Blood Pressure Trajectories From Midlife to Late Life in Relation to Dementia in Women Followed for 37 Years

Erik Joas, Kristoffer Bäckman, Deborah Gustafson, Svante Östling, Margda Waern, Xinxin Guo, Ingmar Skoog

Abstract—Higher midlife blood pressure increases risk for dementia. To further understand the relation between blood pressure and dementia, it is necessary to examine evolution of blood pressure from midlife to late life. We examined blood pressure trajectories using linear mixed models in a representative sample of middle-aged women (N=1462) who were followed from 1968–1969 until 2005–2006 with comprehensive medical and neuropsychiatric examinations. Dementia was diagnosed according to established criteria. Among those not treated with antihypertensives, higher systolic blood pressure at baseline but not blood pressure trajectories from 1968 to 1992 was associated with dementia and Alzheimer disease. Those with history of antihypertensive treatment had higher baseline systolic blood pressure than those who were never treated. In this group, those who developed dementia and Alzheimer disease had lower baseline systolic blood pressure and steeper increase in systolic blood pressure from 1968 to 1992 than those who did not. A steeper decline in systolic blood pressure during the late part of the study was observed in those who developed dementia regardless of antihypertensive treatment. The latter association was attenuated or disappeared when adjusting for body mass index. The association between blood pressure and dementia is complex and influenced by antihypertensive treatment. The findings emphasize the importance of detecting increased blood pressure in midlife and controlling blood pressure in those treated. Whether the trajectory of blood pressure is a risk factor or part of the clinical course of dementia needs to be elucidated. (Hypertension. 2012;59:00-00.) ● Online Data Supplement

Key Words: dementia ■ blood pressure ■ Alzheimer disease ■ hypertension ■ antihypertensives

A life-course perspective when evaluating risk and protective factors for dementia is essential. This may be especially important in relation to blood pressure (BP), which varies with age and in relation to dementia onset and progression. Several studies report that high midlife BP or hypertension increases risk for late-life dementia,1–6 whereas studies on late-life BP have given mixed results.7–9 The relation between BP and dementia is complex. BP decreases the years before dementia diagnosis10,11,12 and is lower in individuals with manifest dementia compared with those without.13–17

Studies on trajectories of BP in relation to dementia have typically been over short periods of time and encompassed late life. An exception is the Honolulu-Asia Aging Study (HAAS), where Japanese American men who developed dementia experienced a steeper increase in systolic BP (SBP) from midlife to late life, followed by a steeper decrease in late life, than those who did not develop dementia.18 An additional increase in midlife SBP18 was only related to dementia in men not treated for hypertension. In addition, several studies report that antihypertensive drugs are associated with lower risk of dementia.19–21 Treatment may, thus, modify the association between BP and dementia. Another factor that may influence BP trajectories in relation to dementia is body mass index (BMI), which is positively related to BP.22 This relationship may be mediated by a number of factors, such as dysregulations of the renin-angiotensin-aldosterone system, the sympathetic nervous system, and the cardiac natriuretic peptide system, as well as insulin resistance, disturbed vascular endothelium function, and low-grade inflammation.23,24 Several of these factors may also be involved in the pathogenesis of dementia disorders, such as Alzheimer disease (AD).25 In HAAS, controlling for weight change attenuated the relationship between SBP decline and incident dementia.18 We have reported recently that midlife BMI increases less with age in those who became demented in this study.26

It is, thus, important to also examine the role of BMI in the relationship between BP and dementia. Finally, it has been suggested that women and men have different BP trajectories throughout life,27 which may influence the association between BP and dementia.

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The aim of this study was to analyze BP trajectories in relation to late-life dementia, with consideration of antihypertensive treatment and BMI, in a representative population sample of women followed from 1968 to 2006. We only included individuals who were examined both in 1968 and 2000–2001 or 2005–2006 to ensure similar lengths of follow-up.

