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Relation of Blood Pressure to Cognitive Impairment and Dementia

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Abstract

Over the past decade several studies have assessed the relation of blood pressure with cognitive function and dementia. While some cross-sectional studies have shown an inverse association between blood pressure levels and cognitive performance or dementia, longitudinal studies yielded controversial results. Most studies relating blood pressure levels in mid-life with late-life risk of cognitive decline or dementia reported a harmful effect of higher blood pressure levels on cognitive function. Studies assessing the effect of late-life blood pressure levels reported that low diastolic and very high systolic levels may increase the risk. Observational studies and randomized cinical trials provide limited evidence for a protective effect of antihypertensive therapy. It seems that the older the person and the more advanced the disease process, the less harmful or even inverted the effect of blood pressure elevation on dementia risk. The reason for this may be that blood pressure declines with age-related pathology, such as vessel stiffening, weight loss, and changes in the autonomic regulation of blood flow.

Keywords

hypertension; cognitive impairment; dementia

EPIDEMIOLOGY OF DEMENTIA, COGNITIVE IMPAIRMENT AND HYPERTENSION

Cognitive impairment and hypertension are among the most common diseases in western societies. The prevalence of dementia increases by a factor of 2 with approximately every five years of age, from about 1% in persons aged 65 years to more than 50% in persons 85 years and older.1 There currently are an estimated 24.3 million people with dementia worldwide, and there emerge about 4.6 million new cases per year. The number of people affected is expected to double every 20 years up to about 80 million cases worldwide in

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2040.2 These figures illustrate the urgency of seeking effective therapeutic interventions for this disease.

Evidence is accumulating that dementia is a heterogeneous disorder and that besides its main neuropathological hallmarks, amyloid beta and neurofibrillary tangles, other factors, especially vascular disease may be involved. One of the most prevalent risk factors in western societies is hypertension. According to the American Heart Association, the prevalence of hypertension amounts to more than 30% in the total US population, meaning that nearly 1 in 3 adults is affected. Its prevalence also increases markedly with advancing age: from less than 30% among persons younger than 60 years of age, to about 63.0% in those aged 60 to 79 years, to over 70% in those aged 80 years or older.3 The evidence relating hypertension or antihypertensive treatment with cognitive impairment and dementia remains controversial. In this review we will re-evaluate the evidence linking both disorders.

DISTINCTION BETWEEN SUBTYPES OF COGNITIVE IMPAIRMENT

Several types of cognitive impairment have been described in research and clinical practice. Dementia, the most severe type, is defined as cognitive impairment in several domains, usually including memory, accompanied also by functional impairment (inability to perform independently in activities of daily living). The most frequently occurring form of dementia is Alzheimer's disease (AD),4 which comprises about 70% of cases. AD is usually identified clinically by short-term memory impairment of slow onset and progression, affecting other cognitive domains (e.g. attention and language), with disease progression, and ultimately causing functional impairment.

The second most prevalent form is vascular dementia (VaD), which has usually been defined as dementia occurring within a short time of a stroke.4 Memory may be affected in VaD, but the main affected cognitive domains are related to executive-frontal abilities. In many cases the temporal relationship between dementia onset and the onset of overt stroke or subclinical cerebrovascular disease is unclear. There is some uncertainty on whether VaD and AD with a cerebrovascular component can be differentiated as distinct diagnostic entities. Studies vary in the proportion of cases of dementia identified as VaD or AD. The co-occurrence of clinical features of both AD and VaD is often referred to as "mixed dementia".

Recently, there has been a growing interest in cognitive impairment in the absence of significant functional impairment. Two terms have been coined to describe this type of cognitive impairment: mild cognitive impairment (MCI), and cognitive impairment-no dementia (CIND). MCI is defined as the presence of memory complaints, detectable memory impairment on neuropsychological tests that is beyond 1.5 standard deviations of the norms, and the absence of functional impairment.5 Most persons with MCI go on to develop AD within 10 years.6 Thus, MCI has become an area of great interest for interventions intended to prevent or slow progression to AD. There are efforts to expand the use of MCI beyond the memory domain to others such as the so called executive frontal abilities.6 Similarly, CIND can be defined as the presence of cognitive impairment in the absence of functional impairment.7

