Title

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Female sex, early-onset hypertension, and risk of dementia

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ABSTRACT

Objective: To evaluate the association of early-adulthood and mid-adulthood hypertension with dementia in men and women.

Methods: We evaluated 5,646 members of a diverse integrated health care delivery system who had clinical examinations and health survey data from 1964 to 1973 (mean age 32.7 years; early adulthood) and 1978–1985 (mean age 44.3 years; mid-adulthood) and were members as of January 1, 1996 (mean age 59.8 years). Hypertension categories based on measurements of blood pressure (BP) and change in hypertension categories between the 2 examinations (e.g., onset hypertension) were used to predict dementia incidence from January 1, 1996, to September 30, 2015. Cox proportional hazard models were adjusted for demographics, vascular comorbidities, and hypertension treatment; inverse probability weighting accounted for differential attrition between first BP measurement and start of follow-up.

Results: A total of 532 individuals (9.4%) were diagnosed with dementia. Early adulthood hypertension was not associated with dementia, though effect estimates were elevated among women. Mid-adulthood hypertension was associated with 65% (95% confidence interval [CI] 1.25–2.18) increased dementia risk among women but not men. Onset of hypertension in mid-adulthood predicted 73% higher dementia risk in women (95% CI 1.24–2.40) compared to stable normotensive. There was no evidence that hypertension or changes in hypertension increased dementia risk among men.

Conclusions: Though midlife hypertension was more common in men, it was only associated with dementia risk in women. Sex differences in the timing of dementia risk factors have important implications for brain health and hypertension management. ***Neurology*® 2017;89:1886–1893**

GLOSSARY

BMI = body mass index; **BP** = blood pressure; **CI** = confidence interval; **EMR** = electronic medical records; **ICD-9** = *International Classification of Diseases-9*; **ISPW** = inverse selection probability weighting; **KPNC** = Kaiser Permanente Northern California; **MHC** = Multiphasic Health Checkups.

Hypertension afflicts 32% of US adults between the ages of 40 and 59 years and 65% of adults over age 60 years.[1] It is more common among men than women in early adulthood yet risk of target organ damage[2] and the amount of cardiovascular disease attributable to hypertension[3] is greater in women than men. Hypertension in midlife is a known risk factor for dementia,[4–7] but possible sex differences in the link between hypertension and dementia have not been evaluated. The effect of hypertension onset before midlife on dementia also remains unknown for either sex. Correctly targeting at-risk populations requires a greater understanding of when the association between hypertension and dementia begins, how changes in blood pressure (BP) increase dementia risk, and if risk factors have different inflection points by sex. Exploration of possible sex differences in risk factors over the life course may help explain why women have higher rates of dementia then men.[8]

The objectives of this study were to determine associations of BP in early adulthood (mean age 33 years) and mid-adulthood (mean age 44 years) with risk of dementia in late life and whether these associations differ by sex.

Supplemental data at Neurology.org

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METHODS

Study population. We included members of the Kaiser Permanente Northern California (KPNC) integrated health care delivery system who participated in the Multiphasic Health Checkups (MHC). MHC was an optional checkup provided to members in San Francisco and Oakland, California, in the 1960s–1980s. MHCs were fielded in successive phases, including 1964–1973 and 1978–1985. KPNC provides care to over 3 million members in Northern California (30% of the geographic region). KPNC membership is generally representative of the overall population of the region, although individuals at extreme tails of the income distribution are underrepresented.[9–11]

During the MHC, information was collected on demographics, lifestyle, and medical history. These analyses use data from the first visit in which an individual was 30–35 years old during the 1964–1973 phase and the first visit in which they were 40+ years old during the 1978–1985 phase. Of the 7,268 individuals who participated in both MHC phases at eligible ages, 360 died before the start of follow-up in 1996, 1,260 stopped being KPNC members before the start of follow-up, and 2 were missing information on education. The final sample includes 5,646 members.

Standard protocol approvals, registrations, and patient consents. This study was approved by the KPNC internal review board.

