Lowering Midlife Levels of Systolic Blood Pressure as a Public Health Strategy to Reduce Late-Life Dementia

Perspective From the Honolulu Heart Program/Honolulu Asia Aging Study

Lenore J. Launer, Timothy Hughes, Binbing Yu, Kamal Masaki, Helen Petrovitch, G. Webster Ross, Lon R. White

Abstract—To estimate the potential benefits of lowering systolic blood pressure (SBP) toward preventing late-life dementia, we estimated the population-attributable risk of elevated SBP for dementia. Analyses are based on the cohort of 8006 Japanese American men (born 1900–1919) followed since 1965 as a part of the Honolulu Heart Program, continued as the Honolulu Asia Aging Study. Midlife cardiovascular risk factors and late-life brain function are well described. We estimated the population-attributable risk of dementia cases attributed to midlife SBP, grouped by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure criteria (<120, 120 to <140, and ≥140 mm Hg), taking into account treatment history, confounding factors, and competitive risk for death. The analysis is based on 7878 subjects, including 491 cases of dementia, with a mean interval of 25 years between measurement of blood pressure and dementia diagnosis. Compared with those with SBP <120 mm Hg, untreated, and <50 years of age at baseline, 17.7% (95% CI: 4.6% to 29.1%) of the cases were attributable to prehypertensive levels (SBP: 120 to <140 mm Hg) of SBP, translating into 11 excess cases per 1000. Among those who did not report taking antihypertensive medication in midlife, 27% (95% CI: 8.9% to 42.1%) of dementia cases can be attributed to systolic BP ≥120 mm Hg, translating into 17 excess cases per 1000. Although population-attributable risk estimates for population subgroups may differ by relative risk for dementia or prevalence of elevated levels of blood pressure, these data suggest that reducing midlife systolic BP is an effective prevention strategy to reduce risk for late-life dementia. (Hypertension. 2010;55:1352-1359.)

Key Words: dementia ■ population-attributable risk ■ hypertension ■ older persons ■ cohort study ■ epidemiology

Dementia causes devastation to the patient and family members and costs millions of dollars in health care. Because the numbers of persons with dementia increases with the aging of the population, preventing this trend is warranted in both human and economic terms. Currently, there are no proven strategies to reduce the occurrence of dementia. High blood pressure (BP) has long been understood to cause stroke. Still evolving is our understanding of the role that increased levels of BP plays in shaping the trajectory to dementia. In the past 10 years, several prospective cohort studies have provided compelling data suggesting that increased levels of BP are associated with an increased risk for dementia. Importantly, the several studies showing this association are based on measures of BP relatively distal to the time that dementia is diagnosed. These studies suggest that high BP not only increases the risk for vascular dementia (VaD) but also Alzheimer disease (AD). Supporting data link high levels of BP to an increased risk for markers of the dementing processes, including cognitive impairment, global and hippocampal atrophy, white matter lesions, neuritic plaques, and cerebral vascular lesions. On the basis of these studies, the following question arises: will a shift in the population distribution of midlife BP to lower levels be associated with lower rates of dementia in the population? The population-attributable risk (PAR) describes the proportion of cases that could be prevented if a specific exposure were eliminated in a target population. In the context of this analysis, the PAR measures the potential impact on dementia rates of reducing elevated levels of BP in the population.

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population. Because dementing processes can begin years before a clinical stage is reached, long periods of follow-up are needed to best identify and estimate the potential of changing risk factor levels to prevent the disease. Observa-
tional longitudinal cohort studies can provide such data, contributing importantly to estimates of the public health impact of interventions and to plans for clinical trials.

Here we present analyses based on the cohort of Japanese American men followed continuously since 1965 as a part of the Honolulu Heart Program (HHP) and since 1991 as a part of the Honolulu Asia Aging Study (HAAS). The long follow-up and serial, standardized assessment of BP, dementia, and other cardiovascular risk factors provide a unique opportunity to estimate the impact on dementia rates of reducing BP levels. Specifically, we estimate the proportion of late-life dementia cases that are attributable to elevated systolic BP (SBP) and could be avoided if normal levels of SBP are maintained in midlife. We account for several factors that contribute to PAR calculations for dementia attributed to elevated levels of SBP, including control for confounding because of other cardiovascular risk factors and disease, and control for the competitive risk for death associated with high levels of SBP. Not accounting for these factors may lead to an overestimate of the PAR for BP levels. In addition, estimates are stratified by history of hypertension treatment to follow published literature suggesting that treatment history is an important modulator of risk for dementia.

