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Blood Pressure, Antihypertensive use, and risk of Alzheimer's and non-Alzheimer's Dementia in late-life: An IPD meta-analysis

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Abstract: Background and Objectives: Previous RCTs and longitudinal studies have indicated that ongoing antihypertensive use in late-life reduces all-cause dementia risk but the specific impact on Alzheimer's (AD) and non-Alzheimer's Dementia risk remains unclear. This study investigates whether previous hypertension or antihypertensive use modifies AD or non-AD risk in late-life as well as the ideal BP for risk reduction in a diverse consortium of cohort studies. Methods: This IPD meta-analysis longitudinal studies of late-life (>60 years) included individuals from 14 nations. The main outcomes were AD and non-AD risk. The main exposures were hypertension history/antihypertensive use and baseline systolic BP (SBP)/diastolic BP (DBP). Mixed effects Cox proportional hazards models were used to assess risk and natural splines were applied to model the relationship between BP and the dementia outcomes. The main model controlled for age, age2, sex, education, racial group and study cohort. Supplementary analyses included a fully adjusted model, an analysis restricting to those with >5 years follow up and models that examined the moderating effect of age, sex and racial group. Results: There were 31,250 participants in the analysis (41% male) with a mean baseline age of 72 (SD=7.5, range=60-110). Participants with untreated hypertension had a 36% (HR=1.36, 95%CI[1.01, 1.83], p=0.0406) and 42% (HR=1.42, 95%CI[1.08, 1.87], p=0.0135) increased risk of AD compared to "healthy controls" and those with treated hypertension respectively. Compared to "healthy controls" both those with treated (HR=1.29, 95%CI[1.03, 1.60], p=0.0267) and untreated hypertension (HR=1.69, 95%CI[1.19, 2.40], p=0.0032) had greater non-AD risk but there was no difference between the treated and untreated groups. Baseline DBP had a significant U-shaped relationship (p=0.0227) with non-AD risk in an analysis restricted to those with 5 years follow up but otherwise there was no significant relationship between baseline BP and either AD or non-AD risk. Discussion: Antihypertensive use was associated with decreased AD risk but not non-AD throughout late-life. This suggests that treating hypertension throughout late-life continues to be crucial in AD risk mitigation. A single measure of BP was not associated with AD risk but DBP may have a U-shaped relationship with non-AD risk over longer periods in late-life.

Title Page

Blood Pressure, Antihypertensive use, and risk of Alzheimer's and non-Alzheimer's Dementia in late-life: An individual participant data meta-analysis

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Abstract

Background and Objectives:
Previous RCTs and longitudinal studies have indicated that ongoing antihypertensive use in late-life reduces all-cause dementia risk but the specific impact on Alzheimer's (AD) and non-Alzheimer's Dementia risk remains unclear. This study investigates whether previous hypertension or antihypertensive use modifies AD or non-AD risk in late-life as well as the ideal BP for risk reduction in a diverse consortium of cohort studies.

Methods:
This IPD meta-analysis longitudinal studies of late-life (>60 years) included individuals from 14 nations. The main outcomes were AD and non-AD risk. The main exposures were hypertension history/antihypertensive use and baseline systolic BP (SBP)/diastolic BP (DBP). Mixed effects Cox proportional hazards models were used to assess risk and natural splines were applied to model the relationship between BP and the dementia outcomes. The main model controlled for age, age^2, sex, education, racial group and study cohort. Supplementary analyses included a fully adjusted model, an analysis restricting to those with >5 years follow up and models that examined the moderating effect of age, sex and racial group.

Results:
There were 31,250 participants in the analysis (41% male) with a mean baseline age of 72 (SD=7.5, range=60–110). Participants with untreated hypertension had a 36% (HR=1.36, 95%CI[1.01, 1.83], p=0.0406) and 42% (HR=1.42, 95%CI[1.08, 1.87], p=0.0135) increased risk of AD compared to "healthy controls" and those with treated hypertension respectively. Compared to "healthy controls" both those with treated (HR=1.29, 95%CI[1.03, 1.60], p=0.0267) and untreated hypertension (HR=1.69, 95%CI[1.19, 2.40], p=0.0032) had greater non-AD risk but there was no difference between the treated and untreated groups. Baseline DBP had a significant U-shaped relationship (p=0.0227) with non-AD risk in an analysis restricted to those with 5 years follow up but otherwise there was no significant relationship between baseline BP and either AD or non-AD risk.

Discussion:
Antihypertensive use was associated with decreased AD risk but not non-AD throughout late-life. This suggests that treating hypertension throughout late-life continues to be crucial in AD risk mitigation. A single measure of BP was not associated with AD risk but DBP may have a U-shaped relationship with non-AD risk over longer periods in late-life.

Background

Hypertension, a disorder that affects an estimated 1.3 billion persons worldwide[1], is the leading cause of strokes and cerebrovascular disease[2]. There is good evidence that mid-life hypertension, but not late-life, increases risk of vascular dementia (VaD)[3]. For Alzheimer's dementia (AD) two meta-analyses[4,5] found no association between late-life or mid-life hypertension and AD, while a third found that mid-life hypertension increased AD risk by 18-25%[6]. More recently, Ou et al[7] (2020) in the largest meta-analysis to date, found that mid-life hypertension was associated with a 19% increased risk of late life AD, whereas late-life hypertension (>65 years) had no significant link to AD.

The consistent meta-analytic findings of no relationship between either categorical or linear late-life blood pressure and either AD or VaD may mask non-linear effects of blood pressure seen in late-life. Van Dalen et al (2021)[8], ran an Individual Participant Data (IPD) meta-analysis (n = 17,286, mean age (SD) = 74.5 (7.3), age range = 55+), to assess the U-shaped relationship between SBP, DBP and dementia outcomes. They found that the low point of risk for dementia was approximately SBP 185 mmHg and DBP 139 mmHg, although this estimate was significantly lower at older ages. As well as changing effects with increasing age, studies have also indicated that the association between BP and AD may be modified by sex[9–16] and ethnicity[17,18]. A study of late-life (>65 years) USA Medicare data[19] (n_{white}=3,121,553, n_{black}=320,720) demonstrated that hypertension was linked to a higher risk of AD in black populations compared to white.

Antihypertensives and Alzheimer's Dementia prevention

Antihypertensives have been associated with a 13% reduced risk of all-cause dementia in a meta-analysis of 7 RCTs of late-life participants[20]. However, few RCTs of antihypertensive use have examined AD specifically as an outcome and the majority of the longitudinal studies focus on all-cause dementia. The Syst-Eur Study[21] (n = 2902, mean follow up = 3.9 years) found a 40% reduction in AD risk for an antihypertensive treatment group, in a population of those aged 60 and older. In contrast, the HYVET-COG Study[22] (n = 3336, mean follow up = 2 years) in those aged 80 and older found no effect of antihypertensive treatment on AD risk. While RCTs are the gold-standard when it comes to assessing the effectiveness of interventions, they often have key limitations of short follow up periods, insufficient power to detect rare events and highly curated participant populations from developed countries that limit generalisability.

