Blood Pressure Levels Before Dementia

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Background: The association between blood pressure (BP) and dementia is not easily interpreted, but some prospective studies suggest that dementia may lower BP.

Objective: To examine the relationship between BP during a 10-year period and the prevalence of dementia.

Design: Comparison of longitudinal BP between participants who had dementia, participants who were cognitively impaired, and unimpaired participants selected from an ongoing cohort study.

Setting: A prepaid health plan in southern California.

Participants: Three hundred participants had dementia, 285 were cognitively impaired, and 585 were unimpaired.

Main Outcome Measures: Retrospective medical record review of up to 3 randomly selected BP measurements per year for the 10 years before cognitive classification of each participant.

Results: Systolic BP increased with time in the unimpaired participants, and increased less in women who developed cognitive impairment and in women who developed dementia. Diastolic BP declined significantly (P<.001) with time in all 3 groups. Compared with unimpaired women, the adjusted rate of decline in diastolic BP was significantly (P = .04) greater for the women who developed dementia.

Conclusions: These findings are consistent with previous findings that the relationship between BP and dementia is affected by age at data collection. Valid inferences about the effect of BP on the development of dementia require prospective data collection in which subjects are free of dementia or cognitive impairment at enrollment.

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Epidemiologic studies of the association between blood pressure (BP) and dementia are not easily interpreted.1 Cross-sectional studies are susceptible to several biases. The results of prospective studies are mixed.2-11 In an analysis of cross-sectional data from a study of dementia in women, we found a lower risk of all dementia and dementia without known cause (probable Alzheimer disease) in women who reported hypertension.12 We took advantage of the availability of medical records for the decade before this cross-sectional assessment to examine the pattern of BP before the time when women were classified as having dementia to explore further the relationship between BP and dementia.

METHODS

The starting point for identification of subjects was the Women's Memory Study, a prospective study whose primary aim is to assess the relationship between hormone therapy (HT) and dementia and Alzheimer disease. Details of recruitment to the study have been published.12

Assembly of the Women's Memory Study cohort involved use of computer-stored prescription data from the Kaiser Permanente Southern California Pharmacy Information Management System to identify women 75 years and older on July 1, 1998, who had at least 1 prescription for oral estrogen filled in a Kaiser Permanente Southern California pharmacy in every calendar year from January 1, 1992, to July 1, 1998 (current HT users) and a comparison group of non-HT users, who were women 75 years and older on July 1, 1998, who did not have prescriptions for estrogen during the same period. Of the 6542 women asked to participate in the study (2930 HT users and 3612 HT nonusers), 3924 (1944 HT users and 1980 HT nonusers) enrolled.

These women, or their proxies, provided demographic and health history information in a baseline interview. Participants were clas-
sified as having dementia, cognitive impairment without demen-
tia, or no impairment based on a multistage testing stra-
egy. This involved use of the Telephone Interview for Cogni-
tive Status–modified,13,14 administered at the baseline inter-
view; the Telephone Dementia Questionnaire,17 which was adminis-
tered to a proxy; and medical record review.

BP SUBSTUDY

The data reported herein derive from a substudy that was con-
ceived after completion of enrollment into the Women’s Memory Study. The substudy involved review of the Kaiser Perma-
nente outpatient medical records of a sample of the Women’s Memory Study participants. The substudy participants in-
cluded all women classified at the baseline assessment as hav-
ing dementia (n=300) or cognitive impairment (n=285), along
with an equal comparison group of women who, at baseline,
were classified as cognitively unimpaired (n=383). The unim-
paired subjects were selected at random from among all women
classified as cognitively unimpaired at the baseline assessment
(n=3339).

The medical record review covered the period from 10 years
before the baseline interview to the day of the baseline inter-
view. The 10-year span began January 15, 1989, and ended Sep-
tember 30, 1999, depending on baseline interview date. For
each year before baseline, data were abstracted on up to 3 BP mea-
surements from among all BP measurements recorded in the
outpatient medical record. Of the 1133 patients with data avail-
able for analysis, 225 (19.9%) had up to 3 BP measurements and
837 (73.9%) had at least 2 BP measurements each year. When
more than 3 measurements were available, 3 were se-
lected to span the full year. From 1989 to 1999, measurement
of BP at adult primary care visits was a routine procedure. Blood
pressure was generally measured with mercury manometers.
Cuffs of different sizes were variably available, and there was
no standard protocol for cuff size choice. There was no special
training in BP measurement.

