Blood Pressure, Pulse Pressure, and Antihypertensive Treatment: Association with Cognitive Decline and Dementia in Elderly Mexican-Americans

by

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INTRODUCTION

1.1 Introduction and Specific Aims

Hypertension, cognitive impairment, and dementia are significant public health problems in the United States (US) and worldwide. Hypertension, one of the most common health problems in adults, affects approximately 65 million individuals in the US in 1999-2000 with a prevalence of 31.3% (1). The prevalence of systolic hypertension is directly proportional to age (2). Among people age 65 years and over in the US, more than half had isolated systolic or combined systolic-diastolic hypertension (2). It is estimated that 48% of hypertensive patients aged 25 or older in the US are either unaware of or untreated for their condition (3).

There will be a dramatic increase in persons with dementia worldwide in the next 30 years: it is estimated that 24.3 million people worldwide had dementia in 2001 and the number of people affected is expected to double every 20 years to 81.1 million by 2040 (4). The prevalence of dementia increases rapidly with advanced age: it is estimated to be below 1% in individuals aged 60–64 years, and doubles every 5 years to exceed 30% in people aged 85 years or older in North American and the US (4).

There is evidence to support a biological relationship between hypertension and cognitive impairment and dementia (5-15). In addition to elevated systolic and diastolic blood pressure, declining or low diastolic blood pressure may also be a risk factor for cognitive impairment and dementia in older age groups (14, 16-21). However, epidemiological studies investigating the relationship between hypertension and lower diastolic blood pressure, and cognitive decline in the elderly have provided inconsistent results (16, 19, 22-32).

The effects of hypertension on cognitive impairment may be modified by age (33). As the difference between systolic and diastolic blood pressure changes with age, it has been suggested that pulse pressure (defined as systolic blood pressure minus diastolic

blood pressure) may provide important information about the effects of blood pressure on cognitive outcomes in the elderly(34-35). Few population-based studies, however, have examined the relationship between pulse pressure in late life and cognitive decline (34).

Randomized clinical trials have shown that antihypertensive treatment produces significant reductions in stroke and cardiovascular risk (36), which have been linked to greater risk of developing dementia (14, 37-44). Longitudinal observational studies and clinical trials examining the association between antihypertensive therapy and dementia, however, do not consistently support the protective effect of antihypertensive treatment on the development of dementia (45-51).

The Sacramento Area Latino Study on Aging (SALSA), a 6-year follow-up study, provided a unique opportunity to assess the impact of blood pressure, pulse pressure, and antihypertensive treatment over time on decline in cognitive function and dementia risk in an older population of Mexican Americans. The Hispanic population is the fastest growing and largest minority population in the US, accounting for one-half of the nations' growth during 2000-2006 (52). The Hispanic population is youthful with approximately 7% of individuals aged 60 and older (52). Mexican Americans, the largest subgroup of Hispanic Americans, make up approximately two-thirds of US Hispanics (52). About 3 million Mexican American adults had hypertension in 1999 to 2000, with prevalence of 29% similar to non-Hispanic white adults (1). The prevalence of dementia in this population was about 5% among those aged 60 and older and 31% among those aged 85 and older, similar to that in non-Hispanic Whites. It is likely that aging in this population will lead to an increase of the prevalence of both conditions in coming years. In addition, studies have shown that Mexican Americans had increased risk of stroke and better post-stroke survival as compared with non-Hispanic Whites (53-54). Higher prevalence of stroke, diabetes and central obesity, lower socio-economic status, poorer access to health cares among Mexican Americans as compared with non-Hispanic Whites present a great challenge to manage these risk factors associated with cognitive impairment (54-56).

This study is the first to focus on the relationship between blood pressure, pulse pressure and antihypertensive treatment to cognitive decline and dementia incidence in the elderly Mexican American population. The data from this study provide a unique

opportunity to better understand the relationship between hypertension and cognition in elderly Mexican-Americans. They may help to identify potentially modifiable risk factors for cognitive decline and dementia and to evaluate the usefulness of the treatment options to these risk factors.

The overall objective of this study is to assess the association between systolic and diastolic blood pressure and pulse pressure with cognitive decline in an elderly Mexican-American population, and to examine the effect of antihypertensive treatment on the incidence of dementia or CIND (clinically impaired but not demented) among elderly Mexican-American hypertensive patients, using a population-based cohort study design. Specific aims and hypotheses are:

Aim 1: To assess the association of baseline and time-dependent systolic and diastolic blood pressure with decline in cognitive function over 6 years of follow-up among older Mexican Americans.

***Hypothesis** 1:* Higher baseline and time-dependent systolic blood pressure are associated with greater increase in errors in the Modified Mini-Mental State Examination (3MSE) and greater decline in the Spanish English Verbal Learning Test (SEVLT) scores over time.

***Hypothesis** 2:* Higher baseline and time-dependent diastolic blood pressure are associated with greater decline in errors in 3MSE and greater increase in SEVLT scores over time.

Aim 2: To test the association of baseline and time-dependent pulse pressure with decline in cognitive function over 6 years of follow-up among older Mexican Americans.

Hypothesis: Higher baseline and time-dependent pulse pressure are associated with greater increase in errors in 3MSE and greater decline in SEVLT scores over time.

Aim 3: To evaluate the association of time-varying antihypertensive treatment with incidence of dementia/CIND over 6 years of follow-up among older Mexican American hypertensive patients*.

Hypothesis: Hypertensive patients receiving antihypertensive therapy over time have a lower incidence of dementia/CIND, compared to untreated hypertensive patients.

* Hypertensive is defined as a systolic blood pressure >=140 mm Hg, or diastolic blood pressure >=90 mmHg, or evidence of treatment with any antihypertensive medication during the study period.

1.2 Background

1.2.1. Blood Pressure, Pulse Pressure, and Hypertension

Blood pressure is determined by cardiac output and peripheral vascular resistance. Systolic blood pressure, which is the peak pressure in the arteries, represents the ejection of blood into the aorta during ventricular systole (57). It is largely determined by stroke volume, the elastic properties of aorta, and the velocity of ejection. Diastolic blood pressure refers to the lowest pressure in the arterial system during diastole. Diastolic blood pressure rises when peripheral vascular resistance increases (57). Blood pressure changes with age. Although the precise mechanism is not understood, the contributing factors of aging to increased blood pressure may include arterial stiffness, atherosclerosis, decreased functional efficiency of the heart, age-related changes in hormone profiles, and salt-sensitivity among older people etc. In some non-industrialized countries, blood pressure is less likely to increase as people age. This difference may be explained by differences in diet and stress, among other things (58).

Burt et al. indicate that the relation between blood pressure and age is rather complex: Systolic blood pressure increases with age for men and women, while diastolic blood pressure rises up to the age of 50-59 years and then begins to decline thereafter for both genders (Figure 1.1, 59). Thus, the difference between systolic and diastolic blood pressure (defined as pulse pressure), increases steeply with age in the elderly population. Increasing evidence suggests that high pulse pressure in the elderly is a marker of increased artery stiffness and widespread atherosclerosis (20-21, 60-61). Elevated pulse pressure is also recognized as an enhanced risk for cardiovascular events (2)

Hypertension, defined by American Heart Association, refers to blood pressure reading of >=140 mm Hg systolic and/or >=90 mm Hg diastolic or any treatment for hypertension (57, 59). For people who are not taking antihypertensive medication, a blood pressure reading of <120 mm Hg systolic and <80 mm Hg diastolic is categorized as “normal” whereas a blood pressure reading of 120-139 mm Hg systolic and/or 80-89 mm Hg diastolic is categorized as “pre-hypertension” (57, 59). The classification of

hypertension for those who are not on antihypertensive treatment consists of two stages: stage 1: blood pressure reading of 140-159 mm Hg systolic and/or 90-99 mm Hg diastolic; and stage 2: blood pressure reading of >=160 mm Hg systolic and/or >=100 mm Hg diastolic (57, 59). Prevalence of systolic hypertension is directly proportional to advancing age (2). It is estimated that more than half of Americans over age 65 years had isolated systolic or combined systolic-diastolic hypertension while fewer than 10% of individuals in this age group had diastolic hypertension in 2005 (2). Hypertension is a well-known independent risk factor for cardiovascular disease, stroke, and renal failure (2).

1.2.2. Antihypertensive Treatment

Several antihypertensive agents are available for treating high blood pressure. The National High Blood Pressure Education Program (NHBPEP) recommended that most patients should use thiazide-type diuretics as their initial therapy for high blood pressure (62). Other first line treatments may include other diuretics, ACEs, ARBs, ß-blockers, calcium channel blockers, or combination (2, 62). Randomized trials have shown that blood pressure lowering produces significant reductions in stroke and cardiovascular risk (36). It has been reported that a decrease of 10-mm Hg in systolic blood pressure or 5-mm Hg in diastolic blood pressure may lead to a risk reduction of 50% to 60% of stroke death and 40% to 50% of death due to cardiovascular disease or other vascular causes (63).

The basic pharmacological mechanisms of the commonly used antihypertensive drug classes are briefly summarized as follows (64): Thiazide-type diuretics, acting on late distal tubule of kidney, help body get rid of extra sodium and fluid. As blood vessels hold less fluid, the volume of blood circulating through the body decreases, which lowers blood pressure. Angiotensin-converting enzyme (ACE) inhibitors lower blood pressure by blocking the production of angiotensin II, a chemical that constricts blood vessels, which in turn makes it easier for blood to flow through the vessels. By blocking the action of angiotensin II, Angiotensin II receptor blockers (ARBs) relax and widen blood vessels, which lowers blood pressure. Both ACE inhibitor and ARBs also increase the release of sodium and water into the urine, which also lowers blood pressure. Beta blockers block the effects of adrenaline (or hormone epinephrine) and lower the amount

of blood the heart pumps out with each beat, which in turn reduces blood pressure. Beta blockers also help improve blood flow by relaxing and widening blood vessels. Calcium channel blockers, by blocking calcium from entering cells of the heart and blood vessel walls, prevent blood vessels from constricting, which lowers blood pressure.

1.2.3. Cognitive Decline

Cognition refers to a range of complex functions of the human mind including learning, concentrating, thinking, perceiving, reasoning, organizing, remembering, and using language, etc (65). Cognitive decline can be aging-related or disease-related. In the National Health and Retirement Study, Plassman et al. found that about 22% of participants aged 71 and over had cognitive impairment that did not reach the threshold for dementia. They estimated that 5.4 million elderly aged 71 and over in the US in 2002 had cognitive impairment without dementia (66). In a study examining the relationship of mild cognitive impairment in different cognitive domains and incident Alzheimer's disease, Aggarwal et al. reported that episodic memory impairment is associated with a substantial and persistent elevation in risk of developing Alzheimer's disease compared to impairment in other cognitive systems such as semantic memory, working memory, perceptual memory, and visuospatial ability (67).

The 3MSE and SEVLT are two validated cognitive exams widely used to screen for cognitive impairment or dementia (68-69). The 3MSE is a measure of global cognitive function that covers a broad range of cognitive abilities including episodic memory, semantic memory, working memory, perceptual memory, and visuospatial ability. This 100 point test also includes orientation to time and space, registration, attention and concentration, recall and delayed recall, verbal fluency and abstract verbal reasoning, visual construction etc. (68). The SEVLT is a delayed word list recall test with five 15-word trials (69) interrupted by a distracter list. As a test of short term verbal recall, it consists of five semantic categories with examples of vegetables, drinks, kitchen utensils, reading materials, and fruit (69). The test score is usually computed as the total number of words recalled after the distracter list.

1.2.4. Dementia

Dementia is characterized by a range of impairment in intellectual and mental abilities that include progressive decline in memory, spatial disorientation and other cognitive abilities (70-72). Dementia has become increasingly prevalent as the population ages.

The most common form of dementia is Alzheimer's disease (AD), accounting for 50% to 70% of all cases (70-71, 73-74). Clinical characteristics of AD include memory loss and cognitive impairment, confusion, mood alterations, and language deterioration. The presence of neuritic plaques and neurofibrillary tangles is the hallmark of neuropathology of AD (75). β-amyloid peptide aggregates in the brain to form extracellular plaques, while tau protein becomes abnormally hyperphosphorylated and aggregates to form intracellular tangles. Both plaques and tangles are present mainly in brain regions involved in learning and memory and emotional behaviours, such as the entorhinal cortex, hippocampus, basal forebrain and amygdale (76). These regions are atrophied as a result of degeneration of synapses and death of neurons.

The second most common form of dementia is vascular dementia (VaD), accounting for about 15%-25% of all cases (70). VaD may result from small and large brain infarcts (eg, strokes), or from subclinical brain pathology such as diffuse subcortical white matter disease (77-78). The primary etiologic element in VaD is ischemia, but the subsequent dementia progression involves a neurodegenerative process very similar to that seen in AD (76, 79)

AD and VaD often coexist and share many risk factors and clinical features (71, 79). For example, studies suggest that the apolipoprotein E4 allele, which is a risk factor for AD, is also associated with VaD; while hypertension, which is a risk factor for VaD, is also associated with AD (80-82). This is termed 'mixed dementia'. Neuropathological studies reported that coexisting vascular pathology occurs in 24%-28% of AD cases (82). Other, less common, forms of dementia include dementia with Lewy Bodies, Pick's Disease etc. There are some relatively rare forms of dementia that are a result of infectious diseases and vitamin B12 deficiency.

Diagnostic and Statistical Manual of Mental Disorder, 4th edition (DSM-IV) criteria are used to diagnose dementia (83). Briefly, the diagnostic criteria include: (i) the

development of multiple cognitive deficits should be manifested by both memory impairment and at least one of the following: aphasia, apraxia, agnosia, disturbances in executive functioning; (ii) the cognitive impairments must be severe enough to cause impairment in social and occupational functioning; (iii) the decline must represent a decline from a previously higher level of functioning; and (iv) the diagnosis of dementia should not be made if the cognitive deficits occur exclusively during the course of a delirium.

Epidemiological studies have classified participants in aging and dementia studies into 3 groups: demented, not demented, and CIND (55, 84). CIND is a clinical syndrome consisting of measurable or evident decline in memory or other cognitive abilities with little effect on day-to-day functioning that does not meet the criteria for dementia as defined by Diagnostic and Statistical Manual of Mental Disorder, 4th edition (85). CIND is diagnosed if the subject does not meet DSM-IV criteria for dementia but has clinically significant impairment in more than one cognitive domain (56).

1.3 Biological Plausibility

1.3.1 Hypertension, Stroke and Cognitive Impairment

Hypertension increases vascular wall tension by decreasing the elasticity of vessels, increasing resistance, and reducing responsiveness to changes in tissue demand (5-7). This pathological process contributes to atherosclerosis. Several studies have reported that atherosclerosis is associated with cognitive impairment and subsequent AD and VaD (8). There are several possible mechanisms by which hypertension might directly lead to cognitive impairment: (i) Ischemic stroke resulting from hypertension increases the risk of dementia (8-9); (ii) Hypertension may cause cerebrovascular damage, such as white matter lesions and multiple small infarcts (10) which contribute to cognitive impairment and dementia, in particular (but not only) VaD (11); (iii) Chronic hypertension leads to vessel wall pathology such as atherosclerosis and arteriolosclerosis, which further induces an insufficient cerebral blood flow and ischemia (12-13). These pathological vessel changes are associated with cognitive dysfunction (12); (iv) Endothelia dysfunction and NO deficiency induced by oxidative stress and inflammatory responses due to longstanding hypertension are involved with the mechanisms of vascular disorders and AD (86-88). . In addition, neuro-pathological studies suggest that

persons with hypertension have increased neurofibrillary tangles and brain atrophy, linking directly the blood pressure and AD (14-15).

There is increasing evidence that stroke is a strong risk factor for AD, vascular and mixed (AD and VaD) forms of dementia (14, 37-44). Studies of the risk factors for stroke have shown that hypertension is a leading contributor to stroke and that the level of blood pressure is directly associated with the risk of stroke (89). People who have hypertension are 4 to 6 times more likely to have stroke (90). Over time, atherosclerosis and hardening of the large arteries induced by hypertension would lead to blockage and weakening of the walls of small blood vessels in the brain, causing ischemic stroke due to clogging of blood vessels, and/or hemorrhagic stroke due to rupture of blood vessels in the brain.

1.3.2 Low Blood Pressure and Cognitive Impairment

Studies have shown that cerebral hypo-perfusion due to lower blood pressure, particularly low diastolic blood pressure in late life, may also play a role in the development of cerebrovascular insufficiency (17-18, 20). Evidence indicates that cerebral hypoperfusion appears to precede the neurodegenerative pathological changes (14), thus, it is likely that low blood pressure may initiate or accelerate disease processes leading to AD and dementia (14, 17, 91). Alternatively, studies suggest that low diastolic blood pressure may be an indicator of increased large arterial stiffness and widespread atherosclerosis in elderly people (20-21, 92). Low diastolic blood pressure resulted from the vessel wall pathology or decrease in cerebral blood flow may give rise to ischemic hypoxia that is linked with cognitive decline and dementia in very elderly populations (31).

1.3.3 Pulse Pressure and Cognitive Impairment

Pulse pressure rises steeply after approximately 60 years of age (59). It is positively associated with arterial stiffness and atherosclerosis (20-21, 60-61, 93), and therefore, it has been linked to an increased risk of cardiovascular diseases including stroke (94-98), which are also risk factors for cognitive dysfunction and dementia (99-102). Oxidative stress and inflammatory responses induced by arterial stiffness are involved with the mechanisms of vascular disorders and AD (87-88). In addition,

clinically silent cerebrovascular lesions, cerebral microcirculation damage, cerebral hypoperfusion, and other vessel pathology resulting from higher pulse pressure appear to predispose individuals to the development of cognitive impairment and subsequent dementia (34-35, 88, 103). Lower pulse pressure most likely contributes to diminished cognitive function and dementia through cerebral hypofusion (35).

1.3.4 Antihypertensive Treatment and Dementia

The precise mechanisms for potential effects of antihypertensive therapy on dementia are not fully understood. Through blood pressure reduction, antihypertensive drugs may lower the risk of progressing into dementia by correcting the underlying blood pressure related mechanisms, such as hypertension induced stroke, cerebrovascular damage, and cerebral hypofusion, and the atherosclerotic process. The non-blood pressure related effects are mediated by mechanisms other than blood pressure reduction. For example, calcium channel blockers prevent calcium influx that may cause neuronal death due to release of intracellular enzymes (47).

1.4 Epidemiological and Clinical Studies

1.4.1 Blood Pressure and Cognitive Decline

Longitudinal studies have been conducted to examine the relationship between blood pressure in midlife and/or late life and decline in cognitive function. The results of these studies are mixed and depend on the age when the blood pressure is measured, length and frequency of follow-up, study population, method of blood pressure collection, and outcome assessments used.

Longitudinal observational studies that investigated midlife blood pressure in relation to late-life cognition decline consistently reported that high blood pressure in midlife, especially high systolic blood pressure, is associated with poor cognitive performance (35, 104-111). These studies often had 20-30 years of follow-up and most concluded that untreated high blood pressure in midlife was a strong risk factor of cognitive impairment in later life (104-106, 109, 112).

Epidemiological studies investigating the relationship between late-life blood pressure and cognitive decline, however, did not consistently support the notion that elevated blood pressure in later life was related to decline in cognition (16, 19, 22-32).

Three studies reported no association between blood pressure and cognitive decline (19, 26-27); five studies reported an inverse association between blood pressure and cognitive performance (28-32); four studies reported a U-shaped relation of systolic or diastolic blood pressure to cognitive decline (16, 23-25); and one study reported that low systolic blood pressure was associated with cognitive deficit (22).

