Association between blood pressure levels and cognitive impairment in older women: a prospective analysis of the Women's Health Initiative Memory Study

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Summary

Background Whether blood pressure (BP), and at what level of controlled BP, reduces risk of cognitive impairment remains uncertain. We investigated the association of BP and hypertension treatment status with mild cognitive impairment and dementia in older women.

Methods We prospectively analysed a sample of 7207 community-dwelling women aged 65–79 years participating in the Women's Health Initiative Memory Study (WHIMS). Participants were recruited between May 28, 1996, and Dec 13, 1999, at 39 US clinical centres, and they were followed up until Dec 31, 2019. Cognitive function was assessed annually. Mild cognitive impairment and probable dementia were defined through a centralised adjudication process. BP was measured by trained and certified staff at baseline. Pulse pressure (PP) was calculated as systolic BP (SBP) minus diastolic BP. Hypertension was defined using the American Heart Association 2017 Guideline for High BP in Adults. Outcomes were (1) mild cognitive impairment, (2) probable dementia, and (3) cognitive loss (the combined endpoint of either mild cognitive impairment or probable dementia, or both). We estimated hazard ratios (HRs) to assess the association between hypertension, SBP, and PP with the risk of study outcomes using Cox proportional hazards regression models, with adjustment for key covariates.

Findings During a median follow-up of 9 years (IQR 6–15), 1132 (15·7%) participants were classified as mild cognitive impairment, 739 (10·3%) as probable dementia, and 1533 (21·3%) as cognitive loss. The incidence rates per 1000 person-years were 15·3 cases (95% CI 14·4–16·2) for mild cognitive impairment, 9·7 cases (9·0–10·4) for probable dementia, and 20·3 (19·3–21·3) for cognitive loss. Elevated SBP and PP were significantly associated with increased risk of mild cognitive impairment and cognitive loss (test for trends across SBP and PP strata, p<0·01). Individuals with hypertension, but with controlled SBP of less than 120 mm Hg did not have a significantly increased risk of mild cognitive impairment (HR 1·33, 95% CI 0·98–1·82, p=0·071), and of cognitive loss (1·09, 0·82–1·44, p=0·57) compared with normotension. Individuals on anti-hypertensive treatment with PP of less than 50 mm Hg did not have a significantly higher risk of mild cognitive impairment (1·26, 0·98–1·62, p=0·07) and of cognitive loss (1·17, 0·94–1·46, p=0·16). There were no significant associations between hypertension, SBP, or PP and probable dementia.

Interpretation Results of our study show significant associations of hypertension and elevated SBP and PP levels with risk of mild cognitive impairment and the combined endpoint of either mild cognitive impairment or probable dementia, suggesting that intensive control of hypertension, SBP, and PP can preserve cognitive health in older women.

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Introduction

Dementia is a global problem. The number of people living with dementia, estimated at 47 million worldwide in 2015, is projected to reach 76 million in 2030 and 135 million by 2050, resulting in huge social and economic costs.[1] Hypertension is one of the most important risk factors for cerebrovascular disorders and dementia.[2–4] Several studies have observed a significant association between midlife hypertension and risk of mild cognitive impairment (a precursor to a progressive dementia), and both midlife and late-life hypertension were associated with risk of dementia.[4–6] For example, results from the Atherosclerosis Risk in Communities (ARIC) study,[4] conducted from 1987–89 through 2011–13 in a cohort of 15744 participants aged 44–66 years at baseline (of whom 27·1% were Black and 72·9% White), show that participants with pre-hypertension (systolic blood pressure [SBP]/diastolic blood pressure [DBP] ≥120/80 mm Hg and SBP/DBP <140/90 mm Hg) or those with hypertension (SBP/DBP ≥140/90 mm Hg) at midlife are at significantly higher risk of dementia.[4] Findings from the Framingham Offspring Study in 1140 participants

Research in context

Evidence before this study

We searched MEDLINE, Embase, and Google Scholar for studies published from 1990 to 2020 assessing the association of blood pressure (BP) and pulse pressure (PP) with risk of mild cognitive impairment and dementia, using key words "blood pressure and cognitive impairment" or "blood pressure and cognitive decline" or "blood pressure and dementia". We did not apply any language restrictions. We noticed that these associations have been tested predominantly by the measures of BP at individuals' middle age and subsequent risk of cognitive impairment at their older age in most observational studies. Findings from these previous studies were inconsistent, probably because of the sample sizes, the heterogeneity in their study populations, variety of the definition of high BP, or a short period of follow-up. Findings from the Systolic Blood Pressure Intervention Trial (SPRINT) provide evidence on risk reduction of mild cognitive impairment and of the combined form of cognitive impairment (mild cognitive impairment or probable dementia) through an intensive control of systolic blood pressure (SBP) at less than 120 mm Hg. Participants in the SPRINT were those at middle and older ages (50 years or older) who had no diabetes or history of stroke and who had SBP between 130 mm Hg and 180 mm Hg at the study screening visit. To date, large-scale population-based studies with sex-specific tests in women were not available. Whether SBP, and at what levels of controlled SBP, is associated with risk reduction of cognitive impairment in older women remains uncertain.

Added value of this study

To our knowledge, the WHIMS is the largest community-dwelling population-based study to examine the association of SBP and PP with the risk of cognitive impairment in older women. Findings from the WHIMS, with a median follow-up of 9 years (IQR 6–15), indicate that hypertension and elevated SBP and PP levels are significantly associated with an increased risk of mild cognitive impairment and cognitive loss (defined as the combined endpoint of either mild cognitive impairment or probable dementia, or both) in older women. The study adds new evidence that older women with controlled hypertension targeting SBP at less than 120 mm Hg or targeting of PP at less than 50 mmHg were not at higher risk for mild cognitive impairment and cognitive loss than were women with normotension.

Implications of all the available evidence

Evidence on whether controlled SBP at less than 120 mm Hg or PP at less than 50 mm Hg are associated with risk reduction of probable dementia remains uncertain. This lack of evidence is probably due to a small sample size of those with diagnosed probable dementia. However, the significant associations of hypertension, elevated SBP, and PP with risk of mild cognitive impairment and cognitive loss support that intensive control of hypertension, SPB, and PP levels can preserve cognitive health in older women.

