High blood pressure at old age : The Leiden 85 plus study

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Chapter 4

The Effect of Age on the Association Between Blood Pressure and Cognitive Function Later in Life

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Abstract

Objectives:
To determine the prospective relationship between blood pressure (BP) and cognitive function across a wide age range.
Design:
Prospective population-based cohort study.
Setting:
The Rotterdam Study and the Leiden 85-plus Study.
Participants:
Three thousand seventy-eight men and women, initial age 55 to 84 from the Rotterdam Study and 276 men and women, initial age 85, from the Leiden 85-plus Study.
Measurements:
Systolic BP (SBP) and diastolic BP (DBP) were measured at baseline, cognitive function was assessed at the end of follow-up using a dedicated neuropsychological test battery. The association between baseline BP levels and cognitive function later in life was assessed in 10-year age groups in the Rotterdam Study and in 85-year-olds of the Leiden 85-plus Study.
Results:
In the youngest participants (<65), SBP and DBP were not associated with cognitive function 11 years later. For persons aged 65 to 74, higher baseline SBP and DBP were related to worse cognitive function 11 years later. In contrast, in older age (≥75), higher SBP and DBP seemed to be related to better cognitive function at the end of follow-up. This effect appeared strongest in the highest age group (85 years).
Conclusion:
High BP was associated with greater risk of cognitive impairment in persons younger than 75 but with better cognitive function in older persons. Age-specific guidelines for BP management are needed, because the current directive that "lower is better" may not apply to BP levels in the very old.

Introduction

Data on the relationship between BP and cognitive function are not consistent, notwithstanding a large number of studies that have investigated the relationship.[1] Most studies report that higher BP levels at middle age relate to cognitive impairment later in life,[2–5] but results on the relationship between higher BP in older age and later cognitive function are conflicting. Some studies have shown a negative effect of higher BP on cognitive function,[6,7] whereas others have not.[8,9] These findings may suggest that age influences the relationship between BP and cognitive function. If this suggestion is correct, it might have consequences for BP management, especially in very old people. Earlier evidence of beneficial effects of BP lowering on cognitive function in older people[10] could not be replicated in recent studies,[11] despite the fact that stroke risk was significantly lower in those studies. Therefore, the effect of age on the relationship between baseline BP and cognitive function later in life was examined over a wide range of age groups in two prospective population-based studies (the Rotterdam Study and the Leiden 85-plus Study). It was hypothesized that the relationship between BP and cognitive function changes with age. Whereas high BP is a risk factor for cognitive impairment at middle age, it might have beneficial effects in old age.

Methods

Populations

The Rotterdam Study is a large, prospective, population-based cohort study conducted in all inhabitants aged 55 and older of Ommoord, a district of Rotterdam, The Netherlands.[12] The medical ethics committee of the Erasmus University of Rotterdam approved the study, and informed consent was obtained from all participants. Of 10,275 eligible subjects, 7,983 (77.7%) participated in the baseline examinations between 1990 and 1993 (mean age 71.2±25.2, range 55–106). All participants were interviewed at home and visited the research center for further examinations. At the fourth survey (2002–2004), cognitive function was extensively assessed using a dedicated neuropsychological test battery.

The Leiden 85-plus Study is a prospective population-based cohort study of 85-year-old inhabitants of Leiden, The Netherlands. The medical ethics committee of the Leiden University Medical Centre approved the study, and informed consent was obtained from all participants. Between September 1997 and September 1999, all 705 inhabitants of Leiden born between 1912 and 1914 were contacted within a month after their 85th birthday; 599 (85.07%) agreed to participate. From age 85 to 90, annual neuropsychological tests were performed during home visits.

Study Sample

In the Rotterdam Study, the sample for this study was restricted to the 6,502 participants aged 55 to 85 with BP measurements at baseline because of the limited number of participants aged 85 and older with follow-up examinations 11 years later (n=4). Of these 6,502 participants, 3,424 (52.7%) did not participate in the fourth survey; 63.7% had died, 29.4% refused the in-person examination or were too ill to visit the research center, and 6.9% could not be contacted. The proportion of participants who did not participate in the fourth survey increased with age, from 30.9% for age 55 to 64 to 54.4% for age 65 to 74 to 87.8% for age 75 to 84. The study sample therefore consisted of 3,078 participants with baseline BP measurements and cognitive measurements 11 years later.