Blood pressure. We included clinical measurements of BP from the 1964–1973 phase, representing early adulthood (30–35 years old), and the 1978–1985 phase, representing mid-adulthood. BP thresholds were based off recommendations from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[12] At each time point, individuals were classified as one of the following: (1) hypotensive (systolic BP <80 mm Hg or diastolic BP <60 mm Hg); (2) normotensive (systolic BP 81–120 mm Hg and diastolic BP 61–80 mm Hg); (3) prehypertensive (systolic BP 120–139 mm Hg or diastolic 80–89 mm Hg); or (4) hypertensive (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg). Hypertension categories were also defined incorporating self-report of hypertension or hypertension medication reported in 1964–1973 MHC and 1978–1985 MHC. In order to understand the effects of changes in hypertension categories between the 2 time points—for example, becoming hypertensive in middle age—we classified individuals into the following 4 categories: (1) stable normotensive, (2) onset hypertension, (3) remitted hypertension, and (4) persistent hypertension. For the purposes of this classification scheme, individuals with prehypertension were considered normotensive.

Dementia diagnosis. Dementia diagnoses between January 1, 1996, and October 1, 2015, were identified from electronic medical records (EMR) consistent with previous studies in this population.[5,13–18] Diagnoses were from inpatient and outpatient visits based on ICD-9 diagnosis codes for Alzheimer disease (331.0), vascular dementia (290.4x), and other/nonspecific dementia (290.0, 290.1x, 290.2x, 290.3, 294.1, 294.2x, and 294.8). A similar set of ICD-9 codes had a sensitivity of 77% and a specificity of 95% compared with a consensus diagnosis of dementia utilizing medical records review, physical examination, structured interviews with informants, and a neuropsychiatric battery.[19]

Mortality. Death was captured through KPNC EMR, the California State Mortality File, and Social Security Death Index records.

Covariates. The 1964–1973 MHC questionnaire captured the following covariates: age, sex, educational attainment (high school or less, trade school or some college or college completion, postgraduate education [reference]), antihypertensives (yes/no), and current smoking (yes/no). The 1978–1985 MHC included clinical measurements of height and weight (used to calculate body mass index [BMI]) and current smoking status. Diabetes, heart failure, or stroke diagnoses occurring before dementia and between January 1, 1996, and September 30, 2015, were considered late-life health exposures (each coded yes/no). These conditions were captured through KPNC's EMR using the ICD-9 codes listed in table e-1 at Neurology.org. KPNC also captured race/ethnicity (white [reference], black, Asian, Hispanic, and other). Missing indicators were used for missing values of current smoking, use of hypertension medication, or BMI.

Method of analysis. First, we examined the distribution of BP, demographics, mid-adulthood health behaviors, and late-life conditions overall and by sex. In primary analyses, we defined hypertension based off BP measurements, self-reported hypertension, and self-reported antihypertensive medications. We implemented weighted Cox proportional hazards models (age as the timescale) to examine the associations between early and mid-adulthood hypertension status and dementia risk later in life. Next, we examined the concurrent effect of hypertension status at both early and mid-adulthood. To understand how changes in hypertension status between early adulthood and mid-adulthood could affect dementia risk, we compared dementia risk among people with stable normotensive BP to those with onset hypertension, remitted hypertension, and persistent hypertension excluding individuals who were hypotensive at either time point. We also examined possible effect modification by sex using interaction terms and stratified models.

We implemented unstabilized inverse selection probability weighting (ISPW) truncated to the 99th percentile to account for differential participation.[20] The final ISPW weight is the product of 3 weights, reflecting the inverse of the probability of (1) participating in an MHC BP measurement during 1978–1985, (2) surviving until the start of follow-up in 1996 conditional on participating in 1978–1985, and (3) KPNC membership in 1996 conditional on participating in 1978–1985 and surviving until 1996. Possible predictors of participation in the 1978–1985 MHC included hypertension status (defined using BP measurements, self-report of hypertension, and self-report of hypertension medication use), demographics, smoking, and BMI from the 1964–1973 MHC. The same variables were obtained from 1964 to 1973 and 1978 to 1985 for predictions of survival and membership until 1996.

Covariates were added in groups starting with sex and race/ethnicity. Late-life diabetes, stroke, and heart failure were grouped together and may be mediators. Individuals were censored at first diagnosis of dementia, gap in membership greater than 90 days, death, or end of study period on September 30, 2015.