A meta-analysis of observational studies found that antihypertensive use reduced risk of AD by 6% but their results were heavily weighted towards a single study[23] and they included participants both in mid-life and late-life (>55 years old). More recently a case-control study of 215,547 italian persons over the age of 65 found that those with intermediate and high exposure to antihypertensives had an 18% and 29% reduction in AD risk[24]. Our group recently published an IPD meta-analysis of 17 studies from 15 countries from around the world (n=34,519)[25]. We found that individuals aged 60 or older with untreated hypertension had a 42% increased risk of all-cause dementia compared to those without hypertension and a 26% increased risk compared to those with treated hypertension. Additionally, there was no association between baseline BP and dementia risk and no significant interaction

between baseline BP and antihypertensive use. AD has distinct familial, genetic and environmental risk factors[26] compared to other dementias, as well as specific symptomatic[27] and disease modifying treatments[28,29]. As such, risk mitigation strategies for AD may need to be different to other dementias and it is important that the particular effect of blood pressure and antihypertensive use on AD risk, in addition to all-cause dementia, be understood. In the current paper, we use international data from 14 diverse, longitudinal cohort studies to investigate how blood pressure and antihypertensive medication use are associated with the risk of both AD and non-Alzheimer's dementia (non-AD).

Methods

Contributing Studies

This analysis incorporated 14 longitudinal studies of ageing (n=31,250) that participated in the Cohort Studies of Memory in an International Consortium (COSMIC) group, a collaborative that has been described in prior papers[25,30–33]. The participants were from 14 countries (USA, Brazil, Australia, China, Japan, Korea, Republic of Congo, Nigeria, Germany, Spain, Italy, France, Sweden and Greece). The follow-up durations varied between 2 and 15 years. Participants younger than 60 were excluded for not being in "late-life". Participants with a dementia diagnosis at baseline were excluded from the analyses. Demographic and follow up information for the individual studies are shown in Table 1. Approval was given by the University of New South Wales Human Research Ethics Committee (HC 12446 and HC 17292). Each participating study had independent ethics approval from their regional ethics board (Table S1). This study is presented according to the PRISMA-IPD guidelines (Table S2)[34].

BP measures, history of hypertension, antihypertensive medication use and covariates

All studies included information on self-reported prior, physician diagnosis of hypertension and the majority had data for antihypertensive use at baseline (12 studies). The studies had up to three measures of BP at baseline, taken while seated and baseline BP was taken to be the average of the multiple measures. Information on BP measurement methods for the studies are in Table S3. Individuals with BP ±3 standard deviations (SDs) from the grand mean (across studies) were excluded as outliers (i.e. SBP<73.1 and >204.1 mmHg, and DBP<45.1 and >114.4 mmHg) (see Table S4). The covariates used in the analyses were age, sex, years of education, racial group, body mass index (BMI), diabetes status, hypercholesterolaemia and smoking status (for details see Tables S5 to S7).

Dementia Outcomes

The two main outcome variables for this study were AD and non-AD dementia. Three studies included in our previous paper did not have AD diagnosis data and were therefore excluded. Across cohorts, the diagnostic criteria used were DSM-IV or DSM III-R for all-cause dementia and NINCDS-ADRDA for AD (Table S8). Individuals diagnosed with all-cause dementia and not AD were defined as non-AD dementia. A subset of those with non-AD were diagnosed with VaD, based on NINDS-AIREN criteria and sensitivity analyses were performed examining specific risk for this outcome. Dementia onset was assigned a date half-way between the assessment date when dementia was first diagnosed and the previous assessment date.

Categorisation of covariates

Education level was provided either as years of education or in a categorical form that was converted to number of years (Table S6) and treated as a continuous variable. Racial group

was treated as a 4-level categorical variable (0–White, 1–Asian, 2–Black, 3–Other). Other covariates included body mass index (BMI) (continuous variable), diabetes status (categorical variable; 0–no diabetes, 1–diabetes), hypercholesterolaemia (categorical variable; 0–no hypercholesterolaemia, 1–hypercholesterolaemia) and smoking status (categorical variable; 0–never smoker, 1–previous smoker, 2–current smoker).

Statistical Analysis

The statistical analyses were pre-specified on Open Science Framework (OSF) (osf.io/rkx79/). For the main analyses, a one-step IPD approach was applied (i.e. models were run for all participants in a combined dataset with a random effect term for study). This approach, rather than the traditional two-step, random effects meta-analysis, was used because our meta-analyses incorporated small studies with low event rates, where investigating interactions effects has limited power in two-step approaches[35]. Hypertension history, as a dichotomous variable, was examined, but because its effect was significantly modified by treatment status (Table S10), the main analysis focussed on a categorical variable based on both hypertension history and antihypertensive use. This variable had four possible groups:

1. No hypertension history while not taking an antihypertensive at baseline ("Healthy Control" participants)
2. No hypertension history while taking an antihypertensive at baseline ("Uncertain hypertension")
3. Reporting hypertension history while taking an antihypertensive at baseline ("Treated hypertension")
4. Reporting hypertension history while not taking an antihypertensive at baseline ("Untreated hypertension")

Individuals in the second group, with uncertain hypertension, were excluded from this part of the analysis (n = 866, 4% of participants). They were removed because they may have been taking an antihypertensive but not been aware or failed to recall that they had been diagnosed with hypertension previously or they may have been taking an antihypertensive for a reason other than hypertension (e.g. heart failure, palpitations, arrhythmias, kidney disease).

This classification was a critical constituent of the analysis and consequently a between-group comparison of characteristics was run, including covariates and baseline MMSE (Table S9). We had BP measures from a single point in time (baseline) and thus did not consider BP in the classification of hypertension given that diagnosis of hypertension requires at least two BP measures taken at least 1 month apart[36].

In assessing baseline BP, SBP and DBP, the measures were centred (SBP at 140 mmHg and DBP at 80 mmHg) and divided by 5 (i.e. measured in units of 5 mmHg) to generate comparable effect sizes to other covariates. Prior publications[8,37] have indicated that BP has a U shaped or parabolic association with AD. Thus, these putative non-linear associations were assessed using natural splines terms for SBP and DBP, with 2 to 4 degrees of freedom according to best fit (using Akaike Information Criteria (AIC) and Bayesian Information

Criteria (BIC)). Studies have similarly found that dementia risk increases quadratically rather than linearly with age[38]. Consequently, age was grand-mean centred (at 73 years) and linear and quadratic age terms (Age and Age^2) were incorporated into every analysis.

Mixed effects Cox proportional hazards survival models were used to examine the association between the independent variables and progression to both Alzheimer's and non-Alzheimer's dementia. Separate cause-specific hazards models were used rather than Fine-Gray models as for the purposes of this study the outcomes were mutually exclusive[39]. The first analysis assessed the risk of AD and non-AD associated with HT/AHT status. The second examined the associations of baseline SBP/DBP to AD and non-AD, utilising the aforementioned natural splines to model the association. Models comprised of both continuous BP parameters and HT/AHT status were attempted but were excluded because of poor model fit, number of excluded participants and a lack of interaction significance.