(53% women) suggest that people with systolic hypertension (SBP ≥140 mm Hg) in midlife (mean age 55 years) are at a significantly higher risk for dementia in late-life (mean age 69 years).[7] Results from the Whitehall II cohort study in 8639 participants (32·5% women) at age 50, 60, and 70 years also show that SBP ≥130 mm Hg at age 50 years is significantly associated with an increased risk of dementia in late-life. However, the associations between SBP and dementia were not significant among older adults aged 60 or 70 years in the Whitehall II cohort study.[6] A recent meta-analysis of 209 prospective studies supports that elevated SBP in midlife is associated with increased risk of cognitive impairment in late-life.[2] In a meta-analysis of six community-based prospective studies, Ding and colleagues[3] observed a significant beneficial effect of anti-hypertensive medication on risk reduction of dementia for those with SBP/DBP equal to or higher than 140/90 mm Hg. Few clinical trials have been done. Results from the Systolic Blood Pressure Intervention Trial (SPRINT) among participants aged 50 years or older with intensive blood pressure (BP) control (SBP <120 mm Hg; n=4678) versus those with standard BP control (SBP <140 mm Hg; n=4683), suggest that intensive BP lowering significantly decreased risk of mild cognitive impairment and of the combined mild cognitive impairment and dementia compared with the control group.[8] In contrast to the SPRINT, the Heart Outcomes Prevention Evaluation-3 (HOPE-3) Study, a double-blind, randomised, placebo-controlled clinical trial, showed that long-term SBP lowering did not affect cognitive decline in older patients.[9] In addition to the study of SBP, several studies have also examined the association between pulse pressure (PP, a measure of arterial stillness) and risk of dementia.[10–12] Both SBP and DBP increase with age up to approximately 60 years, and thereafter SBP continuously increases while DBP starts to decrease, resulting in a steep rise in PP.[10–14] However, studies of the association of SBP and PP with risk of cognitive impairment in older adults are limited or inconsistent.[9–15] Furthermore, to this date, there is paucity of research by sex separately in older adults.[2,3,16–18] In this study, we investigated the association of BP and hypertension treatment status with mild cognitive impairment and dementia in older women using data from the Women's Health Initiative Memory Study (WHIMS).

Methods

Study design and participants

This is a prospective analysis of the WHIMS, which included 7479 female participants aged 65–79 years, who were recruited between May 28, 1996, and Dec 13, 1999. These women were enrolled in the WHI hormone therapy (WHI HT) trials, which included community-dwelling

women from 39 US clinical centres.[19,20] The WHI HT trials consisted of two parallel randomised clinical trials for the evaluation of the effects of oestrogen alone (E-Alone) or the combination of oestrogen plus progestin (E+P) on prevention of heart disease and osteoporotic fractures, and associated risk for breast cancer. The details of the study design of the WHIMS have been reported previously.[21–23] In brief, WHIMS evaluated whether hormone therapy reduced the incidence of all-cause dementia in both trials. Although the WHI E+P trial ended in 2002, and the E-Alone trial ended in 2004, WHIMS participants, recruited from WHI HT trials, continued to receive post-trial cognitive assessments that included an annual cognitive screening with follow-up in clinics for neuropsychological testing and proxy interview plus a neuropsychiatric examination by a specialist physician until 2007. Beginning in 2008, both study cohorts transitioned to the WHIMS–Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO) for post-trial follow-up. Instead of face-to-face evaluation, participants underwent an annual centralised telephone-based cognitive assessment with a validated battery of tests and questionnaires and proxy interviews for continued tracking of changes in cognitive status (see outcome assessment later for more detail).[23,24] In this report, we analysed data from the WHIMS with a follow-up until Dec 31, 2019. Of 7479 participants in the WHIMS, we excluded participants with baseline mild cognitive impairment, with baseline Alzheimer's disease, and those with only baseline survey information, leaving 7207 participants for the analysis.

Exposure assessment

BP was measured by trained and certified staff using standardised procedures in WHI clinics.[25] The average of two readings of BP taken at baseline clinic visit was used for the analysis. We applied the American Heart Association 2017 Guideline for High Blood Pressure in Adults to classify BP into five groups: (1) people with anti-hypertensive medication treatment regardless of their visit measures of BP; (2) people with SBP/DBP ≥140/90 mmHg; (3) people with SBP/DBP ≥130/80 and <140/90 mmHg; (4) people with SBP 120–129 mm Hg and DBP <80 mmHg (ie, elevated SBP), and (5) people with SBP/DBP <120/80 mm Hg (ie, normal BP). PP was the difference between SBP and DBP.[16] PP was categorised in four groups (<50 mm Hg, 50–59 mm Hg, 60–69 mm Hg, and ≥70 mmHg). By taking account of the difference between high SBP (140 mmHg) and high DBP (90 mmHg), we set PP <50 as the reference group, and then tested the effect of every PP increase of 10 mm Hg on the risk of the study outcomes.

Outcome assessment

The study tested three outcomes: mild cognitive impairment, probable dementia, and cognitive loss (defined as the combined endpoint of either mild cognitive impairment or probable dementia or both). All suspected cases were centrally adjudicated in WHIMS. Participants in 1996–2007 were screened annually in person at clinic sites by trained and certified examiners using the Modified Mini-Mental State Examination (3MSE).[26] The 3MSE consists of 15 items, whose scores were summed from 0 to 100, with higher scores reflecting better cognitive functioning. Women who scored below an education-adjusted cut point on the 3MSE (cut points of 80 or lower for participants with ≤8 years of education and 88 or lower for participants with ≥9 years of education. Note that before July 1, 1998, the cut points were 72 and 76)[26] were further administered a modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery of neuropsychological tests and standardised interviews to assess acquired cognitive and behavioural impairments by certified examiners. Additionally, a designated informant (friend or family member) was interviewed separately regarding acquired cognitive and behavioural impairments in the participant. These women were given a neuropsychiatric evaluation by a local board-certified physician with expertise in the field of dementia (ie, geriatrician, neurologist, or geriatric psychiatrist) using a standardised protocol provided by the WHIMS Clinical Coordinating Center (CCC; Wake Forest School of Medicine, Winston-Salem, NC, USA). The physician then classified the WHIMS participant as having no cognitive impairment, mild cognitive impairment, or probable dementia. Beginning with WHIMS-ECHO (2008–21), an annual validated cognitive test battery that included the Telephone Interview for Cognitive Status-modified (TICSm) and other tests of memory, language, executive function, and working memory was administered by telephone by certified examiners. These examiners who were centrally trained by the WHIMS CCC collected all WHIMS specific data[24] 3MSE scores from WHIMS were highly predictive of TICSm scores from WHIMS-ECHO (r=0·82).[24] For women who scored below 31 on the TICSm at any annual assessment during the WHIMS-ECHO follow-up, a reliable and pre-identified informant was interviewed via telephone by using the standardised Dementia Questionnaire to assess the history of cognitive and behavioural changes, functional impairments, and health events that can affect cognitive functioning.[27] This assessment administered by telephone has been evaluated to be reliable and valid.[24] For both WHIMS and WHIMS-ECHO, all participant data were submitted to a central adjudication committee at the WHIMS CCC where a panel of experts in diagnosis of mild cognitive impairment and dementia independently reviewed cases and made classifications. Each triggered case was reviewed independently by two adjudicators with concordance determining final case status. Discordant classifications were submitted to the full adjudication panel for discussion and final consensus classification. Adjudicators followed standardised diagnostic criteria throughout the study. For the classification of mild