Cognitive impairment is often defined by performance in global measures such as the mini mental status exam (MMSE),8 or by studying specific cognitive domains. The most frequently studied domains in adults and the elderly are memory and executive frontal abilities. Memory is the ability to recall an experience after it has been extinguished. Memory problems are probably the most frequent cognitive complaint that bring patients to medical attention. There are several key processes involved in the long-term maintenance of memories. One is consolidation, based in the hippocampal formation, which enables the

laying down of new memories.9 This is the process first and most prominently affected in AD and amnestic MCI, and tested in clinical practice with verbal learning tests, such as the 5 minute recall of 3 items of the MMSE. Another key memory process is retrieval, which is most affected by lesions involving the frontal lobe-subcortical circuits. Pure problems with this process imply an inability to retrieve memory from its long term storage sites (associational cortices) in the absence of problems in consolidation. This process is commonly affected by cerebrovascular disease, and manifests by difficulty in recalling words or objects which can be aided by giving multiple choice options or cues (recognition). A person with abnormal consolidation will not be able to recognize the 3 recall items from the MMSE even when given cues or multiple choices, and may confabulate, while the person with normal consolidation but abnormal retrieval will have difficulty remembering the words, but will recognize them from a list or remember them once a cue is given.

Executive frontal abilities comprise those skills that are used to plan and execute complex tasks and comprise different processes such as attention, working memory, and impulse control. Executive frontal abilities are most often affected by lesions that disrupt the frontal subcortical networks,10 the same system that support memory retrieval. Tests of executive function commonly used in clinical practice include digits span (working memory) and the attention items of the MMSE, but they capture only limited aspects of executive dysfunction. Comprehensive assessment of executive impairment is difficult and there is great interest in development of sensitive instruments.

The natural history of cognitive impairment could be described as onset of cognitive impairment in some cognitive domain, which may worsen over time, present clinically as CIND or MCI, and eventually progress to dementia when functionality is impaired. In the case of AD this usually presents as impairment in recall with memory complaints that worsen progressively, may eventually be identified as MCI or CIND, and subsequently progresses to full blown dementia. In the case of a large or strategic stroke, dementia onset occurs abruptly within a short time of stroke, with or without preceding cognitive impairment. There is growing interest in other forms of vascular cognitive impairment, which may present slowly and incrementally with worsening “subclinical” cerebrovascular disease (white matter hyper-intensities and “silent infarcts”), affect executive abilities and memory retrieval, and may or may not progress to the syndrome of dementia. Some consider that the cognition field has paid more attention to AD to the detriment of the identification of the other forms of cognitive impairment described here, particularly those related to executive abilities.10 The following paragraphs we will review evidence linking hypertension to the cognitive impairment and dementia.

POTENTIAL MECHANISMS LINKING HYPERTENSION TO COGNITIVE IMPAIRMENT

Blood pressure elevation as cause of dementia

There are several mechanisms potentially linking blood pressure to the risk of cognitive impairment. First, hypertension is a risk factor for ischemic cortical infarcts and subcortical white matter lesions (WMLs), and it is plausible that both play a role as end-stage events.11 The risk of stroke increases with increasing blood pressure,12 and stroke – both clinical and subclinical-strongly increases the risk of cognitive impairment and dementia,13–17 potentially by increasing the deposition of amyloid beta, by destruction of brain parenchyma and atrophy,18, 19 or by causing damage in strategic locations that lead to amnestic syndromes, such as thalamic strokes.20 Ischemic WML reflect areas of demyelinisation and moderate loss of axons with incomplete infarction in subcortical structures, accompanied by arteriosclerotic changes with hyalinization or fibrosis of the small penetrating arteries and

arterioles in the white matter.21, 22 Their etiology remains unclear, however, the pattern of brain vascularization suggests that the periventricular white matter harbors an arterial border zone that is particularly susceptible to being injured as a result of systemic or focal decreases in cerebral blood flow. Arteriolosclerosis is almost always detected within areas of small-vessel disease lesions, and may be the substrate for the decreases in blood flow observed in the white matter of hypertensive patients. Cognitive decline and dementia observed in persons with WML have been suggested to be caused by a disconnection of cortical-subcortical pathways,23, 24 leading to a decline in cognitive functions related to subcortical or frontal lobe structures, as described above.25, 26

Second, hypertension may trigger or cause a blood-brain barrier dysfunction, which has been suggested to be involved in the aetiology and pathogenesis of AD.27–29 Chronic hypertension is associated with increased vascular permeability with protein extravasation, 30 leading in turn to chronic edema and tissue necrosis.30 Dysfunction of the blood-brain barrier may induce penetration of substances from the blood into the brain tissue, where they may interact with neuronal or synaptic function or influence accumulation of beta amyloid leading to cognitive impairment.

