results—Blood pressure markedly decreased over 3 years before dementia diagnosis and afterward, whereas no substantial decline was present 3 to 6 years before the diagnosis. However, among subjects with baseline systolic pressure <160 mm Hg, systolic pressure decline ≥15 mm Hg occurring 3 to 6 years before diagnosis was associated with relative risks (95% CI) of 3.1 (1.3 to 7.0) for Alzheimer disease and 3.1 (1.5 to 6.3) for dementia. There was a dose–response relationship between systolic pressure decline and dementia risk in subjects with vascular disease.

Conclusions—Blood pressure starts to decrease only 3 years before dementia diagnosis and continues to decline afterward. A greater decline in systolic pressure occurring 3 to 6 years before diagnosis is associated with an increased risk of dementia only in older people with already low blood pressure or affected by vascular disorders. (Stroke. 2004;35:1810-1815.)

Key Words: Alzheimer disease ▪ blood pressure ▪ dementia ▪ epidemiology

Long-term follow-up studies suggest that elevated blood pressure in midlife is a risk factor for dementia and Alzheimer disease (AD).1–3 However, the relationship between blood pressure and dementia is complicated because an inverse association between level of blood pressure and risk of dementia was also found in numerous follow-up studies.4–6 In addition, we previously reported that blood pressure reduction was associated with concurrently detected cognitive impairment and dementia.7,8 These findings imply 3 possible explanations: (1) the dementing process lowers blood pressure;9,10 (2) low blood pressure and blood pressure reduction increase dementia risk;5,6 and (3) low blood pressure or blood pressure decline and dementia share common risk factors.1,11

Clinicopathologic data showed that blood pressure decreased after AD diagnosis in which blood pressure decline was considered a consequence of degeneration and dysfunction of neurons that regulated blood pressure.12 Indeed, cross-sectional studies frequently indicate an association between low blood pressure and increased dementia prevalence.13–15 The Göteborg longitudinal study revealed that blood pressure started to decline several years before dementia onset;1 however, the East Boston cohort study found that the mean systolic and diastolic pressure varied little by AD status over 15 years of observation.16 Thus, the influence of dementia process on blood pressure remains inconclusive. As the time frame is crucial to disentangle the relation of blood pressure to dementia, in the present study we intended (1) to verify blood pressure variations over a period of 6 years before dementia diagnosis and a period of 3 years thereafter; (2) to examine the association between blood pressure decline occurring 3 to 6 years before diagnosis and risk of subsequent AD and dementia; and (3) to evaluate the potential modifying effects by factors such as initial blood pressure level and vascular disorders.

Subjects and Methods

Study Population
The study population was derived from the Kungsholmen project, a community-based cohort study of aging and dementia that has been...
fully described elsewhere.\textsuperscript{17,18} The project included all inhabitants that were $\geq$75 years in October 1987 and were living in the Kungsholmen district of Stockholm, Sweden. Of all eligible subjects ($n=2368$), 1473 were identified as nondemented by a 2-phase design at baseline (1987 to 1989, Time 1). Of those, 172 subjects either refused to undergo the first follow-up evaluation (1991 to 1993, Time 2) or had moved, and 314 had died before the evaluation. A further 40 subjects were excluded because of missing blood pressure readings. Thus, the current study consisted of 947 baseline nondemented subjects with blood pressure readings at both Time 1 and Time 2. Of these persons, 761 remained free of dementia at Time 2, and only 42 refused to undertake the second follow-up evaluation (1994 to 1996, Time 3). Medical records and death certificates were available for all 167 deceased subjects during second follow-up. All parts of the project received approval from the Ethics Committee at Karolinska Institutet.