The main, partially adjusted analysis incorporated covariates of Age, Age^2, Sex, Education, Racial group and a random intercept term for study. This parsimonious model was used as the main one to minimise participant exclusion, particularly from lower socioeconomic regions, where studies frequently lacked covariates used in the fully adjusted model. Additional analyses were performed to test the robustness of results as follows: First, a fully adjusted analysis was performed, controlling for additional covariates of hypercholesterolaemia, BMI, smoking status and diabetes. Second, a restricted analysis, excluding those with less than 5 years of follow up was run. This approach was needed as dementia progressively develops over years and thus occurrence of dementia within several years of baseline is probably caused by factors substantially prior to study baseline. Third, to assess contributions of individual studies, the main model was run within each study and results were examined for outliers and heterogeneity. Fourth, to assess the putative moderating effects of age, sex and racial group, interactions between the main predictors (HT/AHT status and baseline BP) with these variables were included in separate models. Fifth, to assess the impact of effectiveness of blood pressure control in those with treatment, the main analyses were re-run with the treated hypertension group divided into those with BP <140/90 mmHg (controlled) and those with BP either >140 mmHg SBP or >90 mmHg DBP (uncontrolled). Finally, in order to assess the contributions of VaD to the non-AD results the partially adjusted model, fully adjusted model and >5-year model were repeated with VaD as the main outcome. Interaction analyses for the VaD outcome were not performed because of small event rates.

The Sydney COSMIC team harmonised the data across studies and performed the mixed effects Cox regressions using the coxme[40] and splines packages in R 4.3.1. A significance threshold of $p < 0.05$ was used.

Results

Participant Characteristics

There were 56,821 total participants in the studies, 2884 (5.1%) were excluded for dementia at baseline and 31,250 dementia-free participants (55%) had sufficient data to be included in the analysis. The mean baseline age was 72.1 (SD = 7.5) years and 41% were male (Table 1). The mean follow-up was 4.2 years (SD = 3.9) and the mean years of education was 8.3 years (SD = 5.3). Mean baseline SBP and DBP were 137.8 (SD = 21) mmHg and 79.9 (SD = 11.2) mmHg respectively. Of the hypertensive/antihypertensive groups 35.9% were "healthy controls", 4% were excluded as "uncertain hypertension", 50.7% were treated hypertension, and 9.4% were untreated hypertension. Those with untreated hypertension (compared to healthy controls) were significantly more likely have fewer years of education, be current smokers, less likely to be Asian and have poorer baseline MMSE scores (Table S9). The mean time to AD and non-AD diagnosis was 4.2 (SD = 3.3) and 4.1 years (SD = 3.6) respectively, although these measures varied significantly by study (Table 1). Of the 12 studies that included VaD diagnosis data 35.6% of dementia cases were non-AD, and among them 45.2% were VaD (16.1% of all cases).

History of Hypertension and Antihypertensive Use

In the main analysis, participants with untreated hypertension had significantly higher risk of AD (HR=1.363, 95%CI[1.013, 1.832], p=0.0406) compared to "healthy controls" (Figure 1 and Table 2), whereas those with treated hypertension had no elevated AD risk. However, considering the non-AD outcome, those with either treated hypertension (HR=1.285, 95%CI[1.029, 1.604], p=0.0267) or untreated hypertension (HR=1.693, 95%CI[1.193, 2.403], p=0.0032) had significantly greater non-AD risk than "healthy controls". The untreated hypertension group had significantly higher risk of AD (HR=1.418, 95%CI[1.075, 1.872], p=0.0135) than the treated hypertension group, but risk of non-AD did not differ significantly. In the supplementary analysis (Table S10), hypertension history, without stratifying for treatment status, was associated with greater risk of non-AD (HR=1.366, 95%CI[1.154, 1.616], p=0.0003) but was not associated with AD risk. In the fully adjusted analysis, controlling for other vascular covariates ($N_{studies}$=7), the associations with AD remained significant but associations with non-AD did not. In the analysis restricted to those with >5 years follow up ($N_{studies}$=9) none of the associations remained significant. In the 2-step random effects meta-analysis, comparisons between treated and untreated hypertension groups for AD and non-AD risk showed low heterogeneity (I^2=0% and 7.7%). By contrast, heterogeneity was substantially higher when comparing those with untreated hypertension and "healthy controls" (I^2=32.4% and 63.5%) or those with treated hypertension and "healthy controls" (I^2=11.9% and 78.3%) (Table S11). The results for the VaD analysis were largely similar to that of non-AD with three key differences. First, in the main, partially adjusted analysis those with treated hypertension had no elevated risk of VaD compared to "healthy controls". Second, those with untreated hypertension had significantly greater risk of VaD compared to those with treated hypertension (HR=1.714, 95%CI[1.034, 2.841], p=0.0366). Third, when restricting to those with more than 5 years

follow-up baseline SBP was associated with a positive, approximately linear association with VaD risk (p=0.0092) (Table S12 and Figure S1).

Interaction analyses revealed that the difference in non-AD risk between the treated hypertension group and "healthy controls" significantly diminished with increasing age (p=0.026) (Table S13 and Figure 1). Furthermore, the difference in risk between those with treated hypertension and "healthy controls" was significant in males but not in females (p=0.0327). There were no significant moderating factors for the AD analysis. No moderating effect of race was observed for either AD or non-AD risk.

Baseline BP

In the main, partially adjusted, analysis there was no significant linear or non-linear association between baseline SBP or DBP and either AD or non-AD risk (Table 2 and Figure 2A and B). This finding was supported by the null associations seen in the fully adjusted analysis. However, in the analysis restricted to those with >5 years follow up there was a significant U-shaped association between baseline DBP and non-AD risk (p=0.0227) (Table 2 and Figure 2F). Heterogeneity of the estimates across studies ranged from very small to moderate (I^2 = 0.1% to 58.7%) (Table S10).

The associations between DBP and AD risk as well as SBP and non-AD risk were significantly moderated by age (p=0.0132 and 0.0313 respectively) (Figure 3 and Table S1). Figure 3A suggests that the association between DBP and AD risk inverts with increasing age, with low DBP associated with increased AD risk at 60 and decreased risk by 90. Figure 3B indicates that while the association between SBP and non-AD risk at 60 years of age is U-shaped, it flattens with age. However, in both analyses the main effects were non-significant irrespective of the point at which age was centred (i.e. assessing the effect at 60, 70, 80 or 90), indicating that the interaction may not be meaningful. There were no other significant interactions between age, sex or racial group for the SBP or DBP natural splines terms (Table S14).

Interaction between Baseline BP and HT/AHT Status

There were no significant interactions between either SBP or DBP and the HT/AHT status of participants for either AD or non-AD (Table S15). However, when baseline BP was considered as a binary variable (controlled <140/90 mmHg or uncontrolled >140 mmHg SBP or >90 mmHg DBP), those who had treated hypertension that was uncontrolled had substantially elevated risk of non-AD (HR=1.331, 95%CI[1.04, 1.704], p=0.0233), whereas those with treated, controlled hypertension had no increased risk (Table S16). This result was consistent in those participants restricted to 5 years follow-up but was no longer significant in the fully adjusted analysis. There was no difference in AD risk between those with controlled or uncontrolled treated hypertension.

Discussion

Reduced AD risk in late life associated with antihypertensive use

In this study, the largest meta-analysis in this area to date, there were a number of key insights into the association of late-life hypertension and AD risk. We found that those with untreated hypertension had significantly higher risk of AD than "healthy controls" (+36%) and those with treated hypertension (+42%). This estimate is similar to the 40% greater risk of AD in those with untreated versus treated hypertension found in the Syst-Eur Clinical Trial[21]. However it differs considerably from the 6% estimate from a 2022 meta-analysis[41] of three observational studies. The studies in that meta-analysis used insurance data and included participants from both mid- and late-life, whereas this meta-analysis used data for individuals age 60 or more years from longitudinal studies of ageing. The incidence of dementia is low prior to late-life, and thus including participants less than 60 years old may underestimate the risk of dementia.