We estimated and plotted the cumulative risk of dementia (in 5-year increments from 10 to 25 years) conditional on survival free of dementia to age 60 for hypertension in early adulthood (compared to normotensive BP) for men and women separately using the Practical Incidence Estimator macro.[21] The macro incorporates information on death rates and assumes that individuals who die without a dementia diagnosis never develop dementia. Although our sample includes individuals as young as 51 years in 1996, we chose to estimate the risk of dementia conditional on survival dementia-free to age 60 since very few people in our sample had dementia onset prior to age 60.

In sensitivity analyses, we adjusted for mid-adulthood BMI and current smoking in both early and mid-adulthood. We also conducted sensitivity analyses defining hypertension only by BP

Table 1 Sample characteristics of participants by sex

Characteristic	Women (n = 3,095; 298 cases), n (%) or mean (SD)	Men (n = 2,551; 234 cases), n (%) or mean (SD)	Overall (n = 5,646; 532 cases), n (%) or mean (SD)
Dementia cases	298 (9.63)	234 (9.17)	532 (9.42)
1964–1973 BP			
Systolic BP, mm Hg	118.30 (14.86)	129.87 (16.06)	123.53 (16.45)
Diastolic BP, mm Hg	72.60 (12.34)	73.79 (12.89)	73.14 (12.60)
Hypotensive	38 (1.23)	<5	<50
Normotensive	1,471 (47.53)	544 (21.32)	2,015 (35.69)
Prehypertension	1,142 (36.90)	1,210 (47.43)	2,352 (41.66)
Hypertension	444 (14.35)	796 (31.20)	1,240 (21.96)
1978–1985 BP			
Systolic BP, mm Hg	121.11 (16.48)	126.14 (15.06)	123.38 (16.05)
Diastolic BP, mm Hg	75.67 (10.66)	78.13 (9.81)	76.78 (10.36)
Hypotensive	23 (0.74)	<5	<37
Normotensive	1,291 (41.71)	689 (27.01)	1,980 (35.07)
Prehypertension	1,211 (39.13)	1,214 (47.59)	2,425 (42.95)
Hypertension	570 (18.42)	645 (25.28)	1,215 (21.52)
BP change category			
Stable low	2,273 (73.44)	1,416 (55.51)	3,689 (65.34)
Onset	378 (12.21)	339 (13.29)	717 (12.70)
Remit	252 (8.14)	490 (19.21)	742 (13.14)
Stable high	192 (6.20)	306 (12.00)	498 (8.82)
Age			
1st BP measurement, y	32.71 (1.75)	32.78 (1.76)	32.74 (1.75)
2nd BP measurement, y	44.30 (3.07)	44.21 (2.99)	44.26 (3.03)
At dementia diagnosis	74.8 (5.9)	74.5 (5.7)	74.7 (5.8)
Race/ethnicity			
White	1,543 (49.85)	1,439 (56.41)	2,982 (52.82)
Black	1,084 (35.02)	743 (29.13)	1,827 (32.36)
Asian	302 (9.76)	207 (8.11)	509 (9.02)
Hispanic	110 (3.55)	108 (4.23)	218 (3.86)
Other	56 (1.81)	54 (2.12)	110 (1.95)
≤ High school education	907 (29.31)	559 (21.91)	1,466 (25.97)
Mid-adulthood health behaviors			
Antihypertensive medication in 1964–1973	44 (1.42)	26 (1.02)	70 (1.24)
Antihypertensive medication in 1978–1985	216 (6.98)	160 (6.27)	376 (6.66)
Current smoking in 1964–1973	143 (32.13)	123 (32.45)	266 (32.28)
Current smoking in 1978–1985	759 (43.10)	592 (36.05)	1,351 (39.70)
Late-life health factors			
Heart failure	380 (12.28)	409 (16.03)	789 (13.97)
Diabetes	812 (26.24)	747 (29.28)	1,559 (27.61)
Stroke	489 (15.80)	444 (17.40)	933 (16.52)

Continued

thresholds and adjusted for self-report of hypertension treatment at each MHC phase. Hypertension treatment is a consequence of hypertension and therefore conceptually a potential mediator of the effects of hypertension in these sensitivity analyses.