### Data Collection

#### Blood Pressure

Arterial blood pressure (systolic Korotkoff phase I and diastolic phase V) was measured at baseline and at follow-ups using a mercury sphygmomanometer with the subject in a sitting position after a minimum of 5 minutes of rest.\textsuperscript{13} If the first reading was abnormal (systolic pressure $\geq$160 or diastolic pressure $\geq$95 mm Hg), 2 additional readings were then taken. The mean of the second and third readings was used for analysis. Pulse pressure was defined as the difference between systolic pressure and diastolic pressure.\textsuperscript{19}

#### Baseline Covariates

Demographics (age, sex, and education) were collected following standardized protocols.\textsuperscript{17,18,20} Cognitive functioning was assessed with the Mini-Mental State Examination (MMSE). Information on history of heart disease (International Classification of Diseases, 8th revision) ICD-8 codes 410 to 414, 427, and 428), stroke (ICD-8 codes 430 to 438), and diabetes mellitus (ICD-8 code 250) was derived from the inpatient register system that encompassed all hospitals in Stockholm since 1969. This register system recorded up to 6 different disorders identified during each hospitalization. Functional status was measured with the Katz index of activities of daily living (ADL). Functional disability was defined as the need for assistance in any of the 6 basic ADL. Data on medical drug use in the 2 weeks preceding baseline survey were collected from subjects or informants and verified by inspecting the drug containers and prescriptions.\textsuperscript{21} Antihypertensive drugs were defined as all medicines potentially used for lowering blood pressure (Anatomical Therapeutic Chemical classification, codes C02, C03, and C07). Genomic DNA was prepared from peripheral blood samples, and apoE allelic status was determined using a standard procedure.\textsuperscript{22}

#### Diagnosis of Dementia and Alzheimer Disease

All participants at each follow-up underwent an extensive medical examination and comprehensive cognitive assessments. We used the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised (DSM-III-R) criteria\textsuperscript{23} to define dementia cases with a 3-step diagnostic procedure: two examining physicians independently made a preliminary diagnosis and a third opinion was asked for in case of disagreement.\textsuperscript{17,18} The diagnosis for AD required gradual onset, progressive deterioration, and lack of any other specific causes of dementia. For deceased subjects, 2 physicians made dementia or AD diagnosis by reviewing medical records and death certificates.

### Data Analysis

Data were analyzed in 2 separate lines. First, we plotted line graphics showing variations in mean blood pressure over time by dementia status diagnosed at different follow-ups. To account for the intrasubject correlations among repeated-measures, the linear mixed-effects models were used to statistically verify the effect of dementia on blood pressure. Then, we used Cox models to estimate the association between blood pressure decline from Time 1 to Time 2 and risk of dementia detected at Time 3, in which blood pressure decline was treated as a continuous variable (per 10-mm Hg decrease) or as a categorical variable (no decline, decline 1 to 14, and decline $\geq$15 mm Hg). Statistical interaction was examined by including the independent variables and their cross-product term in the model. Stratified analysis was performed if statistical interaction was suggested. Age, sex, education, vascular disease, baseline MMSE score, antihypertensive drug use, functional disability (indicator variables: no, any, and missing), apoE genotype (indicator variables: e3/e3, e2/e2 or e2/e3, any e4, and missing), and duration of first follow-up were considered as covariates. Dementia and AD were used as separate outcomes in all Cox regression analyses.

### Results

Of the 947 subjects, dementia was diagnosed in 186 subjects (147 with AD) at first follow-up (median, 3.5; range, 1.7 to 5.2 years) and 118 (91 with AD) at second follow-up (median, 3.0; range, 0.1 to 4.8 years). At second follow-up, blood pressure readings were available for 442 nondemented subjects, 59 demented subjects at first follow-up, and 89 demented subjects at second follow-up. Compared with nondemented people, subjects that became demented during follow-ups were older, were more often female, were less educated, had a lower MMSE score, and were more likely to be affected by vascular disease and functional disability, but the 2 groups had no significant differences in the distribution of antihypertensive drug use, systolic pressure, and diastolic pressure (Table 1).

### Variations in Blood Pressure Over 6 Years by Dementia Status

As the Figure shows, at baseline there was no significant difference in mean blood pressure between nondemented individuals and those who became demented at Time 2 or 3. However, both systolic and diastolic pressure markedly decreased over 3 years before dementia diagnosis and continued to decline thereafter. Nondemented subjects also showed a general tendency of decline in blood pressure during the second follow-up period. In the linear mixed-effects models (Table 2), both systolic and diastolic pressure significantly decreased for demented subjects over the 3 years before dementia diagnosis (ie, for terms “Group B\(\times\)Time 2” and “Group C\(\times\)Time 3.” $P<0.01$) and afterward (ie, for the term “Group B\(\times\)Time 3.” $P<0.01$). However, subjects that were demented at second follow-up showed no significant change in either systolic or diastolic pressure during first follow-up (ie, for the term “Group C\(\times\)Time 2.” $P>0.05$).