In the current study, diagnosed hypertension, both treated and untreated, was associated with considerably greater risk of non-AD in late life compared to "healthy controls". There was no difference in overall non-AD risk between the treated and untreated hypertension groups. However, untreated hypertension was associated with a higher risk of VaD. The non-AD and VaD results should be considered with caution as the results of the partially adjusted analysis were not replicated in the fully adjusted analysis or when restricted to more than 5 years of follow-up, indicating that the differences may be better explained by vascular covariates. Nevertheless, our VaD finding is corroborated by the Ou et al (2020) meta-analysis that found a similar association between VaD and hypertension (RR=2.12, 95%CI[1.50–2.99]). The results for VaD are also consistent with the few published clinical trials that have found that the risk of post-stroke dementia is significantly modified by antihypertensive use, reducing risk by up to 34%[42,43]. A challenge to interpreting the differing results of AD, non-AD and VaD is that the delineation of AD from VaD is somewhat arbitrary, and post-mortem studies indicate co-existence of Alzheimer's and vascular pathology is the norm (up to 80% of AD cases)[44].

The subgroup analyses found that males with treated hypertension were at greater risk of non-AD than females (HR_{male} = 1.67, HR_{female} = 1.06, $p_{interaction}$ = 0.033). This finding is consistent with previous research indicating that men are more susceptible to post-stroke dementia than women (RR men 2.7 vs RR women 1.7)[45]. Additionally, we found that the increased non-AD risk associated with treated hypertension diminished with advancing age, whereas untreated hypertension was associated with elevated non-AD risk throughout late life. Previous studies have found that mid-life but not late-life hypertension is associated with late-life VaD[46], but this study clarifies that untreated hypertension continues to convey a greater risk of non-AD in late-life. Regarding racial groups, this study, like others[47,48], found that there were higher rates of hypertension among black individuals. However, the associations of treated and untreated hypertension with AD and non-AD were not significantly different between racial groups, suggesting that antihypertensives are likely to be similarly effective in dementia prevention in different racial groups.

Association between late-life baseline BP and dementia risk

There were no significant associations between baseline SBP or DBP in late-life with AD or non-AD. This is broadly in keeping with numerous previous analyses[4,5,7,25,49–52] showing no association between late-life blood pressure and all-cause dementia or AD. However, when restricting analyses to more than 5 years of follow up there was a significant positive and approximately linear association between SBP and VaD as well as non-linear associations between DBP and both non-AD and VaD risk. For non-AD, low DBP conferred greater risk than high DBP with lowest risk at around 80 mmHg. For VaD high DBP conferred greater risk than low DBP and lowest risk was at around 67 mmHg. Two meta-analyses[7,53] have previously reported low DBP in late-life as a risk factor for all-cause dementia. Furthermore, a meta-analysis by Van Dalen et al (2022)[8] found a U-shaped association between DBP and all-cause dementia, with lowest risk around DBP 139 mmHg. The Chicago Health and Ageing Project (n= 2137) also found a U-shaped association but the lowest risk for dementia was suggested to be a SBP of 138 mm Hg and a DBP of 77 mm Hg[37]. The fact that this finding was only significant in those with more than five years of follow-up is consistent with the years elapsed over which blood pressure causes vascular disease, cognitive impairment and eventual dementia. However, given that other vascular risk factors were not controlled for this result should be interpreted with caution. Animal studies have shown that low DBP, partially caused by vascular disease and diminished vascular elasticity, contributes to poorer cerebral perfusion pressures, likely ischaemia and neurodegeneration[54]. In the future, trials for specific treatments of diastolic hypotension will help to clarify this association in humans and provide insight into best practice management of this condition.

No interaction between history of hypertension/antihypertensive use and baseline BP

We found that baseline BP (systolic and diastolic) did not moderate the association between hypertension/antihypertensive use status for AD risk. This finding is consistent with our previous study[25] and with the Peters et al (2022)[20] meta-analysis of clinical trials, both finding the treatment effect is not modified by baseline BP. This finding indicates that a single measure of baseline BP, being a cross-sectional snapshot of a highly variable[55] biomarker, is of limited practical use when deciding to continue antihypertensive treatment for AD risk reduction. However, those with treated hypertension who had poorly controlled BP had significantly higher non-AD risk than those with well controlled BP. This result should be interpreted with caution as when we controlled for other vascular risk factors in the fully adjusted model the association was no longer significant indicating that the relationship is potentially confounded.

Study Limitations

All included studies used DSM-IV or III-R criteria with three studies additionally using NINCDS-ADRDA criteria. Even when using the NINCDS criteria, validation studies[56] found only a sensitivity of 81% and specificity of 71% in diagnosing “probable” and it cannot discriminate accurately between AD and VaD. Longitudinal studies initiated in more recent

times more frequently include biomarkers of AD, which the cohort studies within our consortium lacked. The variability in dementia diagnostic criteria is part of the larger limitation of cohort study variability. Hypertension definitions varied by location leading to possible discrepancies in diagnosis. Additionally, studies with greater numbers of assessments likely had a better approximation of dementia onset date generating further between-study heterogeneity. Many of the studies report dementia onset shortly after study baseline and given its long prodromal phase this indicates there may have been substantial baseline cognitive impairment. Most of the studies also did not report mortality data and thus our analysis did not account for the competing risks of dementia and death. Many of the participants with baseline hypertension probably had this condition since mid-life, and the results are thus not likely reflective of late-life onset hypertension. There are likely to be non-random differences between those who do and don't take antihypertensives that we could not control for, including socioeconomic status, health literacy, access to medications, poorly managed comorbidities and depression and other mental illnesses that may confound the association between hypertension status and dementia risk. Finally, some studies have indicated that certain classes of antihypertensives[41] may be more effective at reducing AD risk than others and this study lacked data on antihypertensive classes to investigate this putative moderating effect.

Conclusion

To conclude, this IPD meta-analysis, with data from 14 countries, illustrates that throughout late-life those with treated hypertension had a lower risk of AD compared to those with untreated hypertension, suggesting that antihypertensive use should be part of any AD prevention strategy even in late-life. By contrast, both treated and untreated hypertension were associated with elevated non-AD risk, and there were no significant differences in risk between the two groups, although elevated risk of non-AD in the treated group was largely attributable to those with poorly controlled BP. This study suggests that a single measure of SBP or DBP does not predict AD risk, and it is likely that more than one measure is required to guide treatment. DBP may have a U-shaped relationship with non-AD risk over longer time periods.

890

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Access to Data Statement

MJL and DL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing

All aggregate participant data are presented either in the manuscript or appendix. Individual participant data cannot be made publicly available because they are protected by a confidentiality agreement. Data were provided by the contributing studies to COSMIC on the understanding and proviso that the relevant study leaders be contacted for further use of their data and additional formal data sharing agreements be made. Researchers can apply to use COSMIC data by completing a COSMIC Research Proposal Form available from https://cheba.unsw.edu.au/ consortia/cosmic/research-proposals.

Contributors

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Conflicts of Interest

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Isabelle Cairerre and Karen Ritchie have no conflicts to declare.

Assoc Prof Ng Tze Pin, Dr Ma Shwe Zin Nyunt and Dr Qi Gao have no conflicts to declare

All other authors have no conflicts to declare.

Consent Statement

All human subjects provided informed consent to the individual cohort studies that they participated in.