Among the studies reporting no association, Hebert's biracial longitudinal population study suggested that prevalent use of hypertensive medication at baseline (50%) could be a contributing factor to the null effect (19); Tervo et al in their three-year follow-up study of cognitively healthy elderly subjects found that medicated hypertension was related to decline in cognitive performance as treated hypertension might indicate more severe hypertension (26). Among the studies reporting an inverse association, most had a longer follow-up (e.g. >=5 years), or used the higher cut-off of blood pressure measurement (e.g. systolic blood pressure >=160 mmHg) than those studies reporting null results. In particular, the Cardiovascular Heart Study found an association between higher systolic blood pressure and longitudinal decline in cognitive performance (29), and Population Study in Kuopio demonstrated that untreated hypertensive patients were at the highest risk for cognitive decline over 4 years (28). Of the four studies reporting a U shaped relation, the Baltimore Longitudinal Study of Aging had more than two follow-up visits and found that both low and high systolic and diastolic blood pressure were a threat to cognitive function (16). Both Kungsholmen Project and Baltimore Longitudinal Study of Aging revealed that the effects of high systolic blood pressure on cognitive decline were strongest among people who did not taking hypertensive medication (16, 23).

1.4.2 Pulse Pressure and Cognitive Decline

Few population-based studies have examined the relationship between pulse pressure in late life and decline in cognitive function. As far as we are aware, only one study has specifically investigated this relationship despite the theoretic reasons for its importance (34): Waldstein reported that higher pulse pressure was associated with accelerated decline in cognitive function, in particular, learning, memory, and concentration, over time. In addition, three longitudinal studies examined the association of pulse pressure in mid/late life and dementia or AD and the findings were inconclusive:

In the Kungsholmen project, Qiu et al reported a U-shape relationship between level of pulse pressure and risk of AD and dementia in those aged 75 years and older (35). A community-based cohort study, however, found marginal evidence for the association between high pulse pressure and an increased risk of AD in adults aged 65 years and older (45). One study of midlife pulse pressure and incidence of dementia indicated that pulse pressure was not independently associated with dementia incidence (113).

1.4.3 Antihypertensive Treatment and Dementia

The seven longitudinal observational studies that have investigated the relationship between antihypertensive treatment and development of cognitive impairment/dementia in elderly population have reported mixed results (45-51): The East Boston cohort study (46) and the Canadian Study of Health and Aging (45) reported no association between antihypertensive therapy use and AD, and the Baltimore Longitudinal Study of Aging found no association between the use of calcium channel blockers and AD (47). Among four studies reporting protective effects of antihypertensive medications (48-51), the Kungsholmen project showed that using diuretics, the most commonly used therapy, was associated with a significant reduction of dementia risk (48). The results from the Cache County Study also suggested beneficial effects of diuretic use on AD incidence (51). The Rotterdam study (49) demonstrated a substantial effect of antihypertensive therapy in reducing the risk of dementia and VaD, though the results observed in AD patients did not reach statistical significance. While the majority of studies focused on a predominantly Caucasian population, Murray et al. revealed protective effects of antihypertensive drugs on cognitive function in the first and largest longitudinal study focusing on older African Americans (50).

Four large randomized placebo-controlled clinical trials which evaluated the effects of antihypertensive treatment on development of dementia showed inconsistent results (114-118): The Systolic Hypertension in the Elderly Program (SHEP) found no significant reduction of dementia risk in the group receiving active treatment of diuretics and/or β-blocker compared to placebo (114). However, a re-analysis of the data indicated that differential drop-outs may have biased the cognitive assessment and potentially obscured a protective effect of treatment on dementia and cognitive decline (119). In the Systolic Hypertension in Europe (SYST-EUR) trail, active treatment was a

calcium channel blocker (nitrendipine), combined with an ACE inhibitor (enalapril) and/or a diuretic (hydrochlorothiazide) if necessary (115-116). This trial demonstrated that active treatment reduced the development of dementia in elderly people with isolated systolic hypertension by 50% over 2 years (115). The extended trial, in which all participants from the initial trial continued on active treatment for another 2 years, confirmed the original results that long-term antihypertensive therapy reduced the incidence of dementia by 55% (116). In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), participants were assigned to either active treatment (consisting of ACE inhibitor (perindopril) for all participants, or combined with a diuretics (inadpmide)) or a matching placebo (118). After 4 years of follow up, the risk of dementia was reduced by 34% in patients with recurrent stroke. However, no significant effect from the active treatment on the overall risk of dementia was observed. The Study on Cognition and Prognosis in the Elderly (SCOPE) evaluated the role of antihypertensive therapy in preventing cognitive decline and subsequent dementia among the elderly with mild and moderately raised blood pressure (117). The active treatment consisted of ARB candesartan with open-label active antihypertensive therapy added, as needed. After 3.7 years of follow up, no significant difference in dementia incidence and cognitive decline between active treated group and placebo group was observed. This lack of protective effect may be partially explained by the fact that most patients in the placebo group were treated with other antihypertensive drugs for ethical reasons. In addition, two clinical trials examining the effect of antihypertensive therapy and cognitive decline also offered mixed results: The Heart Outcomes Prevention Evaluation (HOPE) study, reported a 41% reduction of cognitive decline related to stroke, using ACE inhibitors (120) while Medical Research Council's treatment trial (MRC) found no significant risk reduction in dementia or cognitive decline in the active treatment group receiving diuretics and/or β-blocker compared to the placebo group (121).

While some longitudinal studies have suggested protective effect of antihypertensive treatment on development of dementia or Alzheimer's disease, evidence from randomized clinical trials is still limited. Factors that may have contributed to the varied results in both types of studies may include antihypertensive agents, study design,

length and frequency of follow-up, study population, sample size, and duration of treatment.

1.5 Methods

1.5.1 Study Population

Sacramento Area Latino Study of Aging (SALSA) is a longitudinal prospective cohort study designed to examine whether risk factors (diabetes, hypertension, smoking and obesity) increase the risk of dementia, memory loss, functional impairment, and decline in cognitive and physical functioning (55). A detailed description of sampling and recruitment in the SALSA study has been described elsewhere (55). The eligible participants were community-dwelling, non-institutionalized Latinos aged 60 years and older in 1998-1999, who lived in the Sacramento area and San Joaquin Valley in California. At baseline, 1789 people were enrolled in the study, and followed from 1998/99 through 2007. The average length of follow-up was 6.11 years and the maximum length was 9 years. Among the 1789 SALSA participants, 115 had dementia or "cognitively impaired not demented" (CIND) at baseline. The analytical sample included 1674 subjects who had no prevalent dementia or CIND at baseline and had available data for at least baseline measurements.

1.5.2 Overview of Analytical Method and Models in the Study

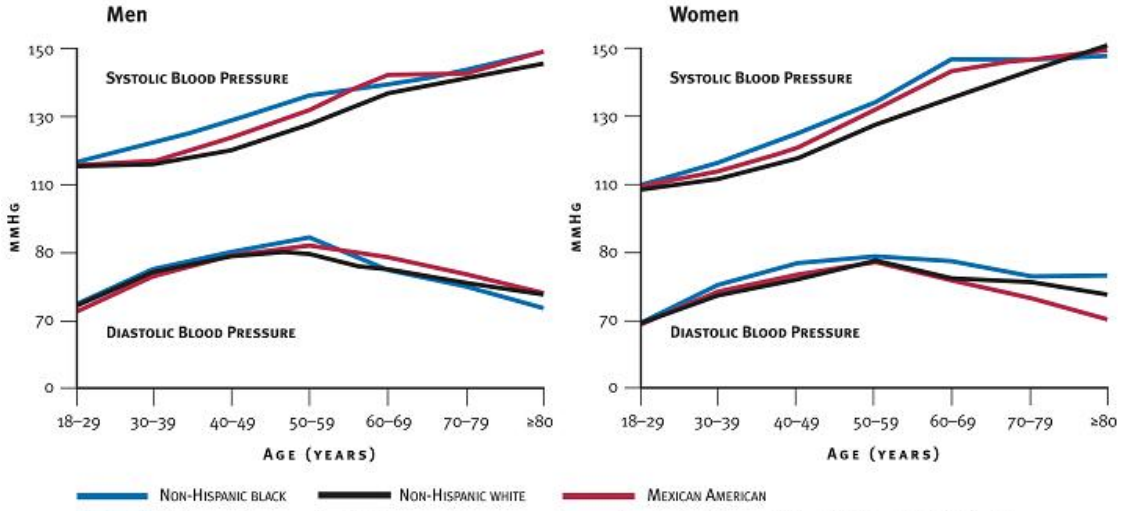
The conceptual models for the 3 aims are presented in Figures 1.2, 1.3, and 1.4. An exposure variable, an outcome variable, potential confounding variables, and effect modifiers for each aim are specified in the conceptual models.

For aim 1 and 2, linear regression models with mixed (fixed and random) effects were used to assess respectively the associations of systolic blood pressure/diastolic blood pressure, or pulse pressure with decline in cognitive function. Such models allowed for the examination of cross-sectional (across all visits or at a given visit) and longitudinal (change over time) relations of an exposure variable (systolic blood pressure, diastolic blood pressure, or pulse pressure) to an outcome variable (errors in 3MSE or SEVLT score). Systolic blood pressure, diastolic blood pressure, or pulse pressure was used as a continuous exposure variable in each of the models while 3MSE or SEVLT performance was used as a continuous outcome variable in each model.

For aim 3, Cox proportional hazard models were applied to test the association between antihypertensive treatment use and risk of dementia/CIND. The use of hypertension medication was included in the COX model as a time varying exposure variable and lagging analysis was performed to reduce ambiguity in the causal ordering (122): time-varying hypertension medication use was measured at the prior visit when dementia/CIND was diagnosed or when last visit was available. It was counted up to and including Visit 5 (out of 6 follow-up visits) with a lag value of hypertension medication use.

1.6 Tables and Figures

Figure 1.1 Systolic and Diastolic Pressure Change with Age.



SBP and DBP by age and race or ethnicity for men and women over 18 years of age in the U.S. population. Data from NHANES III, 1988–1991.

Source: Burt VL, et al. Prevelance of hypertension in the U.S. adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension *1995;25(3):305–13.*

Figure 1.2 Conceptual Causal Model of Systolic or Diastolic Blood Pressure and Cognitive Decline (3MSE or SEVLT) – Aim 1

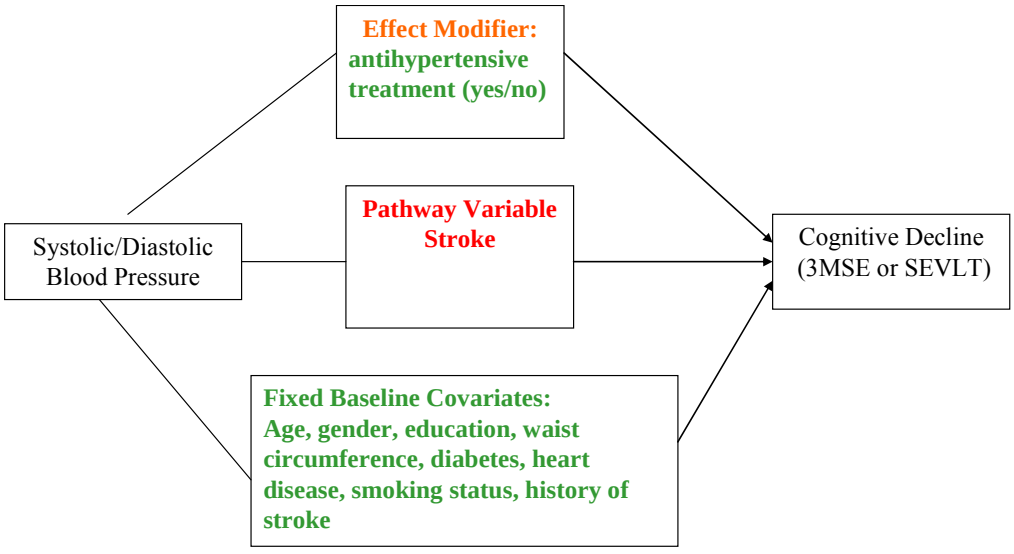


Figure 1.3 Conceptual Causal Model of Pulse Pressure and Cognitive Decline (3MSE or SEVLT) – Aim 2

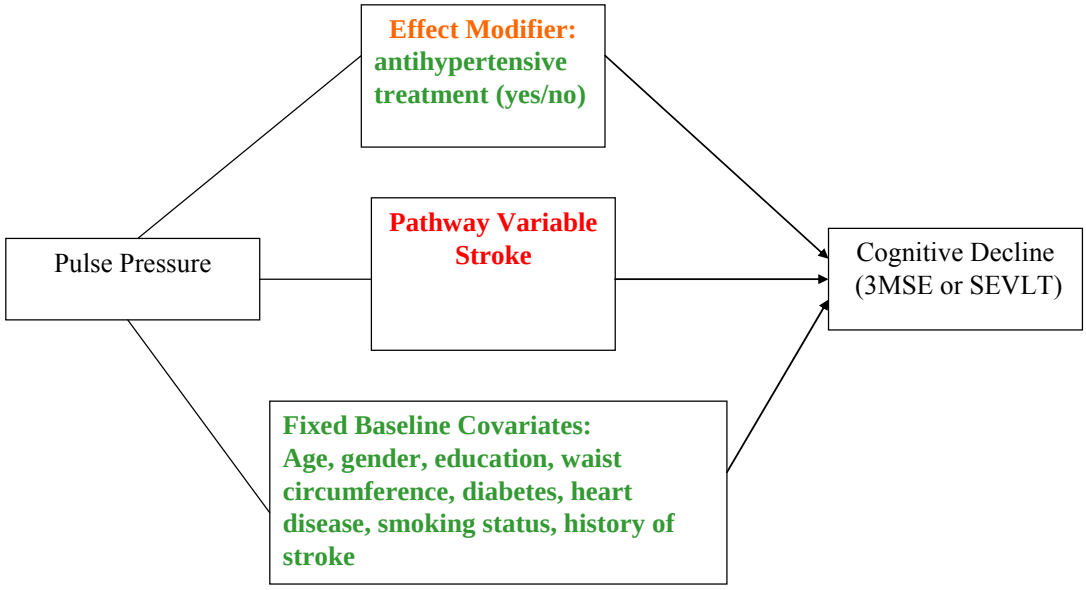
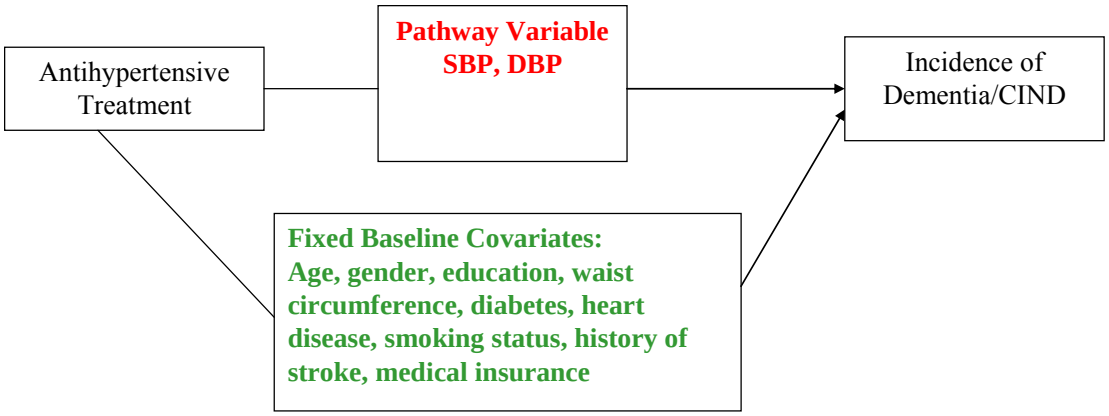


Figure 1.4 Conceptual Causal Model of Antihypertensive Treatment and Incidence of Dementia/CIND – Aim 3



1.7 Appendices

Appendix 1.1. Review of prospective cohort studies of late-life blood pressure in relation to cognitive function change

Author/date	Study	Sample size/age of	BP measure	Outcome measure	Method	Result
Guo et al, 1997	Kungsholmen Project,Sweden	1736 people, age >=75 years, follow-up 3 years	BP measurements in sitting position; if first measurement was abnormal, use the mean of 2nd and 3rd measurements	MMSE score	multiple regression; logistic regression;	U-shape association SBP<=130 mmHg (p<0.05); SBP >=180 mm HG and DBP >=95 mmHg in untreated group is a threat, though p>0.05
Glynn et al, 1999	East Boston cohort study, USA	3657 people, age >=65 years,follow-up 9 years	average of three BP measurements in sitting position;	mental status questionnaire	GEE; Poisson regression	U-shape association error rate of cognitive test associated with BL SBP <130mmHg: 9% (1%, 17%),, with BL SBP >=160 mmHG 7% (0%, 15%)
Tzourio et al, 1999	Epidemiology of Vascular Aging Study, France	1172 people; age 59–71 years, follow-up 4 years	average of two BP measurements	MMSE score	logistic regression	Association of high BP (SPB >=160 mm Hg, DBP >=95 mm Hg) at baseline and cognitive decline at 4-year assessment: 2.8 (1.6, 5.0)
Haan et al,1999	Cardiovascular Health Study, USA	5888 Medicare recipients, age 65 years, followed up to 7 years	average of two BP measurements in sitting position;	3 MSE, digit symbol subtest	GEE	Systolic blood pressure (>158 mm Hg) was associated with decline of 3 MSE score over time (change of score) p<0.001
Bohannon et al,2002	Duke Population Studies of the Elderly, USA	3202 people ,age 65 years, follow-up 3 years	Two- three BP measurements in sitting position and use average the two closest reading	mental status questionnaire	multiple regression	U-shape association of SBP (<110 mm Hg, >165 mm Hg) and cognitive decline for white, not black, p<0.05
Elias et al,2003	Framingham Heart Study, USA	1423 people, age 55–88 years, follow-up 4–6 years	average of two BP measurements in sitting position;	Neuropsychological test battery	multiple regression	for men only (hypertension >=140 mm Hg, high DBP >=90 mm Hg), p<0.05
Reinprecht et al , 2003	Men born in 1914 study	186 men, age 68, follow up 13 years		changes in cognitive function; psychological test battery	multiple regression ANOVA	DBP (tertilles) at age 68 years was inversely related toVerbal. Spatial, and speed performance at age 81
Piguet et al, 2003	Sydney Older Persons Study, Australia	377 people, age >=75; follow up 6 years		Changes in cognitive function; MMSE score	Chi squared statistics, ANOVA	clinically diagnosed hypertension was related to greater decline in MMSE score over 6 years
Hebert et al, 2004	Chicago Health and Aging Project, USA	4284 people, age 65 years, follow-up visit at 3 year and 6 year	average of two BP measurements	immediate and delayed recall; the Symbol Digit Modalities Test, MMSE	linear mixed model	no effect annual change of SBP (p=0.3) or annual change of DBP (p=0.7) on cognitive decline there is nonlinear association of annual change of DBP with cognitive decline (p=0.03)
Tervo et al, 2004	Population study in Kuopio, Finland	806 people, age 60–76 years,follow-up 3 years (1 follow-up visit)	measured at baseline only	cognitive tests	logistic regression	no effect of hypertension (DBP >=95 or SBP >=160): 0.91 (0.49 - 1.69): medicated hypertension: 1.86 (1.05 - 3.29)
Solfrizzi et al, 2004	Longitudinal Study on Aging, Italy	1445 people, age 65–84 years, follow-up 3·5 years	self-reported hypertension, and average of last two of three BP measurements	cognitive tests	Poisson regression	hypertension (SBP >=140 or DBP >=90) 1.44 (0.91-2.35)
Waldstein et al, 2005	Baltimore Longitudinal Study of Aging, USA	847 people; age 60–96 years,followed up to 11 years (1-7 visist)	average of two BP measurements in sitting position	neuropsychological tests	linear mixed model	U shape DBP association with cognitive decline (p <0.05) higher SBP in older individuals (age 80 above) is associated with cognitive decline: p<0.05
Nilsson et al, 2007	Longitudinal study of oldest, Sweden	599 people, age 80-95; follow-up: 4 years	measured after recumbent rest for >=3 min.	MMSE score	logistic regression; linear regression	low SBP is associated with cognitive deficit, beta (LR)=0.986 (0.976, 0.995)

Appendix: 1.2. Review of prospective cohort studies of late-life pulse pressure in relation to cognitive function change

Author/date	Study	Sample size/age of sample Follow-up	BP measure	Outcome measure	Method	Result
Qiu et al, 2003	Kungsholmen Project,Sweden	1270 dementia free subjects, age >=75 years, mean follow-up 4.7 years	BP measurements in sitting position; mean of two sitting measurements	Dementia: DSM III-R; AD: NINCDS-ADRDA;	Cox proportional model	U shape PP association with AD and all dementia: people with high PP (>84) had RR=1.4(1.0, 2.0) for AD and RR=1.3 (0.9, 1.7) for dementia; people with low PP (<70) had RR=1.7 (1.2, 2.3) for AD and RR=1.4 (1.0, 1.9) for dementia, compared with those median tertile PP (70-84)
Morris et al, 2001	East Boston Study	634 subjects free-AD; age >=65; follow-up 4 years	Mean of three sitting measurements	AD: NINCDS-ADRDA	Logistic regression	Marginal association with AD: OR=0.85/10 mm Hg incraese in PP, 0.70-1.02)
Waldstein et al, 2005	Baltimore Longitudinal Study of Aging, USA	1749 people; age>=60; followed up to 14 years (1-8 visist)	average of two BP measurements in sitting position	neuropsychological tests	linear mixed model	High PP was associated with longitudinal decline of several cognitive function tests ($p<0.05$) such as verbal learning, nonverbal memory, working memory et al.