RESULTS The mean age at the first BP measurement during the first phase of the MHC was 32.7 years (SD 1.8 range 30.0–36.0) and at the second phase it was 44.3 years (SD 3.0; range 40.0–55.9) (table 1). The mean follow-up time for dementia (starting in 1996) was 15.3 years (SD 6.1; range 0.1–19.7 years). Early adulthood systolic and diastolic BP were associated with mid-adulthood measures (systolic BP: Pearson correlation coefficient 0.39, $p < 0.001$; diastolic BP: Pearson correlation coefficient 0.34, $p < 0.001$), as was being classified as hypertensive (κ statistic 0.24, $p < 0.001$). During follow-up, 9.4% of the sample was diagnosed with dementia, 15% died without a dementia diagnosis, and 22% was censored due to a lapse in membership. Men were more likely to have been censored due to death than women (16.5% of men vs 13.9% of women). At the end of follow-up, 54% of the sample remained alive, members of KPNC, and dementia-free.

In models including both sexes, adjusting for demographics, early-adulthood hypotension (HR 1.30; 95% confidence interval [CI] 0.42–4.04), prehypertension (HR 1.04; 95% CI 0.86–1.26), and hypertension (HR 1.06; 95% CI 0.85–1.32) were not associated with dementia risk. Similar models examining midlife showed an association between dementia risk and hypertension (HR 1.36; 95% CI 1.10–1.67) but not prehypertension (HR 1.07; 95% CI 0.88–1.30) or hypotension (HR 0.61; 95% CI 0.08–4.48). The estimated effect of midlife hypertension was very similar after adjusting for late-life health conditions (results not shown). The estimated effect of early adulthood hypertension status on dementia risk differed by sex and was only elevated among women (both interaction terms for sex and 4-level hypertension categories at either time point $p < 0.001$; table 2). The effect estimates for prehypertension and hypertension among women in their early 30s were elevated but not significantly different from women with normotensive BP (prehypertension HR 1.24, 95% CI 0.96–1.61; hypertension HR 1.31, 95% CI 0.95–1.79); there was no association in men (table 2). In mid-adulthood, hypertension among women was associated with a 65% increased dementia risk (95% CI 1.25–2.18) compared to normotensive BP, but hypertension among men was not. Effect estimates remained similar for both sexes when further adjusting for late-life conditions (table 2, model 2). A similar set of results was found when the definition of hypertension only included systolic and diastolic cutpoints (table e-2).

Table 1 Continued

Characteristic	Women (n = 3,095; 298 cases), n (%) or mean (SD)	Men (n = 2,551; 234 cases), n (%) or mean (SD)	Overall (n = 5,646; 532 cases), n (%) or mean (SD)
Reason for censoring during follow-up			
Died	431 (13.93)	421 (16.50)	852 (15.09)
Lapse in membership	641 (20.71)	585 (22.93)	1,226 (21.71)

Abbreviation: BP = blood pressure.
A total of 824 members received a questionnaire during the 1964–1973 Multiphasic Health Checkups (MHC) phase including items regarding smoking habits. A total of 3,403 members received a questionnaire during the 1978–1985 MHC phase including items capturing smoking habits.

The 10-, 15-, 20-, and 25-year cumulative risks of dementia by sex and hypertension status conditional on survival to age 60 without dementia (table 3 and figure) were consistently highest among women with hypertension in early adulthood. Cumulative 25-year dementia risk at age 60 was 21% (95% CI 12%–27%) for women with early-adulthood hypertension and 18% (95% CI 14%–21%) for those without.

In models including early and mid-adulthood hypertension status concurrently, the difference in the effect of hypertension status on dementia risk varied by sex (both interaction terms for sex and 4-level hypertension categories at each time point $p < 0.001$). Among women, early-adulthood hypertension was not associated with dementia risk (HR 1.06; 95% CI 0.75–1.50) but mid-adulthood hypertension was associated with 61% elevated risk (95% CI 1.19–2.17; tables e-3 and e-4). Neither early nor mid-adulthood hypertension status was associated with dementia risk among men.