In the Leiden 85-plus Study, BP was measured in 572 participants at age 85; 276 of these underwent neuropsychological testing 5 years later at age 90. Of the remaining 296 individuals (51.7%) who did not participate at age 90, 87.5% had died, and 12.5% refused to participate.

Blood Pressure

In both study samples, systolic BP (SBP) and diastolic BP (DBP) were measured twice at baseline using a sphygmomanometer after 5 minutes of seated rest. The averages of two measurements were used in the analyses. In the Rotterdam Study, the two measurements were separated by a count of the pulse rate. In the Leiden 85-plus Study the two measurements were 2 weeks apart.

Cognitive Function

Global cognitive function was measured in both cohorts using the Mini-Mental State Examination (MMSE; range 0–30, lower scores indicating worse cognitive

function).[13] Only a serial 7s question was used, not the WORLD-backward version. In addition, a dedicated neuropsychological test battery was used to assess executive function and memory. Executive function was assessed using the abbreviated Stroop Test part 3[14] and the Letter Digit Substitution Task (LDST) [15] in both cohorts and the Word Fluency Test (WFT)[16] in the Rotterdam Study only. Memory was assessed using the 15-Word Learning Test (15-WLT) immediate and delayed recall[17] in the Rotterdam Study and the 12-Picture Learning Test (12-PLT) immediate and delayed recall[18] in the Leiden 85-plus Study. Dutch-translated and -validated versions were used for all neuropsychological tests.
MMSE score was used as a measure of global cognitive function. In the Leiden 85-plus Study, executive function and memory were not assessed in participants with a MMSE score of 18 points or lower (n=74) because it was assumed that the tests lack reliability and validity in subjects with severe cognitive impairment. These participants were assigned to the lowest quartile of the distribution to reflect their impaired state of cognitive function.

Additional Measurements

In both study populations, education was measured at baseline and dichotomized into primary education or less versus more than primary education. Antihypertensive drug use was determined at baseline during the home interview (Rotterdam Study) or through pharmacy records (Leiden 85-plus). Smoking status, alcohol intake, history of stroke, history of diabetes mellitus, and history of cardiovascular disease were assessed at baseline.

Statistical Analysis

The association between baseline BP and cognitive function later in life was examined using linear regression models, with BP as independent and cognitive test score as dependent variable. All analyses were adjusted for age (Rotterdam Study only), sex, and education level. Additional adjustments were made for the use of antihypertensive drugs, smoking status, alcohol intake, history of stroke, history of diabetes mellitus, and history of cardiovascular disease. Analyses were conducted using the SPSS statistical package (release 11.1; SPSS, Inc., Chicago, IL).

Results

Table 1 shows the baseline characteristics of participants who did and did not undergo cognitive testing at the follow-up examination for both cohorts. In both studies, the percentage of women was higher, and their proportion increased with age. The level of education was lower in older age (in those who originated from earlier birth cohorts). Average SBP increased and DBP decreased with age, although DBP was highest in the oldest old. The percentage of participants with a history of stroke, diabetes mellitus, or cardiovascular disease increased with age, as did the use of antihypertensive treatment.

In the Rotterdam Study, participants without cognitive assessment at follow-up were older and less educated and had higher SBP and DBP and worse cognitive function at baseline than the participants included in the analyses. This was seen similarly for all age groups from age 55 to 85. In the oldest old (Leiden 85-plus Study), participants who did not undergo cognitive testing at the follow-up examination had lower SBP and DBP and concurrent worse cognitive function at baseline than the participants included in the analyses. In both samples, participants who were not included in the analyses more often had a history of stroke, diabetes mellitus, or cardiovascular disease than participants in the study samples.

Figure 1 shows the effect of age on the association between baseline BP and cognitive function later in life. Individuals up to 65 years of age showed in general little decline in cognitive function over the 11-year follow-up period, and neither baseline SBP nor DBP was related to cognitive function 11 years later. In individuals aged 65 to 74, higher SBP and DBP at baseline were related to worse cognitive function 11 years later. With older baseline age, the effect of BP on cognitive function seemed to invert; in individuals aged 75 and older, higher SBP and DBP at baseline were related to better cognitive function 11 years later, although in the Rotterdam Study, the number of people in this age group was small, and consequently results were not significant for the majority of tests. This effect was even stronger in the highest age group (85 years, subjects from the Leiden 85-plus Study), with higher SBP and DBP related to better cognitive function 5 years later. The shift from risk to benefit of high BP from age 65 to 85 years was observed for all neuropsychological tests (Figure 1).