Appendix 1.3. Review of prospective cohort studies of effect of antihypertensive treatment on dementia

Author/ date	Sample size/age of sample	Follow-up time	Outcome measure	Treatment	Method	Result
Guo et al, 1999	1301 dementia free subjects (224 incident cases; age >=75	3 years;	Dementia: DSM III	Diuretics; Antihypertensive drug	Cox proportional model	Risk reduction in dementia or AD using diuretics HR=0.6 (0.4, 0.9) for monotherapy
Morris et al, 2001	634 subjects free-AD; age >=65	4 years	AD: NINCDS-ADRDA	Diuretics and beta-blockers	Logistic regression	No effect of antihypertensive on risk of AD: OR=0.6 (0.68, 2.61)
In't Veld et al, 2001	6,416 non-dementia-free subjects (118 incident cases); aged >=55	2.2 years	Dementia: DSM III-R; AD: NINCDS-ADRDA; VaD: NINDS-AIREN	Antihypertensive drug	Cox proportional model	Risk reduction in VaD HR=0.3 (0.11, 0.99) and dementia RR=0.67 (0.45, 1.00) using any antihypertensive meds
Lindsy et al, 2002	3894 cognitive function normal subjects (194 incident AD cases); age>=65	5 years	AD: NINCDS-ADRDA	Antihypertensive drug	Multivariate logistic regression model	No effect of antihypertensive agents on AD: OR=0.91 (0.64, 1.30)
Murray et al. 20002	1900 subjects (288 cognitive impairment); age>=65	5 years	Dementia and cognitive impairment: DSM III, ADRDA; MMSE	Antihypertensive drug	Logistic regression	Risk reduction in cognitive impairment using any AHT: OR=0.62 (0.45, 0.84)
Yasar et al. 2005	1092 dementia free subjects(115 incident cases); age>=60	Up to 19 years	AD: DSM III-R	CCB	Cox proportional model	No effect of CCB on risk of AD: HR=0.30 (0.07, 1.25)
Khachaturian et al., 2006	3308 subjects (104 incident AD); age >=65	3 years	Dementia: DSM III-R; AD: NINCDS-ADRDA; 3MSE	Antihypertensive drug; diuretics; beta-blockers, CCB, ACE	Cox proportional model	Risk reduction in AD using any AHT HR=0.64 (0.41, 0.98); using diuretics HR=0.57 (0.33, 0.94); using beta blockers HR=0.53 (0.22, 1.09); no effect of CCB: HR=0.86 (0.45, 1.53)

Appendix 1.4. Review of clinical studies of effect of antihypertensive treatment on dementia

Author/date	Study	Sample size/age/follow-up time	Outcome measure	Treatment	Method	Result
Tzourio et al., 2003	The Perindopril Protection Against Recurrent Stroke Study (PROGRESS)	n1=3051 in treated group and n0=3054 in placebo group; mean age=64; subjects with prior stroke or transient ischemic attack; follow up=3.9 years	Dementia (DSM IV); Cognitive decline (>=3 points in MMSE)	Perindopril (ACE); or Perindopril (ACE) + indapamide (diuretics)	logistic regression	34% risk reduction of dementia (3%, 55%) and 45% risk reduction of cognitive decline (21%, 61%) in recurrent stroke patients
Bosch et al., 2002	Heart Outcomes Prevention Evaluation (HOPE)	n1=4645 in treated group and n0=4652 in placebo group; age >=55 with prior history of CVD and diabetes	Cognitive function (study developed criteria and clinical assessment)	Ramipril (ACE)	Cox regression	41% reduction of cognitive decline related to stroke RR=0.59 (0.37 to 0.94);
SHEP Cooperative Research Group, 1991	The Systolic Hypertension in the Elderly Program (SHEP)	n1=2365 in treated group and n0=2371 in placebo group; age >=60 and and SBP (160-219 mm Hg) and DBP<=90; mean follow-up 4.5 years ;	Dementia (cognitive assessment screening and clinical assessement and ajudication)	Chlorthalidone (diuretics) and /or atenolo (beta blocker)	Cox proportional regression	no significant risk reduction in dementia in the group receiving active treatment of diuretics and/or beta-blockers compared to placebo
Prince et al., 1996	Medical Research Council's treatment trial (MRC)	n1=633 diuretcs group, n2=640 bete blocker group; n0=1311 in placebo group; age (65-74) and SBP (160-209 mm Hg) and DBP < 115 mm Hg; mean follow up: 54 months	Cognitive decline (Paired associate learning test - PALT, and Trail making test - TMT)	Atenolol (beta blocker) Hydrochlorothiazide+ amiloride (diuretcs)	ANOVA	no significant risk reduction in cognitive decline in the group receiving active treatment of diuretics and/or beta-blockers compared to placebo
Forette et al., 1998	Systolic Hypertension in Europe trial (SYST-EUR)	n1=2885 in treated group and n0=2737 in placebo group; age >=60 and SBP (160-219 mm Hg) and DBP<=95; median follow-up 2 years	Dementia (DSM III-R and brian imaging);	Calcium channel blocker (nitrendipine), combined with an ACE inhibitor (enalapril) and/or a diuretic (hydrochlorothiazide), if necessary	KM survival estimates and log rank test; COX regression	reduced dementia in elderly people with isolated systolic hypertension by 50% (p<0.05); on average, MMSE score did not change in either group
Forette et al., 1998, 2002	Systolic Hypertension in Europe trial (SYST-EUR) - extended trial	n1=1485 in treated group and n0=1417 in placebo group; age >=60 and SBP (160-219 mm Hg) and DBP<=95; median follow-up 3.9 years	Dementia (DSM III-R and brian imaging);	Calcium channel blocker (nitrendipine), combined with an ACE inhibitor (enalapril) and/or a diuretic (hydrochlorothiazide), if necessary	KM survival estimates and log rank test; COX regression	reduced dementia in elderly people with isolated systolic hypertension by 55% (p<0.001)
Lithell et al., 2003	The Study on Cognition and Prognosis in the Elderly (SCOPE)	n1=2477 in treated group and n0=2460 in placebo group; age (70-89) and SBP (160-179 mmHg) and/or DBP (90-99 mmHg); mean follow-up of 3.7 years	Cognitive function (MMSE); dementia (clinical assessment and adjudication)	ARB candesartan active AHT was extensively used in the control group (84%)	log rank test; ANCOVA	The proportion of patients who had a significant cognitive decline or development dementia were not different in the treated and control groups

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CHAPTER 2

BLOOD PRESSURE AND CHANGE IN COGNITIVE FUNCTION IN ELDERLY MEXICAN AMERICANS: A POPULATION-BASED COHORT STUDY

2.1 Abstract

OBJECTIVE: The association between blood pressure in late life and cognitive decline has not been conclusively established, and existing studies have not included minority populations, such as non-White Hispanic Americans. The objective of this study was to evaluate the relationship between baseline and time-dependent systolic and diastolic blood pressure and decline in cognitive function over 6 years of follow-up among older Mexican Americans living in the Sacramento, California area.

RESEARCH DESIGN AND METHODS: The Sacramento Area Latino Study of Aging (SALSA) was a longitudinal prospective cohort study with an average length of follow-up of 6.11 years. Participants were 1789 community-dwelling, non-institutionalized Latinos aged 60 years and older in 1998-99. A total of 1674 individuals who had no prevalent dementia and were not "cognitively impaired not demented" (CIND) at baseline and had available data for at least baseline measurements were included in the study. Cognitive assessments using "Modified Mini-Mental State Examination (3MSE)" and "Spanish English Verbal Learning Test (SEVLT)", and measurements of systolic and diastolic blood pressure were performed at baseline and at each of the 6 follow-up visits. Linear regression models with mixed (fixed and random) effects were used to assess respectively, the association between systolic blood pressure (SBP), or diastolic blood pressure (DBP) and cognitive function over time.

RESULTS: Longitudinal findings indicated that (i) higher baseline SBP was associated with longitudinal decline in performance on 3MSE and SEVLT: an annual increase of error in 3MSE was 2% (0.8%, 2.7%) and an annual decline in SEVLT score was -0.04 (-0.07, 0) points, for every 20 mm Hg increase of SBP at baseline; (ii) higher concurrent SBP was related to longitudinal decline in 3MSE performance among untreated

participants: an annual increase of error in 3MSE was 2% (0.6%, 3.2%) for every 20 mmHg increase of concurrent SBP (iii) the annual decline was more pronounced among untreated individuals with uncontrolled SBP (>=140 mmHg): an annual increase of error in 3MSE was 4% (1%, 7%) for every 20 mmHg increase of concurrent SBP; (iv) higher concurrent DBP was associated with longitudinal improvement in performance on both tests and among those with low DBP (<=60 mmHg), the annual increase in SEVLT scores was more pronounced: an annual decline of error in 3MSE was -1% (-1.5%, 1%), an annual increase of SEVLT score was 0.06 (0.03, 0.09) points, and an annual increases of SEVLT scores were 0.4 (0.04, 0.67) points among those with DBP <=60 mmHg, for every 11 mmHg increase in concurrent DBP; (iv) higher baseline DBP was associated with longitudinal improvement in SEVLT scores: an annual increase in SEVLT score was approximately 0.04 (0.01, 0.07) points, for every 11 mmHg increase of DBP at baseline. In addition, cross-sectional findings (across all visits) indicated that higher concurrent SBP was associated with higher mean errors in 3MSE and lower mean scores in SEVLT: a mean error in 3MSE increased by 2% (1%, 3.2%) and a mean score in SEVLT declined by -0.1 (-0.16, -0.04) points, for every 20 mmHg increase of SBP. When treated at baseline, individuals with uncontrolled SBP had 7% (2%, 11%) more mean error in 3MSE as compared to those with controlled SBP. All associations found in this study were fairly small in magnitude.

CONCLUSION: Results of 6 years of follow-up data from the SALSA study demonstrated that higher SBP was associated with longitudinal decline in cognitive function after adjusting for potential confounding variables; untreated individuals with uncontrolled SBP were at highest risk of cognitive impairment. In addition, higher DBP was associated with longitudinal improvement in cognitive function after adjusting for potential confounding variables. This longitudinal improvement was more pronounced among individuals with low DBP. These results suggested that proper use of antihypertensive treatment to keep optimal level of SBP and DBP is important to preserve cognitive function in the elderly.

2.2 Introduction

Hypertension is an important independent risk factor for cardiovascular disease, stroke, and renal failure (1). However, the relationship between hypertension and

cognitive function is not well understood. Seven studies that examined midlife blood pressure in relation to late-life cognitive decline consistently demonstrate that midlife high blood pressure, especially high SBP, is associated with poor cognitive performance (2-10). At least 13 epidemiological studies have examined the association between late-life blood pressure and cognitive decline. However, they do not consistently support the finding that elevated blood pressure in later life is a risk factor for cognitive impairment (11-23). Among these 13 studies, three studies reported no association between blood pressure in late life and cognitive decline (16-18); five studies found an inverse association between blood pressure in late life and cognitive performance (19-23); four studies showed a U-shaped relation of SBP or DBP to cognitive decline in elderly (11, 13-15); and one study indicated that low SBP was associated with cognitive deficit in late life (12).

The hypothesis of an association between blood pressure and cognitive function is best examined using longitudinal data, ideally with multiple follow up measurements of blood pressure and cognitive function (11, 14, 16). The objective of this study was to evaluate the relationship between systolic and diastolic blood pressure and decline in cognitive function over 6 years of annual follow-up among older Mexican Americans living in the Sacramento, California area. To our knowledge, this study was the first to focus on older Mexican Americans, a rapidly growing ethnic population in US.

2.3 Methods

Study population: The Sacramento Area Latino Study of Aging (SALSA) was a prospective longitudinal cohort study designed to examine whether risk factors (diabetes, hypertension, smoking and obesity) increase the risk of dementia, memory loss, functional impairment, and decline in cognitive and physical functioning (24). A detailed description of sampling and recruitment in the SALSA study has been provided elsewhere (24). Eligible individuals were community-dwelling, non-institutionalized Latinos aged 60 years and older in 1998, who lived in the Sacramento area and San Joaquin Valley in California. At baseline, 1789 people were enrolled in the study, and followed from 1998/99 through 2007. The average length of follow-up was 6.11 years and the maximum length was 9 years. Among the 1789 SALSA individuals, 115 had dementia or "cognitively impaired not demented" (CIND) at baseline and were excluded

from this analysis. Thus, the analytical sample included 1674 subjects who had no evidence of dementia or CIND at baseline and had available data for at least baseline measurements.

Data collection: All data for this study at baseline and at follow-up visits were collected by interviews and clinical assessments at home visits every 12-15 months from 1998/99 through 2007. To maintain contact and gather updated information about health status and medication use, a brief telephone interview was added midway between each home visit.

Outcome measurement – 3MSE: The Modified Mini-Mental State Examination (3MSE), a cognitive screening test, was performed for each participant at each home visit. The 3MSE is a 100-point cognitive exam that measures global cognitive function by testing orientation to time and space, registration, attention and concentration, recall and delayed recall, verbal fluency and abstract verbal reasoning, visual construction, etc. (25). Higher test scores indicate better global cognitive performance. The test has been validated in Spanish and widely used as a screening instrument for Alzheimer's disease or dementia (12-13, 19, 26-29). The cognitive assessment was performed at baseline and at each of the 6 follow-up visits.

Outcome measurement - SEVLT: The Spanish English Verbal Learning Test (SEVLT) is a delayed word list recall test with five 15-word trials (30) interrupted by a distracter list. It measures short term verbal recall. The test consists of five semantic categories with examples of vegetables, drinks, kitchen utensils, reading materials, and fruit (30). The test scores range from 0 to 15 with higher scores indicating better performance. The cognitive assessment was performed for each participant at baseline, and at each of the 6 follow-up visits.

Exposure measurement – SBP and DBP: At each home visit, SBP and DBP were measured by trained staff using an automatic digital blood pressure monitor (OMRON MODEL: HEM-747 IC) which was calibrated biannually. Two readings of sitting measurements after 5-minutes rest were taken at baseline and at each annual visit and the average of the two measurements was analyzed. The clinical assessment of SBP and DBP was performed at baseline, and at each of the 6 follow-up visits.

Measurement of Covariates: Eight baseline covariates were initially included in the analyses. Age, measured in years, was calculated from date of birth and baseline visit; gender was collected at baseline; education, measured in years, was collected at the baseline visit; waist circumference, measured at the level of maximum indentation over the abdomen, when the participant bended to the side, was taken in centimeters at baseline and converted to inches; smoking status was assessed by asking each participant to select one of three responses that best described their smoking status at the baseline visit: never smoker, former smoker, or current smoker; history of stroke was determined by self-report of a physician's diagnosis at the baseline visit; history of heart disease was determined by self-report of a physician's diagnosis at baseline by answering "yes" to the questions about myocardial infarction, angina pectoris, or congestive heart failure; diabetes was ascertained if a participant met the following 3 criteria at baseline: fasting plasma glucose (FPG) level ≥126 mg/dL (7.0 mmol/L) (fasting was defined as no caloric intake for at least 8 hours), or use of an anti-diabetic medication, or self-report of a doctor's diagnosis of diabetes.

In addition, hypertension medication use at baseline and at each follow-up visit was included in the analyses as a potential modifier. The use of all prescription drugs, including antihypertensive drugs, was ascertained at each participant's home at baseline and at each follow up visit by direct inspection of all medications. The medication information, including the medication code, dose, number of prescribed pills, and average number of pills taken was entered by trained personnel onto a collection form. This information was then updated by telephone every 6-8 months between home visits. Medication codes were assigned using the Centers for Disease Control (CDC) Ambulatory Care Drug Database System (31). Antihypertensive drugs included all medications potentially used for lowering blood pressure.

Statistical analyses: Linear regression models with mixed (fixed and random) effects were used to assess respectively, the association between SBP or DBP and cognitive function. Such models allowed for the examination of cross-sectional (across all visits or at a given visit) and longitudinal (change over time) relationship between exposure variable (SBP or DBP) and cognitive function. The cross-sectional relationship were indicated by BP main effects or interactions between blood pressure and each of the

covariates, while the longitudinal relationship were represented by interactions between blood pressure and time interval (or three-way interaction of blood pressure, hypertensive medication use, and time interval). The predictors of interest, such as SBP or DBP were entered into the models as fixed effects. Random effects were modeled by taking into account the variability in initial level of 3MSE or SEVLT performance and rate of change between subjects. The initial graphical analysis and univariate test indicated that 3MSE data were skewed since most individuals had high 3MSE scores at baseline. In order to normalize the data, a natural log transformation of error in 3MSE (101-3MSE) was used as the dependent variable in all models. An annual change in 3MSE error, given a standard deviation (SD) unit increase in BP, was calculated as follows: $[(101\text{-}3MSE_2) / (101\text{-}3MSE_1)] = \exp [ß * SD]$, where ß is coefficient of interaction between BP and time. A preliminary graphic analysis and univariate test indicated that SEVLT data had a normal distribution and was directly used as the dependent variable in all models.

Two sets of mixed models were applied to examine the association between systolic blood pressure or diastolic blood pressure and error in 3MSE, or SEVLT score: the first set was baseline models assessing the association of each baseline exposure variable and error in 3MSE or SEVLT score; and the second set was time dependent models assessing the association of each time-dependent exposure variable and error in 3MSE, or SEVLT score. For each set of models, both unadjusted and adjusted effects of the exposure variable were examined. Prior knowledge of biological plausibility as well as the change-in-estimate criterion was applied to determine covariates to be included in the final models. Six baseline covariates (age [years], gender, education [years], diabetes [yes/no], history of stroke [yes/no], and smoking status [current smoker/former smoker/never smoker]) were used for adjustment in the final models.

Use of hypertension medication was examined at baseline or over time to assess whether it would moderate the longitudinal relationship between concurrent SBP and 3MSE or SEVLT performance. This was done by adding three-way interaction of medication use with SBP*time in the model. Stratified analyses were performed if statistical interaction was present. Tests for a nonlinear relationship between SBP or DBP and cognitive function were conducted by including squared blood pressure terms in the models.

All models were fitted using SAS PROC MIXED. Only statistically significant interaction terms ($p<0.05$) were included in the final models.

2.4 Results

Demographic characteristics: The characteristics of individuals at baseline are presented in Table 2.1. The majority of individuals were female (58%), mean age was70 years, and mean education was 7.3 years. Current smokers comprised 11% of the study population. Baseline prevalence of comorbidities included diabetes (32%), stroke (8%) and heart disease (14%). On average, SBP at baseline in the study population was relatively high (138 mmHg), approaching the upper end of the pre-hypertension range, while average DBP at baseline was normal (76 mmHg). There was a high prevalence of hypertension at baseline (61%). Although less than half of individuals used antihypertensive medication at baseline (42%), usage increased over time and reached 52% at the 3rd visit and 70% at the 6th visit. Most of individuals scored well in the 3MSE test at baseline with a median score of 89 out of 100. Average score of SEVLT at baseline was 8.6 out of 15.