Methods
The HHP was started in 1965 as a response to the epidemic of cardiovascular disease in men. The study has been described in many publications over the past 40 years. Briefly, 8006 Japanese American men born between 1900 and 1919; living on Oahu, Hawaii, in 1964; and registered on the selective service rolls participated at baseline. The core HHP was based on 3 exams, carried out in 1965–1968, 1967–1970, and 1971–1974 (Figure), with a mean interval of 6 years between the first and third examination. In this present analysis, these visits constitute the midlife exams. At baseline, participants were aged 45 to 68 years (mean age: 54 years). From the beginning of the HHP, information on incidence of coronary artery disease, stroke, and vital events has been obtained by monitoring local English- and Japanese-language newspapers and by surveillance of hospital discharge records. A follow-up survey in the 1991–1993 examination found that only 5 men could not be traced for mortality information.23

The HAAS began in 1991, on average, 25.1 years after the first HHP examination. The aim of HAAS is to assess diseases of old age, with an emphasis on brain aging and dementia. The long follow-up and serial, standardized assessment of BP, dementia, and other cardiovascular risk factors provide a unique opportunity to estimate the impact on dementia rates of reducing BP levels. Specifically, we estimate the proportion of late-life dementia cases that are attributable to elevated systolic BP (SBP) and could be avoided if normal levels of SBP are maintained in midlife. We account for several factors that contribute to PAR calculations for dementia attributed to elevated levels of SBP, including control for confounding because of other cardiovascular risk factors and disease, and control for the competitive risk for death associated with high levels of SBP. Not accounting for these factors may lead to an overestimate of the PAR for BP levels. In addition, estimates are stratified by history of hypertension treatment to follow published literature suggesting that treatment history is an important modulator of risk for dementia.

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Modified Mini-Mental State Test.24 Those scoring below a predefined cut point on the CASI were further evaluated with a neurological examination, neuropsychological testing, and an informant interview about changes in cognitive function and behavior. In subjects with dementia, a brain image was acquired and routine blood tests conducted. On the basis of these data, a consensus diagnosis of dementia, AD, and VaD, following internationally accepted criteria,25–27 was made by the study neurologist and 2 physicians with expertise in dementia. This consensus conference also diagnosed other dementias, including those attributed to alcohol abuse, brain tumor, subdural hematoma, Parkinson disease, Lewy body disease, Pick disease, trauma, vitamin B12 deficiency, hypothyroidism, progressive supranuclear palsy, and unknown cause. In this study we focus on total dementia, defined to include cases of AD, VaD (the most frequent subtype of dementia), and mixed AD/VaD cases, and excluded other dementias. AD, VaD, and mixed dementia have been shown to be associated with high BP in several observational studies,4 and neuropathologic studies show that demented patients exhibit multiple lesions, with the combination of Alzheimer and vascular lesions being most prevalent.28 The other dementia subtypes are excluded from analyses because, as a group or individually, there is no evidence that risk for these diseases is modulated by high BP.

**BP Measurements**

At each examination, BP was measured 3 times on the left arm with subjects in a seated position. These measures were averaged to get a per-visit mean BP. To obtain a robust measure of exposure, we further averaged the means from examination 1 and examination 3. The midlife SBP levels (in millimeters of mercury) were categorized according to the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines for SBP22; normal (SBP <120); stage 1 hypertension (SBP 120 to <140); and combined stage 1 and stage 2 hypertension (SBP ≥140). Subjects were further classified a priori as (n)ever treated with antihypertensive medication if they reported treatment when asked at the first 3 exams. Treatment has long been known to modulate risk for stroke and mortality. There is also a more recent body of literature suggesting treatment moderates the association of BP to dementia.4 Studies based on the HAAS have consistently shown that the risk for pathological changes in brain function and structure are strongest in those never treated for hypertension.5,8,10,21

**Confounders and Covariates**

To estimate the PAR we controlled for variables shown in previous studies to be significant correlates of dementia2–4,7–9: age; years of education; midlife smoking history; midlife body mass index (BMI); calculated as measured weight [in kilograms] divided by height [in meters] squared); and presence of diabetes mellitus, defined as a history of diabetes mellitus diagnosed by a physician, taking diabetic medications or insulin, or glucose intolerance based on a nonfasting 1-hour glucose level.29 Prevalent coronary heart disease (angina pectoris, myocardial infarction, or coronary insufficiency) and cerebrovascular accidents were ascertained by questionnaire at baseline and updated thereafter through a previously described continuous surveillance of hospital discharge and death records.30 A positive history referred to either a stroke or coronary heart disease before examination 4.

**Analytic Sample**

From the original 8006 cohort members, we excluded 42 with no information after examination 1. Cases (n=86) diagnosed with subtypes of dementia other than AD and VaD were also excluded, as described above. Hence, we had an analytic data set of 7878 subjects, including 439 dementia cases, monitored through October 3, 2000, the date of the last examination included in these analyses (Figure). The 7878 included 346 with no exams after examination 3 and, therefore, no cognitive data and no notification of death. These 346 men were, on average, younger and had less diabetes mellitus and coronary disease but had similar BP levels compared with those who had ≥1 cognitive examination.