Table 1. Baseline Characteristics of Study Samples and Participants without Follow-up Examination

	Rotterdam Study								Leiden 85-plus Study	
	Total sample		Age groups							
			55-64 yrs		65-74 yrs		75-84 yrs		85 years	
Characteristic	Study Sample	No follow-up	Study Sample	No follow-up	Study Sample	No follow-up	Study Sample	No follow-up	Study Sample	No follow-up
Number	3078	3424	1772	791	1126	1341	180	1292	276	296
Age, mean ± SD	64.5 ± 6.0	71.6 ± 7.8	60.2 ± 2.8	60.7 ± 2.8	69.1 ± 2.7	70.3 ± 2.8	77.8 ± 2.3	79.6 ± 2.8	85	85
Female, %	59.1	58.3	58.4	54.9	58.8	54.4	67.8	64.4	72.1	61.8
Low level of education, %	27.9	44.1	23.8	32.9	31.6	40.4	44.9	55.3	62.0	68.3
Use of antihypertensive drugs, %	23.9	37.1	20.2	25.9	27.4	37.4	39.1	43.6	36.2	35.8
SBP, mmHg, mean ± SD	135 ± 20	143 ± 23	131 ± 20	135 ± 21	139 ± 20	144 ± 22	140 ± 19	147 ± 24	158 ± 18	153 ± 19
DBP, mmHg, mean ± SD	74 ± 11	74 ± 12	74 ± 11	76 ± 11	73 ± 11	74 ± 12	71 ± 11	72 ± 13	78 ± 9	75 ± 10
MMSE-score, mean ± SD	28.1 ± 1.5	26.9 ± 2.9	28.2 ± 1.4	27.7 ± 2.1	28.0 ± 1.5	27.4 ± 2.2	27.7 ± 1.6	26.0 ± 3.7	25.7 ± 4.3	22.4 ± 7.2
Ever smoking, %	67	66	69	78	65	70	50	54	43	52
Alcohol intake, U/day ± SD	1.3 ± 1.8	1.3 ± 2.0	1.4 ± 1.9	1.5 ± 2.2	1.3 ± 1.8	1.3 ± 2.0	0.8 ± 1.2	0.9 ± 1.6	0.8 ± 0.8	1.0 ± 0.9
History of stroke, %	1	4	1	2	1	4	3	7	7	13
History of diabetes mellitus, %	6	14	5	7	7	15	10	17	13	19
History of cardiovascular disease, %	18	40	15	25	21	36	25	52	56	68

SBP = systolic blood pressure; DBP = diastolic blood pressure; MMSE = Mini-Mental State Examination
SD = standard deviation