Methods

Participants

The Prospective Population Study of Women in Gothenburg, Sweden, was initiated in 1968–1969 with an examination of 1462 women (participation rate: 90%),27 born 1908, 1914, 1918, 1922, and 1930. Potential participants were systematically sampled from the Swedish Population Register based on birth date. Follow-up examinations were performed in 1974–1975 (n=1302), 1980–1981 (n=1154), 1992–1993 (n=836), 2000–2001 (n=660), and 2005–2006 (n=531).26 Participation rates among survivors were 90%, 83%, 69%, 69%, and 70%, respectively. Only those who participated both in 1968–1969 and in 2000–2001 or 2005–2006 were included in the present study (N=707; for a flowchart, see Figure S1 in the online-only Data Supplement). In addition, those diagnosed with dementia already in 1992 were excluded to have similar observation times before dementia onset in all of the individuals. The study was approved by the ethics committee of Gothenburg University. All of the subjects (or their nearest relatives) gave informed consent to participate.

Examinations

The examinations were performed at an outpatient clinic or in the participant’s home and included social, functional, somatic, neuropsychiatric, and neuropsychological examinations. SBP and diastolic BP (DBP) were measured to the nearest 2 mm Hg with a mercury manometer in the seated position in the right upper arm after 5 minutes of rest using a standard cuff. Information on antihypertensive treatment was obtained by self-report. Further information on the measurement of confounders can be found in the online-only Data Supplement.

Dementia Diagnoses

Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, revised criteria,28 by neuropsychiatrists at consensus meetings using information from neuropsychiatric examinations and close informant interviews.29 Probable and possible AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association30 criteria (“all AD”). AD was further subclassified as “pure AD” (no cerebrovascular or other disease that might contribute to dementia). Details on the neuropsychological tests and the diagnostic procedures can be found in the online-only Data Supplement.

Statistical Methods

Pearson χ² test was used to test relations between categorical variables and dementia. Baseline differences in continuous variables were tested as differences in least-square means on the basis of linear regression models. Logistic regression was used to test for age-adjusted differences of categorical variables.

Linear mixed-effects models were used to analyze BP trajectories in relation to dementia, and the subtype AD diagnosis in 2000–2001 or 2005–2006. SBP and DBP were analyzed separately. The models were fitted with piecewise linear splines, with 2 breakpoints, to allow nonlinear trajectories over time. The location of these break points was chosen on the basis of goodness-of-fit statistics (Akaike Information Criteria). The basic model, model 1, included the effects of age, BMI, and dementia and the interactions between time, age, and dementia to allow for age- and dementia-related differences in BP development over time. Intercept and slopes (time) were included as random effects to account for intraperson heterogeneity. The same analyses were done when analyzing AD instead of dementia.

Results

Of the 1462 who participated in the 1968 baseline examination, 499 died before the 2000–2001 examination, and 6 were excluded because of dementia diagnosed already in 1992. Of those eligible for the examinations in 2000–2001 or 2005–2006 (N=957), 250 refused participation at both examinations. Thus, our sample included 707 individuals (response rate among survivors: 73.9%).

Comparisons among participants, refusals, and those who died before 2000 are given in Table 1. Compared with...
participants, refusals had lower education, higher prevalence of CVDs and smoking, and higher SBP and DBP in 1968–1969. Those who died before 2000 were older, had a higher prevalence of CVD and smoking, and higher SBP, DBP, and BMI in 1968–1969 compared with participants.

Characteristics of the sample in relation to dementia are presented in Table S1 in the online-only Data Supplement. Mean age at baseline was 45.0 years. Among 707 individuals who took part in the study, 144 (20.4%; 103 with all AD, of which 79 were pure AD) were diagnosed with dementia in 2000–2001 or 2005–2006. No associations were found between antihypertensive treatment between 1968 and 1992 and dementia diagnosed in 2000–2006. In unadjusted analyses, those who developed dementia had lower education, higher prevalence of CVD and stroke, and higher SBP, DBP, and cholesterol at baseline and differed regarding birth year. Characteristics in relation to antihypertensive treatment are presented in Table S2.

**BP Trajectories**

The 2 breakpoints considered to best fit the models using Akaike Information Criteria statistics were 1992 and 2000 (mean ages: 69 and 77 years) for SBP and 1980 and 2000 (mean ages: 57 and 77 years) for DBP. Comparisons between those who developed dementia and those who did not regarding BP trajectories are given in Table 2 and Figure 1.