Systolic Blood Pressure

Baseline SBP and cognitive function tests: Table 2.2 presents the relationship between baseline SBP and performance in cognitive function tests. Baseline models indicated that unadjusted SBP at baseline was significantly associated with a higher mean error in 3MSE and lower mean score in SEVLT (model I and III). For every standard deviation (SD=20 mmHg) increase of SBP at baseline, mean error in 3MSE increased by 14%, while mean score in SEVLT decreased by 0.4 points. The relationship between SBP to the actual 3MSE performance is presented in Figure 2.1. Subjects with a lower initial level of 3MSE had a larger drop of 3MSE scores due to the increase in SBP at baseline. There was a longitudinal relationship between baseline SBP and error in 3MSE and SEVLT score after adjusting for all covariates (model II and IV). SBP at baseline was statistically significantly related to change in 3MSE and SEVLT performance over time: an annual increase of error in 3MSE was approximately 2% and an annual decline in SEVLT score was approximately 0.04 points, for every 20 mm Hg increase of SBP at baseline.

Time-dependent SBP and cognitive function tests: Table 2.3 presents the relationship between time-dependent SBP and performance in cognitive function tests. While unadjusted SBP was associated with lower mean score in SEVLT (model I), no association between unadjusted SBP and mean error in 3MSE was observed (model III). There was no longitudinal relationship between time-dependent SBP and performance in 3MSE or SEVLT after adjusting for all covariates (Model II and IV). Cross-sectional findings (across all 7 visits) revealed that adjusted SBP was marginally significantly associated with a higher mean error in 3MSE, and statistically significantly associated with a lower mean score in SEVLT: for every one SD (20 mmHg) increase of SBP, a mean error in 3MSE increased by 2%, and mean score in SEVLT declined by 0.1 points.

Moderation of hypertension medication to the association of SBP and cognitive function: First, the results showed that the relationship between adjusted SBP and change in 3MSE error over time was dependent on concurrent hypertension medication use (Table 2.4). Separate analyses by concurrent medication use indicated that adjusted SBP was statistically significantly related to change in 3MSE error among those who did not take hypertension medication over time: for every 20 mm Hg increase of concurrent SBP, the annual increase of error in 3MSE was approximately 2% among those non-medicated users. Furthermore, among subjects with uncontrolled SBP (>=140 mm Hg) and not taking hypertension medication over time, the annual increase of error in 3MSE was approximately 4% for every 20 mm Hg increase of concurrent SBP (Table 2.4).

There was little evidence that the relationship between concurrent SBP to change in SEVLT was moderated by concurrent hypertensive medication use (P=0.1). Although separate analyses stratified by concurrent medication use did not indicate that concurrent SBP was statistically significantly related to change in SEVLT among either concurrent hypertension medication users or non-users, the direction and size of the relationship are noteworthy: concurrent hypertension medication users might improve SEVLT scores over time while SEVLT performance among non-medicated individuals may be impaired over time, for the same amount of increase in concurrent SBP. Furthermore, it appeared that non-medicated individuals with uncontrolled SBP (>=140 mmHg) tended to have a larger decline in SEVLT scores over time.

Second, the cross-sectional relationship (across all 7 visits) between time-dependent SBP to cognitive function tests was examined to determine if it was dependent on hypertension medication use. Results showed that only the relationship between adjusted SBP and mean 3MSE error was moderated by baseline hypertension medication use after adjusting for all covariates (Table 2.5). In a separate analysis stratified by baseline hypertension medication use, time-dependent SBP was statistically significantly associated with higher mean error in 3MSE among baseline medication users. Within this group of baseline medication users, those who had uncontrolled SBP (>=140 mm Hg) had 7% more mean error in 3MSE as compared to those who had controlled SBP (Table 2.5).

Nonlinear relationship between SBP and cognitive function tests: Nonlinear effects of SBP were examined by including squared SBP in the baseline and time-dependent models. However, there was no evidence of a statistically significant curvilinear relation to either cognitive function test.

Diastolic Blood Pressure

Baseline DBP and cognitive function tests: Table 2.6 presents the relationship between baseline diastolic blood pressure and cognitive function tests. Baseline models indicated that unadjusted DBP at baseline was not associated with mean error in 3MSE and mean score in SEVLT (model I and III), and there was no evidence of a longitudinal relationship between adjusted DBP at baseline and mean error in 3MSE (Model II). However, DBP at baseline was statistically significantly associated with change in SEVLT performance over time after adjusting for all covariates (model IV): for every SD (11 mmHg) increase of DBP at baseline, an annual increase in SEVLT score was approximately 0.04 points.

Time-dependent DBP and cognitive function tests: Adjusted time-dependent models demonstrated a longitudinal relationship between time-dependent DBP and change in 3MSE error and SEVLT score (model II and IV): the annual decline of error in 3MSE was approximately 1% and the annual increase of SEVLT score was approximately 0.06 points, for every SD (11 mm Hg) increase in concurrent DBP (Table 2.7). Figure 2.2 displays how time-dependent DBP influenced mean error in 3MSE at

each visit during the study period from baseline to the 6th year. The study period was also extended beyond year 6 to illustrate the longitudinal impact of concurrent DBP on 3MSE performance over a longer period of time. At baseline, the mean error in 3MSE increased by 5% for every 11 mmHg increase of DBP. With a change in rate (slope) of approximately -1%, the size of the increase in mean error in 3MSE at each follow-up visit attenuated over the study period. After the 6th year, however, the mean error in 3MSE declined at each following visit for every 11 mmHg increase of DBP. Similarly, Figure 2.3 demonstrates how time-dependent DBP influenced SEVLT performance at each visit during the study period from baseline to the 6th year.

Subgroup analyses were also performed to explore if the longitudinal relationship between concurrent DBP and performance in cognitive function tests was stronger among subjects with lower DBP. The restricted analysis revealed that among those with low DBP (<=60 mmHg), the annual increases of SEVLT scores were more pronounced, with approximately 0.4 points per every 11 mmHg increase in concurrent DBP. Although the longitudinal relation to 3MSE error was not statistically significant for those with DBP <=60 mmHg, the magnitude of the inverse relation appeared much larger in this group compare to those with higher DBP.

Moderation of hypertension medication to the association between DBP and cognitive function: There was no interaction between hypertension medication use at baseline or over time with concurrent DBP on change (RX*DBP*time) or mean level (RX*DBP) in 3MSE or SEVLT.

Nonlinear relationship between DBP and cognitive function tests: The nonlinear relationship between DBP and cognitive performance were examined by including squared DBP in both baseline and time-dependent models. There was no statistically significant complex relation to 3MSE performance. There was a marginally significant nonlinear relationship between baseline and concurrent DBP to SEVLT performance in the unadjusted models. However, this nonlinear relationship disappeared after adjustment for potential confounders.

2.5 Discussion

In this community-based longitudinal study of elderly Mexican Americans, we assessed the longitudinal and cross-sectional relationship between SBP and DBP and

cognitive function. Longitudinal findings revealed that higher baseline SBP was associated with longitudinal decline in cognitive performance in both tests, and higher concurrent SBP was related to longitudinal decline in 3MSE performance among untreated individuals. Untreated individuals with uncontrolled SBP were at the highest risk of cognitive decline over time. These data indicated that SBP and DBP displayed a differential relationship with cognitive outcomes in late life. The longitudinal findings revealed that higher concurrent DBP was associated with longitudinal improvement in cognitive performance in both tests, and higher baseline DBP was associated with longitudinal improvement in SEVLT scores. This longitudinal improvement was more pronounced among individuals with low DBP. In addition, cross-sectional findings demonstrated that higher concurrent SBP was associated with lower levels of cognitive performance in both tests, and treated individuals with uncontrolled SBP were more vulnerable to the deleterious effect of high SBP. Additional controlling of baseline SBP and DBP in all time-dependent models did not change our findings.

The results of previous population-based studies of blood pressure and cognitive function have been inconsistent, possibly due to use of different study designs, measurements of cognitive function, timing of blood pressure measurements, and length of follow-up. Among five studies reporting an inverse association between blood pressure in late life and cognitive performance (19-23), the Cardiovascular Health Study, the only study with more than two follow-up visits, found a linear relation between SBP and decline in cognitive function over time. These results are consistent with our finding of an inverse relationship between SBP in the elderly with change in cognitive function over time. The observation that low DBP in late life could be a threat to cognitive function has been documented in two studies (11, 16), although both studies reported a curvilinear relationship between DBP and cognitive performance. Our data suggest a linear relationship between DBP in late-life and change in cognitive function, and adds additional evidence to support of the unfavorable effect of DBP decline over time on cognition in elderly. Tests for nonlinear relation of DBP to cognitive function in this study did not reveal a statistically significant curvilinear relation to either cognitive function test.

Epidemiological studies have demonstrated evidence of a protective role of antihypertensive therapy in preserving cognitive function among elderly: Tzourio et al. reported that untreated hypertensive patients were at the highest risk for cognitive decline over 4 years (19). Waldstein et al. and Guo el al. found that the deleterious effects of high SBP on cognitive decline were strongest among people who did not taking hypertensive medication (11, 13). In addition, clinical trial data from HOPE (The Heart Outcomes Prevention Evaluation), PROGRESS (Perindopril Protection Against Recurrent Stroke Study), and Syst-Eur (Systolic Hypertension in Europe) trial (32-35) showed protective effect of antihypertensive treatment on cognitive decline and development of dementia among systolic hypertensive patients or patients with history of stroke and other vascular diseases. Our results that untreated individuals, and in particular, those with uncontrolled systolic blood pressure, were at highest risk of cognitive decline are consistent with epidemiological studies and clinical trials.

It is noteworthy that all associations found in this study were fairly small in magnitude. This is consistent with results from four studies investigating the relationship between blood pressure in late life and cognitive function (11, 14, 16, 20). These four studies had at least two follow-up visits and applied either GEE or linear mixed model analyses. Our observation of small effect may also be explained, in part, by the fact that the use of hypertension medications was prevalent in this population, which may attenuate the effect of high blood pressure on lower level of cognitive performance.

Potential mechanisms of action by which high systolic blood pressure could lower cognitive performance include ischemic stroke (36-37); cerebrovascular damage such as white matter lesions and multiple small infarcts (38-39); vessel wall pathology such as atherosclerosis and arteriolosclerosis, insufficient cerebral blood flow (40-41); brain atrophy (42-43); and endothelia dysfunction and NO deficiency induced by oxidative stress and inflammatory responses (44-46). The relevant mechanisms of action by which decline in diastolic blood pressure in elderly could negatively affect cognitive performance include cerebral hypo-perfusion, and associated neuron-pathology due to insufficient cerebral perfusion, ischemic hypoxia, and atherosclerosis (28, 42, 47-48). Studies suggest that low diastolic may be an indicator of increased large arterial stiffness and widespread atherosclerosis in elderly people (48-50). It is possible that, over time,

the combination of high systolic blood pressure and low diastolic blood pressure may accelerate the process of cognitive impairment and lead to development of dementia and AD (11).

Important strengths of this analysis include the advantage of a prospective longitudinal design with an average of 6-years follow-up, annual home inspection of medications, in addition to semi-annually phone interviews, annual measurement of blood pressure by trained personnel, and annual measurement of cognitive performance. This study is one of the few that examine blood pressure and cognitive measurements at more than 2 follow-up visits. These factors greatly strengthen measurement reliability and allow for the study of individual change, rather than level of performance at a single point, in cognitive test performance. Thus, these results may provide a more accurate assessment of cognition and its relationship with blood pressure. Limitations of this study include the restriction of the assessment of cognitive function to two tests. It is possible that a broader range of cognitive function testing may provide more definitive results. In addition, there may exist potential residual confounding due to omitted covariates associated with both the exposure and outcome variables. The inclusion of only Mexican American participants in the study may limit the generalization of the study results.

Hypertension and cognitive impairment are significant public health problems. The prevalence of systolic hypertension and cognitive impairment increases substantially with age (1, 51-52). In contrast, diastolic blood pressure rises up to age 50-59 and then starts to drop with age (51). Our findings that higher SBP and lower DBP in elderly were associated with diminished cognitive function over time reinforce the need for and importance of identifying potential modifiable risk factors associated with decline in cognition in the elderly. Future research in this area should include investigating the effect of both high and low blood pressure. Our findings that untreated individuals with uncontrolled systolic blood pressure were at highest risk of cognitive impairments suggest that there is a need to better understand the protective effect of antihypertensive treatment, in particular, the specific class of agents that best preserve cognitive function in late life. Randomized controlled trials will be needed to address these questions.

In addition, this is the first study to focus on the relation of blood pressure and cognitive decline in the elderly Mexican Americans, a young and rapidly growing but understudied ethnic population. It is likely that aging in this population will lead to an increase of the prevalence of hypertension, cognitive impairment, and dementia in coming years. Studies have shown that Mexican Americans had increased risk of stroke and better post-stroke survival as compared with non-Hispanic Whites (53-54). Higher prevalence of stroke, diabetes and central obesity, lower socio-economic status, poorer access to health cares among Mexican Americans as compared with non-Hispanic Whites present a great challenge to manage these risk factors associated with cognitive impairment (24, 54-55). The data from this study provided with a unique opportunity to identify and better understand the potential modifiable risk factors associated with cognitive impairment among elderly Mexican Americans.

2.6 Tables and Figures

Table 2.1 Summary of Baseline Characteristics (a)

Gender [N(%)]	
Male	699 (42)
Female	975 (58)
Age (years)	
Mean (SD)	70 (6.80)
Median (Minimum, Maximum)	69 (59, 98)
Education (Years)	
Mean (SD)	7.3 (5.33)
Median (Minimum, Maximum)	7 (0, 32)
Smoking Status [N(%)]	
Never	762 (46)
Former Smoker	709 (42)
Current Smoker	191 (11)
Missing	12
Waist circumference (inches)	
Mean (SD)	38.19 (5.24)
Median (Minimum, Maximum)	38 (16, 58)
History of Stroke [N(%)]	
Yes	131 (8)
No	1533 (92)
Missing	10
Diabetes [N(%)](b)	
Yes	531 (32)
No	1133 (68)
Missing	10
Heart Disease [N(%)] (c)	
Yes	234 (14)
No	1440 (86)
Systolic Blood Pressure	
Mean (SD)	138 .38(19.30)
Median (Minimum, Maximum)	137 (76, 230)
Diastolic Blood Pressure	
Mean (SD)	76.01 (10.58)
Median (Minimum, Maximum)	76 (34, 119)
Any hypertension drug use [N(%)]	
Yes	696 (42)
No	975 (58)
Missing	3
Hypertension [N(%)](d)	
Yes	1019 (61)
No	517 (31)
Missing	138 (8)
3MSE Score	
Mean (SD)	85.88 (11.56)
Median (Minimum, Maximum)	89 (11, 100)
SEVLT Score	
Mean (SD)	8.6 (2.90)
Median (Minimum, Maximum)	9 (0, 15)

a. Include only the subjects who were dementia/CIND free at baseline
b. Participants were considered to have diabetes if they met any of the following 3 criteria: Fasting plasma glucose (FPG) level >=126 mg/dL (7.0 mmol/L); or use of an antidiabetic medication; or self report of a physician's diagnosis of diabetes.
c. Participants were considered to have heart disease if they had the following 3 medical conditions: MI, angina pectoris, or congestive heart failure.
d. Hypertension was defined as systolic blood pressure >=140 or diastolic blood pressure >=90 or on hypertension medication.

Table 2.2 Relationship between Baseline (BL) Systolic Blood Pressure (SBP) and Cognitive Function Tests

	3MSE (a)		SEVLT (b)	
	Model I	Model II	Model III	Model IV
Parameters	**Unadjusted**	**Adjusted** (c)	**Unadjusted**	**Adjusted** (c)
BL SBP	0.006388****	-0.00048	-0.02222****	-0.00117
(95% CI)	(0.004394, 0.008381)	(-0.00218, 0.001226)	(-0.02852,-0.01592)	(-0.00809, 0.005756)
BL SBP*Time		0.000879****		
(95% CI)		(0.000443, 0.001315)		-0.00201*
				(-0.00366, -0.00035)

**** P value <0.0001; *** P value <0.001; ** P value <0.01; * P value <0.05

a. Dependent variable was defined as natural log of error in measuring 3MSE (ln(101-3MSE)); 3MSE=Modified Mini-Mental State Examination

b. SEVLT (Spanish English Verbal Learning Test) is a delayed word list recall test

c. Adjusted for baseline age, education, gender, diabetes, history of stroke, and smoking status

Table 2.3 Relationship between Time-Dependent (TD) Systolic Blood Pressure (SBP) and Cognitive Function Tests

	3MSE (a)		SEVLT (b)	
	Model I	Model II	Model III	Model IV
Parameters	**Unadjusted**	**Adjusted** (c)	**Unadjusted**	**Adjusted** (c)
TD SBP	0.000765	0.000793* (d)	-0.00815****	-0.00493***
(95% CI)	(-0.00009, 0.001616)	(0, 0.001592)	(-0.01125, -0.00504)	(-0.00794,-0.00192)
TD SBP*Time		0.000203		0.000532
(95% CI)		(-0.00017, 0.000572)		(-0.00089, 0.001958)

**** P value <0.0001; *** P value <0.001; ** P value <0.01; * P value <0.05

a. Dependent variable was defined as natural log of error in measuring 3MSE (ln(101-3MSE))

b. SEVLT (Spanish English Verbal Learning Test) is a delayed word list recall test

c. Adjusted for baseline age, education, gender, diabetes, history of stroke, and smoking status

d. Marginally statistically significant: p value =0.05

Table 2.4 Longitudinal Relationship between Time-Dependent (TD) Systolic Blood Pressure (SBP) and 3MSE Performance (a)

Parameters	Adjusted (b)
Model 1 (c) Longitudinal relation of SBP by moderation of TD hypertension medication use	
TD SBP* Time (95% CI)	-0.00035 (-0.00083, 0.000132)
TD SBP*TD RX Use *Time (95% CI) (d)	0.001351** (0.000575, 0.002127)
Model 2 Among uncontrolled SBP subjects (SBP>=140 mm Hg) who did not take hypertension medication	
TD SBP* Time (95% CI)	0.001861** (0.000517, 0.003204)

**** P value <0.0001; *** P value <0.001; ** P value <0.01; * P value <0.05
a. Dependent variable was defined as natural log of error in measuring 3MSE (ln(101-3MSE))
b. Adjusted for baseline age, education, gender, diabetes, history of stroke, and smoking status
c. Adding three way interaction of SBP*RX*Time to understand if longitudinal effect of time-dependent SBP on 3MSE performance depended on hypertension medication use.
d. Hypertension medication user was reference group

Table 2.5 Cross-Sectional Relationship between Systolic Blood Pressure (SBP) and 3MSE Performance (a)

Parameters	Adjusted (b)
Model 1 (c) Cross-sectional relation of SBP by moderation of hypertension medication use at baseline (BL)	
TD SBP (95% CI)	-0.00016 (-0.00130, 0.000974)
TD SBP* BL RX Use (95% CI) (d)	0.001935* (0.000340, 0.003530)
Model 2 (c) Among BL hypertension medication users	
TD SBP (95% CI) (e)	0.06482** (0.02062, 0.1090)

**** P value <0.0001; *** P value <0.001; ** P value <0.01; * P value <0.05
a. Dependent variable was defined as natural log of error in measuring 3MSE (ln(101-3MSE))
b. Adjusted for baseline age, education, gender, diabetes, history of stroke, and smoking status
c. Longitudinal effect of SBP (SBP*Time) was not statistically significant and not included in the model
d. Non-hypertension medication user was reference group
e. SBP was categorized as two groups: SBP >=140 and SBP <140 mm Hg; SBP<140 was reference group

Table 2.6 Relationship between Baseline (BL) Diastolic Blood Pressure (DBP) and Cognitive Function Tests

	3MSE (a)		SEVLT (b)	
	Model I	Model II	Model III	Model IV
Parameters	**Unadjusted**	**Adjusted** (c)	**Unadjusted**	**Adjusted** (c)
BL DBP	-0.00335	0.001674	0.001778	-0.01874**
(95% CI)	(-0.00703, 0.000333)	(-0.00092, 0.004265)	(-0.00992, 0.01348)	(-0.03150, -0.00598)
BL DBP*Time				
(95% CI)		-0.00062		0.003693*
		(-0.00143, 0.000183)		(0.000635, 0.006752)