cognitive impairment by the adjudicators, WHIMS used the Petersen criteria (1997). These criteria are (1) reported memory problems, (2) an objective memory deficit measured by cognitive tests, (3) normal global cognitive function, (4) absence of significant functional impairment, and (5) absence of dementia. For probable dementia, WHIMS followed the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for dementia and Petersen criteria for mild cognitive impairment.[28,29] Individuals with first identification of mild cognitive impairment or probable dementia were classified as incident mild cognitive impairment or incident probable dementia. An individual could be classified as incident mild cognitive impairment and incident probable dementia because mild cognitive impairment might transition to probable dementia. People with either mild cognitive impairment or probable dementia or both were classified as cognitive loss.

Covariate assessment

See Online for appendix

At baseline, participants completed standardised questionnaires assessing age (years), race and ethnicity (African American, White, and other groups including Hispanic, Asian or Pacific Islander, and American Indian or Alaska Native), education (≤high school, some college, or ≥college (ie, completed a 4-year college or university training with a bachelor's degree or higher), health insurance status (any insurance, yes or no), smoking (never, past, or current smokers), alcohol use (yes or no), physical activity status (yes or no), and history of major chronic conditions (yes or no). Alcohol use was dichotomised as "no" meaning those without any alcohol or with one or less alcohol serving per week, and "yes" meaning those with alcohol use history of two or more alcohol servings per week. Physical activity was classified using expenditure of energy from walking in kcal/week per kg (MET-h/week). If a woman reported 1·5 MET-h/week or more, she was classified as taking part in physical activity; those with less than 1·5 MET-h/week were classified as reporting no physical activity. Self-reported history of diabetes, myocardial infarction, stroke, transient ischaemic attack, congestive heart failure, peripheral arterial disease, and anti-hyperlipidaemic drug status were coded as yes or no. Using self-report to assess chronic conditions has been validated as a reliable and cost-effective approach in large-scale population studies in the USA.[30,31] Height (m) and weight (kg) were measured at baseline to calculate body-mass index (BMI, kg/m²).

Statistical analysis

We first described the baseline characteristics of participants by hypertension status. Differences in continuous variables by hypertension status were tested using *t* tests, and differences in categorical variables were tested using χ^2 tests. Next, we estimated the incidence rates of mild cognitive impairment, probable dementia, and cognitive loss per 1000 person-years. We then applied multivariate adjusted Cox proportional hazards regression analyses to estimate the hazard ratios (HRs) of hypertension, elevated SBP, and PP, and by whether or not individuals were taking anti-hypertensive medication status, for the risk of mild cognitive impairment, probable dementia, and cognitive loss. Duration (days) of the follow-up for each participant was calculated from the participant's enrolment to the day of her first-time classification of mild cognitive impairment or probable dementia, or for those who ended the study earlier due to any other reasons, whichever came first. To control potential confounders, we performed two multivariate-adjusted models. Model 1 was adjusted for age (years), race or ethnicity (Black or African American, White, and the other race or ethnicity group), and WHI HT trial status (ie, conjugated equine oestrogen [CEE] plus medroxyprogesterone acetate or CEE use alone trials). We included the adjustment for WHI HT trial status, because there were differences in age and several baseline variables between the trial status in the participants of the WHIMS (appendix p 1). Model 2 was adjusted for the covariates in Model 1 plus education (≤high school, some college, and ≥college), health insurance status (yes or no), smoking (never, past, or current), alcohol use (yes or no), physical activity (yes or no), history of diabetes (yes or no), and use of anti-hyperlipidaemic medication (yes or no). In Model 2, we did not adjust for history of cardiovascular disease (including those with either myocardial infarction, stroke, transient ischaemic attack, congestive heart failure, or peripheral arterial disease), because it is likely to be a mediator of the association of hypertension, SBP, and PP with risk of mild cognitive impairment, probable dementia, or cognitive loss. Instead, we tested interaction effects of baseline cardiovascular disease and exposures (hypertension, SBP, PP) on mild cognitive impairment, probable dementia, and cognitive loss. Meanwhile, in WHIMS, repeated measures of BP were conducted in annual follow-up at years 1, 3, 6, and 9, which enabled us to examine the associations of SBP and PP variations (assessed by the coefficient of variation, the ratio of the standard deviation to the mean) with risk of the study outcomes.

Finally, we performed two sensitivity analyses: (1) we took into consideration the possibility of reverse causation that is attributable to the incident cases who had incipient cognitive impairment during the early period of follow-up. We repeated our analysis after excluding those with the classification of mild cognitive impairment or probable dementia within the first 1 year of follow-up. This 1 year cutoff makes an assumption that individuals with clinically diagnosed mild cognitive impairment or dementia might have subclinical cognitive impairment at their baseline recruitment. (2) We took into account the possibility of potential competing risks attributable to cardiovascular disease and all other causes of mortality that occurred before the study outcomes (ie, death