### Blood Pressure Decline Over 3 Years and Risk of Subsequent AD and Dementia

As a continuous variable, each 10-mm Hg decrease in systolic pressure led to adjusted relative risks (RR) of 1.09 (95% CI, 1.00 to 1.18; $P=0.04$) for dementia. No significant association between diastolic pressure decline and dementia risk was found. In the categorical analysis, neither systolic nor diastolic pressure decline was significantly associated with subsequent AD and dementia in the entire cohort (the estimated RR varied from 0.7 to 1.2). The categorical analysis results were different from our previous report, in which blood pressure reduction...
was statistically associated with concurrently detected dementing disorders.  

There were statistical interactions between a greater systolic pressure decline (≥15 mm Hg versus no decline) and baseline systolic pressure level (≥160 versus <160 mm Hg) and vascular disease. Multi-adjusted RR related to the interaction term of systolic pressure decline-by-baseline systolic pressure was 0.2 (95% CI, 0.1 to 0.7) for AD and 0.2 (95% CI, 0.1 to 0.6) for dementia. The RR related to the term of systolic pressure decline-by-vascular disease was 2.1 (95% CI, 0.6 to 7.0) for AD and 2.8 (95% CI, 1.0 to 7.4; P=0.04) for dementia. Stratified analyses suggested that systolic pressure decline ≥15 mm Hg was statistically associated with an increased risk of dementia only in people with baseline systolic pressure <160 mm Hg or vascular disease (Table 3). Ten subjects (5 of whom developed dementia during the follow-up period, including 2 AD cases) overlapped between these 2 high-risk subgroups for dementia. Further, among subjects with vascular disease, there was a dose–response relationship between systolic pressure decline and risk of AD (RR per 10-mm Hg decrease, 1.25; 95% CI, 1.00 to 1.57; P=0.06) and dementia (RR per 10-mm Hg decrease, 1.23; 95% CI, 1.03 to 1.48). The RR related to the interaction term of diastolic pressure decline (≥15 mm Hg versus no decline) by vascular disease was 3.4 (95% CI, 1.0 to 12.0; P=0.06) for AD and 2.3 (95% CI, 0.8 to 7.0) for dementia. Stratified analysis showed that subjects with diastolic pressure decline ≥15 mm Hg had a nonsignificantly increased risk for AD and dementia among subjects that were affected by vascular disease (data not shown). No obvious effect modifications by age, sex, education, or antihypertensive drug use were detected.

The pattern of variations in pulse pressure and the association between pulse pressure decline and risk of dementia were similar to those of systolic pressure, as pulse pressure was significantly correlated with systolic pressure (the age- and sex-adjusted correlation coefficient, 0.83; P<0.01).

Discussion

The 6-year follow-up data on a community cohort of older adults showed that blood pressure markedly decreased only 3 years preceding dementia diagnosis and continued to decline thereafter. A greater decline in systolic pressure over a median interval of 3.5 years was associated with an increased risk for subsequent development of AD and dementia only in 2 subgroups: people with previously low systolic pressure, or those affected by vascular disease. Previous studies indicated that patients with dementia had lower blood pressure than nondemented controls.  

The clinoneuroepathologic data showed that blood pressure and pulse pressure decreased during AD course, but sustained decline started from the third or fourth year after diagnosis.  