A third potential explanation for the association are shared risk factors, such as the formation of free oxygen radicals.31 In recent years, considerable data have accrued indicating that the AD brain is under increased oxidative stress. Evidence for this comes from observations of (1) increased levels of trace elements, in particular iron, aluminium, and mercury that are capable of stimulating free radical generation in the AD brain; (2) increased lipid peroxidation and decreased polyunsaturated fatty acids in the AD brain; (3) increased 4-hydroxynonenal, an aldehyde product of lipid peroxidation in AD ventricular fluid; (4) increased protein and DNA oxidation in the AD brain; (5) diminished energy metabolism and decreased cytochrome c oxidase in the brain in AD; (6) advanced glycation end products (AGE), malondialdehyde, carbonyls, peroxynitrite, heme oxygenase-1 and SOD-1 in neurofibrillary tangles or senile plaques; and (7) studies showing that amyloid beta peptide is capable of generating free radicals.32 Indirect evidence supporting an association between increased oxidative stress and dementia comes from a variety of in vitro studies showing that free radicals are capable of mediating neuron degeneration and death. 32

Low blood pressure as a cause of dementia

Low blood pressure has been reported to trigger brain damage and cognitive impairment. Systemic hypotension with reduced cerebral blood flow may give rise to ischemic neuronal damage in vulnerable areas of the brain, especially in watershed areas, and may further lead to ischemic loss of myelin in the white matter. This mechanism could be reinforced by the dysfunction in autonomic nervous system observed in patients with dementia. The brain is involved in blood pressure regulation and pathological brain changes due to dementia disorders may influence blood pressure level.33

Brain changes causing alterations in blood pressure

Several brain changes due to dementia may influence blood pressure regulation. The hypothalamus, the amygdala, the insular cortex, the medial prefrontal cortex, the locus coeruleus, the pons and the medulla oblongata are involved in central blood pressure regulation.34 Several of these areas are affected in dementia. Neurotransmitters involved in blood pressure regulation, such as acetylcholine, serotonine, norepinephrine or glutamate, are also affected in AD.35 In various studies blood pressure declined with dementia severity or in the years before onset of disease.36–39 Thus, it is possible that low blood pressure in persons with dementia is a consequence of pathological brain changes caused by dementia.

STUDIES ON BLOOD PRESSURE AND RISK OF DEMENTIA

The relation between blood pressure, cognitive function, and dementia has been assessed in several epidemiological studies. As interpretations of the findings are dependent on the study design, we review cross-sectional and longitudinal studies separately, and further subdivide into studies assessing blood pressure measured at mid-life and studies assessing the impact of late-life blood pressure on cognitive function and dementia. We focus on population-based studies which are less prone to selection bias than studies on selected samples such as hospital-based cohorts.

CROSS-SECTIONAL STUDIES

Late-life blood pressure and cognition

Several cross-sectional studies assessed the relation of late-life blood pressure to cognition.[36–38,40–52] Cognitive performance was assessed using different neuropsychological instruments: several studies used a cognitive battery covering various cognitive domains,[40,42–44,47,48,50,51,53] and the remaining studies used measures of global cognition such as the mini mental state examination (MMSE) and the cognitive abilities screening instrument. All studies adjusted for age, sex, and education, but only the minority controlled in addition for antihypertensive drug use or other vascular factors.

