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The association between low diastolic blood pressure in middle age and cognitive function in old age. A population-based study

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Abstract

Background: previous longitudinal studies have shown an inverse relation between blood pressure and cognitive function.
Objective: to determine the association between mid-life blood pressure and performance in different areas of cognitive function in late life.
Subjects and methods: we recruited 502 men, aged 69–74 years, from a population-based cohort in Uppsala, Sweden. Blood pressure had been measured at age 50 and we examined performance in 13 psychometric tests about 20 years later.
Results: after the 39 men with a previous stroke had been excluded, there was an inverse relation between diastolic blood pressure at age 50 and performance 20 years later in the digit span test, the trail-making tests and in verbal fluency. The relationships were significant, independently of age, education and previous occupational level. Men within the lowest category of diastolic blood pressure (≤ 70 mmHg, $n = 59$) showed the best results. Baseline blood pressure levels were not linked to performance in tasks on vocabulary, verbal learning and memory or figure copying.
Conclusions: low blood pressure in mid-life indicates a low long-term cerebrovascular risk and is associated with higher late-life performance in cognitive tests that mainly assess subcortico-frontal cognitive functions.

Keywords: *blood pressure, cognitive function, risk factor, trail-making test, verbal fluency*

Introduction

The interest in cognitive decline of vascular origin is steadily increasing because of the possibilities of preventive treatment. Hypertension is the main risk factor for cerebrovascular disease and there is a strong, linear relation between diastolic blood pressure and stroke, even down to low levels (76 mmHg) [1]. We have previously reported [2] an inverse relationship between diastolic blood pressure in middle age and cognitive performance 20 years later—as measured by the Mini-Mental State Examination (MMSE) [3] and the trail-making tests [4].

Hypothetically, low blood pressure might protect from subclinical cerebrovascular lesions causing cognitive impairment. In magnetic resonance imaging studies, subcortical white matter lesions are related mainly to impairment in psychomotor speed, verbal fluency and attention [5–9].

In this study we aimed to investigate the association between low mid-life blood pressure and late-life performance in different areas of cognitive function, with special reference to subcortical functions.

Methods

We recruited the study participants from a cohort of 70-year-old men who had been followed since age 50 with respect to cardiovascular risk factors. The original cohort was defined as all men born in 1920–24 who lived in the municipality of Uppsala in 1970–73

Table 1. The cognitive tests

Test	Area of function	Reference
Vocabulary (WAIS)	Verbal knowledge, general intellectual level	[11]
Digit span test	Verbal immediate memory, attention	[11]
Claeson–Dahl test	Verbal learning and delayed recall	[12]
Block span test	Non-verbal immediate memory, attention	[13]
Trail-making tests A–D	Psychomotor speed and shifting capacity	[4]
Rey–Osterrieth figure	Figure copying and immediate recall	[4]
FAS[a]	Verbal fluency	[13]
Mini-Mental State Examination	Composite: orientation, immediate verbal memory and recall, calculation, language, praxis, figure copying	[3]

WAIS, Wechsler Adult Intelligence Scale.
[a] Subject must write as many words starting with the letters 'F', 'A' and 'S' as possible within time limits.

($n = 2841$). A total of 2322 men (82%) participated in the baseline examination at 50 years of age. From this examination, we collected data on systolic and diastolic blood pressure, measured in the supine position after a 10-min rest to the nearest 0 or 5 mmHg. We also classified subjects according to their occupational level. The cohort was re-examined at age 60 ($n = 1860$), and at age 70. In the latter examination, 1221 men (73% of the 1681 survivors living in Uppsala) took part. Of these, 999 agreed to participate in cognitive testing as well [4], and the first 502 of this group underwent a more extensive test battery.

When the participants were 70 years old, we measured systolic and diastolic blood pressure in the supine position to the nearest 2 mmHg, and calculated the mean of two measurements. An oral glucose tolerance test identified subjects with diabetes mellitus according to the classification of the National Diabetes Data Group [10]. We recorded all pharmacological treatment, and defined antihypertensive treatment as any treatment with drugs that lower blood pressure (i.e. diuretics, β-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors and vasodilators) irrespective of indication. Subjects with a stroke before the cognitive testing were identified by a positive answer to the question "Have you had a stroke—i.e. a cerebrovascular thrombosis or bleeding?" in connection with the testing and/or by data from the Swedish National Inpatient Register, covering all diagnoses in hospitalized patients from 1970 and onwards.