Those who developed dementia did not differ from those who did not regarding SBP at baseline in 1968 or regarding SBP slope from 1968 to 1992, except that those with pure AD experienced an additional increase in SBP in 1968–1992. This increase was borderline significant for model 3 (adjusted for all confounders in model 2 and BMI) and in the age-adjusted analysis for all AD. After 1992, those with dementia, pure AD, and all AD had an additional decline compared with those who did not develop dementia. The decline accelerated after 2000 for dementia, all AD, and pure AD. The models that included BMI and BMI-change eliminated the additional decline attributed to dementia after 2000 and reduced the added decline between 1992 and 2000. Dementia in 2000–2006 was not related to baseline values or trajectories of DBP (see Table S3).

**Stratification by Antihypertensive Treatment**

Comparisons between those who developed dementia and those who did not regarding SBP trajectories stratified by antihypertensive treatment are given in Table 2 and Figure 2. Age-adjusted mean baseline SBP was 143.2 mmHg (95% CI: 140.7–145.7 mmHg) in those who received antihypertensive treatment at any time between 1968 and 1992 and 124.9 mmHg (95% CI: 123.6–126.2 mmHg) in those who did not (t=12.74; degrees of freedom=1; P<0.001). Similar results were found for DBP (data not shown). This difference was
found both among those who became demented and those who did not.

Among those who never received antihypertensive treatment between 1968 and 1992, those who had dementia, all AD, and pure AD in 2000–2006 had higher SBP in 1968 but a similar increase in SBP between 1968 and 2000 compared with those without dementia. After 2000, those with dementia, all AD, and pure AD had an additional decline compared with those without dementia. Adjustment for confounders in model 2 attenuated differences in the slope after 2000 to borderline significance. Added adjustment for BMI (model 3) eliminated the additional decline after 2000 among those who developed dementia compared with those who did not.

Among those on antihypertensive treatment at any time from 1968 to 1992, those with dementia, all AD, and pure AD in 2000–2006 had lower SBP in 1968, a larger additional increase between 1968 and 1992, and an additional decline between 1992 and 2000 compared with those who did not develop dementia. After 2000, the change in SBP was similar in those with and without dementia. The additional decline for those with dementia after 1992 was attenuated when adjusting for BMI.

Among those who were not on antihypertensive treatment, there were no differences regarding DBP between those with dementia and those without, except that the all-AD group had a higher DBP in 1968. Among those on antihypertensive treatment, DBP in 1968 was lower in those who had dementia, all AD, and pure AD in 2000–2006 compared with those who did not develop dementia (data not shown). When adjusting for BMI (model 3), the differences in baseline measurement disappeared.

**Discussion**

We estimated BP trajectories in relation to the development of dementia in a population sample of women followed from 1968 to 2006. We observed a complex pattern influenced by the use of antihypertensive treatment. Among women who did not report the use of antihypertensives from 1968 to 1992, baseline SBP (at age 38–60 years) was higher in those who developed dementia and AD than in those who did not, despite that baseline SBP was considerably lower than among those treated. This may reflect a higher risk for dementia among those with prehypertension in midlife, because higher levels would lead to death before ages when dementia appears. Support for this hypothesis is that those who were lost because of death, as well as those lost because of other causes, had higher SBP and DBP at baseline. On the other hand, among those with a history of antihypertensive treatment, those who later developed dementia had lower SBP at baseline (but still higher than those not treated) and a steeper increase from 1968 to 1992 than those who did not develop dementia. The latter may imply that antihypertensive treatment was less effective in those who later became demented, maybe because of less compliance, less drug effect, or other factors that led to poorer control.

In the later portion of the 37-year follow-up period, we observed a similar relation between SBP and dementia as in another study from our group. In persons born 1901–1902, dementia development between ages 79 and 85 years was associated with higher SBP and DBP at age 70 years, followed by a greater decline between age 75 and 85 years.
We now extend this observation to include midlife SBP levels and show that those who developed dementia tended to increase more in SBP from midlife (mean age: 45 years) to late life (mean age: 69 years) and thereafter declined more. Our findings in Swedish women are also similar to the observation among Japanese American men (born 1900–1919), whereas we who did not had a similar increase thereafter. In contrast, SBP, whereas those who developed dementia and those dementia in the nontreatment group had higher baseline antihypertensive drugs. In our study, those who developed dementia in the nontreatment group had higher baseline SBP, whereas those who developed dementia and those who did not had a similar increase thereafter. In contrast, HAAS reported no associations between BP and dementia in those on antihypertensive treatment, whereas we found that those who became demented among those on antihypertensive treatment had a lower SBP at baseline and a steeper increase in SBP between 1968 and 1992. Differences between the studies may be because of differing patterns of CVD, risk behaviors, and likelihood of having received antihypertensive treatment. However, it may also be because of sex differences, because HAAS only examined men. Compared with men, women have lower SBP levels in early adulthood and higher levels in late life. This emphasizes the importance to analyze men and women separately in studies on BP and dementia.