Key words

Blood pressure, hypertension, Alzheimer's dementia, antihypertensives, longitudinal studies, blood pressure lowering medication

1406

Figure Legends

Figure 1: The association of hypertension history-antihypertensive use (HT/AHT) status with the risk of AD and non-AD dementia (x-axis in log2 scale). The main analysis (partially adjusted) included covariates of Age, Age^2, Sex, Education, Racial group and a random effect for Study. The fully adjusted analysis included additional covariates of BMI, smoking status, history of hypercholesterolaemia and diabetes. Each of the other analyses applied the partially adjusted model. The p-values show the size of the interaction effect for Age, Sex and Racial group with treated hypertension (compared to "healthy controls") and Untreated hypertension (compared to "healthy controls"). Age was treated as a continuous variable, sex as a categorical variable and racial group as a categorical variable with three major groups (White, Asian and Black). The numbers and brackets on the right are the hazard ratios and 95% confidence intervals. The p-values show the significance of the interaction term. The interaction p-values used White participants as the main comparison group in the racial analysis (as this was the largest group included).

Figure 2: The relationship between SBP, DBP and AD/non-AD risk with 95%CIs (shaded areas). In all models SBP and DBP was grand-mean centred (at 140 mmHg and 80 mmHg respectively) and all HRs represent within-group risk relative to this grand-mean. A restricted cubic splines model was applied. Panels A and B show the main analysis (partially adjusted), which included the covariates of Age, Age^2, Sex, Education, Racial group and a random effect for Study. Panels C and D show the fully adjusted analysis which included additional covariates of BMI, smoking status, history of hypercholesterolaemia and diabetes. Panels E and F shows the partially adjusted analysis restricted to those with at least 5 years of follow up.

Figure 3: The relationship between SBP, DBP and AD/non-AD risk with 95%CIs (shaded areas) showing the changing relationship with increasing age. In all models SBP and DBP was grand-mean centred (at 140 mmHg and 80 mmHg respectively) and all HRs represent within-group risk relative to this grand-mean. A restricted cubic splines model was applied. 3A shows the significant moderating effect of age on the relationship between baseline SBP and non-AD risk. 3B shows the significant moderating effect of age on the relationship between baseline DBP and AD risk.

Tables

Author (Year)	Study Name (Abbreviation)	Main Racial Groups	Mean Age (SD)	Sex (M%)	Mean Education Yrs (SD)	Maximum no. Waves	Maximum FU Yrs	Mean FU Yrs (SD)	Mean SBP (SD) (mmHg)	Mean DBP (SD) (mmHg)	HT/AHT Status N (%)[a]	No. AD (%)[a]	Mean time (yrs) to AD diagnosis (SD)	No. non-AD (%)[a]	Mean time (yrs) to non-AD diagnosis (SD)
Xiao et al (2016)[57]	**Chinese Longitudinal Aging Study (CLAS)**	Asian, Chinese	71.1 (7.8)	45.50%	7.7 (5.3)	3	7.2	1.1 (1.6)	129.6 (15.2)	77.9 (8.7)	1 - 1049 (50.5%) 2 - 9 (0.4%) 3 - 913 (44%) 4 - 105 (5.1%)	33 (1.6%)	0.5 (0.1)	23 (1.1%)	0.5 (0.1)
Guerchet et al (2014)[58]	**Epidemiology of dementia in Central Africa (EPIDEMCA)**	Black, African	73.1 (6.6)	41.10%	2 (3.7)	4	2.9	0.8 (1.1)	142.1 (26.7)	80.9 (13.4)	1 - 0 (0%) 2 - 0 (0%) 3 - 33 (41.2%) 4 - 47 (58.8%)	12 (3.7%)	1.8 (0.7)	7 (2.2%)	0.9 (0.6)
Dardiotis et al (2014)[59]	**The Hellenic Longitudinal Investigation of Aging and Diet (HELIAD)**	White, Greek	72.8 (5.5)	40.10%	8.1 (5)	2	7.3	1.7 (1.7)	131.7 (17.7)	77.4 (9.9)	1 - 478 (25.9%) 2 - 165 (8.9%) 3 - 1113 (60.3%) 4 - 89 (4.8%)	53 (2.8%)	1.6 (0.4)	9 (0.5%)	1.5 (0.4)
Hendrie et al (2001)[60]	**Indianapolis-Ibadan Study (Ibadan)**	Black, African	73.6 (5.9)	27.80%	1.2 (3.2)	7	17.7	7.5 (5)	155.3 (32.7)	85.9 (16)	-	258 (15.6%)	4.8 (3.3)	36 (2.2%)	5.3 (3.7)
	Indianapolis-Ibadan Study (Indianapolis)	Black, African-American	75.7 (6)	33.40%	11 (3.1)	7	17.4	6.5 (4.6)	146.9 (22.2)	80.3 (11.8)	-	241 (16.6%)	5 (3.7)	54 (3.7%)	4.6 (3.5)
Katz et al (2011)[61]	**Einstein Aging Study (EAS)**	White/Black, North American	78.1 (5.3)	38.20%	13.2 (3.6)	16	19.6	2.8 (3.4)	134.1 (15.9)	77.4 (8.5)	1 - 591 (29.7%) 2 - 207 (10.4%) 3 - 1018 (51.2%) 4 - 172 (8.7%)	98 (4.8%)	3.8 (3.3)	55 (2.7%)	3.8 (3.4)
Ritchie et al (2010)[62]	**Etude Santé Psychologique Prévalence Risques et Traitement (ESPRIT)**	White, French	73.1 (5.5)	41.60%	10.2 (3.8)	4	9	9.3 (5.6)	140.9 (17.4)	79.7 (9.9)	1 - 1191 (54.8%) 2 - 182 (8.4%) 3 - 765 (35.2%) 4 - 35 (1.6%)	126 (5.8%)	6.7 (4.5)	83 (3.8%)	7.3 (4.4)
Rydberg Sterner et al (2019)[63]	**Gothenburg H70 Birth Cohort Studies (GothenburgH70)**	White, Swedish	73.3 (4.9)	28.90%	9.7 (3.7)	3	10.7	5.9 (4.1)	155.6 (21.8)	84.5 (11.3)	1 - 453 (57.7%) 2 - 79 (10.1%) 3 - 229 (29.2%) 4 - 24 (3.1%)	72 (9.2%)	6.2 (2.9)	52 (6.6%)	5.5 (2.7)
Guaita et al (2013)[64]	**BRAİN AGEİNG İN ABBİATEGRASSO (Invece.Ab)**	White, Italian	72.2 (1.3)	46%	6.8 (3.3)	2	3.3	3.4 (1.4)	141.7 (17.5)	78.9 (8.4)	1 - 443 (34.9%) 2 - 63 (5%) 3 - 729 (57.4%) 4 - 34 (2.7%)	22 (1.7%)	2.3 (1.1)	37 (2.9%)	2.5 (1)
Han et al (2018)[65]	**Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD)**	Asian, Korean	69.9 (6.6)	43.60%	8.2 (5.3)	4	7.1	4 (2.3)	126.2 (14.8)	77.9 (9.2)	1 - 1137 (29.5%) 2 - 161 (4.2%) 3 - 2233 (58%) 4 - 320 (8.3%)	175 (2.8%)	2.7 (1.5)	51 (0.8%)	2.3 (1.5)
Reidel-	**Leipzig Longitudinal**	White,	81.5 (4.9)	25.90%	11.9 (1.7)	7	16	4.8 (3.4)	158.6	86.1	-	135	3.4 (2.2)	94 (9.5%)	4.2 (3.2)