There were an additional 728 men who had ≥1 CASI test that was screen negative who did not participate in any subsequent examination and had no record of death before the end of follow-up. For the main analyses, we imputed case status in these 728 men using age and CASI scores, the main factors associated with risk for dementia. The C index, a measure of how well the independent variables together classify subjects according to outcome, was good (0.81) and did not substantially change with the addition of more variables.31 Imputation was done by calculating the observed proportion of dementia cases in cells defined by CASI score (<60, 60 to 79, and 79 and above)32 and 5-year age groups separately for examination 4, 5, and 6. Using those percentages we then randomly selected subjects within the CASI/age cells in the 728 subjects. This resulted in 82 case subjects who, compared with examined cases, were on average younger (56.0 [SD: 5.4 years of age] versus 54.0 years of age [SD: 4.2 years of age]) but otherwise similar in midlife BP levels and other risk factors associated with high BP. There was no change in the proportion of cases across the BP groups, but among the imputed cases there was a higher proportion of those who were treated with antihypertensive medications.

**Time to Event**

Censoring events included dementia diagnosis, death if it occurred before a dementia diagnosis, or no dementia or death by the end of the follow-up date. Time to event was defined as follows: (1) for the cases identified at examination 4, we assumed a time of onset 2 years before the examination 4 date, which is approximately midway between the time of dementia diagnosis and institutionalization or death19; (2) for the incident measured and imputed cases, we assumed a time of onset in the midpoint between the examination at which the diagnosis was made and the previous examination; (3) for those who died, the censor date was date of death; (4) for those with unknown status after examination 3 (n=346), the date of examination 3 was used for censoring; and (5) all of the others were censored at October 3, 2000.

**Analytic Strategy**

Because high BP is a strong risk factor for death,39 we calculated the relative risk with a proportional hazard competing risk model that accounts for the possibility that someone dies before reaching the clinical dementia end point or the end of the follow-up. Not taking competing risk into account may lead to an overestimate of the risk for dementia, specifically when the second outcome, in this case death, is associated with the main exposure of interest.20 The model is based on the method of Fine and Gray33 and was implemented in the program function crr in the R package cmprsk.34

**Stratification of the Cohort**

We a priori stratified the sample by treated versus not treated in midlife, as described above. Because the R program does not allow for delayed entry, the cohort was further stratified by baseline age (<50 and ≥50 years old), giving 9 BP/age/treatment cells. The statistical package also requires other confounders be entered into the model as dichotomous variables. This was done as follows: education (<12 or ≥12 years); smoking (ever or never); BMI (<25 versus ≥25); and presence/absence of diabetes mellitus, coronary heart disease, and stroke.

**Estimation of Parameters**

For the estimation of relative risk we chose as our reference group the cell at the lowest risk for death or dementia associated with SBP level: those aged <50 years at baseline who had normal BP and did not report taking antihypertensive medication (see Table S1, available in the online Data Supplement at http://hyper.ahajournals.org). The relative risk of developing dementia was calculated within each of the 8 other BP level/age/treatment cells (see Appendix 1 in the online Data Supplement for details of the statistical methods) so that all of the comparisons were made to the same reference group.

Within each age/treatment strata, the attributable fraction was obtained for each level of BP by multiplying the cell-specific risk...
Launer et al  Blood Pressure and PAR for Dementia 1355

Results

The total cohort mean age at baseline was 54.0 years (SD: 5.6 years); the mean age of the <50 group was 48.0 years, and of the ≥50.0 group was 56.5 years. There were 41.3% of men with systolic midlife prehypertension and 37.4% with systolic hypertension. The prevalence of all of the cardiovascular risk factors and disease (BMI, diabetes mellitus, coronary heart disease, and stroke) increased with increasing SBP group (Table 1). However, there were proportionately more dementia cases in the systolic prehypertension group.

Overall, 41.3% of the subjects reported taking antihypertensive medication, including 24.6% in the prehypertension and 80.0% in the hypertension groups. Compared with those who were treated, those who were not treated had lower SBP, diastolic BP, and BMI; were less likely to have cardiovascular disease; and a lower proportion of the group died (see Table S1 in the online Data Supplement). Compared with the rest of the cohort, the reference group (those who were untreated normotensive and <50 years old at baseline) had lower SBP and diastolic BP and less cardiovascular disease. The highest proportion of deaths occurred in the hypertensive group (72.8%), followed by those in the prehypertension group (57.0%); mortality was lowest in those with normal levels of SBP (53.6%). Compared with the men in the reference group, those with hypertensive levels of SBP had a significantly higher risk for death. Mortality in the prehypertension group did not differ significantly from the normotensive group (Table 2; see Table S2 for an analysis by BP/treatment/age group).