The following diagnoses according to the codes of the International Classification of Diseases, versions 8 or 9, were used for classification of stroke: intracerebral haemorrhage (431), thrombo-embolic stroke (433–434), transient ischaemic attack (435) and acute 'ill-defined' cerebrovascular disease (436). Educational level was stratified as low (elementary school only, 6–7 years), medium (secondary school) or high (university studies). The main previous occupational level was also divided into three categories: low (e.g. manual workers and small farm holders), medium (e.g. foremen, clerks, salesmen) and high (e.g. professionals, business managers).

Cognitive tests

The tests and areas of cognitive function are shown, in the order that they were administered, in Table 1.

In the vocabulary subtest from the revised Wechsler Adult Intelligence Scale [11], the subject is asked to explain the meaning of a total of 35 words. In the digit span, he is asked to repeat a series of numbers in the right order. We noted the total number of correct answers in digits forwards and backwards. In the Swedish Claeson–Dahl test, a list of 10 common words is read to the subject, and is repeated until he can correctly recall all of them or a maximum of 10 times [12]. We tested retention after 10–15 min (after the trail-making tests). The block span test is the spatial counterpart to the digit span—the examiner points at a series of blocks in a given order [13]. The task in the FAS word fluency test is to write as many words, starting with the letters 'F', 'A' and 'S', as possible, in 1 min per letter [13]. The trail-making tests are designed to measure executive control functions, such as psychomotor speed and shifting capacity. To the standard trail-making tests A (digits 1–25) and B (digits and letters: 1-A-2-B . . . K-12-L-13), tests C (letters A–Z) and D (following arrows indicating the order) were added. The maximum time set for trail-making tests A, B and C was 240 s. We used the Rey–Osterrieth complex figure for testing visuo-spatial functions: figure copying and immediate recall. The MMSE is a composite screening test for dementia and cognitive decline [2]. We added it to the protocol after the start, which is why the number of participants was lower for this than the other tests ($n = 393$).

Table 2. Description of the study population of 502 at the time of the cognitive testing

	n (%)
Educational level	
Low	280 (55.9%)
Medium	152 (30.3%)
High	69 (13.8%)
Occupational level	
Low	199 (39.7%)
Medium	209 (41.7%)
High	93 (18.6%)
Antihypertensive treatment	190 (37.8%)
Previous stroke	39 (7.8%)
Diabetes mellitus (oral glucose tolerance test)	70 (14.1%)

We obtained informed consent from all participants, and the study was approved by the ethics committee of Uppsala University.

Statistical methods

The distribution of the scores in the MMSE was highly skewed, which is why the median values with the ranges from the 10th to the 90th percentiles are presented, and the Spearman partial correlation, a non-parametric equivalent to analysis of covariance, was used in the analyses. The other variables were normally distributed after a logarithmic transformation. We used Student's unpaired *t* test and the χ^2 test in univariate analyses, and applied analysis of covariance in multivariate models.

Results

The mean age (± SD) of the 502 participants was 72.2 ± 1.1, range 69.8–74.0 years. Details of their health and educational and occupational levels are presented in Table 2. The rate of antihypertensive treatment was 37.8%, and 7.8% had sustained a stroke before the testing. The participants did not differ in baseline blood pressure or socio-economic status from the other survivors from the original cohort, i.e. non-responders in Uppsala and men who had moved from Uppsala (Table 3).

The median score in the MMSE was 29 points (range 21–30). The most frequent errors in the MMSE were in word recall, in counting backwards (from 100 in 7s), and in spelling backwards. There were strong positive relations between educational level and performance in all tests, except for the figure copying task. Subjects with a previous stroke ($n = 39$) had higher baseline

Table 3. Baseline characteristics in participants in the cognitive testing and in surviving non-participants

	Participant		
Variable	Yes ($n = 502$)	No ($n = 1372$)	*P*
Socio-economic status			
Low	45.2%	42.9%	
Medium	38.4%	41.9%	
High	16.4%	15.2%	
Mean blood pressure ± SD, mmHg (and range)			
Systolic	131 ± 16 (100–210)	132 ± 17 (95–235)	0.509
Diastolic	83 ± 10 (60–125)	83 ± 11 (50–140)	0.920

blood pressure and markedly lower results in all tests, except in the vocabulary test and in figure copying. They were excluded from the rest of the analyses.