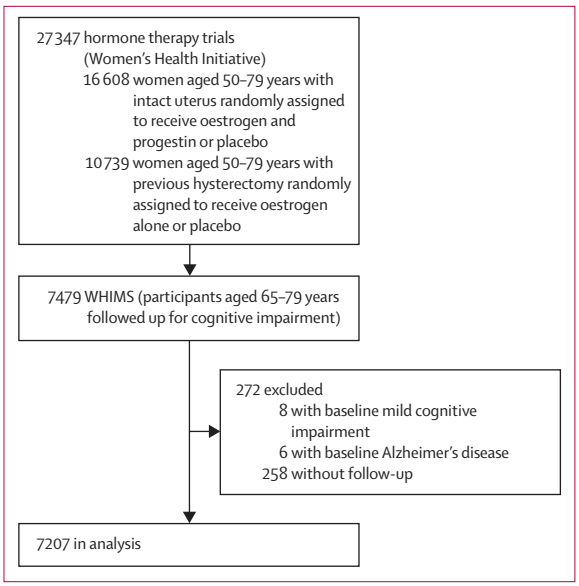

Figure 1: **Sample size of the study participants**

	No hypertension (n=3932)	Hypertension (n=3275)	p value
Age in years, mean (SD)	69·7 (3·7); n=3932	70·5 (3·9); n=3275	<0·0001
BMI, kg/m², mean (SD)	27·5 (5·3); n=3907	29·7 (5·9); n=3261	<0·0001
Modified Mini-Mental state score, mean (SD)	95·6 (4·1); n=3888	94·9 (4·4); n=3245	<0·0001
Race or ethnicity	..	..	<0·0001
Black	180 (4·6%)	326 (10·0%)	..
White	3520 (89·5%)	2755 (84·1%)	..
Others*	232 (5·9%)	194 (5·9%)	..
Education†	..	..	<0·0001
≤High school	1076 (27·5%)	1048 (32·1%)	..
Some college	1545 (39·4%)	1352 (41·4%)	..
≥College	1298 (33·1%)	866 (26·5%)	.
Health insurance†, yes	3648 (93·4%)	3065 (94·5%)	0·054
Smoking status†	..	..	0·052
Never	2031 (52·4%)	1763 (54·6%)	..
Past	1557 (40·2%)	1268 (39·3%)	..
Current	287 (7·4%)	199 (6·2%)	..
Alcohol consumption†, yes	1163 (29·7%)	777 (23·8%)	<0·0001
Physical activity†, yes	2312 (59·0%)	1775 (54·3%)	<0·0001
Medical history, yes			
Diabetes	204 (5·2%)	387 (11·8%)	<0·0001
Myocardial infarction	86 (2·2%)	160 (4·9%)	<0·0001
Stroke	39 (1·0%)	78 (2·4%)	<0·0001
Transient ischaemic attack	71 (1·8%)	129 (3·9%)	<0·0001
Congestive heart failure	22 (0·6%)	47 (1·4%)	<0·0001
Peripheral arterial disease	52 (1·3%)	98 (3·0%)	<0·0001
Anti-hyperlipidaemic drug	543 (13·8%)	754 (23·0%)	<0·0001

Data are mean (SD); n or n (%). Women in the hypertension group either had SBP/DBP of 140 /90 mm Hg or higher or were taking anti-hypertensive medication treatment. BMI=body-mass index. SBP/DBP=systolic blood pressure/diastolic blood pressure. *Including Hispanic, Asian or Pacific Islander, and American Indian or Alaska Native. †Missing data for education status (n=22), health insurance (n=59), smoking (n=102), alcohol consumption (n=17), and physical activity (n=16) are excluded.

Table 1: **Baseline characteristics of participants**

impedes the occurrence of mild cognitive impairment or probable dementia). We conducted competing risk analyses using the Fine-Gray Cox regression model. Furthermore, because hypertension might cause non-fatal cardiovascular disease first and then lead to cognitive impairment, we repeated the competing risk analyses among those who had no baseline cardiovascular disease and no incident cardiovascular disease.

All data analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). Statistical significance was defined as a p value lower than 0·05 in a two-sided test.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 7479 participants, we excluded eight participants with baseline mild cognitive impairment, six with baseline Alzheimer's disease, and 258 with only baseline survey information. The final sample size included in the analysis was 7207 (figure 1).

Individuals with hypertension had significantly higher mean ages, higher BMI, and lower baseline mean 3MSE scores than did those without hypertension (p<0·0001; table 1). In women with hypertension compared with those without hypertension, there was a higher proportion of Black/African Americans, a higher proportion of women with lower education attainment (≤high school), a lower proportion of women reporting alcohol consumption and physical activity, as well as a higher proportion of women with diabetes, myocardial infarction, stroke, transient ischaemic attack, congestive heart failure, peripheral arterial disease, and anti-hyperlipidaemic medication use.

Of 7207 participants, with a mean of 11 years follow-up (median 9 years [IQR 6–15]), 1132 (15·7%) developed mild cognitive impairment, 739 (10·3%) developed probable dementia, and 1533 (21·3%) were classified as having cognitive loss. The incidence rates per 1000 person-years were 15·3 cases (95% CI 14·4–16·2) for mild cognitive impairment, 9·7 cases (9·0–10·4) for probable dementia, and 20·3 cases (19·3–21·3) for cognitive loss.

The prevalence of those with SBP/DBP 130–139/80–89 mm Hg was 24·1% (1733 of 7207), and the prevalence of hypertension (SBP/DBP ≥140/90 and those with anti-hypertensive medication use) was 45·4% (3275 of 7207; table 2). After adjusting for age, race or ethnicity, and hormone use in WHI HT trials, the HRs of those under anti-hypertensive medication treatment versus those with normal BP (SBP/DBP <120/80 mm Hg) were 1·33 (95% CI 1·15–1·54, p=0·0001) for cognitive loss, 1·44 (1·21–1·71, p<0·0001) for mild cognitive

	Population at risk	Number of cases	Model 1*		Model 2†	
			HR (95% CI)	p value	HR (95% CI)	p value
Risk of cognitive loss						
SBP/DBP, mm Hg	..	..	..	..	..	..
<120/<80	1321	272	1 (ref)	..	1 (ref)	..
120–129/<80	878	179	1·03 (0·85–1·24)	0·78	1·01 (0·83–1·22)	0·93
130–139/80–89	1733	366	1·10 (0·94–1·29)	0·22	1·08 (0·92–1·27)	0·33
≥140/90	682	152	1·21 (0·99–1·48)	0·065	1·20 (0·98–1·47)	0·074
Hypertension taking anti-HTN	2593	564	1·33 (1·15–1·54)	0·0001	1·27 (1·09–1·48)	0·002
Test for HR trend	..	..	..	<0·0001	..	0·0004
Risk of mild cognitive impairment						
SBP/DBP, mm Hg	..	..	..	..	..	..
<120/<80	1321	187	1 (ref)	..	1 (ref)	..
120–129/<80	878	138	1·15 (0·92–1·43)	0·21	1·13 (0·91–1·41)	0·28
130–139/80–89	1733	260	1·13 (0·93–1·36)	0·21	1·11 (0·92–1·35)	0·27
≥140/90	682	112	1·28 (1·01–1·62)	0·042	1·25 (0·98–1·59)	0·069
Hypertension taking anti-HTN	2593	435	1·44 (1·21–1·71)	<0·0001	1·35 (1·13–1·62)	0·001
Test for HR trend	..	..	..	<0·0001	..	0·0005
Risk of probable dementia						
SBP/DBP, mm Hg	..	..	..	..	..	..
<120/<80	1321	147	1 (ref)	..	1 (ref)	..
120–129/<80	878	86	0·89 (0·69–1·17)	0·41	0·89 (0·68–1·17)	0·41
130–139/80–89	1733	182	1·00 (0·80–1·24)	0·98	1·00 (0·80–1·25)	0·96
≥140/90	682	78	1·13 (0·86–1·49)	0·39	1·16 (0·88–1·54)	0·29
Hypertension taking anti-HTN	2593	246	1·06 (0·86–1·30)	0·58	1·06 (0·85–1·31)	0·63
Test for HR trend	..	..	..	0·29	..	0·29

Data are adjusted HR (95% CI), unless otherwise stated. Cognitive loss was the combined endpoint of either mild cognitive impairment or probable dementia, or both. A participant might have had incident mild cognitive impairment first, then transitioned to probable dementia. Anti-HTN=anti-hypertensive medication. BMI=body-mass index. HR=hazard ratio. SBP/DBP=systolic blood pressure/diastolic blood pressure. *Model 1: adjusted for age, race and ethnicity, and hormone therapy in the WHI HT trial. †Model 2: adjusted for model 1 plus education, health insurance, BMI, smoking status, alcohol consumption, and diabetes, and anti-hyperlipidaemic medication use.