For each woman whose records were included, the mean
BP in the calendar year before the baseline interview and in each
of the 9 years before the baseline interview was calculated. The
group mean BP in the dementia status groups (dementia, cog-
nitive impairment, and unimpaired) was then calculated for each
year before the baseline interview.

A BP measurement was considered invalid if the recorded sys-
tolic BP (SBP) was lower than the diastolic BP (DBP), if the DBP
was less than 10 points lower than the SBP, or if the SBP was higher
than 300 mm Hg. Invalid BP measurements were excluded.

ANALYSIS

The statistical significance of differences in the characteristics
of women by dementia classification was tested using the χ²
statistic.

To determine whether the change over time differed among
the dementia classification groups, we performed a repeated-
measures analysis of covariance with mean BP over time as the
repeated outcome variable. This model was fitted using de-
mentia group, year before the dementia diagnosis, and an in-
teraction term for dementia classification and year, adjusting
for age at interview. Separate models were constructed for sys-
tolic and diastolic measurements. A procedure (MIXED) with
a statement (REPEATED) in the 1999 version of SAS statisti-
cal software (SAS Institute Inc, Cary, NC) was used to fit the
repeated-measures data. Least squares means estimates of SBP
and DBP in the 3 dementia classification groups based on re-
peated-measures analysis of covariance were conducted. Dif-
fences were statistically significant at P<.05 (2-tailed).

A total of 1170 women were identified for inclusion in the
substudy. The outpatient medical records of 18 women
could not be located, and the medical records of 19 women
had no BP values recorded during the 10-year span. This
left 1133 women for the analysis. Table 1 shows selected
characteristics of women whose records were included ac-
cording to classification as having dementia, having cog-
nitive impairment, or being unimpaired at the 1999 as-
seessment. Compared with unimpaired women, those with
dementia were older. The mean (SD) ages of the 3 groups
(unimpaired women, those with cognitive impairment, and
those with dementia) were 78.6 (3.3), 79.9 (3.8), and 81.0
(4.5) years, respectively. The age difference among the 3
groups was significant (P<.001). Those with dementia had
less education, and were more likely to have a history of stroke,
myocardial infarction, Parkinson disease, or diabetes mel-
itus. A lower percentage of women with dementia
had a history of hypertension, as previously reported.12

Of the women in the analysis, 55.9% had at least 1 BP
measurement recorded in each of the 10 years of data ab-
straction; 92.5% had at least 1 reading for at least 5 of
the 10 years. In no year was there less than 81.4% of the
women in the analysis with at least 1 BP measurement.
Of the 25850 documented BP measurements recorded
during data abstraction, 9 were excluded because they
were invalid.

Table 2 shows the unadjusted mean BP 9 and 5 years
before assessment and in the year of the assessment by
dementia classification at assessment. Nine years before
the assessment, the mean (SD) SBP was slightly higher
for women who developed dementia compared with
women who remained unimpaired. At assessment, the
mean (SD) SBP in women who developed dementia
was lower than in women who remained unimpaired.

Figure 1 and Figure 2 show least squares means estimates of SBP and DBP, respectively, and can be viewed
as a reconstruction of longitudinal measures of BP in a
cohort oversampled to include women who developed
dementia or cognitive impairment. The adjusted SBP in-
creased with time in the unimpaired women (Figure 1).
The adjusted SBP increased less in the women who de-
veloped cognitive impairment and in the women who de-
volved dementia. The difference in the adjusted rate of
change over time in SBP between the women who de-
volved dementia and the unimpaired women was sta-
tistically significant (P<.001). The difference in the
adjusted rate of change in SBP between the cognitively
impaired women and the unimpaired women was of mar-
ginal significance (P=.04). The difference between
the women who developed dementia and those who were cog-
nitively impaired was not significant (P=.07). The effect
of time on SBP was statistically significant in the unim-
paired women and in the cognitively impaired women
(P<.001 for both), but only marginally significant
(P=.04) in the women who developed dementia.