Most of the studies reported a harmful effect of high blood pressure on cognitive function,[45–50, 53, 54] whereas three studies did not find an association.[42–44] The studies that reported an association usually used cut-offs for systolic blood pressure (SBP) of at least 160 mm Hg to define hypertension, or clinically diagnosed hypertension (medical history, use of antihypertensive drugs, or blood pressure measures). This association was also supported by two studies, which suggested a U-shaped association between blood pressure and poor cognitive performance.[51, 52] Even among young people (<40 years), high SBP was associated with poorer performance on cognitive tasks (eg, verbal learning and attention).[55, 56] Among AD patients, hypertension was related to a greater cognitive impairment in an African-American sample.[57] Five studies reported an association between low blood pressure and poor global cognitive functioning.[36–38, 58,59]

Late-life blood pressure and dementia

Seven studies have examined the cross-sectional association between late life blood pressure and risk of prevalent AD and dementia.[39, 52, 60–64] Of these, five studies observed an inverse association. Two reported an association between low blood pressure levels and high prevalence of dementia and AD,[39, 52] and three studies observed an association of self-reported or clinically diagnosed hypertension with a lower prevalence of dementia.[60, 63, 64] Two studies found no association between blood pressure and prevalent dementia and AD.[61, 62] The Kuopio Study analysed blood pressure as a continuous variable, which might have masked a non-linear relation between blood pressure and risk of prevalent AD.[61]

In summary, some cross-sectional studies seem to support the notion that severe hypertension impairs cognitive functioning. The finding of low blood pressure or decline in blood pressure in association with cognitive impairment may reflect the necessity of a certain level of blood pressure for older adults to maintain cerebral perfusion, and thereby to preserve cognitive ability. However, it is also possible that low blood pressure in fact is a correlate or consequence of cognitive impairment. This is supported by clinical studies showing that most individuals with dementia have low blood pressure levels,[22, 34, 65, 66] and by population studies reporting a decrease in blood pressure with dementia onset and increased dementia severity.[67, 68] However, in the interpretation of these cross-sectional

studies it has be taken into account that inverse associations may also be caused by biases such as survival bias related to blood pressure.

LONGITUDINAL STUDIES

Midlife blood pressure and cognition

Several studies that measured blood pressure 20–30 years before cognitive assessment, consistently reported a harmful effect of midlife high blood pressure on late-life cognition (table 1).[36, 41, 69–78] The Framingham Study reported an association between midlife hypertension and low late-life cognitive performance in particular in persons without antihypertensive treatment.[74, 79] The Honolulu-Asia Aging Study consistently reported that midlife high SBP was associated with late-life poor cognitive functioning in untreated people.[36] In this cohort, the effect was strongest in apolipoprotein Eε4 carriers.[80] A Swedish cohort of men observed an association between high DBP at age 50 years and cognitive impairment at age 70 years. This association was again strongest in persons without antihypertensive treatment.[41, 75] The Kuopio Study, in which MCI was used as the outcome, did not detect a significant association. However, in this study high SBP in combination with high total cholesterol in mid-life doubled the risk of late-life MCI.[76]

Midlife blood pressure and dementia

An association between raised midlife blood pressure and increased risk of late-life dementia and AD has been reported in four of five studies (table 1).[69, 70, 76–78] In all studies, the association was strongest when blood pressure levels of at least 160/95 mmHg were used as cut-offs. Autopsy and neuroimaging data from the Honolulu-Asia Aging Study further supported these findings by observing a higher burden of neuritic plaques, neurofibrillary tangles and hippocampal atrophy, neuropathological markers potentially underlying dementia etiology, in persons with high blood pressure in midlife.[81] One study, the Hiroshima study, did not find an association between midlife increased SBP and late-life AD.[69] In summary, these studies strongly suggest that mid-life high blood pressure increases the risk of late-life cognitive impairment, dementia and AD.

Late-life blood pressure and cognition

The main longitudinal studies that investigated the relation between late-life blood pressure and cognition are summarised in table 2. The results of these studies are inconsistent. Seven studies reported a positive effect of high blood pressure or hypertension on cognitive impairment or cognitive decline.[51, 82–87] Three studies reported a U-shaped relation between SBP and cognitive function.[37, 88, 89] Three studies reported no significant effect of high blood pressure on cognition.[90–92]