**** P value <0.0001; *** P value <0.001; ** P value <0.01; * P value <0.05

a. Dependent variable was defined as natural log of error in measuring 3MSE (ln(101-3MSE))

b. SEVLT (Spanish English Verbal Learning Test) is a delayed word list recall test

c. Adjusted for baseline age, education, gender, diabetes, history of stroke, and smoking status

Table 2.7 Relationship between Time-Dependent (TD) Diastolic Blood Pressure (DBP) and Cognitive Function Tests

	3MSE (a)		SEVLT (b)	
	Model I	Model II	Model III	Model IV
Parameters	**Unadjusted**	**Adjusted** (c)	**Unadjusted**	**Adjusted** (c)
TD DBP	0.001266	0.005119***	-0.01016***	-0.03121****
(95% CI)	(-0.00026, 0.002795)	(0.002357, 0.007882)	(-0.01573, -0.00459)	(-0.04190, -0.02052)
TD DBP*Time				
(95% CI)		-0.00069* (d)		0.005253****
		(-0.00140, 0)		(0.002552, 0.007954)

**** P value <0.0001; *** P value <0.001; ** P value <0.01; * P value <0.05

a. Dependent variable was defined as natural log of error in measuring 3MSE (ln(101-3MSE))

b. SEVLT (Spanish English Verbal Learning Test) is a delayed word list recall test

c. Adjusted for baseline age, education, gender, diabetes, history of stroke, and smoking status

d. Marginally statistically significant: p value =0.05

Figure 2.1 Relationship between Baseline SBP and 3MSE Performance (per 20 mm Hg Increase in SBP at Baseline)

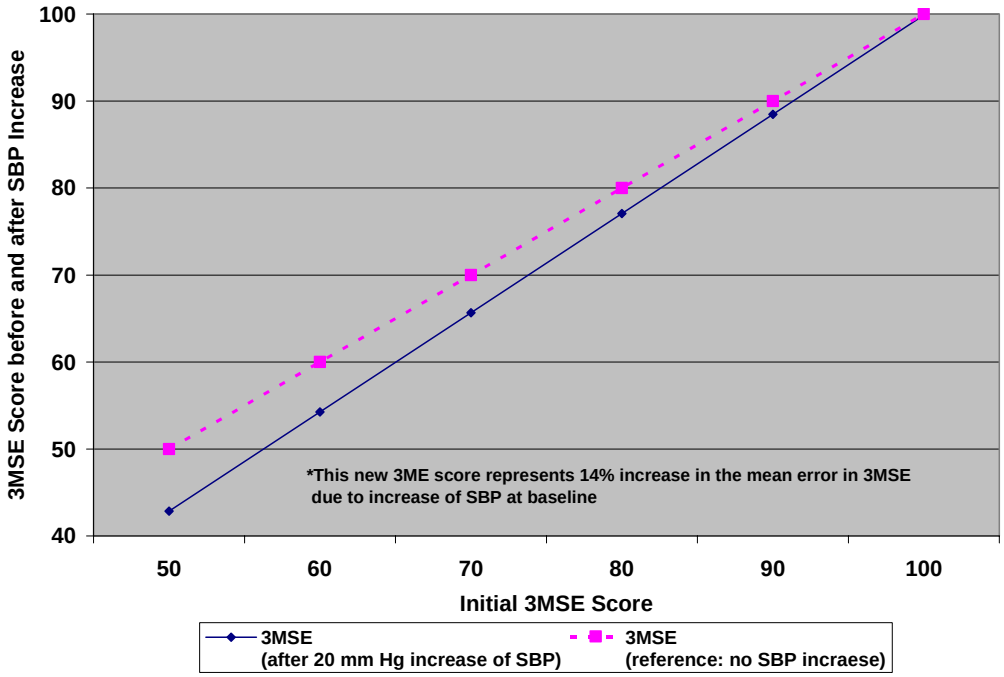


Figure 2.2 Longitudinal and Cross-Sectional Relationship between Concurrent DBP and 3MSE Performance (Per 11 mmHg Increase in Concurrent DBP)*

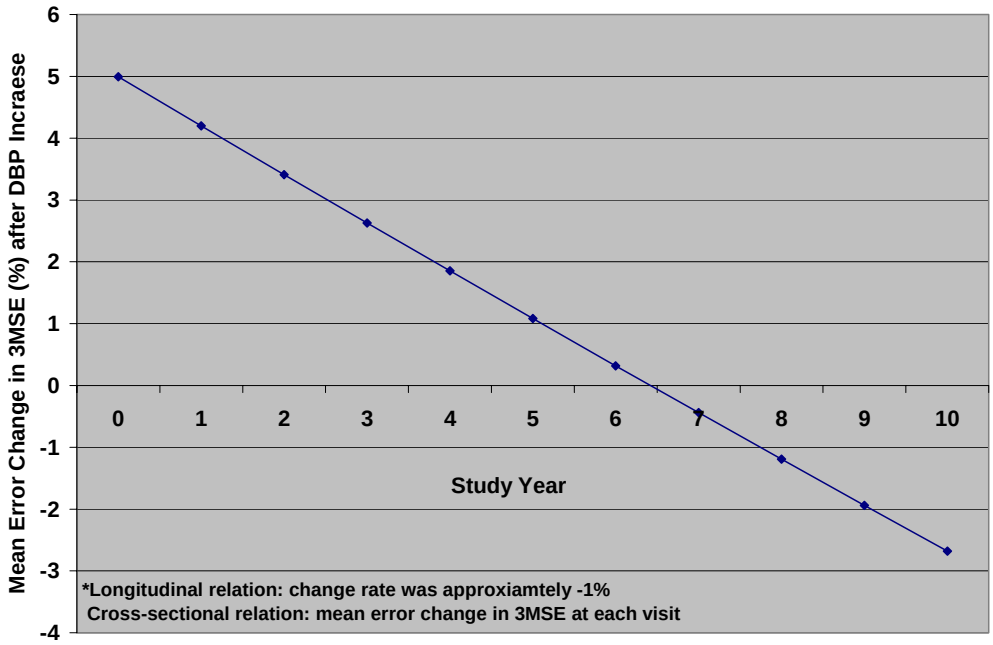
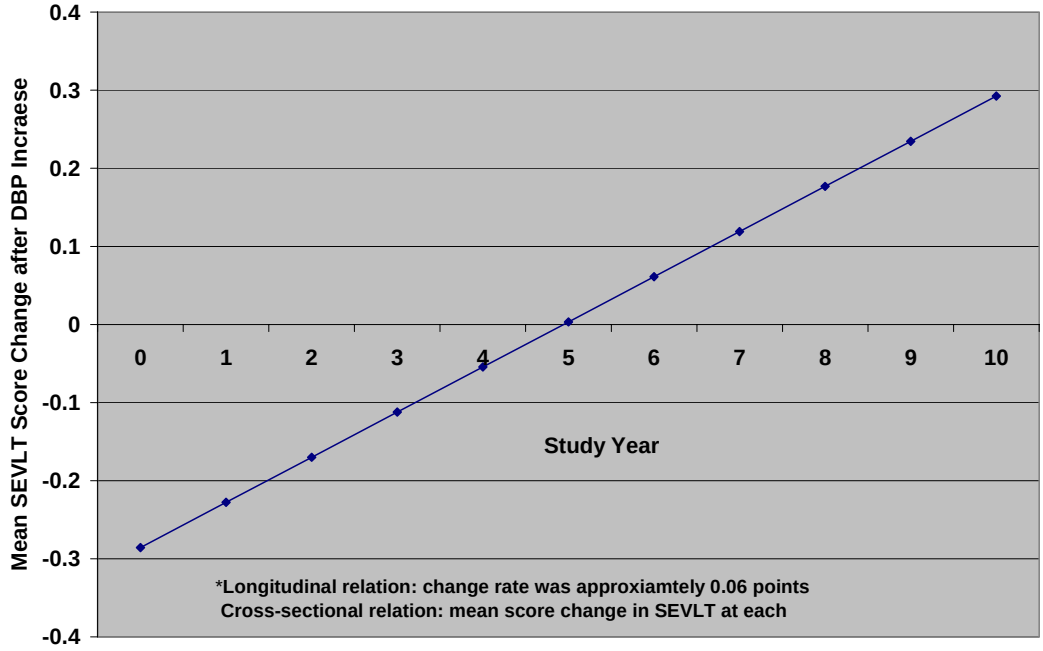


Figure 2.3 Longitudinal and Cross Sectional Relationship between Concurrent DBP and SEVLT Performance (Per 11 mmHg Increase in Concurrent DBP)*



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CHAPTER 3

PULSE PRESSURE AND CHANGE IN COGNITIVE FUNCTION IN ELDERLY MEXICIAN AMERICANS: A POPULATION-BASED COHORT STUDY

3.1 Abstract

OBJECTIVE: Few population-based studies have examined the relationship between pulse pressure in late life and decline in cognitive function. The objective of this study was to test the association between baseline and time-dependent pulse pressure and decline in cognitive function over 6 years of follow-up among older Mexican Americans living in the Sacramento, California area.

RESEARCH DESIGN AND METHODS: The Sacramento Area Latino Study of Aging (SALSA) was a prospective longitudinal cohort study with an average length of follow-up of 6.11 years. Eligible community-dwelling, non-institutionalized Latinos aged 60 years and older in 1998-99 (n=1768) were enrolled in the study, and followed from 1998/99 through 2007. A total of 1674 individuals who had no prevalent dementia and were not "cognitively impaired not demented" (CIND) at baseline and had available data for at least baseline measurements were included in the study. Cognitive assessments using "Modified Mini-Mental State Examination (3MSE)" and "Spanish English Verbal Learning Test (SEVLT)", and measurements of systolic blood pressure and diastolic blood pressure were performed at baseline and at each of the 6 follow-up visits. Pulse pressure was calculated as the difference of systolic and diastolic blood pressure. Linear regression models with mixed (fixed and random) effects were used to assess the association between pulse pressure and cognitive function.

RESULTS: Longitudinal findings indicated that (i) higher baseline pulse pressure was associated with longitudinal decline in both cognitive performance tests: an annual increase of error in 3MSE was 2% (1.4%, 3.1%) and an annual decline of SEVLT score was -0.07 (-0.1, -0.03) points, for every 18 mm Hg increase in PP at baseline; (ii) higher concurrent pulse pressure was associated with longitudinal decline in 3MSE

performance: an annual increase of error in 3MSE was 1% (0.3%, 1.8%) for every 18 mm Hg increase in PP; (iii) higher concurrent pulse pressure was related to longitudinal decline in both tests among untreated participants: an annual increase of error in 3MSE was 2% (0.8%, 3.5%), an annual decline in SEVLT score was -0.06 (-0.11, -0.01) points, for every 18 mm Hg increase in pulse pressure; (iv) the annual decline was more pronounced among untreated individuals with higher pulse pressure (>=70 mm Hg): an annual increase of error in 3MSE was 4.5% (1%, 8.2%) for every 18 mm Hg increase in pulse pressure. In addition, cross-sectional findings (across all visits) indicated a U shaped relationship between concurrent pulse pressure and cognitive performance: both low and high pulse pressure were associated with a higher mean error in 3MSE and lower mean score in SEVLT. All associations found in this study were fairly small in magnitude.

CONCLUSION: Results of 6 years of follow-up data from the SALSA study demonstrated that higher pulse pressure was associated with longitudinal decline in cognitive function after adjusting for potential confounding variables; and untreated individuals with high pulse pressure were at highest risk of cognitive impairments. The results also revealed a U shaped relationship between concurrent pulse pressure with mean errors in 3MSE and mean scores in SEVLT: both low and high pulse pressure were associated with poor cognitive performance. These results suggested an important role of optimal pulse pressure to preserve cognitive function in the elderly.

3.2 Introduction

Increasing evidence suggests that hypertension may contribute to diminished cognitive function (1-14). The effects of hypertension on cognitive impairment, however, may be modified by age as systolic blood pressure increases with age for men and women, while diastolic blood pressure increases up to age 50-59 and then begins to decline with age for both genders (15). The difference between systolic blood pressure and diastolic blood pressure (defined as pulse pressure), thus, increases steeply among older people as they continue to age.

High pulse pressure in the elderly is a marker of increased artery stiffness and widespread atherosclerosis (16-19) that has been linked with a risk of cognitive impairment and dementia. It is therefore possible that higher pulse pressure is associated

with worse cognitive performance in elderly over time. However, few population-based longitudinal studies have examined the effects of the pulse pressure on cognitive decline in the elderly population (20-21). The Baltimore Longitudinal Study reported that higher pulse pressure in late life was associated with accelerated decline in cognitive function, in particular, learning, memory, and concentration, over time (20). In addition, two other epidemiological studies investigated the relationship between pulse pressure and risk of dementia and Alzheimer's disease. Kungsholmen project found a U-shape relation between level of pulse pressure and risk of Alzheimer's disease and dementia in those aged 75 and older (21). The East Boston Study, a community-based cohort study, however, found marginal evidence of the association between high pulse pressure and an increased risk of Alzheimer's disease in adults aged 65 and older (22).

The objective of this study was to assess the association between baseline and time-dependent pulse pressure and decline in cognitive function over 6 years of follow-up among older Mexican Americans living in the Sacramento, California area.

3.3 Methods

Study population: A detailed description of sampling and recruitment in the Sacramento Area Latino Study of Aging (SALSA) has been described elsewhere (23). SALSA was a prospective longitudinal cohort study designed to examine whether risk factors (diabetes, hypertension, smoking and obesity) increase the risk of dementia, memory loss, functional impairment, and decline in cognitive and physical functioning (23). At baseline, a total of 1789 eligible community-dwelling, non-institutionalized Latinos aged 60 years and older, who lived in the Sacramento area and San Joaquin Valley in California, were enrolled in the study and followed from 1998/99 through 2007. The average length of follow-up was 6.11 years and the maximum length was 9 years. Among 1789 SALSA participants, 115 had dementia or "cognitive impairment not demented" (CIND) at baseline and were excluded from this analysis. Thus, the analytical sample included 1674 subjects who had no prevalent dementia or CIND at baseline and had available data for at least baseline measurements.

Outcome measurement – 3MSE and SEVLT: The Modified Mini-Mental State Examination (3MSE) and the Spanish English Verbal Learning Test (SEVLT) were performed for each participant at each home visit and at each of the 6 annual follow-up

visits. The 3MSE is a 100 point cognitive exam that measures global cognitive function by testing orientation to time and space, registration, attention and concentration, recall and delayed recall, verbal fluency and abstract verbal reasoning, visual construction, etc. (24). Higher test scores indicate better global cognitive performance. It has been validated in Spanish and widely used as a screening instrument for Alzheimer's disease or dementia (1, 25-30). The SEVLT is a delayed word list recall test with five 15-word trials (31) interrupted by a distracter list. It measures short term verbal recall. The test consists of five semantic categories with examples of vegetables, drinks, kitchen utensils, reading materials, and fruit (31). The test scores range from 0 to 15 with higher scores indicating better performance.

Exposure measurement – pulse pressure: Pulse pressure was calculated as the difference between systolic and diastolic blood pressure at baseline and at each of the 6 follow-up visits. At baseline and at each of 6 annual visits, systolic and diastolic blood pressures were measured by trained staff using an automatic digital blood pressure monitor (OMRON MODEL: HEM-747 IC) calibrated biannually. Two readings of sitting measurements after a 5-minute rest were taken and the average of the measurements was analyzed.

Measurement of Covariates: A total of eight baseline covariates were included in the initial analyses. Age, measured in years, was calculated from dates of birth and baseline visit; sex and education, measured in years, were collected at the baseline visit; waist circumference, measured at the level of maximum indentation over the abdomen, when the participant bended to the side, was taken in centimeters at baseline and converted to inches; smoking status was assessed by asking each participant to select one of three responses that best described their smoking status at the baseline visit: never smoker, former smoker, or current smoker; history of stroke was determined by self report of a physician's diagnosis at the baseline visit; history of heart disease was determined by self report of a physician's diagnosis at baseline by answering "yes" to the questions about MI, Angina pectoris, or congestive heart failure; diabetes was ascertained if a participant met the following 3 criteria at baseline: fasting plasma glucose (FPG) level ≥126 mg/dL (7.0 mmol/L) (fasting was defined as no caloric intake

for at least 8 hours), or use of an anti-diabetic medication, or self-report of a doctor's diagnosis of diabetes.

In addition, antihypertensive medication use at baseline and over time was included in the analyses as a potential modifier. Antihypertensive drugs included all medications potentially used for lowering blood pressure. The use of antihypertensive drugs was ascertained at each participant's home at baseline and at each follow up visit by direct inspection of all medications. Trained personnel entered the medication information such as medication code, dose, number of prescribed pills, and average number of pills taken onto the collection form. This information was then updated by telephone every 6-8 months between home visits. Medication codes were assigned using the Centers for Disease Control (CDC) Ambulatory Care Drug Database System (32).

Statistical analyses: The association between pulse pressure and cognitive function was assessed by linear regression models with mixed (fixed and random) effects. These models allowed for the examination of both the cross-sectional (across all visits or at a given visit) and longitudinal (change over time) relationships between pulse pressure and cognitive function. The cross-sectional relationship was indicated by pulse pressure main effects or interactions between pulse pressure and each of the covariates, while the longitudinal relationship was represented by interactions between pulse pressure and time interval (or three-way interaction of pulse pressure, hypertensive medication use, and time interval). The predictors of interest such as pulse pressure were entered as fixed effects into the models. Random effects were modeled by taking into account the variability in initial level of 3MSE or SEVLT performance and rates of change between subjects. The initial graphical analysis and a univariate test indicated that 3MSE data was skewed since most participants had high scores in their 3MSE test at baseline. Therefore, a natural log transformation of error in 3MSE (101-3MSE) was used as a dependent variable in all models to normalize the data. A preliminary graphic analysis and a univariate test indicated that SEVLT data had a normal distribution and was directly used as the dependent variable in all models.

Two sets of mixed models were applied to examine the association between pulse pressure and error in 3MSE, or SEVLT score: the first set were baseline models testing the association between baseline pulse pressure and error in 3MSE or SEVLT score; and

the second set were time dependent models assessing the association between time-dependent pulse pressure and error in 3MSE, or SEVLT score. For each set of models, both unadjusted and adjusted effects of pulse pressure were examined. Prior knowledge of biological plausibility as well as the change-in-estimate criterion was applied to determine covariates to be included in the final models. Six baseline covariates including age (years), gender, education (years), diabetes (yes/no), history of stroke (yeas/no), and smoking status (current/former/never smoker) were used for adjustment in the final models.

The moderation effects of hypertension medication used at baseline or over time were tested. Stratified analyses were performed if a statistical interaction was suggested. Nonlinear relationship between pulse pressure and cognitive function was tested by including squared pulse pressure terms in the models. In addition, based on tertile of pulse pressure, a categorical analysis was performed using concurrent pulse pressure as a categorical variable (<54 mm Hg, 54-69 mm Hg, and >=70 mmHg) to examine if there is nonlinear relationship between pulse pressure and cognitive function performance.

All models were fit using SAS PROC MIXED. Only statistically significant interaction terms ($p<0.05$) were included in the final models.

3.4 Results

Demographic characteristics: The characteristics of individuals at baseline are presented in Table 3.1. More than half of the participants were female (58%), mean age was 70 years, and mean education was 7.3 years. Majority of individuals were not current smokers (88%). Baseline prevalence of comorbidities included diabetes (32%), stroke (8%), and heart disease (14%). On average, systolic and diastolic blood pressure at baseline was 138 mm Hg and 76 mm Hg respectively. Mean pulse pressure was 62 mm Hg. Hypertension at baseline was prevalent (61%). Although less than half of individuals used anithypertensive medication at baseline (42%), usage increased over time and reached 52% at the 3rd visit and 70% at the 6th visit. Most of individuals scored well in the 3MSE test at baseline with a median score of 89 out of 100. Average score of SEVLT at baseline was 8.6 out of 15.