Accounting for the competitive risk for death, and compared with the reference group, the <50-year olds had a moderately elevated risk for dementia, which was significant ratio by the total number dementia cases. Individual cell-attributable fractions were added up for estimates of PAR by BP level. The excess/prevented number of dementia cases was calculated by multiplying the number of dementia cases within each age/treatment strata by the attributable fraction for those in the normotensive, prehypertensive, and hypertensive SBP groups, separately.

Confidence levels were estimated for each risk ratio and PAR estimates by bootstrapping with 1000 bootstraps on 80% subsets. SAS version 9.1.3* was used to calculate the PAR and bootstrapped 95% CIs.

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Accounting for the competitive risk for death, and compared with the reference group, the <50-year olds had a moderately elevated risk for dementia, which was significant
in the untreated group (Table 3; see Table S3 for a sensitivity analysis that excludes the 52 imputed dementia cases).

On the basis of the combination of risk and number of cases, 27.0% (95% CI: 8.9% to 42.1%) of dementia cases can be attributed to untreated midlife levels of SBP ≥120 mm Hg; this translates into 17 excess cases per 1000. There are 17.7% (95% CI: 4.6% to 29.1%) of cases that are attributable to prehypertensive levels (SBP 120 to <140 mm Hg) of BP, regardless of treatment status, which translates into 11 excess cases per 1000 (Table 4).

Discussion

Our PAR analyses suggest that 17% of late-life dementia cases are attributable to midlife SBP levels between 120 and 140 mm Hg. Among those who did not report taking antihypertensive medication in midlife, 27% of dementia cases can be attributed to SBP levels of ≥120 mm Hg. These estimates are based on >25 years of follow-up, take into account the presence of other correlated factors suspected to increase the risk for dementia, and account for the competing risk of mortality associated with high BP.

These are the first data to provide adjusted estimates of the potential impact of reducing BP on rates of dementia based on a long period of observation of a population-based cohort. There are several factors related to the internal and external validity of the finding, however, that need to be considered when evaluating these PAR estimates and generalizing them to other samples and studies.

Internal Validity

This study is based on a well-described, large population-based cohort that has been followed for >25 years. Standardized assessment of BP, continual surveillance of mortality, and well-characterized dementia cases make the HHP/HAAS a unique cohort on which to base estimates of the PAR for dementia attributed to high blood. However, several assumptions had to be made in the analysis, which need to be noted.

First, the 346 subjects for whom we had no data after examination 3 were censored at examination 3, essentially assigning them the status of nondemented. These men were healthier than those who had ≥1 cognitive examination; the bias introduced depends on the extent to which these men were at even higher risk for dementia or death than those in the sample; given their favorable health status, the error introduced is likely to be small. Similarly, we do not know the error introduced by imputing dementia status in the men with incomplete follow-up after examination 4. However, we did have a cognitive score from a previous examination, and we based the imputation on age and CASI score, which are the most important predictors of whether someone will develop dementia. Including this group results in a decrease in the PAR, so our estimates are conservative.

Second, treatment is defined as ever having used an antihypertensive medication. The study did not collect data on the indication for taking the medication, the dosage of prescribed medication, or whether the medications were taken continuously. However, we did find expected differences in the cardiovascular risk factor profile between the treated and untreated groups. Several factors can account for the differences in risk and benefit between the treated and untreated groups; they may reflect differences in SBP level and variability, the effect of a particular medication, or some third factor, yet unknown, that was correlated with answering positively to question about treatment. Clearly, additional research is needed to answer this question.

Table 3. Proportional Hazard Competing Risk of Dementia by Midlife SBP, Treatment Status, and Age Strata: HHP/HAAS

<table>
<thead>
<tr>
<th>SBP, mm Hg</th>
<th>Treated With Antihypertensive Medications</th>
<th>Untreated</th>
<th>Total, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;50 Years Old (n=631)</td>
<td>≥50 Years Old (n=2602)</td>
<td>&lt;50 Years Old (n=688)</td>
</tr>
<tr>
<td>Reference†</td>
<td>RR*</td>
<td>95% CI†</td>
<td>RR*</td>
</tr>
<tr>
<td>Normotensive (&lt;120)</td>
<td>1.04</td>
<td>0.96 to 1.13</td>
<td>0.92</td>
</tr>
<tr>
<td>Prehypertension (120 to &lt;140)</td>
<td>1.12</td>
<td>0.90 to 1.40</td>
<td>1.19</td>
</tr>
<tr>
<td>Hypertension (≥140)</td>
<td>1.19</td>
<td>0.85 to 1.66</td>
<td>1.19</td>
</tr>
</tbody>
</table>

*Data were adjusted for competing risk of death and confounding factors; RR indicates risk ratio.
†There were total of 1000 bootstrapped 95% CIs for all of the competing risk RRs.
‡Reference group (n=493) includes untreated men with normal BP who were <50 years of age at baseline in 1965.