Compared to women who remained normotensive during early- and mid-adulthood, onset of hypertension and persistent hypertension were associated with 73% (95% CI 1.24–2.40; table 4) and 63% (95% CI 1.11–2.40) increased risk of dementia among women. Among women, remitted hypertension was not associated with elevated risk of dementia. The elevated risk of dementia among women with onset and persistent hypertension persisted after further adjustment for late-life health conditions. There was no evidence that changes in hypertension status from early to mid-adulthood affected risk of dementia among men. The estimated effects of changes in hypertension on dementia risk did not significantly differ by sex (interaction term sex × 4 level changes $p = 0.11$). In models defining hypertension by BP cutpoints only, onset of hypertension was associated with dementia risk among women and there was no association between changes in hypertension status and dementia risk among men (table e-5).

The association between mid-adulthood hypertension and dementia risk among women remained significant after further adjusting for mid-adulthood BMI and early or mid-adulthood smoking (HR 1.59; 95% CI 1.19–2.13). Neither hypotension (HR 0.76; 95% CI 0.10–5.70) nor prehypertension (HR 0.97; 95% CI 0.74–1.28) elevated dementia risk among women. There were too few men with hypotension to estimate an effect on dementia. Neither prehypertension nor hypertension in mid-adulthood was associated with dementia among men

Table 2 Overall and sex-specific adjusted hazard ratios (aHR) for dementia by hypertension status as defined by blood pressure thresholds, self-reported hypertension, and self-reported antihypertensive medication in early adulthood and mid-adulthood modeled separately[a]

	Women (n = 3,095; 298 cases)		Men (n = 2,551; 234 cases)	
	Model 1, aHR (95% CI)	Model 2, aHR (95% CI)	Model 1, aHR (95% CI)	Model 2, aHR (95% CI)
Early adulthood (overall mean age 32.74 years)				
Hypotensive	1.53 (0.50–4.72)	1.63 (0.52–5.09)	—	—
Normotensive	Ref	Ref	Ref	Ref
Prehypertensive	1.24 (0.96–1.61)	1.25 (0.96–1.62)	0.83 (0.62–1.11)	0.83 (0.62–1.10)
Hypertensive	1.31 (0.95–1.79)	1.25 (0.90–1.73)	0.85 (0.62–1.17)	0.84 (0.61–1.15)
Mid-adulthood (overall mean age 44.26 years)				
Hypotensive	0.72 (0.10–5.37)	0.79 (0.11–5.85)	—	—
Normotensive	Ref	Ref	Ref	Ref
Prehypertensive	1.00 (0.77–1.31)	1.02 (0.77–1.33)	1.12 (0.84–1.51)	1.13 (0.84–1.52)
Hypertensive	1.65 (1.25–2.18)	1.61 (1.21–2.15)	1.13 (0.83–1.55)	1.12 (0.81–1.54)

Abbreviation: CI = confidence interval.
[a] Hazard ratios estimated by Cox proportional hazards model with age as the time scale and weighted by the inverse of the probability of being in the final analytic sample. Model 1 adjusted for demographics. Model 2 adjusted for demographics and late-life health conditions. Due to small sample size, estimates for the association between hypotensive blood pressure and dementia were not examined for men.

Table 3 Estimates of cumulative risk (CR) of dementia incorporating death rates by sex and hypertension status in early adulthood, conditional on survival free of dementia to age 60

	Women		Men	
	Hypertensive in early adulthood, CR (95% CI)	Normotensive in early adulthood, CR (95% CI)	Hypertensive in early adulthood, CR (95% CI)	Normotensive in early adulthood, CR (95% CI)
10-year risk	3.33 (1.67-4.94)	1.86 (1.27-2.44)	2.49 (1.30-3.63)	2.23 (1.43-3.01)
15-year risk	8.62 (5.91-11.16)	4.72 (3.75-5.63)	6.18 (4.20-7.97)	5.12 (3.87-6.29)
20-year risk	14.71 (10.65-18.26)	9.96 (8.36-11.40)	10.59 (7.44-13.23)	11.02 (8.92-12.87)
25-year risk	20.60 (12.12-27.02)	17.70 (14.22-20.55)	17.53 (11.33-22.26)	19.61 (14.97-23.24)

Abbreviation: CI = confidence interval.

(prehypertension HR 1.13; 95% CI 0.84–1.52; hypertension HR 1.12; 95% CI 0.81–1.54).