Baseline pulse pressure and cognitive function tests: Table 3.2 presents the relationship between baseline pulse pressure and cognitive function tests. Unadjusted

baseline pulse pressure was statistically significantly associated with a higher mean error in 3MSE and lower mean score in SEVLT: for every one standard deviation (SD=18 mm Hg) increase in baseline pulse pressure there was a 17% increase in mean error in 3MSE and 0.5 points drop in mean score in SEVLT (model I and III). There was a longitudinal relationship between baseline pulse pressure and 3MSE and SEVLT performance after adjusting for all covariates (model II and IV): an annual increase of error in 3MSE was approximately 2% and annual decline of SEVLT score was approximately 0.07 points, for every 18 mm Hg increase in pulse pressure at baseline.

The baseline models including higher-order terms for pulse pressure did not demonstrate a statistically significant quadratic relationship with both cognitive function tests.

Time-dependent pulse pressure and cognitive function tests: Table 3.3 presents the relationship between time dependent pulse pressure and cognitive function tests. First, adjusted time-dependent model revealed a cross-sectional relationship between nonlinear pulse pressure and 3MSE performance (model II). Both low and high pulse pressure appeared to be linked to a higher level of predicted errors in 3MSE. Furthermore, Figure 3.1 shows that pulse pressure influenced 3MSE performance differently for people with low and high pulse pressure at baseline: given a 18 mm Hg increase in pulse pressure at baseline, subjects with initial pulse pressure of 30 mm Hg had a 8% decline in mean error in 3MSE, whereas subjects with initial pulse pressure of 100 mm Hg had a 4% increase in mean error in 3MSE.

Second, this nonlinear time-dependent model also revealed a longitudinal relationship between concurrent pulse pressure and change in error in 3MSE: the annual increase of error in 3MSE was approximately 1% for every 18 mm Hg increase in pulse pressure. It should be noted that, while the longitudinal relationship between concurrent pulse pressure and 3MSE performance was linear, the size and direction of the influence of concurrent pulse pressure to 3MSE performance at each visit differed by the initial pulse pressure level of each subject (Figure 3.2), for the same amount of increase in pulse pressure. For example, an 18 mm Hg increase in pulse pressure was beneficial to the 3MSE performance of individuals with an initial level of pulse pressure equal to 30 mm Hg, as mean error in 3MSE declined at each visit; whereas the same amount of increase

in pulse pressure adversely affected the performance of those with an initial level of pulse pressure equal to 80 mm Hg, as mean error in 3MSE increased at each visit. However, over time, the size of change in 3MSE performance favorable to people with low pulse pressure attenuated while the size of the change unfavorable to people with high pulse pressure increased.

Third, in the unadjusted time-dependent model, the concurrent pulse pressure was statistically significantly associated with SEVLT score: for an 18 mm Hg increase in concurrent pulse pressure, mean score in SEVLT dropped by 0.1 points (model III). In the adjusted model, neither cross-sectional nor longitudinal relationship between pulse pressure and the mean score or change in SEVLT was observed (model IV). Nonlinear effects of pulse pressure were tested by including squared pulse pressure in the time-dependent models, but no evidence of a statistically significant complex relationship to SEVLT performance was observed.

Moderation effect of antihypertensive medication on the association of pulse pressure and cognitive function tests: Antihypertensive medication use at baseline and over time was examined to determine if it moderated the cross-sectional and longitudinal relationship between concurrent pulse pressure and cognitive function tests. The results indicated that the influence of concurrent pulse pressure on changes in 3MSE performance over time was dependent on concurrent hypertensive medication use. The separate analysis by antihypertensive medication use indicated that an annual increase of error in 3MSE per 18 mm Hg increase concurrent pulse pressure was approximately 2% among the non-users of hypertension medication. Further restricting the analysis to those non-users with high pulse pressure (>=70 mm Hg) demonstrated that an 18 mm Hg increase in concurrent pulse pressure corresponded to an annual increase of error in 3MSE of approximately 4.5% (Table 3.4).

Although the influence of concurrent pulse pressure on longitudinal SEVLT performance in the entire sample was not dependent on either concurrent or baseline hypertension medication use, the restricted analyses demonstrated that there was a longitudinal relationship between concurrent pulse pressure and SEVLT performance among non-users of hypertension medication at baseline or over time (Table 3.5): for every 18 mm Hg increase in concurrent pulse pressure, the annual decline in SEVLT

score was approximately 0.06 points and 0.05 points respectively, among those not taking antihypertensive medication over time and at baseline.

Categorical analysis of the association between pulse pressure and cognitive function: Using the median tertile (54<=pulse pressure<70) as the referent group, we found a U-shaped relationship between concurrent pulse pressure and mean error in 3MSE and mean score in SEVLT (Table 3.6): an individual with a pulse pressure <54 mm Hg had 9% higher mean error in 3MSE and 0.2 points lower mean score in SEVLT than an individual with a pulse pressure between 54 and 69 mm Hg; an individual with a pulse pressure >=70 mm Hg had a 6% higher mean error in 3MSE and 0.2 points lower mean score in SEVLT than an individual with a pulse pressure between 54 and 69 mm Hg. The longitudinal association between time-dependent pulse pressure and change in SEVLT score was statistically significant when comparing untreated individuals with higher pulse pressure (>=70 mm Hg) to untreated individual with a pulse pressure between 54 and 69 mm Hg: the annual decline in SEVLT score was approximately 0.1 point.

3.5 Discussion

In this community-based longitudinal study of elderly Mexican Americans, the longitudinal and cross-sectional relationship between pulse pressure and cognitive function was assessed. The longitudinal findings revealed that higher baseline pulse pressure was associated with longitudinal decline in cognitive performance in both tests, higher concurrent pulse pressure was related to longitudinal decline in 3MSE performance, and higher concurrent pulse pressure was related to longitudinal decline in both cognitive performance tests among untreated participants. The annual decline most adversely affected the cognitive performance of untreated individuals with high pulse pressure (>=70 mm Hg). In addition, cross-sectional findings suggested a U shaped relationship between concurrent pulse pressure and mean errors in 3MSE and mean scores in SEVLT: both low and high pulse pressure was associated with poor cognitive performance in both tests. Statistical significance of the observed associations persisted when additional adjustment for SBP and DBP was included in all adjusted models. Controlling of baseline pulse pressure in the time-dependent models did not change the study results.

The association between high pulse pressure and longitudinal decline in cognitive function is consistent with that reported by the Baltimore Longitudinal Study (16), the only study which has specifically examined the association of pulse pressure in late life and cognitive decline over time. Although our study population was older, considerably less educated and of Mexican decent (versus a predominantly white population in the Baltimore study), our results presented a similar pattern between pulse pressure and change in cognitive function over time. However, there were two differences noted. First, while we found a statistically significant relation between high pulse pressure and cognitive decline over time using the 3MSE in our study, this was not the case in the Baltimore Longitudinal Study which used the MMSE (Mini-Mental State Examination). This may suggest that 3MSE, a modified MMSE, with broader variety of cognitive function and wider range of difficulty levels may have an enhanced ability to detect subtle changes in cognitive function associated with vascular risk, such as high pulse pressure (20, 24). Second, a U-shaped relationship between concurrent pulse pressure and mean errors in 3MSE and mean scores in SEVLT was observed in our study, whereas no such relationship was evident in the Baltimore Longitudinal Study (20). This may be explained in part by the difference in populations studied. Our participants were older than those in the Baltimore Longitudinal Study (mean=70 vs. mean=57). It is possible that lower pulse pressure linked to inadequate cerebral perfusion may be a bigger threat to older people. The Kungsholmen project, a longitudinal study of elderly persons aged 75 and older, found a U-shape relationship between the level of pulse pressure and risk of AD and all dementias (21), which is consistent with our findings.

Among longitudinal studies investigating the relationship between pulse pressure and cognitive impairment, none have examined the role of antihypertensive therapy in preserving cognitive function among elderly. Our study results may be the first to demonstrate that untreated individuals, in particular, those with high pulse pressure (>=70 mmHg), may be at highest risk of cognitive impairment.

It is noteworthy that all associations found in this study were fairly small in magnitude. This is consistent with the findings observed in the Baltimore Longitudinal Study, which had more than two follow-up visits and used linear mixed model analyses. Our modest results may be explained, in part, by the fact that the use of hypertension

medications was prevalent in our population, which may have attenuated the relationship between high pulse pressure and poor cognitive performance.

High pulse pressure is positively associated with arterial stiffness and atherosclerosis (16-19, 33). Thus, it has been linked to an increased risk of cardiovascular diseases including stroke (34-38), which are also risk factors for cognitive decline and dementia (39-42). Studies have also shown that oxidative stress and inflammatory responses induced by arterial stiffness are involved with the mechanisms of vascular disorders and AD (43-44). In addition, clinically silent cerebrovascular lesions, cerebral microcirculation damage, cerebral hypoperfusion, and other vessel pathology resulting from high pulse pressure appear to predispose individuals to the development of cognitive impairment and subsequent dementia (20-21, 44-45). Low pulse pressure most likely contributes to the diminished cognitive function and dementia through cerebral hypofusion (21). Both low and high pulse pressure may be precursors to chronic cerebral oxygen deprivation that is linked to cognitive decline and dementia in very elderly populations (4).

Strengths of this study include the prospective collection of data over a 6-year period, annual home inspection of medications in addition to semi-annually phone interviews, annual measurement of blood pressure by trained personnel, annual measurement of cognitive performance, and wider age range from 59-98 years to better capture the change of pulse pressure in the elderly. Our study measured pulse pressure and cognitive measurements at 6 follow-up visits. This method of data collection strengthens measurement reliability and permits the examination of individual change in cognitive performance over time. Therefore, it is likely to provide a more accurate measure of cognition and its relationship to pulse pressure. Limitations of this study include the restriction of the assessment of cognitive function to two tests. It is possible that a broader range of cognitive function testing may provide more definitive results. In addition, there may exist potential residual confounding due to omitted covariates associated with both the exposure and outcome variables. The inclusion of only Mexican American participants in the study may limit the generalization of the study results.

Our finding that higher pulse pressure, a marker of arterial stiffness, is associated with the diminished cognitive function over time underscores the importance of

identifying the potentially modifiable risk factors for cognitive decline in the elderly and emphasizes the need to expand research in this area. The additional finding that untreated individuals with higher pulse pressure were at highest risk of cognitive impairment suggests the need to further understand the protective effect of the antihypertensive treatment, and specific classes of agents in treating the risk factors associated with high pulse pressure in late life. Future studies to examine the benefit of early intervention with appropriate pharmacological treatment, life-style changes, and diet to maintain an optimal cognitive level in the elderly may play an important role in reducing and/or delaying the onset of cognitive impairment and dementia.

3.6 Tables and Figures

Table 3.1 Summary of Baseline Characteristics (a)

Gender [N(%)]	
Male	699 (42)
Female	975 (58)
Age (years)	
Mean (SD)	70 (6.80)
Median (Minimum, Maximum)	69 (59, 98)
Education (Years)	
Mean (SD)	7.3 (5.33)
Median (Minimum, Maximum)	7 (0, 32)
Smoking Status [N(%)]	
Never	762 (46)
Former Smoker	709 (42)
Current Smoker	191 (11)
Missing	12
Waist circumference (inches)	
Mean (SD)	38.19 (5.24)
Median (Minimum, Maximum)	38 (16, 58)
History of Stroke [N(%)]	
Yes	131 (8)
No	1533 (92)
Missing	10
Diabetes [N(%)](b)	
Yes	531 (32)
No	1133 (68)
Missing	10
Heart Disease [N(%)] (c)	
Yes	234 (14)
No	1440 (86)
Systolic Blood Pressure	
Mean (SD)	138 .38(19.30)
Median (Minimum, Maximum)	137 (76, 230)
Diastolic Blood Pressure	
Mean (SD)	76.01 (10.58)
Median (Minimum, Maximum)	76 (34, 119)
Pulse Pressure	
Mean (SD)	62.36 (17.55)
Median (Minimum, Maximum)	60 (20, 151)
Any hypertension drug use [N(%)]	
Yes	696 (42)
No	975 (58)
Missing	3
Hypertension [N(%)](d)	
Yes	1019 (61)
No	517 (31)
Missing	138 (8)
3MSE Score	
Mean (SD)	85.88 (11.56)
Median (Minimum, Maximum)	89 (11, 100)
SEVLT Score	
Mean (SD)	8.6 (2.90)
Median (Minimum, Maximum)	9 (0, 15)

a. Include only the subjects who were dementia/CIND free at baseline
b. Participants were considered to have diabetes if they met any of the following 3 criteria: Fasting plasma glucose (FPG) level >=126 mg/dL (7.0 mmol/L); or use of an antidiabetic medication; or self report of a physician's diagnosis of diabetes.
c. Participants were considered to have heart disease if they had the following 3 medical conditions: MI, angina pectoris, or congestive heart failure.
d. Hypertension was defined as systolic blood pressure >=140 or diastolic blood pressure >=90 or on hypertension medication.

Table 3.2 Relationship between Baseline (BL) Pulse Pressure (PP) and Cognitive Function Tests

	3MSE (a)		SEVLT (b)	
	Model I	Model II	Model III	Model IV
Parameters	**Unadjusted**	**Adjusted** (c)	**Unadjusted**	**Adjusted** (c)
BL PP	0.008927****	-0.00207	-0.02748****	0.004949
(95% CI)	(0.006755, 0.01110)	(-0.00423, 0.000085)	(-0.03438,-0.02059)	(-0.00282, 0.01272))
BL PP*Time		0.001228****		-0.00372****
(95% CI)		(0.000785, 0.001671)		(-0.00553,-0.00191)

**** P value <0.0001; *** P value <0.001; ** P value <0.01; * P value <0.05

a. Dependent variable was defined as natural log of error in measuring 3MSE (ln(101-3MSE))
b. SEVLT (Spanish English Verbal Learning Test) is a delayed word list recall test
c. Adjusted for baseline age, education, gender, diabetes, history of stroke, and smoking status

Table 3.3 Relationship between Time-Dependent (TD) Pulse Pressure (PP) and Cognitive Function Tests

	3MSE (a)		SEVLT (b)	
	Model I	Model II	Model III	Model IV
Parameters	**Unadjusted**	**Adjusted** (c)	**Unadjusted**	**Adjusted** (c)
TD PP	0.000537	-0.00866****	-0.00740****	0.003156
(95% CI)	(-0.00047 0.001547)	(-0.01312, -0.00421)	(-0.01107, -0.00372)	(-0.00342,0.009731)
TD PP*Time		0.000586**		-0.00136 (e)
(95% CI)		(0.000172, 0.000999)		(-0.00296,0.000236)
TD PP*TD PP		0.000046**		
(95% CI) (d)		(0.000015, 0.000076)		

**** P value <0.0001; *** P value <0.001; ** P value <0.01; * P value <0.05

a. Dependent variable was defined as natural log of error in measuring 3MSE (ln(101-3MSE))
b. SEVLT (Spanish English Verbal Learning Test) is a delayed word list recall test
c. Adjusted for baseline age, education, gender, diabetes, history of stroke, and smoking status
d. TD PP*TD PP*Time was not statistically significant and not included in the final model
e. P vlaue =0.09

Table 3.4 Longitudinal Relationship between Time-Dependent (TD) Pulse Pressure (PP) and 3MSE Performance (a)

Parameters	Adjusted (b)
Model 1 (c) Longitudinal relation of linear PP by moderation of TD hypertension medication use	
PP* Time (95% CI)	0.000123 (-0.00041, 0.000650)
PP* RX Use *Time (95% CI) (d)	0.001244** (0.000361, 0.002127)
Model 2 Among high PP subjects (PP >=70 mm Hg) who did not take hypertension medication	
PP* Time (95% CI)	0.002470** (0.000571 0.004369)

**** P value <0.0001; *** P value <0.001; ** P value <0.01; * P value <0.05

a. Dependent variable was defined as natural log of error in measuring 3MSE (ln(101-3MSE))

b. Adjusted for baseline age, education, gender, diabetes, history of stroke, and smoking status

c. Adding three way interactions of PP*RX*Time to understand if longitudinal relation of linear PP to 3MSE performance depended on time-dependent hypertensive medication use.

d. Hypertension medication user was reference group

Table 3.5 Longitudinal Relationship between Time-Dependent (TD) Pulse Pressure (PP) and SEVLT (a)

Parameters	Adjusted (b)
Model 1 (c) Longitudinal relation of PP by moderation of TD hypertension medication use	
PP* Time (95% CI)	-0.00308* (-0.00579, -0.00036)
PP* RX Use *Time (95% CI) (d)	0.002793 (-0.00058, 0.006164)
Model 2 Among non-hypertension medication users	
PP* Time (95% CI)	-0.00323* (-0.00599, -0.00048)
Model 3 (c) Longitudinal relation of PP by moderation of BL hypertension medication use	
PP* Time (95% CI)	-0.00284* (-0.00509, -0.00059)
PP* RX Use *Time (95% CI) (e)	0.002942 (-0.00027, 0.006159)
Model 4 Among non-hypertension medication users	
PP* Time (95% CI)	-0.00263* (-0.00491, -0.00035)

**** P value <0.0001; *** P value <0.001; ** P value <0.01; * P value <0.05
a. SEVLT (Spanish English Verbal Learning Test) is a delayed word list recall test
b. Adjusted for baseline age, education, gender, diabetes, history of stroke, and smoking status
c. Adding three way interactions of PP*RX*Time to understand if longitudinal relation of concurrent PP on SEVLT performance depended on time-dependent (TD) or baselien (BL) hypertensive medication use.
d. Non-hypertension medication user was reference group: P value=0.1
e. Non-hypertension medication user was reference group: P value=0.07

Table 3.6 U – Shaped Relationship between Time-Dependent (TD) Pulse Pressure (PP) and Cognitive Function – Categorical Analysis (a)

Parameters	Adjusted Model I (b)	Adjusted Model II (b)
	3MSE	**SEVLT**
1:PP< 54 (95% CI)	0.08711**** (0.05077, 0.1235)	-0.1618* (-0.2961, -0.02748)
2:PP>=70 (95% CI)	0.06089*** (0.02497, 0.09681)	-0.1590* (-0.2923, -0.02565)
3:54<=PP<70 (95% CI)	Reference	Reference

**** P value <0.0001; *** P value <0.001;
a. Dependent variable was defined as natural log of error in measuring 3MSE (ln(101-3MSE))
b. Adjusted for baseline age, education, gender, diabetes, history of stroke, and smoking status

Figure 3.1 Cross-Sectional Relationship between Nonlinear Pulse Pressure and 3MSE Performance at Baseline (Per 18 mmHg Increase in Pulse Pressure)