Among the studies showing an association, two observed a linear association between high SBP and cognitive decline,[51, 84] and one an association between high DBP and lower cognitive performance.[83] In the French Epidemiology of Vascular Aging study those who had persistently high blood pressure and were not treated with antihypertensive drugs had the highest risk for cognitive decline over 4 years.[85] A U-shaped relation was reported from the Kungsholmen project, the East Boston Study and the Duke study.[37, 89,88] Of the three studies reporting no association, the Kuopio Study showed no relation with high blood pressure, but reported that treated high bood pressure, which might indicate more severe hypertension, was associated with MCI.[91] The other two cohorts, one derived from a mixed white and African-American cohort in which antihypertensive therapy was highly prevalent (around 50%),[92] and the ILSA did not detect an association between hypertension and MCI or hypertension and progression from MCI to dementia.[90]

Late-life blood pressure and dementia

Many longitudinal studies have examined the relation between late-life blood pressure and risk of incident AD and dementia (table 3).[93–105] Eight studies did not find a significant association between high blood pressure or hypertension and risk of dementia and AD,[96–103] but some studies did report an association with VaD.[99, 101] In most of these studies, hypertension was ascertained as self-reported high blood pressure or a history of hypertension.

The Gothenburg H-70 study found significantly higher SBP and DBP in individuals who developed dementia after 9–15 years than in those who remained free of dementia.[95] Consistent with this finding, the Kungsholmen project reported that very high SBP >180 mm Hg was associated with a greater than 50% increased risk of dementia and AD, independent of previous cognitive status.[39, 93]

Four studies reported an inverse increased incidence of dementia and AD in individuals with low DBP or SBP,[93, 94, 104, 105] three studies had more than 4 years of follow-up.[93, 94, 105] The Kungsholmen project showed that low DBP <70 mm Hg was associated with an increased risk of dementia and AD, especially in those taking antihypertensive drugs,[93] or in individuals carrying an *APOE*ε4 allele.[106] Similarly, the pooled 3-year follow-up data of the Gothenburg H-70 and the Rotterdam studies found that the inverse association between SBP and DBP and risk of dementia was confined to individuals taking antihypertensive medications.[104] The Bronx Aging Study on community-dwelling volunteers showed that over 21 years follow-up, low DBP (≤70 mm Hg) was associated with a nearly twofold increased risk of AD and dementia, and dementia risk was even higher for individuals with persistently low blood pressure.[105] In addition, the Kungsholmen project also suggested that a greater decline in SBP was predictive of dementia and AD among participants who had initial SBP of less than 160 mmHg or who were affected by vascular disorders such as stroke and diabetes mellitus.[107]

In summary, these studies do not show a consistent pattern in the relation between blood pressure and cognition. However, they clearly indicate that the relation between late-life blood pressure and cognitive performance is different from the findings of studies addressing mid-life blood pressure in relation to late-life cognitive functioning. There is no strong evidence to indicate that raised blood pressure in later life is a risk factor for dementia and AD, although an increased dementia risk among individuals with high blood pressure, especially very high SBP (eg, ≥180 mm Hg), has been reported. Rather, more studies have shown a risk effect of low blood pressure in later life on the development of dementia and AD.

METHODOLOGICAL ISSUES

Some methodological issues need to be taken into account in interpretation of these findings. First, cross-sectional studies are limited in determining the direction of an association because both exposure and outcome are assessed simultaneously. Longitudinal studies provide an opportunity to assess the temporal relation between blood pressure and cognition and dementia, however, the length of follow-up remains -due to the long pre-clinical period of dementia- relevant. Second, cognitive impairment and dementia are likely to represent a clinically and pathologically heterogeneous syndrome, and definitions of subtypes are not clearly established diagnostic entities. The frequency of dementia in a group of individuals with cognitive impairment is the result of both the definition of the disorder and the underlying pathophysiology. Different definition of dementia subtypes thus may lead to different results. Third, most studies used standardised criteria to define dementia and its main subtypes on the basis of extensive neuropsychological and clinical assessments. As

neurodegenerative markers and vascular lesions in the brain are very common in elderly people, the finding of an association with AD in some studies may actually indicate an association with the mixed type of dementia. Finally, lack or insufficient control of antihypertensive therapy and vascular comorbidities such as diabetes mellitus and obesity, and variability in exposure assessments may partly explain the discrepancies among studies.