There was an inverse relation between diastolic blood pressure at baseline and performance in the digit span test, the trail-making tests A–C and in the FAS test of verbal fluency (Table 4). Men whose blood pressure was within the lowest category (≤ 70 mmHg) showed the best performance in these tests. The linear associations were weak, but statistically significant after adjusting for age, educational and occupational levels. The relations between diastolic blood pressure and results in the digit span, trail-making test C and verbal fluency were significant also after adjusting for diabetes mellitus. Men within the lowest fifth of systolic blood pressure (≤ 115 mmHg, $n = 83$) had significantly better results in the digit span (13.5 *versus* 12, $P < 0.01$) and in verbal fluency (30 *versus* 26, $P = 0.01$) than the others; otherwise there was no relation between systolic blood pressure and cognitive scores. Performance in the MMSE, vocabulary test and block span test, in verbal learning and retention, and in figure copying and recall was not related to baseline blood pressure levels.

Low diastolic blood pressure at baseline was associated with low diastolic blood pressure, a low rate of antihypertensive treatment and diabetes mellitus at follow-up (Table 5). Cognitive performance did not differ between men who were treated with antihypertensive agents at the time of testing and untreated men. Many subjects were treated with two or more antihypertensive agents. Of the treated men, 50% received β-blockers, 38% diuretics, 35% calcium antagonists, 18% angiotensin-converting enzyme inhibitors and 6% other drugs. Cognitive test results were not affected by the choice of antihypertensive agent. Among men with hypertension (defined as having diastolic blood pressure ≥ 95 mmHg and/or receiving treatment) at baseline, performance did not

Table 4. Cognitive performance at age 70 in relation to diastolic blood pressure at age 50 (stroke cases excluded)

Cognitive test	Score[a], by diastolic blood pressure at 50 years (mmHg) ≤ 70 ($n = 59$)	75 ($n = 80$)	80 ($n = 128$)	85 ($n = 75$)	≥ 90 ($n = 121$)	*P*
MMSE[b]	29 (27–30)	28 (26–30)	29 (26–30)	29 (25–30)	28 (26–30)	0.269
Vocabulary	51	49	49	49	49	0.408
Digit span	14.1	13.0	13.1	12.9	12.8	0.032[c]
Block span	13.9	14.5	14.5	13.9	14.0	0.419
Verbal learning[d]	122	144	141	138	129	0.670
Verbal retention	6.3	6.1	6.2	6.1	6.2	0.366
Trail-making tests[d]						
A	37	41	41	41	42	0.049[c]
B	96	107	114	111	111	0.042[c]
C	55	64	70	67	69	0.015[c]
D	18	22	20	19	20	0.909
Figure copying	34	33	33	33	33	0.108
Figure retention	17	17	18	17	18	0.610
Verbal fluency	33	31	30	29	29	0.018[c]

[a] Adjusted for age, education, and occupation (analysis of covariance with diastolic blood pressure as a continuous variable).
[b] Median values (10–90%); all others are mean values.
[c] Adjusting also for diabetes: digit span, $P = 0.033$, trail-making test A, $P = 0.062$; test B, $P = 0.076$; test C, $P = 0.022$; verbal fluency, $P = 0.031$.
[d] High scores indicate low performance.

differ between men with and without hypertension at follow-up.

Discussion

In this elderly stroke-free population, low diastolic blood pressure at age 50 was associated with better performance 20 years later in cognitive tests measuring verbal attention, verbal fluency, psychomotor speed and shifting capacity, independently of age, education and occupation. On the other hand, there was no relation between mid-life blood pressure levels and later performance in tests measuring vocabulary, non-verbal attention, verbal learning and recall or visuo-constructional functions.