In comparable multivariate analyses of DBP (Figure 2),
the adjusted rate of decline in DBP was marginally signifi-
cantly greater for the women who developed dementia
(P=.04) compared with the unimpaired women. The dif-
difference between the unimpaired women and the women who were cognitively impaired was not significant ($P = .33$).

The difference between the women who developed dementia and those who were cognitively impaired also was not significant ($P = .37$). Diastolic BP declined significantly with time in all 3 groups ($P < .001$ for all).

**COMMENT**

In our study, SBP increased less over time in women who developed dementia than in women who remained unimpaired. Diastolic BP declined in women who developed dementia and in those who remained unimpaired, but it declined less in women who remained unimpaired. The results suggest that dementia modifies the effect of aging on BP. Our findings are consistent with those of Skoog et al., who reported on 15 years of follow-up in 382 individuals without dementia who were enrolled in the Swedish Longitudinal Population Study. At enrollment into that study at the age of 70 years, individuals who later developed dementia had higher SBP (178 vs 164 mm Hg) and DBP (101 vs 92 mm Hg) va-

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**Table 1. Characteristics of Women in the Analysis by Dementia Classification at Assessment**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unimpaired (n = 568)</th>
<th>Cognitive Impairment Without Dementia (n = 274)</th>
<th>Dementia (n = 291)</th>
<th>$P$ Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td>.002</td>
</tr>
<tr>
<td>&lt;High school</td>
<td>77 (13.6)</td>
<td>60 (21.9)</td>
<td>63 (21.6)</td>
<td></td>
</tr>
<tr>
<td>High school graduate</td>
<td>171 (30.1)</td>
<td>90 (32.8)</td>
<td>96 (33.0)</td>
<td></td>
</tr>
<tr>
<td>Some college or trade school</td>
<td>211 (37.1)</td>
<td>78 (28.5)</td>
<td>77 (26.5)</td>
<td></td>
</tr>
<tr>
<td>College plus</td>
<td>108 (19.0)</td>
<td>44 (16.1)</td>
<td>49 (16.8)</td>
<td></td>
</tr>
<tr>
<td>Refused to answer or do not</td>
<td>1 (0.2)</td>
<td>2 (0.7)</td>
<td>6 (2.1)</td>
<td></td>
</tr>
<tr>
<td>know</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td>.14</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>11 (1.9)</td>
<td>3 (1.1)</td>
<td>7 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>29 (5.1)</td>
<td>17 (6.2)</td>
<td>18 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>21 (3.7)</td>
<td>17 (6.2)</td>
<td>22 (7.6)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>498 (87.7)</td>
<td>231 (84.3)</td>
<td>232 (79.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8 (1.4)</td>
<td>5 (1.8)</td>
<td>9 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.2)</td>
<td>1 (0.4)</td>
<td>3 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>348 (61.3)</td>
<td>166 (60.6)</td>
<td>152 (52.2)</td>
<td>.06</td>
</tr>
<tr>
<td>Medication</td>
<td>303 (53.3)</td>
<td>145 (52.9)</td>
<td>119 (40.9)</td>
<td>.004</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>62 (10.9)</td>
<td>46 (16.8)</td>
<td>39 (13.4)</td>
<td>.06</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>45 (7.9)</td>
<td>40 (14.6)</td>
<td>34 (11.7)</td>
<td>.009</td>
</tr>
<tr>
<td>Stroke</td>
<td>22 (3.9)</td>
<td>37 (13.5)</td>
<td>47 (16.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>6 (1.1)</td>
<td>7 (2.6)</td>
<td>11 (3.8)</td>
<td>.02</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of each group. Some percentages may not add up to 100 because some people will have more than 1 medical condition.

†Comparing the 3 classification groups.