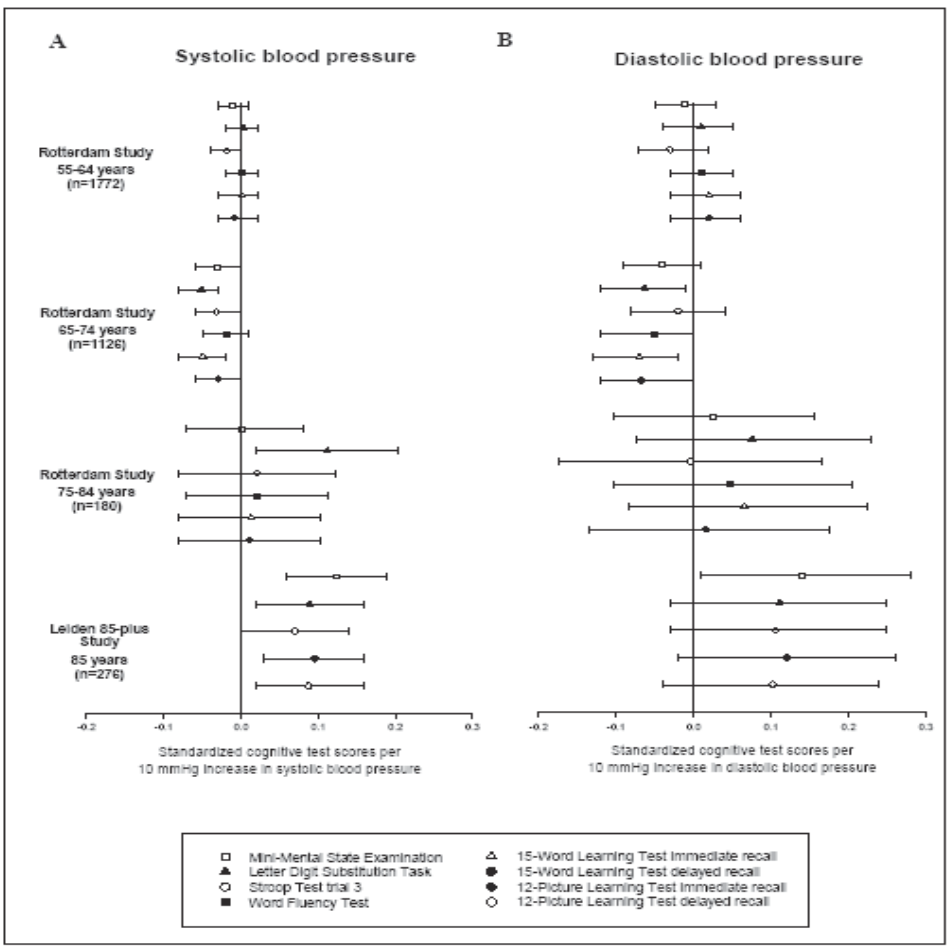

Figure 1. The effect of age on the association of baseline blood pressure and cognitive function later in life. Symbols represent the mean standardized cognitive test scores and 95% confidence intervals per 10 mmHg increase in systolic (A) and diastolic (B) blood pressure. For graphical reasons, the estimates for the Stroop test were inversed because a higher Stroop score reflects worse cognitive function. Analyses were adjusted for age (Rotterdam Study only), sex and level of education.

Additional adjustments for the use of antihypertensive drugs, smoking status, alcohol intake, history of stroke, history of diabetes mellitus, or history of cardiovascular disease did not markedly change any of these results (data not shown).

Discussion

These data show that age has an important effect on the relationship between BP and cognitive function later in life. In participants younger than 75, higher SBP and DBP were associated with worse cognitive function 11 years later. This relationship reversed in older participants, in whom higher SBP and DBP at baseline were associated with better cognitive function later in life.

The detrimental effect of higher BP levels on cognitive performance in middle-aged people is well established,[2–5] and the results from the analyses in the 65- to 74-year age group in the Rotterdam Study sample were consistent with these previous findings. The mechanisms behind this association may involve atherosclerotic changes in large and hyaline degeneration in small cerebral vessels, ischemic brain lesions, and disturbances in endothelial or brain cell permeability,[1–5] although in the oldest-old participants in the Rotterdam Study, high BP at baseline was related to better cognitive function later in life, and when the analyses were replicated in the 85-year-old participants of the Leiden 85-plus Study sample, similar results were found.

In the current study, participants with low BP and good cognitive function at baseline were more likely to be included in the study sample than participants with higher BP and worse cognitive function at baseline. One might expect that this selective attrition could have influenced the results, especially in the oldest age group of the Rotterdam Study, in which a large proportion (87.8%) of the participants who were present at baseline were not available at follow-up. Although selective attrition may have attributed to the formation of a selective group of survivors in the oldest age group of the Rotterdam Study, this does not necessarily diminish the importance of the findings that, in this group of individuals, high BP was related to better cognitive function later in life.

The results on the relationship between BP and cognitive function from the Leiden 85-plus Study, with data available on the oldest old (aged 85 years), confirmed those from the Rotterdam Study. Although the proportion of participants in the Leiden 85-plus sample who were not available at follow-up was also considerable (51.72%), these participants had predominantly lower BP levels and worse cognitive function than those included in the analyses. This concurs with previous findings that high BP is not a risk factor for mortality in the oldest old.[19,20]

Although the observations cannot be interpreted that BP management should be changed in old individuals, they underscore the need for further elucidation of risks and benefits of BP lowering therapy in the oldest old.