Table 2: **Association between hypertension and risk of cognitive loss, mild cognitive impairment, and probable dementia**

impairment, and 1·06 (0·86–1·30, p=0·58) for probable dementia in Model 1. These associations for cognitive loss and mild cognitive impairment remained significant after additional adjustment in Model 2 (1·27, 1·09–1·48, p=0·002 for cognitive loss and 1·35, 1·13–1·62, p=0·001 for mild cognitive impairment), and remained not significant for probable dementia (1·06, 0·85–1·31, p=0·63). Among individuals not taking anti-hypertensive medication but with SBP/DBP ≥140/90 mm Hg, there was no significantly increased risk for cognitive loss (1·20, 0·98–1·47, p=0·074), or mild cognitive impairment (1·25, 0·98–1·59, p=0·069). Overall, higher BP was significantly associated with an increasing risk of cognitive loss and mild cognitive impairment (test for trend of cognitive loss across the SBP/DBP strata, p=0·0004, and of mild cognitive impairment, p=0·0005) but was not significant with probable dementia (test for trend, p=0·29).

Of 2593 participants taking anti-hypertensive medication, 739 (28·5%) had SBP controlled to less than 130 mm Hg, and 1365 (52·6%) had SBP controlled to less than 140 mm Hg (table 3). Elevated SBP (ie, ≥120 mm Hg) was significantly associated with risk of cognitive loss and mild cognitive impairment (test for trend, p=0·0005 for cognitive loss, p=0·002 for mild cognitive impairment), but not for probable dementia (p=0·35).

There were no significant interaction effects between SBP and baseline cardiovascular disease or between SBP and age on the risk of cognitive loss, mild cognitive impairment, and probable dementia (p values >0·05; table 3).

Increased PP was associated with an increasing risk of cognitive loss (test for trend, p=0·0002) and mild cognitive impairment (test for trend, p=0·0005; table 4). Among those not taking anti-hypertensive treatment, individuals with PP of 70 mm Hg or higher were at a significantly higher risk of cognitive loss and of mild cognitive impairment than were those with PP lower than 50 mm Hg. Those with hypertension (ie, on anti-hypertensive treatment) and with PP of 50 mm Hg or higher had significantly higher risk for cognitive loss and mild cognitive impairment than did those without hypertension and with PP lower than 50 mm Hg. There was no significant association between PP and probable dementia (test for trend, p=0·20). There were no significant interaction effects between PP and baseline cardiovascular disease and between PP and age on the risk of cognitive loss, mild cognitive impairment, and probable dementia (p>0·05).

SBP variation (assessed by coefficient of variation) was significantly associated with risk of cognitive loss (HR 1·10, 95% CI 1·04–1·17, p=0·0009) and mild cognitive impairment (1·10, 1·03–1·18, p=0·005), but not with probable dementia (1·07, 0·98–1·16, p=0·14; table 5). There were no significant associations between PP variation and the three study outcomes (p>0·05).

The risk of cognitive loss and mild cognitive impairment was significantly associated with elevated SBP (figure 2A, B) and with elevated PP (figure 2C, D). Overall, an increase in every 10 mm Hg of SBP was associated with a 5% increased risk of cognitive loss, and a 4% increased risk of mild cognitive impairment. An increase in every 10 mm Hg of PP was associated with a 7% increased risk of cognitive loss and of mild cognitive impairment.

In our sensitivity analyses, we considered a potential reverse causality. We first repeated our analyses to examine the associations of hypertension, SBP, and PP with risk of the study outcomes by excluding participants with mild cognitive impairment or probable dementia diagnosed within the first year from baseline. The results were similar to the analyses without this exclusion (data not shown).

Second, we analysed the cause-specific risks of hypertension (defined by SBP/DBP) for fatal cardiovascular disease and all other causes of death, and for

cognitive loss, mild cognitive impairment, and probable dementia (appendix p 2). The overall results of the association between hypertension and the study outcomes were consistent with the findings without including competing risk analyses (table 2), except that those with SBP/DBP 140/90 mm Hg or higher had a significant risk for cognitive loss (HR 1·24, 95% CI 1·02–1·52, p=0·035) and for mild cognitive impairment (1·32, 1·04–1·68, p=0·022) in the competing risk analysis. The appendix (pp 3–4) shows the results of the cause-specific competing risk analysis of the associations of SBP and PP with fatal cardiovascular disease, all other causes of death, and with cognitive loss, mild cognitive impairment, and probable dementia. The results are consistent with the analyses in tables 3 and 4, showing that elevated SBP or PP remained significantly associated with increased risk of cognitive loss and mild cognitive impairment, but not with risk of probable dementia. These results also indicate that hypertension, elevated SBP, and PP were significantly associated with risk of mortality from cardiovascular disease and all other causes of death (appendix pp 2–4). In a subsample of participants who had MRI measures of total brain volume, we further observed that there were significant associations of elevated SBP and PP with decreased total brain volume (appendix p 5). We also repeated the analyses by exclusion of non-fatal cardiovascular disease, and similar results to those without this exclusion (tables 2–4) were observed (data not shown).

Discussion

The main findings of the study were that, first, during a median follow-up of 9 years (IQR 6–15), among women aged 65–79 years at baseline, those with hypertension and those with SBP of 120 mm Hg or higher and taking anti-hypertensive medication were at significantly higher risk of cognitive loss and mild cognitive impairment than those with normotension. Second, women with hypertension being treated and with an SBP lower than 120 mm Hg did not have a significantly increased risk of cognitive loss and mild cognitive impairment compared with those with normotension. Third, women who were not on anti-hypertensive treatment and who had a PP of 70 mm Hg or higher, or those on anti-hypertensive treatment and a PP of 50 mm Hg or higher were at significantly higher risk of cognitive loss and mild cognitive impairment than were those with a PP lower than 50 mm Hg. Finally, hypertension, elevated SBP, and PP were not associated with an increased risk of probable dementia.