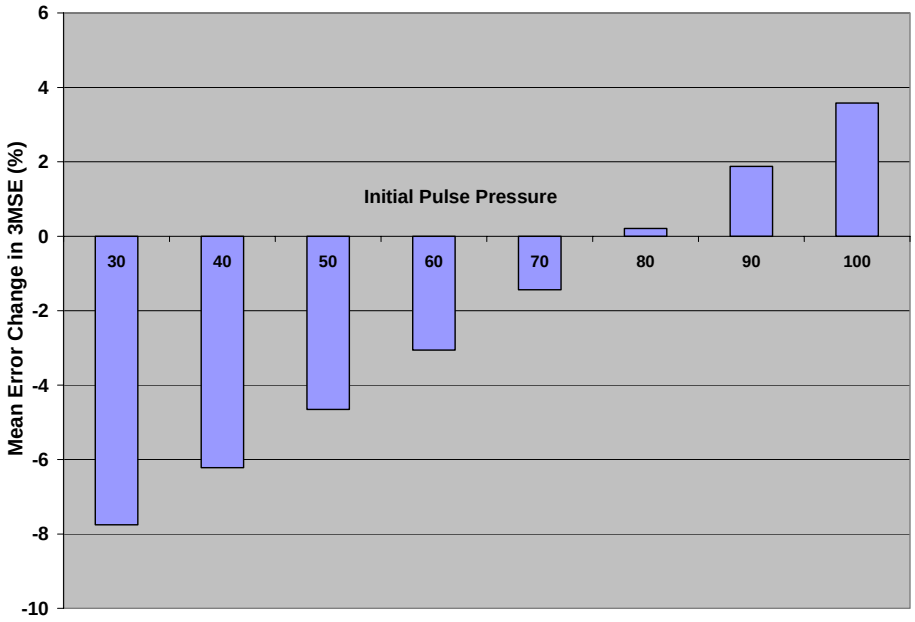
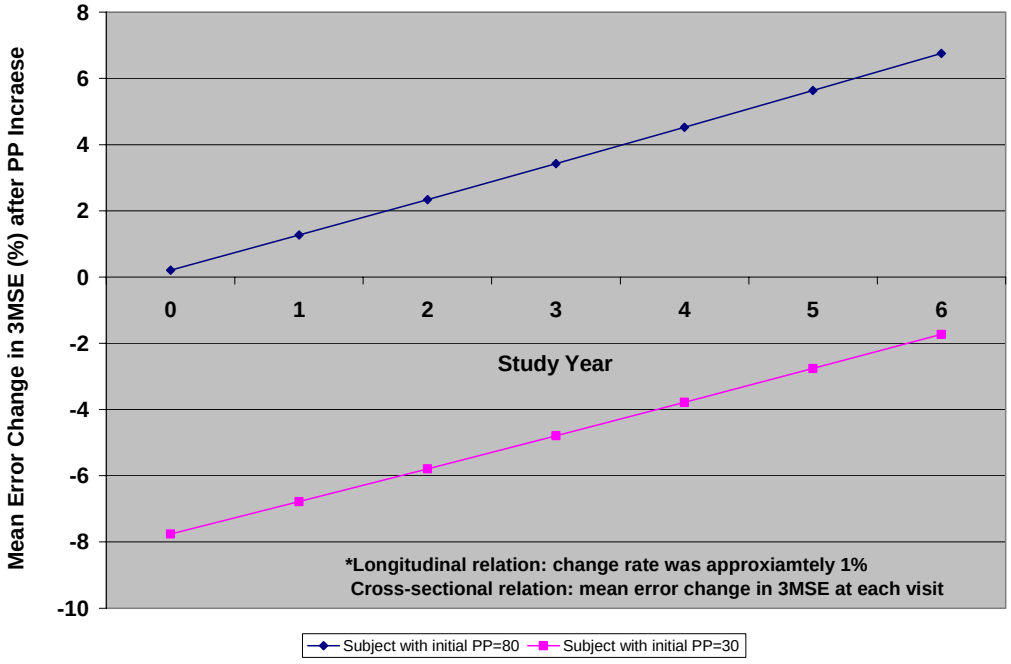


Figure 3.2 Longitudinal and Cross-Sectional Relationship between Concurrent Pulse Pressure and 3MSE Performance (Per 18 mmHg Increase in Concurrent PP)



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CHAPTER 4

THE ASSOCIATION BETWEEN ANTIHYPERTENSIVE TREATMENT AND INCIDENCE OF DEMENTIA/CIND IN HYPERTENSIVE PATIENTS: A POPULATION-BASED COHORT STUDY OF ELDERLY MEXICAN AMERICANS

4.1 Abstract

OBJECTIVE: Longitudinal observational studies examining the relationship between antihypertensive treatment and the development of cognitive impairment/dementia in the elderly have produced inconsistent results. Existing studies have been limited in their assessment of medications by class. The objective of this study was to evaluate the association between uses of any antihypertensive treatment and specific class of agents with incidence of dementia/CIND, over 6 years of follow-up among older Mexican American hypertensive patients living in the Sacramento, California area.

RESEARCH DESIGN AND METHODS: The Sacramento Area Latino Study of Aging (SALSA) was a prospective longitudinal cohort study with an average length of 6.11 year follow-up. Among 1789 eligible community-dwelling, non-institutionalized Latinos aged 60 years and older enrolled in 1998-99, 1434 hypertensive patients who were free dementia or "cognitively impaired not demented" (CIND) at baseline were included in the analysis. A multistage process was used to evaluate participants for cognitive impairment and dementia at baseline and at six follow-up examinations. At baseline and each follow-up visit, Modified Mini-Mental State Examination (3MSE) and the Spanish and English Verbal Learning Test (SEVLT) were used for screening, and the Spanish English Neuropsychological Assessment Scales (SENAS *battery*) and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) were used to determine the need for a neuro-clinical evaluation. Clinical assessment and adjudication, as well as further magnetic resonance imaging and appropriate laboratory tests were performed to establish a dementia case. In this analysis, dementia and CIND were combined into one

outcome variable: dementia/CIND. Antihypertensive medication use was ascertained at each participant's home at baseline and each follow-up visit by direct inspection of all medication and coded by the Centers for Disease Control (CDC) protocol. Any antihypertensive drug use, as well as use of each antihypertensive drug class including diuretics, beta blockers, ACE inhibitors, and calcium channel blockers was used as an exposure variable in the analysis. Cox proportional hazard models, using age as time-scale, were applied to assess the association between use of antihypertensive treatment as well as each antihypertensive drug class and the risk of dementia/CIND.

RESULTS: Any antihypertensive medication use was associated with lower incidence of dementia/CIND after adjustment for potential confounders: hazard ratio (HR=0.42, 95% CI=0.28, 0.62). Diuretics, beta blocker, and ACE Inhibitor use were associated with lower incidence of dementia/CIND: (HR=0.52, 95% CI=0.34, 0.81) for diuretics; (HR=0.54, 95% CI =0.33, 0.88) for beta blockers; (HR=0.64, 95% CI =0.43, 0.98) for ACE Inhibitors. Calcium channel blockers were not associated with incidence of dementia/CIND: (HR=0.93, 95% CI =0.59, 1.47).

CONCLUSION: In this large population-based study in which antihypertensive medication use was prevalent, any antihypertensive medication use was associated with lower incidence of dementia/CIND. In particular, use of diuretics, beta blockers and ACE Inhibitors was associated with a lower incidence of dementia/CIND. Use of calcium channel blockers was not associated with incidence of dementia/CIND. The findings provided additional evidence to support the protective effects of antihypertensive treatment and specific drug class on dementia and added to our understanding to potential treatment options to preserve cognitive function. Future epidemiological and clinical studies to examine the possible neuro-protective effects of these drugs in diversified population are suggested.

4.2 Introduction

Several classes of antihypertensive agents are available for treating high blood pressure. Randomized clinical trials have shown that blood pressure-lowering produces significant reductions in stroke and cardiovascular risk (1). It was reported that a decrease of 10-mm Hg in systolic blood pressure or 5-mm Hg in diastolic blood pressure could lead to a risk reduction of 50% to 60% of stroke death and 40% to 50% of death

due to cardiovascular disease or other vascular causes (2). Stroke and underlying causes of cardiovascular disease such as atherosclerosis and arteriolosclerosis have been linked to a greater risk of dementia and Alzheimer's disease (5-13). However, clinical and epidemiological studies investigating the effect of antihypertensive treatment on cognitive impairment have provided varied results (14-25), mostly depending on class of antihypertensive agents used, study design, length of follow-up, study population, and duration of treatment, etc.

Given the evident beneficial effect of antihypertensive medication in preventing stroke and cardiovascular disease, it will be a challenge to conduct placebo-controlled clinical trials to examine the relationship of antihypertensive therapy and dementia due to ethical complication (18). Thus epidemiological studies involving longer follow-up and multiple visits, larger sample of demented cases, and diversified population will add value to a better understanding with the treatment to the modifiable risk factor of cognitive dysfunction. Our objective in this study was to evaluate the association of antihypertensive treatment including specific class of agents with incidence of dementia/CIND, over 6 years of annual follow-up among older Mexican American hypertensive patients living in the Sacramento, California area.

4.3 Method

Study population: The Sacramento Area Latino Study of Aging (SALSA) was a prospective longitudinal cohort study designed to examine whether risk factors (diabetes, hypertension, smoking and obesity) increase the risk of dementia, memory loss, functional impairment, and decline in cognitive and physical functioning (26). A detailed description of sampling and recruitment in the SALSA study has been described elsewhere (26). The eligible participants were community-dwelling, non-institutionalized Latinos aged 60 years and older in 1998-1999, who lived in the Sacramento area and San Joaquin Valley in California. At baseline, a total of 1789 people were enrolled in the study, and followed from 1998/99 through 2007. The average length of follow-up was 6.11 years and the maximum length was 9 years. Among the 1789 SALSA participants, 115 had dementia or CIND at baseline and were excluded from this study. This analysis was confined to hypertensive patients whose systolic blood pressure was ≥140 mm Hg and/or diastolic blood pressure was ≥90 mm Hg or who took any antihypertensive drugs,

at baseline or over 6 years of follow-up. Thus, the analytical sample included 1434 participants who met the criteria of hypertensive patient and were free dementia/CIND at baseline.

Data collection: All baseline and follow-up data were collected by interviews and clinical assessments at home visits every 12-15 months from 1998/99 through 2007. To maintain contact and gather updated information about health status and medication use, a brief telephone interview was added midway between each home visit.

Outcome measurement –Dementia or CIND: A multistage process was used to evaluate participants for cognitive impairment and dementia at baseline and at the annual follow-up examination. The details of this process are described elsewhere (26). Briefly, in the first stage, a participant who had the screen score below the 20^{th} percentile on either 3MSE or SEVLT was referred for further neuropsychological examination. At each follow-up visit, a participant was referred for neuropsychological testing if the 3MSE score or SEVLT score declined by more than 8 points or 3 points from baseline respectively, or if the current 3MSE or SEVLT score was $<20^{th}$ percentile. In the second stage, the SENAS battery and IQCODE were used to determine if a subject was in need of a neuro-clinical evaluation with the study geriatrician or a neurologist. A participant was referred for neurological examination if he/she scored below the 10^{th} percentile on at least one neuropsychological test and less than 20^{th} percentile on the IQCODE, or scored below the 10^{th} percentile on at least 4 neuropsychological tests and less than 40^{th} percentile on the IQCODE. In the third stage, diagnoses of dementia, CIND, or normal were adjudicated by a team of neurologists and a neuropsychologist. Finally, demented cases were referred for further magnetic resonance imaging (MRI) and appropriate laboratory tests. Diagnostic and Statistical Manual of Mental Disorder, 4^{th} edition (DSM-IV) criteria were used to establish a diagnosis of dementia (27). For this study, dementia and CIND were combined into one outcome variable: dementia/CIND (28).

Exposure measurement - Antihypertensive Treatment: Antihypertensive medication use was ascertained at each participant's home at baseline and at each annual visit by direct inspection of all medication. The medication information was entered by trained personnel onto a collection form, and included the medication code, dose, number of prescribed pills, and average number of pills taken. This information was then updated

by telephone every 6-8 months between home visits. Medication codes were assigned using the Centers for Disease Control (CDC) Ambulatory Care Drug Database System (29). Antihypertensive medications included all medication potentially used for lowering blood pressure. In addition, the class of each antihypertensive drug (diuretics, beta blockers, ACE inhibitors, and calcium channel blockers) was also used as an exposure variable in the analysis.

Covariate measurement: The measurements of nine baseline covariates were included in the analyses. They include age, measured in years, calculated from dates of birth and baseline visit; sex; education, measured in years, collected at the baseline visit; waist circumference, measured at the level of maximum indentation over the abdomen, when the participant bended to the side, taken in centimeters at baseline and converted to inches; smoking status, assessed by asking each participant to select one of three responses that best described their smoking status at the baseline visit: never smoker, former smoker, or current smoker; medical insurance, assessed by asking each participant if he/she had medical insurance and types of insurance (e.g. HMP/PPO, MEDI-CAL/Supplement, Medicare, Others) that he/she had; history of stroke, determined by self report of a physician's diagnosis at the baseline visit; history of heart disease, determined by self report of a physician's diagnosis at baseline by answering "yes" to the questions about MI, angina pectoris, or congestive heart failure; diabetes, ascertained if a participant met the following 3 criteria at baseline: fasting plasma glucose (FPG) level ≥126 mg/dL (7.0 mmol/L) (fasting was defined as no caloric intake for at least 8 hours), or use of an anti-diabetic medication, or self-report of a doctor's diagnosis of diabetes.

Statistical analyses: Descriptive statistics were used to compare baseline characteristics between treated and untreated hypertensive patients. The crude incidence rates were calculated as the number of dementia/CIND patients divided by the follow-up time (person-years at risk). Cox proportional hazard models, using age as time-scale (30-31), were applied to assess the association between antihypertensive treatment use and risk of dementia/CIND. This time scale considered participants at risk for dementia/CIND beginning with their age at entry in the study and allowed adjustment for left truncation (30). Participants who developed dementia/CIND during the follow-up contributed information up to their age at diagnosis. Those who did not develop

dementia/CIND during the study were censored at the age of their last available follow-up visit. The use of hypertension medication was included in the COX model as a time-varying exposure variable. Lagging was used in the analysis to reduce ambiguity in the causal ordering (30): time-varying hypertension medication use was measured at the prior visit when dementia/CIND was diagnosed or when the last visit was available. It was counted up to and including Visit 5 (out of 6 follow-up visits) with a lag value of hypertension medication use.

Both unadjusted and adjusted effects of antihypertensive treatment use were examined. Prior knowledge of biological plausibility, the change-in-estimate criterion, and differences in baseline characteristics in treated and untreated groups were considered when determining covariates to be included in the final models. The covariates used for adjustment in the final models were gender, education (years) diabetes (yes/no), history of stroke (yes/no), heart disease (yes/no), smoking status (current/former/never smoker), medical insurance, and waist circumference (inches) at baseline.

All models were fit using SAS PROC PHREG for COX models. Results were considered as statistically significant if $P<0.05$.

4.4 Results

Demographic characteristics: The baseline characteristics of all hypertensive patients at baseline are presented in Table 4.1. The two groups (treated vs. untreated) were balanced with respect to gender, education and diastolic blood pressure. Patients in the treated group were older, had higher systolic blood pressure, higher pulse pressure, and proportionally more had a history of heart disease, diabetes, stroke, and abdominal obesity. A larger proportion of the patients in the treated group had medical insurance and fewer treated patients were current smokers.

Antihypertensive medications use: Figure 4.1 shows antihypertensive medication use among hypertensive patients over time. The proportion of hypertensive patients using any antihypertensive drugs increased during the 6-years of follow up period from 49% at baseline to 74% at 6^{th} visit. The use of the medication by class (diuretics, ACE inhibitor, and beta blockers) in this group followed the same upward trend with an

increase in use from 21%, 17%, and 11% at baseline to 38%, 32%, and 28% at 6th visit, respectively. The use of calcium channel blockers, however, changed little over time.

Crude Incidence of Dementia/CIND, Death, and Loss- to-Follow-up: Among 1434 hypertensive patients without prevalent dementia/CIND at baseline, 139 patients developed dementia/CIND over 6 years of follow-up. Table 4.2 presents the crude incidence rates of dementia/CIND by gender and by hypertension medication use at baseline. The crude rate ratio of users vs. non users was 1.15 for men and 1.2 for women. Table 4.3 provides a summary of the number of incident dementia/CIND cases by visit, as well as the number of deaths, and number of participants who were lost-to-follow-up.

Time-Dependent Model: Table 4.4 presents the unadjusted and adjusted results from COX proportional hazard model using time-varying antihypertensive treatment as an exposure variable: in the unadjusted model (model 1), any antihypertensive drug use significantly reduced the risk of dementia/CIND by 47% compared with persons not using any antihypertensive treatments; after adjusting for baseline stroke and diabetes (model 2), the magnitude of this reduction in risk of dementia/CIND among antihypertensive treatment users increased further (58%); when further adjusting for all potential confounders in the model (model 3), the magnitude of the reduction in the risk of dementia/CIND remained unchanged (58%).

Table 4.5 presents the association between use of individual antihypertensive medication subclasses and incidence of dementia/CIND among hypertensive patients. Use of diuretics, the first line therapy for hypertension, led to the largest reduction (48%) in incidence of dementia/CIND compared to those who did not use diuretics. Use of beta-blockers and ACE inhibitors, also resulted in a significant reduction (46% and 36%, respectively) in the risk of dementia//CIND respectively compared to non-users of these classes of drugs. A non-significant risk reduction for dementia/CIND among users of calcium channel blockers was observed.

4.5 Discussion

In this community-based prospective cohort study of Mexican Americans aged 60 and older, the association between use of antihypertensive treatment and the risk of developing dementia/CIND among hypertensive patients was examined. Results revealed a significantly reduced risk of dementia/CIND among patients routinely using

any antihypertensive medication. By class, use of diuretics, beta blockers, and ACE inhibitors were associated with lower incidence of dementia/CIND. Use of calcium channel blockers, however, was not associated with a reduction in the incidence of dementia/CIND. Statistical significance persists in all adjusted models, regardless of whether duration of study or age at diagnosis was used as a time-scale in the analysis. Controlling for baseline systolic blood pressure and diastolic blood pressure in all models did not change the results.

Among four epidemiological studies that reported protective effects of antihypertensive medications (17-20), the Kungsholmen project showed that diuretic use, the most commonly used therapy, was associated with a significant reduction of dementia risk (17). The Cache County Study suggested beneficial effects of diuretic use, in particular, potassium-sparing diuretics, and a marginal protective influence from beta blockers, on Alzheimer's disease incidence (20). The Rotterdam study (18) demonstrated a substantial effect of antihypertensive therapy in reducing the risk of dementia and vascular dementia. In a longitudinal community-based study of African Americans, protective effects of antihypertensive drugs on cognitive impairment were observed (19). Our findings in this study are consistent with these results. On the other hand, the Baltimore Longitudinal Study of Aging, which prospectively collected the use of calcium channel blockers for up to 19 years, and both the Cache County Study and a community-based study of African Americans, found no association between use of calcium channel blockers and Alzheimer's disease or cognitive impairment (16, 19-20). Although all three studies indicated a trend toward risk reduction with use of calcium channel blockers, results for this class of medication (including ours) were not statistically significant.

Six large randomized placebo-controlled trials that have evaluated the effects of antihypertensive treatment on cognitive decline and development of dementia have produced divergent results (21-25, 32-33): The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) and the Heart Outcomes Prevention Evaluation (HOPE) study reported respectively a 34% reduction of dementia in recurrent stroke patients, and a 41% reduction of cognitive decline related to stroke, using ACE inhibitors in both trials, or combined ACE inhibitor with diuretics in the PROGRESS (25, 32). The Systolic

Hypertension in the Elderly Program (SHEP) and Medical Research Council's treatment trial (MRC) found no significant risk reduction in dementia or cognitive decline in the group receiving active treatment of diuretics and/or beta-blockers compared to placebo (21, 33). However, re-analysis of SHEP data indicated that differential drop-out may have biased the cognitive assessment and obscured a protective effect of treatment on dementia and cognitive decline (34). In the Systolic Hypertension in Europe trial (SYST-EUR), active treatment was a calcium channel blocker (nitrendipine), combined with an ACE inhibitor (enalapril) and/or a diuretic (hydrochlorothiazide), if necessary (22-23). This trial demonstrated that active treatment reduced dementia in elderly people with isolated systolic hypertension by 50% and 55%, respectively in the initial and extended trials (22-23). The Study on Cognition and Prognosis in the Elderly (SCOPE) evaluated the role of ARB candesartan in preventing cognitive decline and subsequent dementia among elderly with mild and moderately raised blood pressure (24) and failed to observe a significant difference in dementia incidence and cognitive decline between the active treated and placebo groups. This lack of protective effect may be partially explained by the fact that most patients in the placebo group were treated with other antihypertensive drugs for ethical reasons. In general, our findings appear consistent with results from these trials in that there is protective effect from ACE inhibitors and there likely exists potential protective effect from diuretics and beta-blockers.

The precise mechanisms by which antihypertensive therapy affects dementia incidence are not fully understood. Through blood pressure reduction, antihypertensive drugs may lower the risk of progressing into dementia (including both Alzheimer's disease and vascular dementia) by correcting the underlying blood pressure-related mechanisms such as hypertension-induced stroke, cerebrovascular damage, and cerebral hypofusion, and by disrupting the atherosclerotic process. For example, the PROGRESS study showed that the antihypertensive treatment comprised of an ACE inhibitor (perindopril) and a diuretic (indapamide) reduced white matter lesion progression among patients with a history of cerebrovascular disease (35), which provides neuron protection against cognitive decline and subsequent dementia. The non-blood pressure related effect is mediated by mechanisms other than blood pressure reduction. For example, calcium

channel blockers prevent calcium influx that may cause neuronal death due to release of intracellular enzymes (16).