Heller et al (2001)[66]	**Study of the Aged (LEILA)**	German							(24.3)	(16.2)		(13.7%)			
Anstey et al (2012)[67]	**Personality and Total Health Through Life Study (PATH)**	White, Australian	62.5 (1.5)	51.50%	13.7 (2.8)	4	13.9	9.7 (4.5)	139.8 (19.5)	83 (10.7)	1 - 1455 (58.7%) 2 - 0 (0%) 3 - 820 (33.1%) 4 - 202 (8.2%)	34 (1.3%)	9.5 (1.8)	46 (1.8%)	8.4 (3)
Haan et al (2003)[68]	**Sacramento Area Latino Study on Aging (SALSA)**	Mixed, Mexican	70.4 (6.8)	41.60%	7.3 (5.3)	7	9.4	5.5 (3.2)	138.5 (19.3)	75.9 (10.6)	1 - 548 (32.3%) 2 - 0 (0%) 3 - 719 (42.4%) 4 - 429 (25.3%)	69 (4.1%)	3.9 (1.6)	47 (2.8%)	1 (0)
Scazufca et al (2008)[69]	**São Paulo Ageing & Health Study (SPAH)**	Mixed, Brazilian	72.1 (6.2)	39.20%	2.5 (3)	2	4.1	1.8 (0.9)	146 (25.9)	85.9 (13.6)	1 - 355 (19.9%) 2 - 0 (0%) 3 - 1074 (60.2%) 4 - 356 (19.9%)	0 (0%)	0 (0)	37 (2.1%)	2 (0)
Lobo et al (2005)[70]	**Zaragoza Dementia Depression Project (ZARADEMP)**	White, Spanish	73.9 (9.3)	42.90%	7.1 (3.8)	3	6.7	2.9 (2.1)	141.3 (18.7)	79.1 (11.2)	1 - 122 (6.9%) 2 - 0 (0%) 3 - 1397 (79.2%) 4 - 245 (13.9%)	87 (2%)	2.2 (1.2)	50 (1.1%)	2.1 (1.2)
	Total		72.1 (7.5)	41%	8.3 (5.3)			4.2 (3.9)	137.8 (21)	79.9 (11.2)	1 - 7822 (35.9%) 2 - 866 (4%) 3 - 11043 (50.7%) 4 - 2058 (9.4%)	1415 (4.5%)	4.2 (3.3)	681 (2.2%)	4.1 (3.6)

Table 1: Summary Table of racial groups, demographics at baseline and dementia rates of the 14 studies included in COSMIC after exclusions. The Indianapolis-Ibadan Study consisted of two separate cohorts (one in Africa and one in the USA), hence they are classified as separate studies.

[a]Classes for HT/AHT status 1 – No history of hypertension and not taking antihypertensives ("Healthy controls"); 2 – No history of hypertension but taking antihypertensives("uncertain hypertension"); 3 – History of hypertension and taking antihypertensives ("treated hypertension"); 4 – History of hypertension and not taking antihypertensives ("untreated hypertension").

HT/AHT Status and Dementia risk						
Alzheimer's Dementia						
	HR (95%CI)	**P**	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**
	Main Analysis (n = 19251, nevent = 615)		**Fully Adjusted Analysis (n = 7610, nevent = 295)**		**Restricting to >5 years FU (n = 4707, nevent = 151)**	
Treated hypertension (comp "healthy controls")	0.961 (0.801, 1.152)	0.6644	0.853 (0.653, 1.113)	0.2411	1.115 (0.771, 1.612)	0.5618
Untreated hypertension (comp "healthy controls")	1.363 (1.013, 1.832)	**0.0406**	1.705 (1.114, 2.609)	**0.014**	1.467 (0.841, 2.56)	0.1768
Untreated hypertension (comp Treated hypertension)	1.418 (1.075, 1.872)	**0.0135**	1.999 (1.318, 3.032)	**0.0011**	1.316 (0.779, 2.223)	0.3051
Non-Alzheimer's Dementia						
	Main Analysis (n = 18975, nevent = 414)		**Fully Adjusted Analysis (n = 7645, nevent = 200)**		**Restricting to >5 years FU (n = 4704, nevent = 89)**	
Treated hypertension (comp "healthy controls")	1.285 (1.029, 1.604)	**0.0267**	1.256 (0.915, 1.724)	0.158	1.561 (0.984, 2.477)	0.0588
Untreated hypertension (comp "healthy controls")	1.693 (1.193, 2.403)	**0.0032**	1.389 (0.755, 2.558)	0.2909	1.202 (0.53, 2.724)	0.6594
Untreated hypertension (comp Treated hypertension)	1.318 (0.953, 1.822)	0.0949	1.106 (0.608, 2.013)	0.741	0.77 (0.347, 1.706)	0.5197
Baseline BP and Dementia risk						
Alzheimer's Dementia						
	Main Analysis (n = 25457, nevent = 905)		**Fully Adjusted (n = 9251, nevent = 333)**		**Restricting to >5 years FU (n = 7182, nevent = 294)**	
SBP (mmHg)		0.4234		0.8655		0.7029
100	1.007 (0.752, 1.35)		1.09 (0.697, 1.704)		0.997 (0.703, 1.416)	
120	1.073 (0.947, 1.214)		0.981 (0.854, 1.127)		0.981 (0.904, 1.064)	
140	0.986 (0.924, 1.052)		1.023 (0.943, 1.111)		1.047 (0.976, 1.124)	
160	0.912 (0.777, 1.07)		1.012 (0.809, 1.265)		1.021 (0.899, 1.16)	
180	0.921 (0.81, 1.048)		0.863 (0.627, 1.189)		0.862 (0.722, 1.029)	
DBP (mmHg)		0.2217		0.9985		0.8592
60	1.001 (0.809, 1.239)		0.979 (0.688, 1.394)		1.098 (0.799, 1.51)	
70	1.095 (1, 1.2)		0.989 (0.879, 1.113)		1.004 (0.901, 1.12)	
80	0.99 (0.956, 1.024)		1.005 (0.931, 1.084)		1.007 (0.967, 1.049)	
90	0.907 (0.823, 0.999)		1.012 (0.884, 1.159)		1.003 (0.888, 1.133)	
100	0.975 (0.819, 1.16)		1.003 (0.549, 1.831)		0.906 (0.635, 1.291)	
Non-Alzheimer's Dementia						
	Main Analysis (n = 25531, nevent = 531)		**Fully Adjusted (n = 9310, nevent = 272)**		**Restricting to >5 years FU (n = 7181, nevent = 143)**	
SBP (mmHg)		0.3136		0.6522		0.3293
100	1.114 (0.798, 1.555)		1.232 (0.772, 1.968)		1.079 (0.488, 2.384)	
120	0.908 (0.838, 0.985)		0.994 (0.878, 1.125)		0.899 (0.783, 1.033)	
140	1.004 (0.941, 1.072)		0.949 (0.861, 1.046)		0.989 (0.83, 1.18)	
160	1.137 (1.024, 1.262)		1.024 (0.847, 1.239)		1.176 (0.96, 1.441)	
180	1.12 (0.969, 1.295)		1.172 (0.952, 1.442)		1.344 (1.149, 1.572)	
DBP (mmHg)		0.1922		0.4589		**0.0227**
60	1.045 (0.789, 1.385)		1.044 (0.686, 1.588)		1.813 (1.159, 2.838)	
70	0.965 (0.866, 1.076)		0.969 (0.833, 1.128)		0.98 (0.826, 1.162)	
80	0.954 (0.89, 1.022)		0.954 (0.855, 1.063)		0.86 (0.75, 0.985)	
90	1.038 (0.923, 1.166)		1.049 (0.893, 1.232)		1.045 (0.863, 1.266)	
100	1.229 (0.968, 1.561)		1.295 (0.962, 1.743)		1.348 (1.01, 1.8)	