DISCUSSION Although elevated BP is more common among men than women in early and mid-adulthood, our results suggest that hypertension in mid-adulthood is a risk factor for dementia only for women. Hypertensive women in their 30s were at 31% increased risk of dementia, though not significantly higher than their counterparts with normotensive BP. Hypertension among women in their 40s was associated with 65% higher risk. All of these associations were null for men. The 10- to 25-year cumulative risks of dementia conditional on being alive and dementia-free at age 60 were consistently highest among women with hypertension in early adulthood.

Women who developed hypertension in their 40s experienced 73% higher risk of dementia compared to women who were normotensive in early and mid-adulthood. Women who experienced hypertension during both life periods had 63% higher risk of dementia compared to women who were normotensive at both time points. Remitted hypertension was not associated with risk of dementia. There was also no evidence of an association between remitted hypertension or BP at either time point and dementia risk among men.

While the association between hypertension in one's 50s and dementia risk is well-established,[4–7,22,23] the association with early-adulthood BP and dementia remains unclear in the prior literature. Studies of BP and dementia risk in Sweden[24] and Japan[23] included people in their 30s at baseline but enrolled people up to 60 and 70 years old. Although both studies found an association between BP and dementia, the wide age range obscured the effect of BP specifically in one's 30s on dementia risk. Our findings suggest that BP in one's 40s, and possibly in one's 30s, is a risk factor for dementia among women only.

Figure Estimates of the cumulative risk of dementia by sex and early adulthood hypertension status, conditional on survival dementia-free until age 60 and incorporating death rates

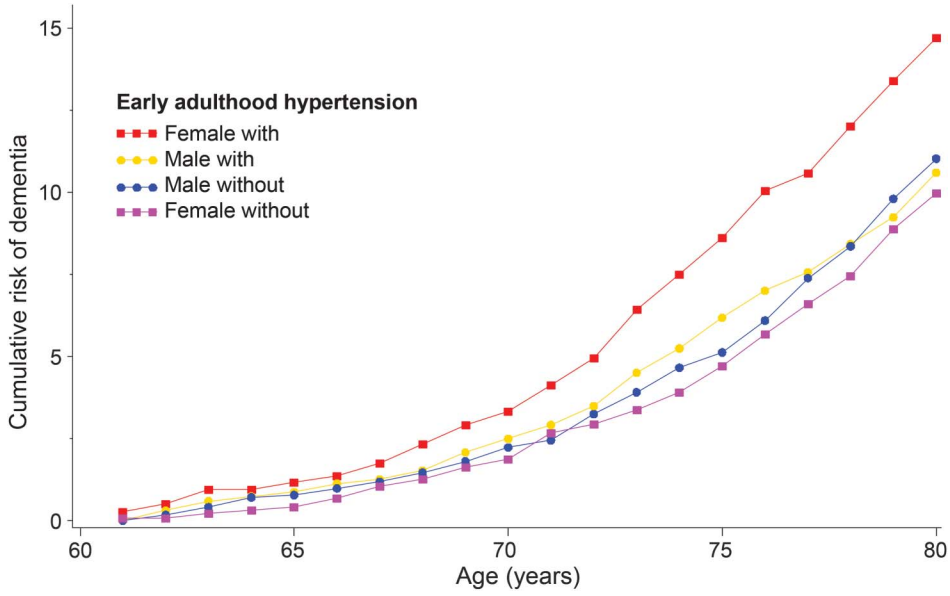

Table 4 Hazard ratios (HR) for dementia by changes in hypertension status defined with blood pressure, self-reported hypertension, and self-reported antihypertensive medication use from early adulthood to early midlife[a]

	Women (n = 3,036; 294 cases)		Men (n = 2,547; 234 cases)	
	Model 1, HR (95% CI)	Model 2, HR (95% CI)	Model 1, HR (95% CI)	Model 2, HR (95% CI)
Stable normotensive	Ref	Ref	Ref	Ref
Onset hypertension	1.73 (1.24–2.40)	1.68 (1.20–2.34)	1.08 (0.73–1.60)	1.05 (0.71–1.58)
Remitted hypertension	1.16 (0.69–1.97)	1.10 (0.64–1.89)	0.82 (0.52–1.30)	0.81 (0.51–1.28)
Persistent hypertension	1.63 (1.11–2.40)	1.58 (1.07–2.33)	1.01 (0.68–1.50)	1.00 (0.68–1.48)

Abbreviation: CI = confidence interval.
[a] HRs estimated by Cox proportional hazards model with age as the time scale and weighted by the inverse of the probability of being in the final analytic sample. Model 1 adjusted for demographics. Model 2 adjusts for demographics and late-life health conditions.