The associations of BP with cognitive function and dementia have been studied in recent decades. Studies in which a cutoff of SBP ≥140 mm Hg was applied suggest that midlife high blood pressure is a risk factor for late-life cognitive impairment.[32,33] Therefore, treatment of high SBP during midlife might be an effective strategy to reduce the risk of late-life cognitive impairment.[32–35]

	Population at risk	Number of cases	Adjusted HR (95% CI)*	p value
Risk of cognitive loss				
Not taking anti-HTN				
<120 (normal SBP)	1386	288	1 (ref)	..
120–129	1115	227	1·03 (0·86–1·23)	0·75
130–139	1010	219	1·09 (0·91–1·30)	0·36
≥140	1103	235	1·14 (0·95–1·36)	0·15
Hypertension taking anti-HTN				
<120 mm Hg	283	61	1·09 (0·82–1·44)	0·57
120–129 mm Hg	456	102	1·33 (1·05–1·67)	0·018
130–139 mm Hg	626	134	1·35 (1·09–1·67)	0·006
≥140 mm Hg	1228	267	1·25 (1·05–1·49)	0·012
Test for HR trend	..	..	..	0·0005
Risk of mild cognitive impairment				
Not taking anti-HTN				
<120 mm Hg (normal SBP)	1386	198	1 (ref)	..
120–129 mm Hg	1115	172	1·12 (0·91–1·37)	0·30
130–139 mm Hg	1010	155	1·14 (0·92–1·41)	0·24
≥140 mm Hg	1103	172	1·16 (0·94–1·43)	0·18
Hypertension taking anti-HTN				
<120 mm Hg	283	52	1·33 (0·98–1·82)	0·071
120–129 mm Hg	456	77	1·38 (1·05–1·81)	0·021
130–139 mm Hg	626	98	1·37 (1·06–1·75)	0·015
≥140 mm Hg	1228	208	1·32 (1·08–1·62)	0·008
Test for HR trend	..	..	..	0·002
Risk of probable dementia				
Not taking anti-HTN				
<120 mm Hg (normal SBP)	1386	158	1 (ref)	..
120–129 mm Hg	1115	109	0·89 (0·68–1·17)	0·41
130–139 mm Hg	1010	110	1·00 (0·80–1·25)	0·96
≥140 mm Hg	1103	116	1·17 (0·88–1·54)	0·29
Hypertension taking anti-HTN				
<120 mm Hg	283	22	0·72 (0·45–1·16)	0·18
120–129 mm Hg	456	46	1·04 (0·70–1·53)	0·85
130–139 mm Hg	626	64	1·06 (0·82–1·36)	0·67
≥140 mm Hg	1228	114	1·21 (0·91–1·62)	0·19
Test for HR trend	..	..	..	0·35
Interaction effect				
SBP*CVD on cognitive loss	..	..	1·07 (0·75–1·52)	0·73
SBP*CVD on mild cognitive impairment	..	..	1·04 (0·70–1·55)	0·85
SBP*CVD on probable dementia	..	..	0·80 (0·46–1·39)	0·42
SBP*Age on cognitive loss	..	..	0·81 (0·66–1·01)	0·056
SBP*CVD on mild cognitive impairment	..	..	0·83 (0·65–1·06)	0·13
SBP*Age on probable dementia	..	..	0·85 (0·62–1·16)	0·30

Cognitive loss was the combined endpoint of either mild cognitive impairment or probable dementia, or both. A participant might have had incident mild cognitive impairment first, then transitioned to probable dementia. Anti-HTN=anti-hypertensive medication. BMI=body-mass index. CVD=baseline cardiovascular disease. HR=hazard ratio. SBP=systolic blood pressure. *Adjusted for age, race and ethnicity, and hormone therapy in the WHI HT trial, education, health insurance, BMI, smoking status, alcohol consumption, physical activity, anti-hyperlipidaemic medication use, and diabetes.

Table 3: **Association of SBP with risk of cognitive loss, mild cognitive impairment, and probable dementia by anti-HTN status**

	Population at risk	Number of cases	Adjusted HR (95% CI)	p value
Risk of cognitive loss				
Not taking anti-HTN				
<50	1729	351	1 (ref)	..
50–59	1321	252	0·97 (0·82–1·14)	0·68
60–70	900	205	1·14 (0·96–1·36)	0·15
≥70	664	161	1·22 (1·00–1·47)	0·048
Hypertension taking anti-HTN				
<50	538	112	1·17 (0·94–1·46)	0·16
50–59	692	152	1·33 (1·09–1·61)	0·005
60–70	582	127	1·19 (0·96–1·46)	0·11
≥70	780	173	1·31 (1·08–1·59)	0·005
Test for HR trend	..	..	..	0·0002
Risk of mild cognitive impairment				
Not taking anti-HTN				
<50	1729	215	1 (ref)	..
50–59	1321	184	1·01 (0·84–1·23)	0·89
60–70	900	138	1·07 (0·86–1·32)	0·55
≥70	664	124	1·30 (1·04–1·63)	0·020
Hypertension taking anti-HTN				
<50	538	89	1·26 (0·98–1·62)	0·067
50–59	692	115	1·37 (1·09–1·71)	0·01
60–70	582	101	1·27 (1·00–1·61)	0·049
≥70	780	130	1·29 (1·04–1·62)	0·023
Test for HR trend	..	..	..	0·0005
Risk of probable dementia				
Not taking anti-HTN				
<50	1729	174	1 (ref)	..
50–59	1321	134	1·00 (0·79–1·26)	0·98
60–70	900	107	1·18 (0·92–1·51)	0·20
≥70	664	78	1·15 (0·87–1·51)	0·34
Hypertension taking anti-HTN				
<50	538	47	0·97 (0·70–1·36)	0·88
50–59	692	72	1·28 (0·96–1·69)	0·09
60–70	582	48	0·92 (0·66–1·28)	0·61
≥70	780	79	1·25 (0·95–1·65)	0·12
Test for HR trend	..	..	..	0·20
Interaction effect of				
PP*CVD on cognitive loss	..	..	1·13 (0·78–1·62)	0·52
PP*CVD on mild cognitive impairment	..	..	1·18 (0·79–1·81)	0·40
PP*CVD on probable dementia	..	..	0·92 (0·53–1·61)	0·78
PP*Age on cognitive loss	..	..	0·83 (0·67–1·02)	0·073
PP*Age on mild cognitive impairment	..	..	0·87 (0·69–1·11)	0·26
PP*Age on probable dementia	..	..	0·88 (0·65–1·20)	0·42

Cognitive loss was the combined endpoint of either mild cognitive impairment or probable dementia, or both. Anti-HTN=anti-hypertensive medication. BMI=body-mass index. CVD=baseline cardiovascular disease. HR=hazard ratio. PP=pulse pressure. *Adjusted for age, race and ethnicity, and hormone therapy, in the WHI HT trial, education, health insurance, BMI, smoking status, alcohol consumption, physical activity, anti-hyperlipidaemic medication use, and diabetes.