Table 2: Summary of Cox Proportional Hazards Models examining relationship between HT/AHT status, baseline BP and both AD and non-AD risk. The models were all adjusted for Age, Age^2, Sex, Education and Racial group and a random effect term for study. There were 12 studies included in the main analysis for HT/AHT status (CLAS, EAS, EPIDEMCA, ESPRIT, H70, HELIAD, Invece.Ab, KLOSCAD, PATH, SALSA, SPAH, and ZARADEMP). There were 7 studies included in the fully adjusted analysis for HT/AHT status (EAS, EPIDEMCA, ESPRIT, Invece.Ab, KLOSCAD, PATH and SALSA). The fully adjusted analysis included additional covariates of

BMI, smoking status, history of hypercholesterolaemia and diabetes. There were 9 studies included in the restricted >5 year follow up analysis for HT/AHT status (CLAS, EAS, ESPRIT, H70, HELIAD, KLOSCAD, PATH, SALSA, and ZARADEMP). For the main analysis of the measures of baseline BP there were 14 studies included (CLAS, EAS, EPIDEMCA, ESPRIT, H70, HELIAD, Indianapolis-Ibadan, Invece.Ab, KLOSCAD, LEILA, PATH, SALSA, SPAH, and ZARADEMP). There were 7 studies included in the fully adjusted model for baseline BP (EAS, EPIDEMCA, ESPRIT, Invece.Ab, KLOSCAD, PATH and SALSA,). There were 11 studies included in the >5 year follow up analysis for baseline BP (CLAS, EAS, ESPRIT, H70, HELIAD, Indianapolis-Ibadan, KLOSCAD, LEILA, PATH, SALSA, and ZARADEMP). P-values for the baseline BP natural splines were computed by comparing the model fit of the model with and without the natural splines terms.

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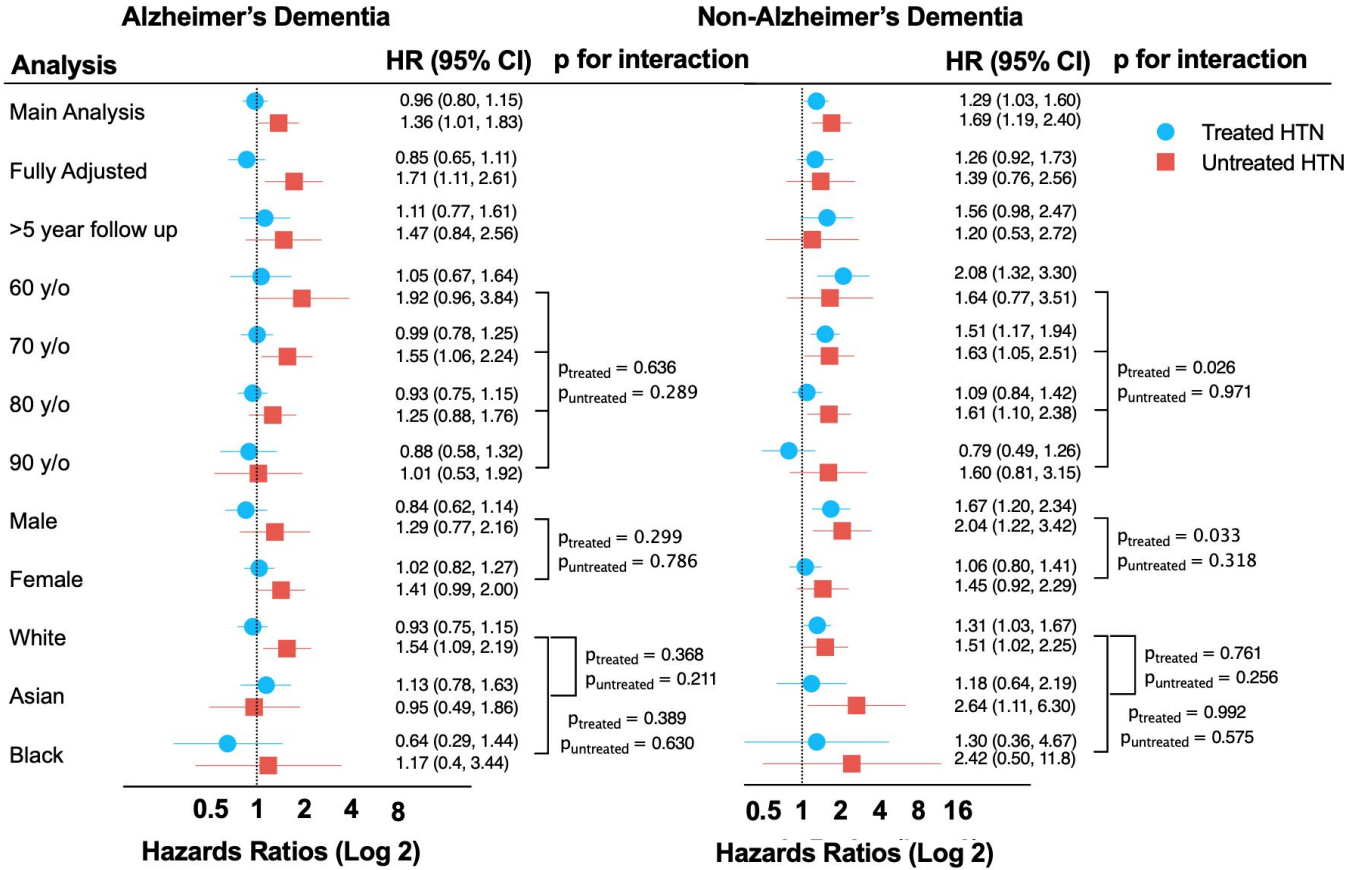
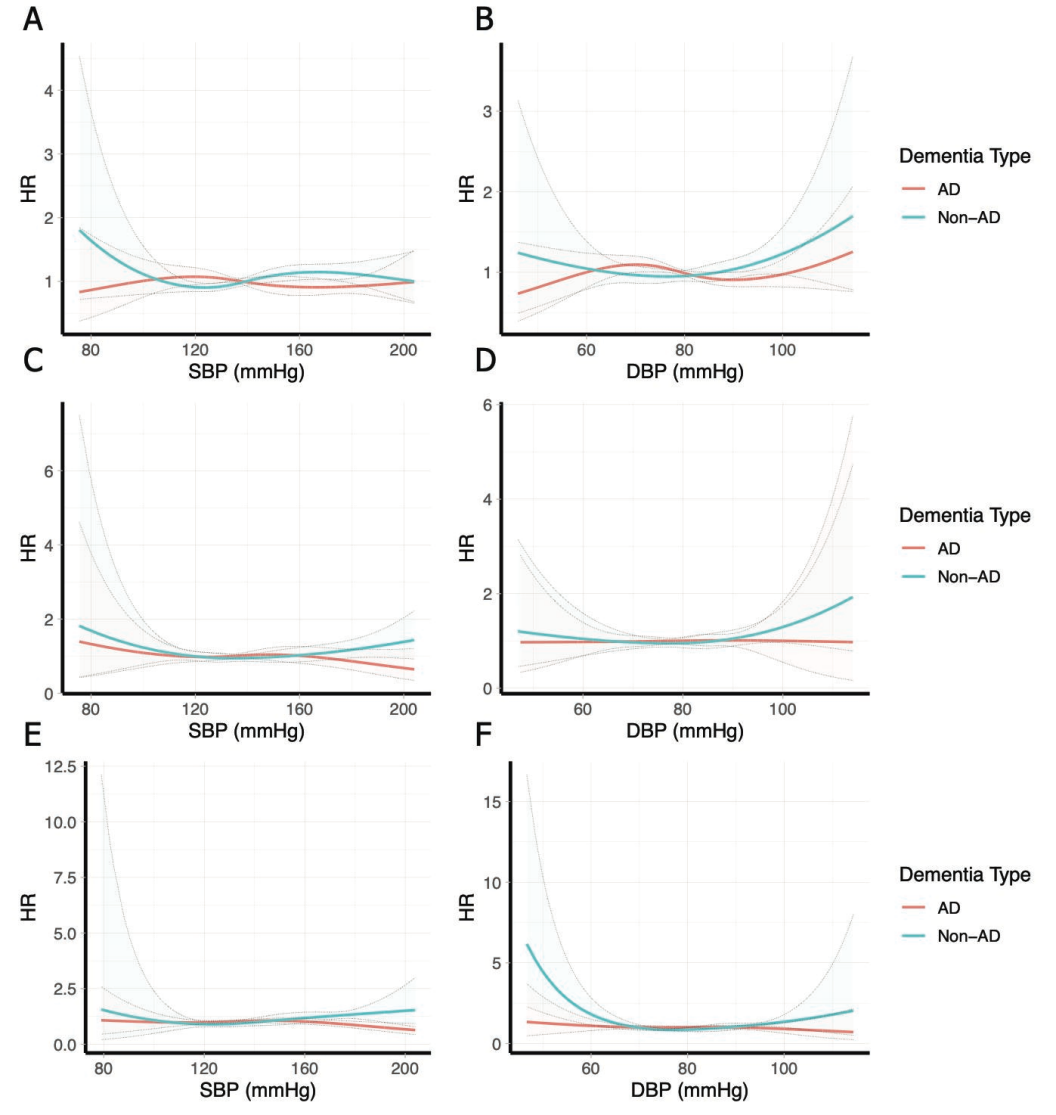
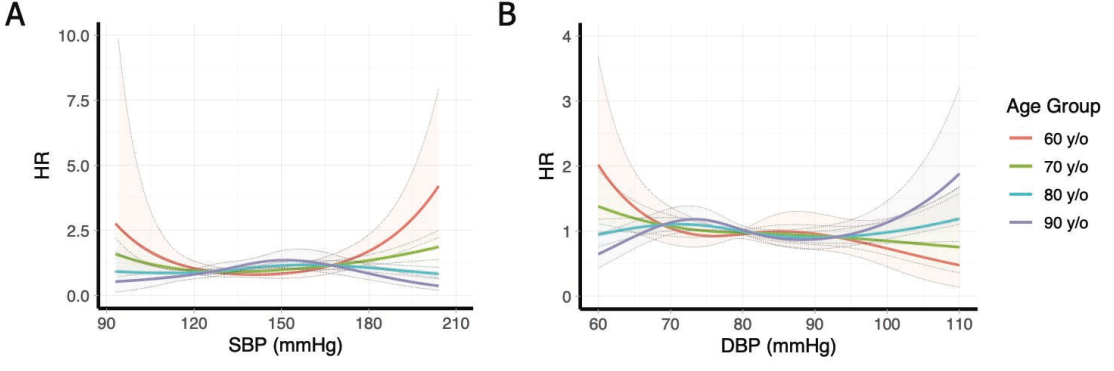