Both in our study and in the HAAS Study, the main findings were related to SBP. High SBP may be an indicator of large artery stiffness, which has been related to increased risk of dementia, whereas DBP is a marker of peripheral resistance, which is related to ischemic white matter lesions.

BP decrease was more accentuated in the later part of the study, the years before dementia onset, as also reported by others. Interestingly, this accentuated decline was observed earlier in those who received antihypertensive treatment. It has also been reported that BP declines during the course of dementia. Reasons for the decline could be that BP regulation may be disturbed by neurodegeneration decades before dementia onset, that hypotension may cause or initiate degenerative processes, or both.

There is a positive relation between BP and BMI. This relationship may be mediated by a number of factors, such as dysregulations of the renin-angiotensin-aldosterone system and the sympathetic nervous system, as well as insulin resistance, disturbed vascular endothelium function, and low-grade inflammation. These factors may also be involved in the pathogenesis of dementia disorders, such as AD. It is noteworthy that the second additional decline in BP, but not the first, in those who developed dementia disappeared after controlling for BMI, suggesting that a general hypometabolic state may be responsible for the second decline and partly influences the first decline in those with dementia. We have reported recently that BMI initially, in midlife, increases less and/or 2005–2006. Thus, all of the individuals were followed up to age ≥70 years, at which age they had a reasonable possibility of developing dementia. This approach also provided a similar length of BP trajectories in all of the groups. Thus, as in all of the studies of late-life dementia, this is a survival sample. Survival bias may, thus, explain some of the findings. Baseline BP was higher in those who died or refused than in participants. This indicates that associations between high BP and dementia may be underrated in studies with long follow-ups, because both hypertension and dementia are related to an increased mortality rate. Fourth, we do not know the length of antihypertensive treatment or duration of obesity or BP over recommended cutoffs. Fifth, antihypertensive treatment was assessed by self-report. We can, thus, not exclude the possibility that there might have been underreporting because of recall bias. However, bias because of cognitive dysfunction or incipient dementia is probably low, because assessment was done ≥8 years before dementia onset.

Strengths of this study include the population-based sample, the comprehensive examinations, and the long follow-up. Furthermore, we used linear mixed models to analyze trajectories of BP, enabling us to analyze changes in the BP-dementia relationship over time in 1 model. There are also some limitations and methodological issues. First, we only measured BP once at each examination, which may lead to larger variance. However, SDs are consistent with other studies. Furthermore, BP trajectories with age in our study are similar to those reported in the literature, where DBP increases until age 50 to 59 years and then decreases, whereas SBP increases to age ≥70 years. Second, some subgroups were small, for example, the number of participants on antihypertensive treatment. This resulted in low statistical power and, thus, less possibility to find significant differences. Third, we only included persons who survived and participated in examinations in 2000–2001 and/or 2005–2006. Thus, all of the individuals were followed up to age ≥70 years, at which age they had a reasonable possibility of developing dementia. This approach also provided a similar length of BP trajectories in all of the groups. Thus, as in all of the studies of late-life dementia, this is a survival sample. Survival bias may, thus, explain some of the findings. Baseline BP was higher in those who died or refused than in participants. This indicates that associations between high BP and dementia may be underrated in studies with long follow-ups, because both hypertension and dementia are related to an increased mortality rate. Fourth, we do not know the length of antihypertensive treatment or duration of obesity or BP over recommended cutoffs. Fifth, antihypertensive treatment was assessed by self-report. We can, thus, not exclude the possibility that there might have been underreporting because of recall bias. However, bias because of cognitive dysfunction or incipient dementia is probably low, because assessment was done ≥8 years before dementia onset.