Table 4: **Association of PP with risk of cognitive loss, mild cognitive impairment, and probable dementia by anti-HTN status**

	Adjusted HR (95% CI)*	p value
CV of systolic blood pressure		
Cognitive loss	1·10 (1·04–1·17)	0·0009
Mild cognitive impairment	1·10 (1·03–1·18)	0·005
Probable dementia	1·07 (0·98–1·16)	0·14
CV of pulse pressure		
Cognitive loss	1·02 (0·99–1·06)	0·27
Mild cognitive impairment	1·02 (0·98–1·07)	0·27
Probable dementia	1·01 (0·96–1·06)	0·68

Cognitive loss was the combined endpoint of either mild cognitive impairment or probable dementia, or both. HR was estimated based on every 5-rise of CV (ie, estimated CV/5) associated with cognitive impairment, mild cognitive impairment, and probable dementia. BMI=body-mass index. CV=coefficient of variation. HR=hazard ratio. PP=pulse pressure. SBP=systolic blood pressure. *Adjusted for age, race and ethnicity, hormone therapy, in the WHI HT trial, education, health insurance, BMI, smoking status, alcohol consumption, physical activity, anti-hyperlipidaemic medication use, and diabetes.

Table 5: **Adjusted HRs of SBP and PP variation for cognitive loss, mild cognitive impairment, and probable dementia**

However, the impact of different cutoffs on the control of cognitive impairment were not consistent across the studies.[33–39] In the SPRINT trial, which included 9361 individuals aged 50 years or older, participants were randomly assigned to an intensive treatment group (SBP <120 mm Hg) or a standard treatment group (SBP <140 mm Hg). The results show that intensive treatment for SBP (SBP <120 mm Hg) was significantly associated with risk reduction of mild cognitive impairment and with the combined endpoint of mild cognitive impairment or probable dementia (but not probable dementia alone) among the study participants over a median follow-up of 5·11 years.[8] However, the SPRINT was a clinical trial with selection of participants in middle and older age, and it had a relatively small sample size of female participants (36%).[8,40] Findings from our study extended previous studies by using data from the WHIMS and demonstrating that older women with hypertension and with control of SBP to less than 120 mm Hg had no significantly increased risk of cognitive loss and mild cognitive impairment. Meanwhile, SBP variation was significantly associated with risk of cognitive loss and mild cognitive impairment, but not with probable dementia. However, the association between PP variation and the study outcomes was not significant. This non-significant association between PP variation and the study outcomes might be affected by changes in DBP.

Several studies examined the association between high BP in midlife and risk of dementia in late-life.[41,42] However, few studies addressed sex differences. Findings from the Honolulu-Asia Aging Study suggest that the association of increased midlife BP on late-life dementia was present only among men who were never treated with anti-hypertensive drugs.[41] In the SPRINT trial, there was no significant association between an intensive control of SBP lower than 120 mm Hg and risk of probable dementia.[8] We did not observe a significant

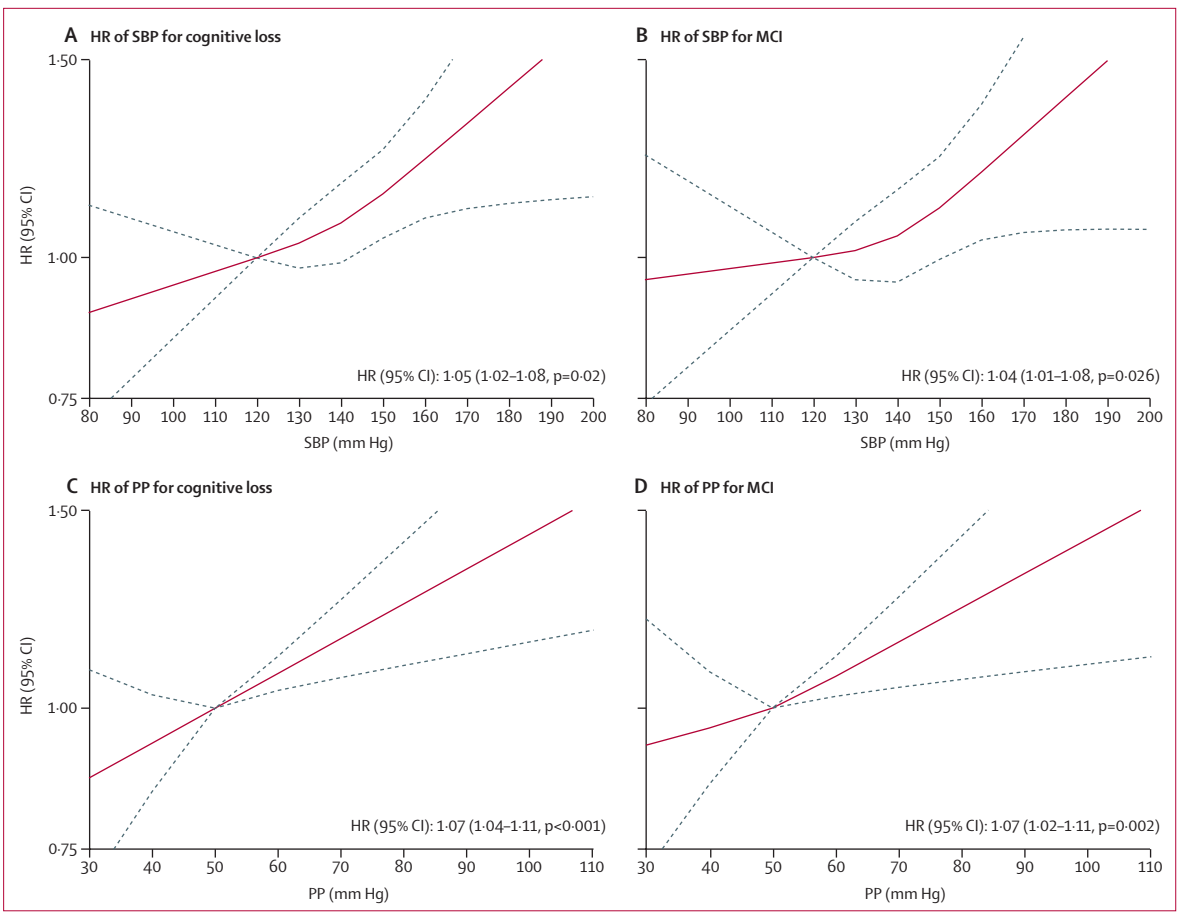

Figure 2: **Relative hazards of SBP for cognitive loss and mild cognitive impairment (A, B), and of PP for cognitive loss and mild cognitive impairment (C,D)**
Solid line: the estimated relative hazards for cognitive loss compared with the reference value as a function of SBP levels (A and B) or of PP levels (C and D). Dotted lines are the 95% CIs of the relative hazard lines. Summary hazard ratios are calculated for each 10 mm Hg increase in SBP or PP. Overall, an increase in every 10 mm Hg of SBP was associated with an increased risk of cognitive loss by 5%, and an increased risk of mild cognitive impairment by 4%. An increase in every 10 mm Hg of PP was associated with an increased risk of cognitive loss and of mild cognitive impairment by 7%. SBP=systolic blood pressure. PP=pulse pressure. HR=hazard ratio.