Table 4. PAR for Dementia Attributed to Midlife SBP: HHP/HAAS

<table>
<thead>
<tr>
<th>SBP (mm Hg)</th>
<th>Treated With Antihypertensive Medications, %</th>
<th>Untreated, %</th>
<th>Total, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAR</td>
<td>95% CI*</td>
<td>PAR</td>
</tr>
<tr>
<td>Prehypertension (120 to &lt;140)</td>
<td>−1.41</td>
<td>−6.46 to 3.17</td>
<td>19.14</td>
</tr>
<tr>
<td>Hypertension (≥140)</td>
<td>−11.00</td>
<td>−27.70 to 5.46</td>
<td>7.94</td>
</tr>
<tr>
<td>Combined 120 mm Hg and higher</td>
<td>−12.40</td>
<td>−34.68 to 8.57</td>
<td>27.08</td>
</tr>
</tbody>
</table>

Risk estimates are adjusted for confounding factors and competitive risk for death.
*There were a total of 1000 bootstrapped 95% CIs for all of the PARs.
External Validity
Data are based on men born from 1900 to 1919, which defines the extent to which these analyses are generalizable to others. First, the cohort was middle age in the 1960s, and treatment patterns reflect the state of the art at that time. At that time, the main goal was to treat diastolic BP. Isolated systolic hypertension was not a strong indication for treatment, and levels of BP indicating treatment were higher than the current standards.

Second, these estimates are based on Japanese American men. In this cohort, the incidence of dementia is similar to that reported for cohorts of mainly white origin and the prevalence of and mortality associated with prehypertension are similar to those reported in National Health and Nutrition Examination Survey and the relationship of midlife BP and late-life dementia has been replicated in cohorts of men and women from different race/ethnic groups. Nevertheless, the population distributions of SBP do vary by sex, race/ethnic group, socioeconomic status, diet, the force of mortality associated with elevated BP, and other factors. Therefore, as for any PAR, separate calculations would have to made for significant subgroups in the population.

Third, these are data that show the predicted midlife-attributable risk for dementia, without taking into account subsequent changes in BP levels or treatment. However, the finding that high BP increases the risk for dementia has been most consistent in studies where the study interval was long and BP was measured at midlife. There is increasing awareness about the difficulties in interpreting relative risks for dementia associated with BP measured close to the time that dementia is diagnosed. The issues that plague interpretation include the lowering of measured BP that is the consequence of dementing processes and the increasing prevalence of pathological hypotension in older populations. In addition, the strength of this analysis is the demonstration that, regardless of what happens in the intervening period, from a public health prevention perspective, treatment of BP in midlife is indicated in programs aimed to reduce the burden of dementia in late-life dementia. Whether reducing SBP in late age reduces the risk for dementia or conversion from mild cognitive impairment to dementia can be addressed in clinical trials such as the Hypertension in the Very Elderly Trial.

Finally, a randomized trial to test the efficacy of BP control to prevent dementia is needed. There are few trials examining the efficacy of treating BP with particular drugs and the risk for dementia. However, follow-up was short, they achieved very small differences in BP between placebo and control, and they were not powered for dementia outcomes. The design of the study should take into account findings from observational studies that suggest that longer treatment and follow-up may be important factors for prevention success.

In this cohort, the PAR for hypertension is lower than for prehypertension. This group is the smallest proportion of the sample and is at significantly increased risk for death compared with others. It may not be surprising that hypertension is associated with risk for dementia. What this study shows is that those with prehypertension in midlife have a higher attributable risk for dementia than either the normotensive or hypertensive men. This reflects the combination of a moderately raised risk for dementia, a similar risk for death compared with normotensives, and a higher number of prehypertensive men within that group of cases.

Efforts to control hypertension have been well on their way for decades. Risk factors and outcomes in persons with hypertension are the most likely to change with changes in detection and treatment practices. It is only recently that the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has modified its classification to include the term “prehypertension.” The new designation is intended to identify those individuals who would benefit from early intervention to reduce BP, slow down the rate of progression of BP to hypertensive levels, or prevent hypertension entirely. Our findings suggest that there may also be a benefit for the prevention of dementia.

Implications
Although secular trends documented through the National Health and Nutrition Examination Survey studies show that the prevalence of hypertension has decreased and the use of antihypertensive medication has increased over time, recent studies suggest some worrying trends. For instance, a large proportion of those with hypertension are not aware of their condition, are aware but have not sought treatment, or have been treated but unsuccessfully. Furthermore, the rates of obesity and diabetes mellitus, both important comorbidities with hypertension, are increasing, particularly in children. With these trends, the number of people with prehypertension in midlife will inevitably increase. The changes in medical practice, coupled with the changes in lifestyle that occur with time, argue for a broad surveillance system that can monitor the end impact of population changes in BP levels and changes in the incidence of dementia. Although the PAR estimates may differ among subgroups in the population, these data are clearly suggestive of the need to consider midlife SBP level as a modifiable risk factor for dementia.