Perspectives

We followed Swedish women for 37 years and found that late-life dementia, especially AD, was related to higher midlife SBP in those not treated with antihypertensive drugs and with increasing SBP in those who were on treatment. This emphasizes the importance of detecting increased BP in middle-aged women and controlling BP in those treated. Our findings should be seen in light of the fact that women have been a neglected group regarding prevention of cardiovascular risk factors and regarding research on these risk factors. The importance of carefully monitoring BP is further emphasized by the finding that BP started to decrease in the years before dementia onset. In addition, our study shows the importance of stratifying for use of antihypertensives in studies on BP and dementia. Whether changes in SBP trajectories before dementia onset are part of the course of the disease or increases risk remains to be determined.

Sources of Funding

Disclosures

Dr Skoog has received speaking fees from the following companies: Nycomed, Lundbeck, Janssen, Eisai, Shire and Pfizer, all below $10,000. Dr Skoog has also done consultancy work for Nycomed, also for less than $10 000.

References


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Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2012/02/13/HYPERTENSIONAHA.111.182204.DC1

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Blood pressure trajectories from mid- to late-life in relation to dementia in women followed for 37 years

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Methods

Measurement of confounders

Body height was measured to the nearest cm and weight to the nearest 0.1 kg. BMI was calculated as kg/m^2. Smoking was classified as never smoker or ever smoker in 1968. Education was dichotomized as compulsory (6 years in those born 1908-22, and seven years in those born 1930), or more than that. Diagnosis of myocardial infarction was based on self-report, ECG findings, medical records and death certificates. Coronary heart disease was defined as fulfilling one or more of the following criteria: angina pectoris according to the Rose criteria obtained by self-report; myocardial infarction; ECG-evidence of ischemia, i.e. complete left bundle branch block or major Q-waves; pronounced ST-depression and/or negative T-waves. Diabetes mellitus was defined as a diagnosis told by a doctor, or being on anti-diabetes therapy (insulin and/or tablets), or having fasting venous or capillary whole blood glucose values $\geq 7.0$ mmol/l, or according to death certificates. Information on stroke/TIA was derived from self-reports, key informants and the Swedish hospital discharge register. Information on frequent or constant psychological stress in 1968, 1974 or 1980 was obtained by self-report. Participants who stated that they had experienced stress at any of these examinations were deemed to have experienced stress. Blood samples were drawn in the fasting state, and serum-cholesterol measured.

Diagnosis of dementia

Extensive neuropsychiatric examinations and close informant interviews began when participants became aged 70 years or older. Neuropsychiatric examinations were performed by psychiatrists in 1992, and by experienced psychiatric nurses in 2000 and 2005, and included components of the Alzheimer’s Disease Assessment Scale- cognitive subscale (ADAS-Cog), other tests of mental functioning (described in the following section), activities of daily living, and personality changes. Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Third edition, revised (DSM-III-R) criteria by neuropsychiatrists at consensus meetings using information from neuropsychiatric examinations and close informant interviews. Participants must have evidenced significant impairment in social or occupational functioning representing significant decline from a previous level of functioning for a diagnosis.
Description of mental functioning tests

Assessment of Memory:

Observed recent and episodic memory was rated on a seven-step scale, with zero score assigned to unimpaired performance and one to six reflecting increasing levels of impaired performance.

Remembering the last two prime ministers in Sweden, and orientation to time, place, and person was also assessed

Language and aphasia:

Poverty of speech, spoken language ability, comprehension of spoken language and word-finding difficulties during the examination was rated on a seven-step scale, with zero score assigned to unimpaired performance and one to six reflecting increasing levels of impaired performance.

Language performance was also tested by naming 12 objects which were shown to the participant,

Visuospatial:

The participant was asked to copy the following items on paper: a cube, overlapping pentagons, a rhomb, overlapping quadrants and a cross

Executive function (planning, organizing, abstract thinking)

Understanding proverbs: The participants were told four proverbs and asked to explain their meaning

Following commands of increasing complexity, from one to five steps.

Word Fluency: naming as many animals as possible in one minute

Apraxia (inability to carry out motor activities despite intact function)

Asking the participant to perform a pantomime (eating with cutlery, combing their hair, light a match) or to use certain objects (a pen etc)

Ideational apraxia: The participant was given an envelope, a paper and a stamp and was asked to prepare it for a mail, i.e. fold the paper, seal the envelope, put on a stamp and write the address on the envelope.