Alzheimer's Dementia
Non-Alzheimer's Dementia
Analysis
HR (95% CI)
p for interaction
HR (95% CI)
p for interaction
Treated HTN
Untreated HTN
Main Analysis
0.96 (0.80, 1.15)
1.36 (1.01, 1.83)
1.29 (1.03, 1.60)
1.69 (1.19, 2.40)
Fully Adjusted
0.85 (0.65, 1.11)
1.71 (1.11, 2.61)
1.26 (0.92, 1.73)
1.39 (0.76, 2.56)
>5 year follow up
1.11 (0.77, 1.61)
1.47 (0.84, 2.56)
1.56 (0.98, 2.47)
1.20 (0.53, 2.72)
60 y/o
1.05 (0.67, 1.64)
1.92 (0.96, 3.84)
2.08 (1.32, 3.30)
1.64 (0.77, 3.51)
70 y/o
0.99 (0.78, 1.25)
1.55 (1.06, 2.24)
1.51 (1.17, 1.94)
1.63 (1.05, 2.51)
80 y/o
0.93 (0.75, 1.15)
1.25 (0.88, 1.76)
1.09 (0.84, 1.42)
1.61 (1.10, 2.38)
90 y/o
0.88 (0.58, 1.32)
1.01 (0.53, 1.92)
0.79 (0.49, 1.26)
1.60 (0.81, 3.15)
$p_{treated} = 0.636$
$p_{untreated} = 0.289$
$p_{treated} = 0.026$
$p_{untreated} = 0.971$
Male
0.84 (0.62, 1.14)
1.29 (0.77, 2.16)
1.67 (1.20, 2.34)
2.04 (1.22, 3.42)
Female
1.02 (0.82, 1.27)
1.41 (0.99, 2.00)
1.06 (0.80, 1.41)
1.45 (0.92, 2.29)
$p_{treated} = 0.299$
$p_{untreated} = 0.786$
$p_{treated} = 0.033$
$p_{untreated} = 0.318$
White
0.93 (0.75, 1.15)
1.54 (1.09, 2.19)
1.31 (1.03, 1.67)
1.51 (1.02, 2.25)
Asian
1.13 (0.78, 1.63)
0.95 (0.49, 1.86)
1.18 (0.64, 2.19)
2.64 (1.11, 6.30)
Black
0.64 (0.29, 1.44)
1.17 (0.4, 3.44)
1.30 (0.36, 4.67)
2.42 (0.50, 11.8)
$p_{treated} = 0.368$
$p_{untreated} = 0.211$
$p_{treated} = 0.389$
$p_{untreated} = 0.630$
$p_{treated} = 0.761$
$p_{untreated} = 0.256$
$p_{treated} = 0.992$
$p_{untreated} = 0.575$
0.5 1 2 4 8
0.5 1 2 4 8 16
Hazards Ratios (Log 2)
Hazards Ratios (Log 2)


A
B
C
D
E
F
HR
SBP (mmHg)
DBP (mmHg)
Dementia Type
AD
Non–AD


A
10.0
7.5
5.0
2.5
0.0
HR
90
120
150
180
210
SBP (mmHg)
B
4
3
2
1
0
HR
60
70
80
90
100
110
DBP (mmHg)
Age Group
60 y/o
70 y/o
80 y/o
90 y/o