Our data showed no substantial differences in mean baseline blood pressure between nondemented persons and those that

### Table 1. Baseline Characteristics of the Study Participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Demented at Time 2 (n=186)</th>
<th>Demented at Time 3 (n=118)</th>
<th>Nondemented up to Time 3 (n=643)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>82.9 (4.9)</td>
<td>81.9 (4.0)</td>
<td>80.1 (4.4)</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>86.0</td>
<td>77.1</td>
<td>74.5</td>
</tr>
<tr>
<td>Education &lt;8 years, %</td>
<td>73.7</td>
<td>58.5</td>
<td>53.5</td>
</tr>
<tr>
<td>MMSE* score, mean (SD)</td>
<td>25.0 (3.1)</td>
<td>27.0 (1.6)</td>
<td>27.5 (1.6)</td>
</tr>
<tr>
<td>Vascular disease, † %</td>
<td>21.0</td>
<td>28.0</td>
<td>14.2</td>
</tr>
<tr>
<td>Antihypertensive drug use, %</td>
<td>38.2</td>
<td>41.5</td>
<td>42.3</td>
</tr>
<tr>
<td>Functional disability, ‡ %</td>
<td>33.3</td>
<td>22.9</td>
<td>15.9</td>
</tr>
<tr>
<td>APOE genotype, ‡ %</td>
<td>e3/e3</td>
<td>46.6</td>
<td>52.6</td>
</tr>
<tr>
<td>e2/e2 or e2/e3</td>
<td>9.7</td>
<td>11.0</td>
<td>12.9</td>
</tr>
<tr>
<td>any e4</td>
<td>25.8</td>
<td>30.5</td>
<td>22.1</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg), %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;140</td>
<td>20.4</td>
<td>15.2</td>
<td>15.6</td>
</tr>
<tr>
<td>140–159</td>
<td>31.7</td>
<td>39.0</td>
<td>35.1</td>
</tr>
<tr>
<td>≥160</td>
<td>47.9</td>
<td>45.8</td>
<td>49.3</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg), %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90</td>
<td>71.0</td>
<td>76.2</td>
<td>70.0</td>
</tr>
<tr>
<td>90–94</td>
<td>15.0</td>
<td>11.9</td>
<td>14.6</td>
</tr>
<tr>
<td>≥95</td>
<td>14.0</td>
<td>11.9</td>
<td>15.4</td>
</tr>
</tbody>
</table>

*MMSE indicates Mini-Mental State Examination; MMSE score was from 0 (worst) to 30 (best).
†At least 1 case of heart disease (n=118), stroke (n=50), and diabetes mellitus (n=21) was present.
‡Numbers of subjects with missing values were 24 for functional status and 137 for apoE genotype.

AD and 2.3 (95% CI, 0.8 to 7.0) for dementia. Stratified analysis showed that subjects with diastolic pressure decline ≥15 mm Hg had a nonsignificantly increased risk for AD and dementia among subjects that were affected by vascular disease (data not shown). No obvious effect modifications by age, sex, education, or antihypertensive drug use were detected.

The pattern of variations in pulse pressure and the association between pulse pressure decline and risk of dementia were similar to those of systolic pressure, as pulse pressure was significantly correlated with systolic pressure (the age- and sex-adjusted correlation coefficient, 0.83; P<0.01).
TABLE 2. Estimates of Effects of Dementia Status Over Time on Systolic and Diastolic Pressure From Linear Mixed-Effects Models

<table>
<thead>
<tr>
<th></th>
<th>Estimate (β)</th>
<th>SE (β)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model II—Diastolic pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>99.222</td>
<td>5.051</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at different follow-ups</td>
<td>–0.234</td>
<td>0.063</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td>1.873</td>
<td>0.648</td>
<td>0.004</td>
</tr>
<tr>
<td>Time 1 (Baseline)*</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Time 2 (First follow-up)</td>
<td>0.933</td>
<td>0.565</td>
<td>0.099</td>
</tr>
<tr>
<td>Time 3 (Second follow-up)</td>
<td>–1.599</td>
<td>0.677</td>
<td>0.018</td>
</tr>
<tr>
<td>Group A (nondemented until Time 3)*</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Group B (demented at Time 2)</td>
<td>–0.334</td>
<td>0.894</td>
<td>0.709</td>
</tr>
<tr>
<td>Group C (demented at Time 3)</td>
<td>–1.317</td>
<td>1.057</td>
<td>0.213</td>
</tr>
<tr>
<td>Group B×Time 2</td>
<td>–3.246</td>
<td>1.078</td>
<td>0.003</td>
</tr>
<tr>
<td>Group B×Time 3</td>
<td>–5.741</td>
<td>1.487</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Group C×Time 2</td>
<td>0.157</td>
<td>1.296</td>
<td>0.904</td>
</tr>
<tr>
<td>Group C×Time 3</td>
<td>–5.651</td>
<td>1.351</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Reference category.