Agnosia (failure to identify or recognize objects despite intact sensory function)

Asking the participant to name their fingers (finger agnosia) and to identify a coin and a key by their fingers
References


Table S1. Characteristics of the study sample of women in relation to dementia and Alzheimer’s disease (AD) in 2000-2006

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No dementia</th>
<th>Dementia‡</th>
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<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Total†</strong></td>
<td>563 (79.6)</td>
<td>144 (20.4)</td>
<td>103 (14.6)</td>
<td>79 (11.2)</td>
<td>707 (100)</td>
</tr>
<tr>
<td><strong>Birth Cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1930</td>
<td>231 (41.0)</td>
<td>13 (9.0)</td>
<td>10 (9.7)</td>
<td>9 (11.4)</td>
<td>244 (34.5)</td>
</tr>
<tr>
<td>1922</td>
<td>174 (30.9)</td>
<td>42 (29.2)</td>
<td>26 (25.2)</td>
<td>21 (26.6)</td>
<td>216 (30.6)</td>
</tr>
<tr>
<td>1918</td>
<td>130 (23.1)</td>
<td>60 (41.7)</td>
<td>45 (43.7)</td>
<td>34 (43.0)</td>
<td>190 (26.9)</td>
</tr>
<tr>
<td>1914</td>
<td>25 (4.4)</td>
<td>25 (17.4)</td>
<td>19 (18.4)</td>
<td>14 (17.7)</td>
<td>50 (7.1)</td>
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<td>1908</td>
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<td>3 (2.9)</td>
<td>1 (1.3)</td>
<td>7 (1.0)</td>
</tr>
</tbody>
</table>

**Confounders**

| Antihypertensive treatment 1968-1992 | 109 (19.4) | 38 (26.4) | 25 (24.3) | 14 (17.7) | 147 (20.8) |
| Smoking in 1968 (ever)              | 246 (43.7) | 56 (38.9) | 32 (31.1)* | 29 (36.7) | 302 (42.7) |
| Diabetes mellitus 1968-2000         | 61 (10.8)  | 14 (9.7)  | 11 (10.7) | 9 (11.4)  | 75 (10.6) |
| Cardio vascular disease 1968-2000   | 184 (32.7) | 63 (43.8)* | 38 (36.9) | 22 (27.8) | 247 (34.9) |
| Education (more than compulsory) in 1968 | 204 (36.3) | 37 (25.7)* | 26 (25.2)* | 21 (26.6) | 241 (34.1) |
| Stroke                               | 86 (15.3)  | 48 (33.3)** | 20 (19.4) | 5 (6.3)*  | 134 (19.0) |
| Stress 1968-1980                     | 207 (36.8) | 50 (34.7) | 40 (38.8) | 33 (41.8) | 257 (36.4) |

Mean (SD) Mean (SD) Mean (SD) Mean (SD) Mean (SD)

| Systolic blood pressure (mm Hg) in 1968 | 127.5 (17.4) | 133.6 (19.4)** | 134.8 (19.0)*** | 131.5 (16.1) | 128.7 (18.0) |
| Diastolic blood pressure (mm Hg) in 1968 | 80.7 (9.7) | 83.2 (9.2)** | 83.5 (9.3)*** | 81.8 (8.8) | 81.2 (9.7) |
| Body mass index in 1968                | 23.7 (3.4) | 23.8 (3.5) | 24.0 (3.7) | 23.7 (3.7) | 23.7 (3.4) |
| Cholesterol in 1968                    | 6.6 (1.0) | 7.1 (0.9)** | 7.1 (0.9)*** | 7.0 (0.9)*** | 6.7 (1.0) |

Significant differences between those who developed dementia and those who did not among confounders and baseline measures: *=p<0.05, **=p<0.01, ***=p<0.001

†Row percentages are presented for the total sample; all other percentages presented are column percentages.