**Table 2. Unadjusted BP Measurements in Selected Years Before Assessment by Dementia Classification at Assessment**

<table>
<thead>
<tr>
<th>Time Before Assessment</th>
<th>Unimpaired (n = 568)</th>
<th>Cognitive Impairment Without Dementia (n = 274)</th>
<th>Dementia (n = 291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minus 9 y</td>
<td>n = 476</td>
<td>n = 220</td>
<td>n = 226</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>137.0 (15.9)</td>
<td>137.3 (15.7)</td>
<td>138.5 (15.4)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>78.7 (8.1)</td>
<td>78.3 (7.6)</td>
<td>78.8 (7.7)</td>
</tr>
<tr>
<td>Minus 5 y</td>
<td>n = 506</td>
<td>n = 235</td>
<td>n = 254</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>139.7 (16.3)</td>
<td>140.0 (16.1)</td>
<td>141.0 (16.9)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>78.0 (8.1)</td>
<td>77.3 (8.1)</td>
<td>77.4 (8.5)</td>
</tr>
<tr>
<td>Minus 0 y</td>
<td>n = 519</td>
<td>n = 253</td>
<td>n = 253</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>144.2 (16.8)</td>
<td>142.2 (19.5)</td>
<td>140.0 (18.6)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>75.8 (8.6)</td>
<td>74.7 (8.9)</td>
<td>74.8 (8.5)</td>
</tr>
</tbody>
</table>

Abbreviation: BP, blood pressure.

*Data are given as mean (SD) unless otherwise indicated. The “n” values are women with available BP measurements.
ues. However, there was no BP difference between individuals with dementia and those without dementia at the end of the 15-year follow-up.

Burke et al\textsuperscript{15} reported that preclinical dementia is associated with pathologic changes that cause BP dysregulation. This provides a mechanistic explanation for our observations. We hypothesize that pathologic neural changes affect the slope of BP change and the development of dementia.

Our findings explain the lower odds ratio for dementia in women who reported hypertension at enrollment into our study: either clinical hypertension did not develop or clinical hypertension resolved. This phenomenon may provide an explanation for some of the contradictory and confusing findings in other cross-sectional studies and in case-control studies.

Several studies suggest that an elevated BP measured in midlife increases the risk of dementia or accelerates age-related cognitive decline. Mechanistic explanations are abundant.\textsuperscript{17-21} Our study does not rule out a relationship between hypertension, especially uncontrolled hypertension in midlife, and the development of dementia.\textsuperscript{5,6,10}

High and low BP in midlife may affect dementia risk. In the Kungsholmen Project, for example, severe uncontrolled hypertension increased the risk for all dementia, and BP below a certain level (SBP, $\leq 140$ mm Hg; or DBP, $\leq 75$ mm Hg) also increased the risk for Alzheimer disease and all dementia.\textsuperscript{10} We attempted to use our data to explain the relationship between dementia and BP classified in categories (optimal BP, healthy BP, mild hypertension, moderate or severe hypertension, and isolated systolic hypertension). Because BP category changed over time and was related to antihypertensive treatment, we could not identify their separate effects.

Our study and the analysis have limitations. Mortality due to the complications of hypertension in midlife may have biased BP among those who survived to enroll into the study. Our analysis did not directly measure person-specific paths of change in BP nor did it control for baseline BP. The study population comprised women who were almost exclusively white, were all long-term enrollees in a single health plan, and were more likely than elderly women in the general population to use HT.

Our results have methodologic implications. They suggest that valid inferences about the effect of BP on the development of dementia will require prospective data collection in which subjects are free of dementia and cognitive impairment at study enrollment. Studies will need to enroll subjects at ages when dementia has not affected BP.

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**Author Contributions:** Study concept and design: Petitti and Buckwalter. Acquisition of data: Petitti and Crooks. Analysis and interpretation of data: Petitti, Crooks, Buckwalter, and Chiu. Drafting of the manuscript: Petitti and Crooks. Critical revision of the manuscript for important intellectual content: Petitti, Crooks, Buckwalter, and Chiu. Statistical analysis: Buckwalter and Chiu. Obtained funding: Petitti and Buckwalter. Administrative, technical, and material support: Petitti and Crooks. Study supervision: Petitti.

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**REFERENCES**