Perspectives
Dementia has high individual, societal, and economic costs. It is an age-related disease, and as the proportion of older persons in the population increases, proportionately more cases will develop. Prevention is a priority, but to date there is no accepted prevention strategy. In this regard, 2 concepts are becoming crystallized in experimental, clinical, and epidemiological studies: first, clinical dementia is the end of processes that begin many years before a diagnosis is made, and, second, cardiovascular risk factors are associated with an increased risk for late-life dementia. Together, these concepts suggest that early intervention on cardiovascular risk factors may be one approach to prevent late-life dementia. Use of population-based longitudinal studies, such as the HHP/HAAS, can contribute importantly to identifying the most relevant cardiovascular risk factors, the long-term effect on the brain of these risk factors, and the possible effects of intervening early on late-life dementia outcomes. This current study shows that ≈20% of dementia cases are attributed to higher levels of SBP. BP control is an intervention that is...
known to benefit for many other reasons, and this study shows that it may also help reduce dementia in late life. The study also shows, similar to cardiovascular outcomes, that the risk for dementia is raised even in persons with SBP levels in the prehypertension range. These data, in combination with results from clinical trials, should provide the basis for developing monitoring and evaluation tools to track trends in dementia as it relates to changes in the population distribution of BP.

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Disclosures
None.

References
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Lowering mid-life levels of systolic blood pressure as a public health strategy to reduce late-life dementia:

Perspective from the Honolulu Heart Program/Honolulu Asia Aging Study

Supplemental Information

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Appendix. Method to estimate the attributable risk of elevated levels of midlife systolic blood pressure on dementia in the presence of death

The population attributable risk is calculated using the weighted-sum approach for multi-level multi-factor exposures across strata [1]. Let \( E = 0, \ldots, K \), be the primary exposure variable with \( K+1 \) levels and \( D = 0 \) or \( 1 \) be the binary variable for disease.

1. **Single stratum**

For binary exposure \((K=1)\), AR can be written as [2]

\[
AR = \frac{\Pr(E)(RR - 1)}{1 + \Pr(E)(RR - 1)} = P(E = 1 \mid D = 1) \frac{RR - 1}{RR}
\]  

where \( RR = P(D=1 \mid E=1) / P(D=1 \mid E=0) \). When the exposure variable has multiple categories \((K>1)\), then the level-specific attributable risk is given by [3]

\[
AR^{(k)} = \frac{\Pr(E)(RR_k - 1)}{1 + \sum_{k=1}^{K} \Pr(E)(RR_k - 1)} = P(E = k \mid D = 1) \frac{RR_k - 1}{RR_k}
\]

where \( RR_k = P(D = 1 \mid E = k) / P(D = 1 \mid E = 0) \). The overall AR of the \( K \)-level exposure is given by

\[
AR = \sum_{k=1}^{K} P(E = k)(RR_k - 1) = \sum_{k=1}^{K} P(E = k \mid D = 1) \frac{RR_k - 1}{RR_k}
\]

Thus the overall \( AR = \sum_{k=1}^{K} AR^{(k)} \). Equation (1) is a special case of (3) when \( K=1 \).

The AR can be interpreted as the proportion of cases (diseases) in the population which can be attributed to the exposure. The excess number of cases (EC) that can be attributed to the exposure can be calculated as

\[
EC = \text{Total number of cases} \times AR.
\]

The excess number of cases due to exposure level \( k \) is calculated as

\[
EC^{(k)} = \text{Total number of cases} \times AR^{(k)}.
\]

Hence, \( EC = \sum_{k=1}^{K} EC^{(k)} \).

2. **Multiple Strata**

When there are confounders \( X \), e.g., age, BMI group, smoking and disease history, the data are usually stratified into multiple groups. Let \( i \) be the index of the strata, \( i=1,\ldots,G \).
First, within each stratum $i$, the cumulative risks of developing dementia for each exposure (hypertension) level in the presence of death, $P(D=1 | E=k, X=i), k=0,\ldots,K$, are calculated using the function crr in the R package cmprsk [3]. Because hypertension is a known risk factor for death, the hypertensive subjects may die earlier. If we treat death as censored, then there are more censoring cases for hypertensive people. The approach by Fine and Gray [2] considered the competing risk of death and calculated the cumulative probability of having dementia in the presence of death.