CONCLUSION

While the association between elevated mid-life levels of blood pressure and late-life cognitive impairment is relatively consistent across cohorts, the association between late-life blood pressure levels and cognitive decline remains inconsistent. Closer analysis of the inconsistencies between cross-sectional and longitudinal studies suggests that the discrepancies among them may be accounted for by elements of the study design, specifically a combination of the duration of time between the measurement of blood pressure and brain function, and the ages at which the measurements were made. In general, it seems that the older the person and the more advanced the disease process, the less harmful or even inverted the effect of blood pressure elevation on dementia risk. The reason for this may be that blood pressure declines with age-related pathology, such as vessel stiffening, weight loss, and changes in the autonomic regulation of blood flow.

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Table 1

Studies on mid-life hypertension and risk of cognitive decline and dementia

Study	Setting	Participants	Main results
Studies on Cognition			
Elias et al,74 1993	Framingham Study, USA	1702 persons, age 55–88 years, BP measured 20 years earlier	High BP and chronic hypertension associated with lower cognitive function
Launer et al,36 1995	HAAS, USA	3735 Japanese-American men, mean age 78 years, BP measured 25 years earlier	Each 10-mm Hg increase in SBP associated with an increase in risk for intermediate cognitive function of 7% (95% CI 3% to 11%) and for poor cognitive function of 9% (95% CI 3% to 16%)
Swan et al,73 1998	Cohort of male twins, USA	392 men, age 68–79 years, BP measured at 43–53 years	SBP ≥140 mmHg related to increased decline in cognitive function over 10 years
Swan et al,72 1998	Western Collaborative Group Study, USA	717 white men, mean age 75 years; BP measured at mean age 45 years	Persistent high SBP (≥140 mmHg) related to reduced verbal learning and memory performance
Kilander et al,41 1998	Male cohort in Uppsala, Sweden	999 swedish men, age 69–75 years; BP measured at age 50 years	DBP at age 50 years inversely related to global cognitive function at age 70 years
Kilander et al,75 2000	Male cohort in Uppsala, Sweden	502 swedish men, age 69–74 years; BP measured at age 50 years	Low DBP (≤70 mmHg) related to better performance on tests assessing the subcortical-frontal cognitive functions
Kivipelto et al, 762001	Kuopio and Joensuu Study, Finland	1449 people, age 65 years, follow-up 21 years	Higher SBP associated with lower cognitive function, no association with DBP
Elias et al,71 2004	Maine-Syracuse Longitudinal Study, USA	529 persons, age 18–83 years; BP measured up to 20 years earlier	BP inversely related to visualisation/fluid composite score
Studies on Dementia			
Launer et al,70 2000	HAAS, USA	3703 Japanese-American men, age 65 years; BP was measured at age 45–68 years	Midlife high BP ≥ 160/95 mmHg increased risk of dementia in later life in men not treated with antihypertensive drugs
Kivipelto et al,76 2001	Kuopio and Joensuu Study, Finland	1449 people, age ≥65 years, follow-up 21 years	Higher SBP and lower DBP associated with dementia
Wu et al,77 2003	Linxian County, China	602 persons, age ≥65 years; BP measured over 15 years earlier	Hypertension ≥160/95 mmHg in midlife associated with higher risk of AD in late life
Yamada et al.69 2003	Adult Health Study in Hiroshima, Japan	1774 persons, age ≥60 years, BP assessed >25 years ago	High SBP related to risk of VaD but not AD
Whitmer et al,78 2005	Kaiser Permanente Medicare Program of Northern California	8845 persons, mean age 69 years, hypertension assessed at mean age of 42 years	Hypertension weakly related to higher risk of dementia