association of hypertension, SBP, and PP with risk of probable dementia as well. This non-significant association with probable dementia in our study might be partly due to a relatively small sample size of those who were diagnosed having probable dementia or due to a more complicated impact of hypertension, SBP, and PP with ageing effect on dementia.

In our study, participants with hypertension (SBP/DBP ≥140/90 mm Hg or SBP ≥140 mm Hg) but not taking anti-hypertensive medication had a borderline significant association with risk of cognitive loss and mild cognitive impairment. This borderline significant result could be explained by a few possible reasons. For example, these individuals might have had a newly diagnosed hypertension. Meanwhile, in the Framingham Offspring study, investigators observed that in individuals with lower to normal SBP/DBP (≤140/90 mm Hg) at middle ages, a steep decline in SBP during their midlife to late-life was associated with an increased risk of dementia. We are unable to test this association because we have no data for the measures of BP in women's midlife.

We observed a significant association of elevated PP with risk of mild cognitive impairment and cognitive loss. These findings are consistent with several reports, including from the SPRINT.[11,43–45] However, our results add new evidence to the research of BP and cognitive health in the study of older women.

Mild cognitive impairment, a collection of heterogeneous conditions, might represent a pre-dementia state in some people, or a transient and reversible state in other people. The observation of the non-significant association of SBP and PP with probable dementia in our study could partly be explained by two factors. First, given the small sample size of incident cases of probable dementia, the study might have been underpowered to test this association. Second, this non-significance might partly be attributable to the risk reduction of mild cognitive impairment from high BP treatment and subsequently to a risk reduction of probable dementia.

In addition, anti-hypertensive treatment could have neuroprotective properties separate to its BP lowering capabilities. For example, findings from the Honolulu-Asia Ageing Study suggest that longer duration of anti-hypertensive treatment was associated with a reduced risk of dementia.[46] However, the risk reduction by anti-hypertensives seen for dementia was not observed by the other studies, such as the East Boston Established Populations for Epidemiologic Studies of the Elderly and the Canadian Study of Health and Aging.[47,48]

The mechanisms by which hypertension and elevated SBP and PP could lead to cognitive impairment could be through several potential pathophysiological pathways.[32,33,49] First, cardiovascular disorders (myocardial infarction, heart failure, stroke, peripheral arterial disease, and atrial fibrillation) are more prevalent in individuals with hypertension, which predisposes for (silent) brain infarction. Second, studies have shown a significant association between increased BP and white matter abnormalities, suggesting that elevated BP might play a role in the pathogenesis of cognitive impairment by affecting the development of neuropathological lesions or brain atrophy.[38,39,45,50] In our subsample analysis using data for those with MRI measures of total brain volume (a possible marker of neuronal injury and neurodegeneration status), we observed that hypertension, elevated SBP, and PP were significantly associated with decreased total brain volumes (test for trend, $p<0·05$, appendix p 5). Third, studies have also demonstrated a significant association of elevated SBP and PP with cerebral amyloidosis, tau-mediated neurodegeneration, cerebral amyloid retention, and the prediction of hippocampal atrophy.[49,51,52] These pathological progressions commonly take time for years.

Our study has several strengths regarding its contributions to BP and cognitive impairment research. The results are based on a large-scale population-based longitudinal study. Cases of mild cognitive impairment and probable dementia were classified by a centralised and standardised adjudication process, which reduced potential misclassification of the study outcomes. A set of robust analysis approaches were applied in the study, which demonstrate a consistent result. However, several limitations in the study also need to be kept in mind when interpreting these findings. First, findings of the study were pertinent to the measures of BP in early late-life exposures among women aged 65–79 years. No corresponding data on midlife exposures were collected in the WHIMS. Therefore, the findings may limit generalisation to younger women. Second, the study participants consisted of mainly White women, which limits the generalisability to other racial and ethnic groups. Third, the study focused on hypertension, SBP and PP, but not DBP. Therefore, findings from the study do not directly elucidate any association of DBP alone, although PP has been proposed as an indicator to assess arterial stiffness status. Fourth, we applied the American Heart Association 2017 Guideline for High BP in Adults to classify BP levels for the purpose of staying with the updated guideline. This classification, however, might limit its application to the other settings that do not use this guideline. Fifth, the measures of cognitive impairment were conducted in older women, either at clinical sites or through telephone assessment. Potential bias might occur due to the exclusion of participants who had significant hearing impairment, although this exclusion was less than 1% among the total participants of the study. Finally, because of the long-term follow-up study, residual confounding attributable to unmeasured factors is possible.

In summary, older women with hypertension, with elevated SBP or elevated PP, were at higher risk of cognitive loss and mild cognitive impairment than were women with normotension. Older women taking anti-hypertensive treatment with SBP lower than 120 mm Hg or with PP less than 50 mm Hg did not have elevated risk of cognitive loss and mild cognitive impairment. These results add new evidence that decreased SBP and PP levels might have a pivotal role in preserving cognitive health in older women.

Contributors

LL conceived and designed the study. SRR, KMH and SW-S reviewed and edited the study conception and design. LL and SRR had full access to all the data in the study. LL performed the analysis, interpreted data, drafted the first report, and revised the final report. SRR, KMH, and SW-S interpreted data and reviewed the report. NSM, BH, ZL, VWH, J-CC, and EJG interpreted the data and reviewed the report. All authors discussed the analysis approaches and results and contributed to the report.

Declaration of interests

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Data sharing

Individual, deidentified participants data from the WHIMS used in these analyses can be obtained by request from any qualified investigators following a standard application process and approval of a protocol and signed data access agreement via the WHI Presentation and Paper Committee.

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For the **listing of WHI investigators** see http://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Short%20List.pdf

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