There is growing evidence that the harmful effect of hypertension may be stronger among women compared to men for some outcomes. Previous work has shown a stronger association among women than men between hypertension and microabluminuria,[2] left ventricular hypertrophy,[2] and baroreceptor reflex sensitivity,[25] and greater reductions in systolic and diastolic function.[26] However, limited work has examined possible sex differences in the association between mid-adulthood BP and dementia risk with inconsistent results. In our analyses, the relationship between hypertension in mid-adulthood (and early adulthood) and dementia risk was present only among women. This is surprising given that previous studies examining midlife hypertension as a risk factor for dementia have found no difference by sex[5,27] or a stronger association among men.[27] Studies including only men[6,28] or women[24] have also found a midlife BP–dementia relationship. Differences in the age range of participants may partially explain inconsistencies across studies. The mean age at mid-adulthood in our sample was 44.26 while the mean age of other studies examining midlife is often in the 50s.[6,7,22]

Another possible reason our analyses did not find evidence of an association among men is remaining selection bias not mitigated with the ISPW, though our weights used multiple baseline characteristics to account for differential participation in MHC studies, survival, and KPNC membership in 1996. Of note, prior studies of midlife hypertension and dementia did not address possible selection bias through methods such as inverse probability weighting.[5–7,22,23] Differential survival during follow-up by sex may also lead to differences in the estimated effect of hypertension on dementia risk across sexes. Indeed, 16.5% of men in our sample were censored due to death, compared to 13.9% of women. This means we were unable to follow a greater proportion of men than women until the end of the study to determine if they would have received a dementia diagnosis between 1996 and 2015 had they not died. Furthermore, men with hypertension in early adulthood or mid-adulthood were more likely to die than men without hypertension (early adulthood hypertension: 18% vs 16%; mid-adulthood hypertension: 22% vs 14%). Thus the risk of dementia associated with hypertension may be underestimated among men.

Hypertension is associated with cognitive impairment,[29] stroke,[30] and brain atrophy.[31] In general, mechanisms would accumulate risk of dementia over the life course. This is consistent with the reduced effect estimate of early adult life BP when both time points are modeled concurrently, signaling that midlife BP may partially mediate the association between early adulthood hypertension and dementia risk.

Strengths of our study include a diverse sample with equal access to health care, the ability to look over several decades with a long follow-up period, repeated clinical measurements of BP, self-report of hypertension and of antihypertensive medication in early and mid-adulthood, and information on health behaviors and comorbidities in early adulthood through late life. We implemented inverse probability weights to mitigate selection bias taking into account differential participation and survival from the first MHC phase to the start of follow-up. Subclinical dementia in early adulthood and midlife is highly unlikely, ensuring the temporal order of interest. Though we do not have information on type and dose of antihypertensive use, only 12% of individuals with hypertension in the United States were receiving effective antihypertensive medication in the 1970s.[23] Developments in screening protocol for high BP and in antihypertensive medication have occurred since 1964, limiting the generalizability of these results current middle-aged cohorts. We do not have neuroimaging or pathology data so we are unable to examine specific dementia subtypes or subclinical vascular brain injury. Nor could we explore cerebrovascular-specific mechanisms for the association between hypertension and dementia.

This study suggests that hypertension is a risk factor for dementia among women starting in their early 40s but not for men. Further research is needed to disentangle possible sex-specific pathways through which elevated BP over the life course accelerates brain aging.

AUTHOR CONTRIBUTIONS

Rachel A. Whitmer and Paola Gilsanz contributed to the conception and design of the study. Paola Gilsanz was responsible for the analysis of the data. All coauthors interpreted the data and contributed substantially to the manuscript.

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DISCLOSURE

P. Gilsanz, E. Mayeda, M. Glymour, C. Quesenberry, and D. Mungas report no disclosures relevant to the manuscript. C. DeCarli is a consultant to Novartis Pharmaceuticals. A. Dean and R. Whitmer report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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