Then the relative risks are calculated as
\[ RR_{k,i} = \frac{P(D=1 | E=k, X=i)}{P(D=1 | E=0, X=i)}. \]

The overall estimate of the common relative risk is calculated as the adjusted logit estimate:
\[ RR_k = \exp \left( \frac{\sum_i p_i \log(RR_{k,i})}{\sum_i p_i} \right), \]

where $p_i = n_i/n$ is the proportion of subjects in the $i$-th stratum. The attributable risk due to exposure level $k$ in stratum $i$ is
\[ AR^{(k)}_i = \frac{P(E=k | X=i)(RR_{k,i} - 1)}{1 + \sum_{k=1}^{K} P(E=k | X=i)(RR_{k,i} - 1)} = P(E=k | D=1, X=i) \frac{RR_{k,i} - 1}{RR_{k,i}}. \]

Here we use the former equation because the estimates $P(E=k|X=i)$ has smaller variance than $P(E=k|D=1,X=i)$.

Let $C_i = \# \{ D=1, X=i \}$ be the number of cases, and let $EC^{(k)}_i$ be the excess number of cases due to exposure level $k$ in stratum $i$. The total aggregate number of cases $C = \sum_{i=1}^{I} C_i$. Then the aggregate attributable risk for exposure level $k$ is defined as
\[ AR^{(k)} = \sum_{i=1}^{I} EC^{(k)}_i / C = \sum_{i=1}^{I} C_i \times AR^{(k)}_i / C = w_i AR^{(k)}_i \]

where $w_i = C_i/C$ is the proportion of cases in stratum $i$. The overall population attributable risk (AR) is then
\[ AR = \sum_{k=1}^{K} AR^{(k)} \]

1. Confidence Intervals
The confidence intervals of AR can be calculated using Bootstrap. First, a stratified bootstrap sample is generated for each stratum, and the AR and $AR^{(k)}$ are calculated for each bootstrap sample. Then the procedure is repeated $B$ (=1000) times and the empirical confidence interval is constructed based on the resulted AR from the $B$ samples.

References


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt;50 yrs old</th>
<th>≥50 yrs old</th>
<th>&lt;50 yrs old*</th>
<th>≥50 yrs old</th>
<th>Reference</th>
<th>Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=631)</td>
<td>(n=2602)</td>
<td>(n=688)</td>
<td>(n=3464)</td>
<td>(n=493)</td>
<td></td>
</tr>
<tr>
<td>Age (yrs) (mean ± SD)</td>
<td>48.0 (±0.9)</td>
<td>56.9 (±5.1)</td>
<td>47.9 (±1.0)</td>
<td>56.0 (±4.8)</td>
<td>48.0 (±0.9)</td>
<td></td>
</tr>
<tr>
<td>Mid-life Systolic BP (mmHG) (mean ± SD)</td>
<td>146.0 (±15)</td>
<td>152.6 (±17.8)</td>
<td>130.7 (±7.9)</td>
<td>125.7 (±12.7)</td>
<td>112.7 (±5.7)</td>
<td></td>
</tr>
<tr>
<td>Mid-life Diastolic BP (mmHG) (mean ± SD)</td>
<td>92.7 (±8.2)</td>
<td>90.9 (±9.5)</td>
<td>82.3 (±5.3)</td>
<td>77.4 (±7.4)</td>
<td>73.8 (±5.8)</td>
<td></td>
</tr>
<tr>
<td>Mid-life Systolic BP category [n, %]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>normotensive (&lt; 120)</td>
<td>19 [3.0]</td>
<td>44 [1.7]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prehypertension (120- &lt;140)</td>
<td>212 [33.6]</td>
<td>582 [22.4]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypertension (&gt;= 140)</td>
<td>400 [63.4]</td>
<td>1976 [75.9]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &gt;25 [n, %]</td>
<td>331 [52.5]</td>
<td>1123 [43.2]</td>
<td>275 [40.0]</td>
<td>843 [24.3]</td>
<td>134 [27.2]</td>
<td></td>
</tr>
<tr>
<td>History of stroke [n, %]</td>
<td>12 [1.9]</td>
<td>134 [5.2]</td>
<td>2 [0.3]</td>
<td>32 [0.9]</td>
<td>1 [0.2]</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------</td>
<td>-----------</td>
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<td>----------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>Event Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death [n, %]</td>
<td>320 [50.7]</td>
<td>1946 [74.8]</td>
<td>279 [40.6]</td>
<td>2235 [64.5]</td>
<td>189 [38.3]</td>
<td></td>
</tr>
<tr>
<td>Number of follow-up years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead (mean ± SD)</td>
<td>22.9 (±8.5)</td>
<td>19.8 (±8.3)</td>
<td>23.1 (±8.4)</td>
<td>21.2 (±8.6)</td>
<td>24.1 (±8.2)</td>
<td></td>
</tr>
<tr>
<td>Demented (mean ± SD)</td>
<td>28.1 (±2.9)</td>
<td>26.2 (±3.1)</td>
<td>28.6 (±2.9)</td>
<td>27.0 (±3.3)</td>
<td>29.3 (±3.7)</td>
<td></td>
</tr>
<tr>
<td>Not demented (mean ± SD)</td>
<td>26.9 (±10.8)</td>
<td>26.8 (±10.0)</td>
<td>27.8 (±10.3)</td>
<td>26.7 (±10.6)</td>
<td>29.1 (±9.1)</td>
<td></td>
</tr>
<tr>
<td>Person years of follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>7317.8</td>
<td>38435.6</td>
<td>6435.9</td>
<td>47446.2</td>
<td>4555.4</td>
<td></td>
</tr>
<tr>
<td>Demented</td>
<td>758.4</td>
<td>4394.4</td>
<td>829.5</td>
<td>6837.0</td>
<td>410.4</td>
<td></td>
</tr>
<tr>
<td>Not demented</td>
<td>7650.5</td>
<td>13083.4</td>
<td>10547.9</td>
<td>26025.7</td>
<td>8428.2</td>
<td></td>
</tr>
</tbody>
</table>