‡Dementia includes all dementia cases. ‘All AD’ includes all probable and possible AD cases. ‘Pure AD’ includes only AD cases with no cerebrovascular or other disease that might contribute to dementia.
**Table S2. Characteristics of the study sample of women in relation to any antihypertensive treatment between 1968 and 1992**

<table>
<thead>
<tr>
<th>Characteristics</th>
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<th>Any antihypertensive treatment</th>
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</thead>
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<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
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<tr>
<td>1914</td>
<td>36 (6.4)</td>
<td>14 (9.5)</td>
<td>50 (7.1)</td>
</tr>
<tr>
<td>1908</td>
<td>5 (0.9)</td>
<td>2 (1.4)</td>
<td>7 (1.0)</td>
</tr>
<tr>
<td><strong>Confounders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia in 2000 or 2005</td>
<td>106 (18.9)</td>
<td>38 (25.9)</td>
<td>144 (20.4)</td>
</tr>
<tr>
<td>Smoking in 1968 (ever)</td>
<td>251 (44.8)</td>
<td>51 (34.7)*</td>
<td>302 (42.7)</td>
</tr>
<tr>
<td>Diabetes mellitus 1968-2000</td>
<td>46 (8.2)</td>
<td>29 (19.7)***</td>
<td>75 (10.6)</td>
</tr>
<tr>
<td>Cardio vascular disease 1968-2000</td>
<td>161 (28.8)</td>
<td>86 (58.5)***</td>
<td>247 (34.9)</td>
</tr>
<tr>
<td>Education (more than compulsory) in 1968</td>
<td>208 (37.2)</td>
<td>33 (22.4)***</td>
<td>241 (34.1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>85 (15.2)</td>
<td>49 (33.3)***</td>
<td>134 (19.0)</td>
</tr>
<tr>
<td>Stress 1968-1980</td>
<td>202 (36.1)</td>
<td>55 (37.4)</td>
<td>257 (36.4)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg) in 1968</td>
<td>124.6 (14.3)</td>
<td>144.3 (21.6)***</td>
<td>128.7 (18.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg) in 1968</td>
<td>78.9 (7.9)</td>
<td>90.0 (10.9)***</td>
<td>81.2 (9.7)</td>
</tr>
<tr>
<td>Body mass index in 1968</td>
<td>23.4 (3.1)</td>
<td>25.1 (4.1)***</td>
<td>23.7 (3.4)</td>
</tr>
<tr>
<td>Cholestrol in 1968</td>
<td>6.6 (1.0)</td>
<td>6.9 (1.2)***</td>
<td>6.7 (1.0)</td>
</tr>
</tbody>
</table>

Significant differences between those reporting any antihypertensive treatment between 1968 and 1992 those who did not among confounders and baseline measures of blood pressure: * = p<0.05, ** = p<0.01, *** = p<0.001

† Row percentages are presented for the total sample; all other percentages presented are column percentages.
Table S3. Differences in baseline values and slopes of diastolic blood pressure in relation to dementia and Alzheimer’s disease (AD) 2000-2006 in women followed from 1968-9 to 2000-1 or 2005-6.

<table>
<thead>
<tr>
<th>(N=individuals (dementia cases))</th>
<th>Difference at baseline (mm Hg)</th>
<th>Difference in rate of change (mm Hg/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Model 1* (N=707 (144))</td>
<td>0.42 (-1.42, 2.26)</td>
<td>0.66</td>
</tr>
<tr>
<td>Model 2† (N=702 (142))</td>
<td>0.32 (-1.49, 2.13)</td>
<td>0.73</td>
</tr>
<tr>
<td>Model 3‡ (N=702 (142))</td>
<td>0.72 (-1.03, 2.46)</td>
<td>0.42</td>
</tr>
<tr>
<td>Dementia subtypes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure AD* (N=642 (79))</td>
<td>-0.68 (-2.98, 1.62)</td>
<td>0.56</td>
</tr>
<tr>
<td>All AD* (N=666 (103))</td>
<td>0.67 (-1.42, 2.76)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

* Model 1 Adjusted for: Age
† Model 2 Adjusted for: Age + education, cardiovascular disease, diabetes, smoking, cholesterol, stress and stroke
‡ Model 3 Adjusted for: Age + education, cardiovascular disease, diabetes, smoking, cholesterol, stress and stroke + BMI.
Figure S1. Participation in PPSW

1968
N=1462

N=23 dropouts*

1974
N=137 declined
N=1302 participants

N=52 dropouts*

1980
N=233 declined
N=1154 participants

N=183 dropouts*

1992
N=368 declined
N=836 participants

N=241 dropouts*

N=6 excluded
Due to dementia in 1992

2000
N=303 declined
N=654 participants

N=224 dropouts*

2005
N=225 declined
N=531 participants

Study sample:
N=707

*Dead or moved from Sweden