The previous studies that associated higher BP in middle-age with worse cognitive function later in life[2–5] suggested that antihypertensive treatment might prevent or delay the onset of impaired cognitive function, but data from randomized clinical trials on the beneficial effects of antihypertensive treatment on cognitive function are not consistent.[7,10,21–23] From these earlier studies, only the Syst-Eur trial,[10] which studied the effect of treatment with nitrendipine with the possible addition of enalapril and hydrochlorothiazide on incidence of dementia, showed benefit that could not be replicated in the Hypertension in the Very Elderly Trial (HYVET).[11] This large, double-blind, placebo-controlled trial included 3,336 participants aged 80 and older and showed that antihypertensive treatment with indapamide with the option of perindopril did not reduce incidence of dementia.[11] Although the short follow-up, owing to the early termination of the trial, could have affected this result, the alternative explanation is that there is no clear benefit in correspondence with the observational data presented here. Alternatively, the use of the relatively insensitive Mini-Mental State Examination as an outcome measure for cognitive impairment or decline could also have contributed to the inconsistent findings in clinical trials. Another explanation is that the oldest old in whom impaired cognitive function is most prevalent were underrepresented in these studies.

It is tempting to speculate why BP lowering is consistently associated with a lower risk of stroke, whereas this benefit is not reflected in consistent preservation of cognitive function. Although counterintuitive, the aggregated data from the observational and experimental studies suggest that, in the oldest old, higher BP may have also have a benefit with respect to cognitive function, possibly through

the necessity of maintaining adequate cerebral perfusion.[24–26] Local regulation of cerebral blood flow tightly regulates cerebral perfusion over a wide range of BP.[27] A combination of myogenic and neurogenic mechanisms mediates this autoregulation of cerebral blood flow.[28] With older age, basal cerebral blood flow decreases, possibly caused by impaired cerebral autoregulation through atherosclerosis or endothelial dysfunction.[29,30] In the oldest old, higher BP may therefore be required to prevent cerebral hypoperfusion and preserve cognitive function. Individuals with greater risk of morbidity and mortality are present in the population-based prospective studies but are less likely to be included in randomized clinical trials. Participants of the HYVET[11] who were randomized to placebo had a mortality risk less than half that of the general population, indicating the recruitment of relative healthy people into the trial.

The current study had several strengths. Data on BP and cognitive function were available from two independent Dutch prospective population-based studies. These two cohorts are complementary and allowed the association between BP level and cognitive function from age 55 onward to be examined. The dedicated neuropsychological test batteries that were used in both studies were comparable and assessed several cognitive domains, including global cognitive function, executive function, and memory. Some of the participants in the oldest age group (Leiden 85-plus Study) could not undergo all the cognitive tests that were available because of their severely impaired cognitive status (MMSE score≤18). Rather then excluding these persons from the analyses, the information on the cognitive status of these participants that was available (MMSE score) was used to infer their scores on the other cognitive tests.

There were also some limitations. The associations between BP and cognitive function were based on the assessment of BP at baseline and the measurement of cognitive function 11 years (Rotterdam Study) or 5 years (Leiden 85-plus Study) later. The difference in follow-up length between the two study samples warrants some caution in the comparison and interpretation of the results, because the Rotterdam Study results are based on 11 years of follow-up, compared with 5 years of follow-up in the Leiden 85-plus Study. Despite the long follow-up periods, extension of these periods may have revealed even stronger associations between baseline BP and cognitive function later in life, because the effect of BP on cognitive function is thought to be long-term.[1] This may especially play a role up to the age of 65, for which the follow-up period may just have been too short.

However, a longer follow-up, especially in older age, would also lead to further dropout of participants and consequently to limited statistical power, as well as the potential of survival bias.

In conclusion, this study shows that the relationship between baseline BP levels and cognitive function later in life differs across age groups. Although there is not a clear age cut-off at which the relationship between BP and cognitive function later in life inverses, there seems to be a gradual shift with age from high BP being a risk factor for cognitive impairment to high BP potentially helping to preserve cognitive function in the oldest old, presumably through maintaining perfusion pressure. The data illustrate that it should not simply be assumed that advice to 65-year-olds on target BP should be the same as advice to 85-year-olds and underscore the need for further elucidation of risks and benefits of BP lowering therapy in the oldest old.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

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