The important strengths of this analysis include the advantage of a prospective longitudinal design with an average of 6-years follow-up, annual home inspection of medications in addition to semi-annually phone interviews, annual assessment of cognitive function, clinical evaluation and adjudications of potential dementia/CIND cases, and further examination of demented cases by magnetic resonance imaging and appropriate laboratory tests. In addition, higher prevalence of antihypertensive medication use in this population allowed for the examination of effects of specific classes of antihypertensive agents. Our study is one of the few longitudinal studies which examined the use of antihypertensive medications, measured cognitive performance, and evaluated dementia incidence at more than 2 follow-up visits. This method of data collection strengthened measurement reliability and may have provided a more accurate evaluation of the association between antihypertensive treatment and incidence of dementia/CIND. Limitations in this study include the relatively small number of dementia cases, which did not allow for the examination of the association between antihypertensive therapy and Alzheimer's disease and vascular dementia, separately, and the potential for differential drop-out due to health problems such as severe hypertension or dementia. Additional limitations may include competing risk from death and the potential for residual confounding due to omitted covariates associated with exposure and outcome. This study only included elderly Mexican Americans, which may limit the generalizability of the results to other elderly populations.

Identifying appropriate therapeutic strategies to prevent or delay the onset of dementia and the progression from cognitive impairment to dementia is of great public health importance given that the projected size of the dementia population is expected to double every 20 years to 81.1 million worldwide by 2040 (36). This study provides additional evidence to support the protective effects of antihypertensive treatment, specifically, diuretics, beta-blockers, and ACE inhibitors, on reducing the risk of dementia/CIND. These findings need to be replicated in future studies with longer follow-up and multiple measurements of cognitive function and drug usage, and in larger

and more diversified populations; ideally, in the interventional studies specifically designed to address the association of each drug class (or drug) and dementia risk.

4.6 Tables and Figures

Table 4.1 Summary of Baseline Characteristics of Hypertensive Patients (a)

	Treated (b) N=696	**Untreated** N=736	**p value**
Gender [N(%)]			
Male	285 (41)	323 (44)	0.2
Female	411 (59)	409 (56)	
Age (years)			
Mean (SD)	71.03 (7.05)	69.61 (6.35)	<0.0001
Median (Minimum, Maximum)	70 (60, 98)	68.61 (59, 92)	
Education (Years)			
Mean (SD)	7.43 (5.27)	7.47 (5.35)	0.8956
Median (Minimum, Maximum)	7.0 (0, 32)	7.0 (0, 24)	
Smoking Status [N(%)]			
Never	309 (44)	330 (45)	0.008
Former Smoker	323 (46)	301 (41)	
Current Smoker	64 (10)	103 (14)	
Waist circumference (inches)			
Mean (SD)	39.13 (5.25)	37.64 (5.21)	<.0001
Median (Minimum, Maximum)	39 (18, 58)	38.0 (16, 55)	
Medical Insurance [N(%)]			
Yes	658 (95)	647 (88)	<0.0001
No	38 (5)	85 (12)	
History of Stroke [N(%)]			
Yes	76 (11)	40 (5)	0.0002
No	620 (89)	694 (95)	
Diabetes [N(%)] (c)			
Yes	325 (47)	160 (22)	<0.0001
No	371 (53)	574 (78)	
Heart Disease [N(%)] (d)			
Yes	169 (24)	49 (7)	<0.0001
No	527 (76)	587 (93)	
Systolic Blood Pressure			
Mean (SD)	142.49 (19.53)	138.05 (18.34)	<.0001
Median (Minimum, Maximum)	140 (90, 230)	138.0 (99, 215)	
Diastolic Blood Pressure			
Mean (SD)	76.62 (11.47)	76.50 (9.83)	0.8282
Median (Minimum, Maximum)	77 (40, 113)	76.0 (34, 119)	

a. Hypertensive patient is defined as a patient who had SBP >=140 mm Hg, or DBP >=90 mmHg, or was on any hypertension medication during the study period
b. Any hypertension medication use at baseline. Two patients had missing hypertension medication use at baseline.
c. Participants were considered to have diabetes if they met any of the following 3 criteria: Fasting plasma glucose (FPG) level >=126 mg/dL (7.0 mmol/L); or use of an antidiabetic medication; or self report of a physician's diagnosis of diabetes.
d. Participants were considered to have heart disease if they had the following 3 medical conditions: MI, angina pectoris, or congestive heart failure.

Table 4.2 Summary of Crude Incidence of Dementia/CIND by Gender and Antihypertensive Medication (AH) Use at Baseline

	Gender	
	Male	**Female**
	Incidence (per 1000 PY)	**Incidence (per 1000 PY)**
AH Use = Yes	N=25 14.6 per 1000 PY	N=46 17.8 per 1000 PY
AH Use = No	N=27 12.7 per 1000 PY	N=41 14.7 per 1000 PY
Total Rate	N=52 13.5 per 1000 PY	N=87 16.2 per 1000 PY
Crude Rate Ratio	1.15	1.12

Table 4.3 Dementia, Death, Lost to Follow-up by Visit among Hypertensive Patients (a)

	BL	**AV1**	**FV2**	**FV3**	**FV4**	**FV5**	**FV6**
	N=1434	**N=1429**	**N=1359**	**N=1314**	**N=1205**	**N=1004**	**N=883**
Dementia/CIND (b)	0	19 (1.3%)	9 (0.7%)	33 (2.5%)	31 (2.6%)	26 (2.6%)	21 (2.4%)
Death	0	25 (1.7%)	27(2.0%)	39 (3.0%)	87 (7.2%)	64 (6.4%)	50 (5.7%)
Lost to follow-up (c)	2 (0.3%)	26 (1.8%)	9 (0.7%)	37 (2.8%)	83 (6.9%)	31 (3.1%)	17 (1.9%)

a. Participant with baseline dementia and CIND were excluded
b. Inclide 22 dementia patients who died
c. Include drop-out and lost to follow-up

Table 4.4 Association between Antihypertensive Medication Use and Incidence of Dementia/CIND among Hypertensive Patients (a)

Model/Varaible (b)	**Hazard Ratio**	**95 % Confidence Interval**		**P Value**
Model 1 (Unadjusted)				
Any Hypertension Drugs	0.53	0.370	0.758	0.0005
Model 2 (Adjusted) (c)				
Any Hypertension Drugs	0.424	0.292	0.614	<.0001
Model 3 (Adjusted) (d)				
Any Hypertension Drugs	0.418	0.284	0.616	<.0001

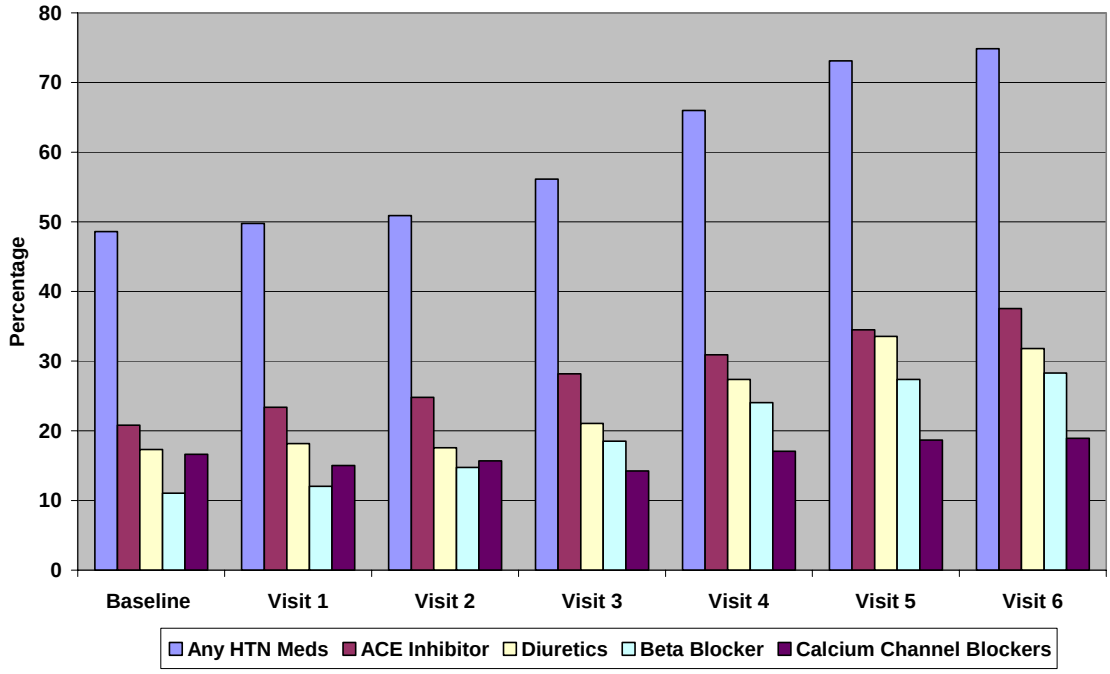
a. Hypertensive patient is defined as a patient who had SBP >=140 mm Hg, or DBP >=90 mmHg, or was on any hypertension medication during the study period
b. Cox proportional hazard models: any hypertensione medications use was a time dependent variable. The medication use at the prior vsist (lag value) was used in the models. Age was used as time scale.
c. Adjusted for baseline diabetes and history of stroke
d. Adjusted for baseline education, gender, diabetes, history of stroke, heart disease, smoking status, waist circumference, medical insurance

Table 4.5 Association between Antihypertensive Medication Use and Incidence of Dementia/CIND among Hypertensive Patients – by Drug Class (a)

Model/Varaible (b)	**Hazard Ratio**	**95 % Confidence Interval**		**P Value**
Model 1 (c)				
Diuretics	0.524	0.339	0.808	0.004
Model 2 (c)				
ACE Inhibitor	0.644	0.425	0.975	0.038
Model 3 (c)				
Beta Blocker	0.538	0.329	0.880	0.014
Model 4 (c)				
Calcium Channel Blockers	0.93	0.587	1.472	0.754

a. Hypertensive patient is defined as a patient who had SBP >=140 mm Hg, or DBP >=90mmHg, or was on any hypertension medication during the study period
b. Cox proportional hazard models: any hypertensione medications use was a time dependent variable. The medication use at the prior vsist (lag value) was used in the models. Age was used as time scale.
c. Adjusted for baseline education, gender, diabetes, history of stroke, heart disease, smoking status, waist circumference, medical insurance

Figure 4.1 Antihypertensive Medication Use among Hypertensive Patients



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CHAPTER 5

SUMMARY AND CONCLUSION

5.1 Major Findings

In this community-based prospective cohort study of elderly Mexican Americans, the relationships between systolic blood pressure, diastolic blood pressure, and pulse pressure and cognitive decline, and antihypertensive treatment and the risk of developing dementia/CIND were examined. The major findings are outlined below.

The association between systolic blood pressure and cognitive decline: (i) Higher baseline systolic blood pressure was associated with longitudinal decline in cognitive performance assessed by 3MSE and SEVLT; (ii) Higher concurrent systolic blood pressure was related to longitudinal decline in 3MSE performance among untreated participants and the annual decline in 3MSE performance was more pronounced among untreated individuals with uncontrolled systolic blood pressure; (iii) Higher concurrent systolic blood pressure was associated with lower mean level of cognitive performance assessed by 3MSE and SEVLT and treated individuals with uncontrolled systolic blood pressure were more vulnerable to the deleterious effect of high systolic blood pressure.

The association between diastolic blood pressure and cognitive decline: (i) Higher concurrent diastolic blood pressure was associated with longitudinal improvement in cognitive performance assessed by 3MSE and SEVLT and this longitudinal improvement appeared more pronounced among individuals with low diastolic blood pressure; (ii) Higher baseline diastolic blood pressure was associated with longitudinal improvement in SEVLT scores.

The association between pulse pressure and cognitive decline: (i) Higher baseline pulse pressure was associated with longitudinal decline in cognitive performance assessed by 3MSE and SEVLT; (ii) Higher concurrent pulse pressure was related to longitudinal decline in 3MSE performance; (iii) Higher concurrent pulse pressure was related to longitudinal decline in cognitive performance assessed by 3MSE and SEVLT

among untreated participants and the annual decline of cognitive performance in both tests was more pronounced among untreated individuals with higher pulse pressure (>=70 mmHg); (iv) There was a U shaped relationship between concurrent pulse pressure and mean level of cognitive performance assessed by 3MSE and SEVLT: both low and high pulse pressure was associated with poor cognitive performance.

The association between antihypertensive treatment and dementia/CIND: (i) There was a statistically significant reduction in the incidence of dementia/CIND among any antihypertensive treatment users compared to non-users after adjustment for all potential confounders; (ii) Use of diuretics, beta-blockers, and ACE inhibitors was associated with a lower incidence of dementia/CIND after adjusting for potential confounders; (iii) Use of calcium channel blockers was not associated with the incidence of dementia/CIND after adjusting for potential confounders.

5.2 Public Health Implications

Hypertension, cognitive impairment, and dementia are major threats to the health of elderly persons. Among people aged 65 years and over in the US, more than half have isolated systolic or combined systolic-diastolic hypertension (1). Dementia, on the other hand, affects about 5% of the elderly population aged 65 and older in the US, and its prevalence doubles every 5 years to exceed 30% in people aged 85 years and older (2-3). In addition, the prevalence of cognitive impairment without dementia among individuals aged 71 and older was 22.1%, comprising approximately 5.4 million elderly in US in 2002 (4).

The mechanisms that link elevated systolic blood pressure, low diastolic blood pressure, and high pulse pressure in late life to cognitive decline and dementia are biologically plausible. This study adds to the growing evidence that supports the contribution of higher systolic blood pressure, lower diastolic blood pressure, and higher pulse pressure to a decline in cognitive function over time in elderly persons. The findings that antihypertensive therapy, specifically, diuretics, beta-blockers, and ACE inhibitors, may have protective effects, support on-going efforts to identify appropriate therapy to prevent or delay the onset of dementia and the progression from cognitive impairment to dementia. The results of this study point to likely modifiable risk factors

for cognitive decline and dementia and add to our understanding of the potential usefulness of the treatment options.

Dementia and cognitive impairment, while adversely affecting patients' quality of life, add a significant burden to patients' caregivers and to the current health care system. Given the high prevalence of hypertension and dementia in the elderly and the association between these two conditions, the beneficial effect of early intervention can be substantial, even if there is only a small reduction in risk or slight delay to the onset of cognitive loss and dementia (6). Based on current projections for Alzheimer's disease prevalence over the next half century, a 6 month delay in the onset of Alzheimer's disease, would result in almost 400,000 fewer cases by 2047 and a 5-year delay in onset would reduce the prevalence by half (5).

Furthermore, few studies investigating the relationship between blood pressure, pulse pressure, or antihypertensive treatment and cognitive dysfunction have included the non-White Hispanic population, one of the fastest growing ethnic populations in the US. This study provides important information on this rarely studied but rapidly expanding population of elderly persons.

5.3 Limitations

Several limitations of this study are worth noting. First, the measurement of cognitive decline was restricted to two tests. It is possible that a broader range of cognitive function testing may have captured more occurrences of cognitive decline. It is likely that this outcome misclassification is non-differential (not dependent on exposure), which would have the effect of attenuating the relationship between blood pressure/pulse pressure and cognitive function over time.

Second, the relatively small sample of dementia cases did not permit for a separate investigation of the association between antihypertensive treatment and Alzheimer's disease and vascular dementia. Therefore, the conclusions of this study apply broadly to all dementia cases in this population.

Third, as with all observational studies of certain duration, this analysis may be vulnerable to the differential drop out of participants due to severe hypertension and dementia. If proportionally fewer treated hypertensive patients drop out of the study due

to severe hypertension and dementia than untreated patients, this may lead to an underestimate of the protective effect of antihypertensive treatment. Similarly, if proportionally more participants with higher systolic blood pressure drop out of the study due to hypertension or cognitive impairment than those with normal blood pressure, this may lead to an underestimate of the documented inverse association between higher systolic blood pressure and decline in cognitive function.

Fourth, there may be a competing risk from death due to the very advanced age and medical condition of this population. When using the COX proportional model, competing risk from death was taken into account by examining the association between antihypertensive treatment and risk of dementia/CIND by event type (7). The impact of competing risk from death on the relationship between blood pressure and pulse pressure and decline in cognitive function, is difficult to quantify due to lack of available exposure and outcome information for those who died. Previous studies indicate that systolic blood pressure increases with age for men and women, while diastolic blood pressure begins to decline after the age of 60 for both genders (8). Among the elderly persons who died due to age and medical conditions, cognitive function could have declined if they were alive. Thus, a possible impact of competing risk from death may be an attenuation of the association between blood pressure and pulse pressure, and decline in cognitive function over time.

Fifth, there may continue to be residual confounding due to unknown or unmeasured covariates associated with both exposure and outcome. The direction of the bias due to an unknown or unmeasured confounder depends on the relationship of the confounder with exposure and outcome. The confounder may positively confound the estimated association if the confounder-exposure (C-E) association and the confounder-outcome (C-O) association are in the same direction, which would underestimate the protective effect of antihypertensive treatment, or overestimate the inverse association between blood pressure and pulse pressure and decline in cognitive function. The confounder may negatively confound the estimated association if the C-E or C-O associations are in opposite directions, which would overestimate the protective effect of antihypertensive treatment, or underestimate the inverse association between blood pressure and pulse pressure and decline in cognitive function (9).

Lastly, this study was confined solely to elderly Mexican Americans, which may limit the generalizability of the results to other elderly populations.

5.4 Directions for Future Research

These findings that there is a protective effect of antihypertensive treatment on the risk reduction in dementia/CIND, and untreated individuals with uncontrolled systolic blood pressure or higher pulse pressure have the highest risk of cognitive impairment suggest the need to further understand the beneficial effect of antihypertensive treatment, in particular, the specific class of agents most capable of preserving cognitive function in late life. Antihypertensive treatment as primary prevention or as treatment of cognitive impairment will require further study. Future clinical trials specifically designed to address the association between each drug class (or drug) and the risk of dementia and cognitive impairment would be best able to accomplish these goals.

The findings that higher systolic blood pressure and lower diastolic blood pressure in late life are associated with cognitive decline over time raise the need to further understand and quantify the optimal blood pressure that preserves cognitive function. While treatment of hypertension and high pulse pressure may prevent arterial stiffness and preserve cognitive function, excessive blood pressure reduction in the elderly may be deleterious to cerebral perfusion which may in turn affect cognition. Thus, future studies investigating the association between antihypertensive treatment and cognitive function in elderly should explore how factors such as treatment duration, cumulative dosage, age, blood pressure change over time, and cerebrovascular and cardiovascular risk influence this association.

Given the evident beneficial effect of antihypertensive medication in preventing stroke and cardiovascular disease, it will be a challenge to conduct placebo-controlled clinical trials to examine the relationship of antihypertensive therapy and dementia for ethical reasons (10). Thus, larger and long term epidemiological studies in heterogeneous populations will have to be designed to allow for repeated measurements of drug use (including dose and duration) and cognitive evaluation. Such studies will increase our understanding of the optimal treatments to address the modifiable risk factors for cognitive impairment.

5.5 Conclusion

Results of 6 years of follow-up data from the SALSA study demonstrate that higher systolic blood pressure and higher pulse pressure were associated with longitudinal decline in cognitive function after adjusting for potential confounding variables; and untreated individuals with uncontrolled systolic blood pressure and high pulse pressure were at highest risk of cognitive impairment. There was a U shaped relation of concurrent pulse pressure to cognitive function: both low and high pulse pressure were associated with poor cognitive performance. In addition, the results show that higher diastolic blood pressure was associated with longitudinal improvement in cognitive function after adjusting for potential confounding variables and this longitudinal improvement was more pronounced among individuals with low diastolic blood pressure.

Furthermore, the results of this study indicate that any antihypertensive medication use was associated with lower incidence of dementia/CIND. In particular, use of diuretics, beta blockers and ACE Inhibitors was associated with a lower incidence of dementia/CIND. Use of calcium channel blockers was not associated with incidence of dementia/CIND.

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