*The data in this column are for those with prehypertension or hypertension; the normotensives are in the reference column.
### Table S2: Risk* of Death by mid-life systolic blood pressure, treatment status, and age strata: HHP/HAAS

<table>
<thead>
<tr>
<th>Systolic BP (mmHG)</th>
<th>Treated with anti-hypertensive meds</th>
<th>&lt;50 yrs old</th>
<th>&gt;50 yrs old</th>
<th>Total Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>HR (95% CI)</td>
<td>n</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Normotensive (&lt;120)</td>
<td>493</td>
<td>reference†</td>
<td>493</td>
<td>reference†</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>0.72 (0.32-1.64)</td>
<td>44</td>
<td>1.29 (0.88-1.90)</td>
</tr>
<tr>
<td>Prehypertension (120 - &lt;140)</td>
<td>212</td>
<td>1.06 (0.82-1.38)</td>
<td>582</td>
<td>0.97 (0.81-1.17)</td>
</tr>
<tr>
<td>Hypertension (≥ 140)</td>
<td>400</td>
<td>1.74 (1.43-2.13)</td>
<td>1976</td>
<td>1.22 (1.04-1.43)</td>
</tr>
<tr>
<td>Untreated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHG)</td>
<td>T</td>
<td>&lt;50 yrs old</td>
<td>&gt;50 yrs old</td>
<td>Total Untreated</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>HR (95% CI)</td>
<td>n</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Normotensive (&lt;120)</td>
<td>493</td>
<td>reference†</td>
<td>1153</td>
<td>0.86 (0.73-1.01)</td>
</tr>
<tr>
<td>Prehypertension (120 - &lt;140)</td>
<td>596</td>
<td>1.04 (0.86-1.26)</td>
<td>1831</td>
<td>0.90 (0.77-1.06)</td>
</tr>
<tr>
<td>Hypertension (≥ 140)</td>
<td>92</td>
<td>1.54 (1.11-2.14)</td>
<td>480</td>
<td>1.08 (0.90-1.30)</td>
</tr>
</tbody>
</table>

* Hazard Ratio (95% CI)

† Reference group (n = 493) includes untreated men with normal blood pressure who are < 50 years of age at baseline in 1965
Table S3: Proportional hazard competing risk* of dementia by mid-life systolic blood pressure, treatment status and age strata before imputation of case status: HHP/HAAS

<table>
<thead>
<tr>
<th>Systolic Blood Pressure (mmHG)</th>
<th>Treated with anti-hypertensive meds</th>
<th>Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;50yrs old</td>
<td>≥50 yrs old</td>
</tr>
<tr>
<td></td>
<td>RR* (95% CI)†</td>
<td>RR* (95% CI)†</td>
</tr>
<tr>
<td></td>
<td>reference‡</td>
<td>reference‡</td>
</tr>
<tr>
<td>Normotensive (&lt;120)</td>
<td>1.10 (1.01-1.20)</td>
<td>0.95 (0.90-1.01)</td>
</tr>
<tr>
<td>Prehypertension (120 - &lt;140)</td>
<td>1.29 (1.03-1.62)</td>
<td>0.89 (0.79-1.01)</td>
</tr>
<tr>
<td>Hypertension (≥ 140)</td>
<td>1.46 (1.05-2.08)</td>
<td>0.84 (0.71-1.02)</td>
</tr>
</tbody>
</table>

* Adjusted for competing risk of death; imputed cases set to non-demented and censored at the date of their last HAAS exam

† 1000 bootstrapped 95% CI for all competing risk RR

‡Reference group (n = 493) is the same for all RR and includes untreated men with normal blood pressure who are < 50 years of age at baseline in 1965