Table 2

Studies on late-life blood pressure and risk of cognitive decline

Study	Setting	Participants	Main results
Guo et al,37 1997	Kungsholmen Project, Sweden	1736 persons, age ≥75 years, followed for 3 years	U-shaped relation with lower performance on MMSE
Glynn et al,89 1999	East Boston cohort study, USA	3657 persons, age ≥65 years, followed for 9 years	U-shaped relation with lower performance on mental status questionnaire test
Tzourio et al,85 1999	Epidemiology of Vascular Aging Study, France	1172 persons, age 59–71 years, followed for 4 years	High BP ≥160/95 related to poorer cognitive performance (OR 2.8, 95% CI 1.6–5.0)
Haan et al,84 1999	Cardiovascular Health Study, USA	5888 Medicare recipients age ≥65 years, followed for 7 years	Each 1 SD increase (22 mmHg) in SBP related to 0.96 points decline in MMSE over 7 years
Knopman et al,86 2001	Atherosclerosis Risk in Communities, USA	10963 persons, age 47–70 years, followed up for 6 years	Hypertension (≥140/90) or use of antihypertensive medication related to increased decline on digit symbol subtest of WAIS
Bohannon et al.88 2002	Duke Population Studies of the Elderly, USA	3202 persons, age ≥65 years, followed for 3 years	U-shaped relation in white persons, no association in African-Americans
Piguet et al,87 2003	Sydney Older Persons Study, Australia	377 persons, age ≥75 years, followed for 6 years	Hypertension associated with greater decline in MMSE over time
Reinprecht et al,83 2003	Men born in 1914 Study, Sweden	186 men, assessments at age 68 and 81 years	DBP in tertiles at age 68 inversely related to verbal, spatial and speed performance at 81 years
Elias et al,82 2003	Framingham Heart Study, USA	1423 persons, age 55–88 years, followed for 4–6 years	Hypertension (≥140/90 mmHg) related to a lower total neuropsychological test score in men, not in women
Herbert et al,92 2004	Chicago Health and Aging Project, USA	4284 persons, age ≥65 years, followed up for 6 years	No association between BP and cognitive function
Tervo et al,91 2004	Cohort Study in Kuopio, Finland	806 persons 60–76 years, followed- up for 3 years	High BP (>160/95 mmHg) not related to MCI, weak association between treated hypertension and MCI
Solfrizzi et al,90 2004	ILSA, Italy	1445 persons, age 65–84 followed- up for 3.5 years	No association between hypertension and cognitive function
Waldstein et al,51 2005	Baltimore Longitudinal Study on Aging, USA	847 persons, age 60–96 years, followed up to 11 years	High SBP related to poorer cognitive performance and increased cognitive decline

Table 3

Studies on late-life blood pressure and dementia

Study	Setting	Participants	Main results
Yoshitake et al,99 1995	Hisayama Study, Japan	828 non-demented persons, age 65- 98 years, followed for 7 years	Hypertension (≥160/95) not related to AD but to VaD
Skoog et al,95 1996	Gothenburg H-70 Study, Sweden	382 persons, age 70 years, followed up to 15 years	Higher SBP and DBP levels at baseline associated with increased risk of dementia
Brayne et al,100 1998	Cambridge Cohort Study, UK	376 persons, age ≥75 years, followed for 2.4 years	History of hypertension not associated with dementia
Tyas et al,98 2001	Cohort study in Manitoba, Canada	694 persons, age ≥65 years followed for 5 years	Self reported high BP not related to AD
Ruitenberg et al,104 2001	Gothenburg H-70 and Rotterdam Studies	6985 persons, age ≥55 years, followed for 3 years	BP inversely related to dementia risk in users of antihypertensive drugs
Morris et al,94 2001	East Boston study, USA	378 persons, age ≥65 years, followed for 13 years	Association of increased SBP but not DBP levels with lower risk of dementia
Posner et al,101 2002	WHICAP, USA	1259 Medicare recipients, age ≥65 years followed for 5 years	Hypertension history related to VaD but not AD
Lindsay et al,97 2002	Canadian Study of Health and Aging	3566 persons, age ≥65 years, followed for 5 years	Self reported high BP not related to AD
Kuller et al,102 2003	Cardiovascular Health Study, USA	3275 Medicare recipients in four clinical centers, age ≥65 years, followed for 7 years	History of hypertension not associated with dementia
Verghese et al,105 2003	Bronx Aging Study, USA	488 community volunteers, age ≥75 years, mean follow-up 6.7 years	Low diastolic pressure associated with higher risk of dementia
Qiu et al,93 2003	Kungsholmen Project, Sweden	1270 persons, age ≥75 years, followed over 5 years	Both low DBP and SBP associated with an increased risk of AD and dementia
Borenstein et al,96 2005	Kame Project, USA	1859 Japanese Americans, age ≥65 years, mean follow-up 9 years	Self-reported hypertension not related to AD
Pettiti et al,103 2005	Women's Memory Study, USA	1133 women, age ≥75 years, followed for 7 years	SBP and DBP measured 5 or 9 years before dementia diagnosis not significantly different between demented and control groups