were demented 3 to 6 years later. However, at the diagnosis, the blood pressure level for demented subjects was lower than that of nondemented people, and blood pressure continuously decreased with dementia progression. Our findings are inconsistent with the East Boston study, in which little variation in blood pressure was noticed from 13 years before AD diagnosis to 2 years after the diagnosis. Different patterns in blood pressure decline among studies may suggest that the dementia-related blood pressure decline is age-dependent. The tendency of a slight decline in blood pressure during the second follow-up period for those subjects who remained nondemented at second follow-up may be explained by the fact that some people in this group were already in the preclinical phase of dementia.

Clinical trials in individuals with systolic hypertension show that reduction in blood pressure with antihypertensive drugs reduces dementia risk. However, epidemiologic studies suggest that a decrease in blood pressure may be related to an increased risk of dementia. A follow-up study on a male cohort found that a decrease in systolic pressure over a 30-year interval was related to poor performance on a psychomotor speed test in late life. In the Kungsholmen project, low blood pressure and decline in blood pressure were both associated with increased risk of concurrently detected cognitive impairment and dementia, which are in line with the view that low blood pressure is correlated with a dementia course. Two recent follow-up studies further linked low (diastolic) blood pressure to an elevated risk of AD and dementia, suggesting that low blood pressure is predictive of clinical dementia. Community-based studies addressing the longitudinal relationship between blood pressure changes and dementia risk are currently unavailable. In the present study, we found that apparent reduction in systolic pressure over the 3 to 6 years preceding dementia diagnosis was associated with an increased risk for subsequent AD and dementia only in selected older people, ie, those with initial low systolic pressure or with vascular disorders. These findings indicate a possible threshold level in systolic pressure, especially for subjects with vascular disease in whom further reduction of blood pressure under this level may precipitate dementia onset. Although antihypertensive drug use did not substantially modify the effect of blood pressure decline on dementia, caution is needed in the use of these drugs for older people with low diastolic pressure.

How could blood pressure decline affect the dementing process? Neuropathological studies found that many Alzheimer patients had consistent or episodic hypotension. Clinical data support the view that low blood pressure or frequent episodic hypotension could result in poor cerebral perfusion that may play a role in dementia and AD. In further support of this notion, population-based cohort studies show that low blood pressure is predictive of clinical dementia. These observations indicate a potential pathway that subtle neurodegenerative lesions in strategic locations of the brain that regulate blood pressure may initiate blood pressure decline. Then, the extensive decline in blood pressure may lead to deficits in cerebral perfusion, which in turn may accelerate the already started neurodegenerative process if the brain perfusion cannot be promptly and sufficiently remedied, especially for persons with initial low blood pressure or vascular disorders. Therefore, blood pressure decline can be considered an accelerating factor of clinical dementia and AD, rather than an initiator of the dementing process. In addition, as evidence shows that vascular disorders may promote clinical manifestation and pathogenesis of neurodegeneration, we cannot rule out the possibility that multiple cerebrovascular damages (eg, severe atherosclerosis and brain infarcts) may be responsible for both the decline in blood pressure and the development of clinical AD and dementia.

Our study has limitations. First, the diagnosis of dementia or AD was made clinically without using neuroimaging data, which could affect the diagnostic accuracy for AD but not for dementia. However, neuroimaging data may help detect cerebrovascular lesions but may not be able to indicate a causative relation with dementia. Second, as blood pressure may be affected decade(s) before dementia is clinically manifested, we were unable to determine when blood pressure decline was initiated by the dementing process with only
a 6-year follow-up time. Finally, as our study population consisted of subjects with a minimum age of 75 years at entry, caution is needed when generalizing our findings to younger populations.

In summary, our data show that blood pressure markedly decreases over the 3-year preclinical phase of dementia. A greater decline in systolic pressure is predictive of clinical dementia in subjects with low blood pressure or affected by vascular disorders. These findings have relevant implications for clinical practice and dementia prevention and for understanding the complex relationship between blood pressure and dementia.

Acknowledgments

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References


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