Table 5. Educational level, diastolic blood pressure and rate of treatment at age 70 years according to diastolic blood pressure category at age 50 years (stroke cases excluded)

	Value, by diastolic blood pressure at 50 years (mmHg) ≤70 ($n = 59$)	75 ($n = 80$)	80 ($n = 128$)	85 ($n = 75$)	≥90 ($n = 121$)
Proportion with low education	59.3%	63.8%	60.9%	41.3%	52.9%
Mean diastolic blood pressure at 50 years	69 ± 2	75 ± 0	80 ± 0	85 ± 0	96 ± 8
Proportion receiving treatment at 50 years	1.7%	0%	2.3%	1.3%	5.8%
Mean diastolic blood pressure at 70 years					
All	79 ± 10	83 ± 9	83 ± 9	85 ± 8	89 ± 7
Untreated	78 ± 9	82 ± 8	82 ± 7	84 ± 8	88 ± 6
Treated	86 ± 10	88 ± 12	85 ± 12	87 ± 9	90 ± 8
Proportion perceiving treatment at 70 years	13.6%	23.8%	28.1%	38.7%	64.5%
Prevalence of diabetes at 70 years	3.4%	16.5%	10.4%	12.2%	22.7%

Baseline blood pressure was measured only once, but low baseline blood pressure still indicated a low long-term vascular risk, with low blood pressure and a low rate of treatment and diabetes mellitus at follow-up. As previously reported, there was no relation between cross-sectional measurements of office blood pressure and test scores, while high ambulatory 24-h diastolic blood pressure was associated with poorer performance in the MMSE and the trail-making tests [2].

This was a healthy population, with a median MMSE score of 29 points. The differences in test scores between blood pressure categories were small, and cannot be interpreted as markers of early dementia. However, a slight impairment of word-finding abilities and executive functions are common complaints among otherwise healthy elderly people.

Baseline blood pressure levels and socio-economic status did not differ between the participants in the cognitive study and the other surviving men from the original cohort. Thus, there was no evidence of a major selection bias. However, the rate of antihypertensive treatment is likely to be higher in subjects under medical health control than in non-responders. The relationships between blood pressure and cognitive function in a general population might be even stronger. We measured cognitive functions at one occasion only. Therefore, no clear conclusions regarding causality may be drawn. One possibility is that low blood pressure is associated with a higher baseline cognitive reserve. However, since there was no correlation between blood pressure and educational level, this explanation seems less probable. The other interpretation is that low blood pressure, or other factors associated with low blood pressure, may have beneficial effects in keeping cognitive functions intact.

Our results are in concordance with findings in other longitudinal studies. In the Framingham study, untreated hypertensive subjects had low results as measured by a composite score from eight psychometric tests [14]. In the Honolulu–Asia Aging Study, a high mid-life systolic blood pressure was associated with later poor performance in the MMSE [15]. Interestingly, hypertension at age 70 predicted Alzheimer's disease, as well as vascular dementia, in a population of 85-year-olds [16].

If there is a causal link between low blood pressure and high cognitive performance late in life, independent of manifest stroke, what could the pathophysiological mechanisms be? On a group basis, hypertension is related to cerebral white matter lesions, but causality in the complex of hypertension, white matter lesions and cognitive impairment is still unclear [17].

Some previous studies have investigated correlations between white matter lesions visualized by magnetic resonance imaging and performance in different cognitive areas. In patients with Alzheimer's disease, widespread white matter lesions were associated with poorer performance, particularly in tests on attention (the digit span test), cognitive speed and visual recognition [5]. The following studies included only neurologically healthy, non-demented elderly men. Subjects with leukoaraiosis performed worse in tests measuring attention and speed of mental processing (trail-making test A), while memory and language functions were unimpaired [6]. In the Rotterdam study, white matter lesions correlated with poorer results in the trail-making tests A and B and verbal fluency, and in delayed recall [7]. Similarly, in another study, subjects with white matter hyperintensities performed worse in the trail-making test B [8]. One study was able to show a link between white matter lesions, high systolic blood pressure, reduced cerebral glucose metabolism and lower scores on tests of verbal fluency (FAS), trail-making test B and visual memory [9].

Together, low performance in the trail-making tests and tests of attention and verbal fluency seem to be more indicative of subcortical pathology than tests on other cognitive areas. This is in accordance with our findings—low blood pressure was related to better performance in attention (digit span), verbal fluency and in the trail-making tests, while there was no such relation to performance in tests of other cognitive domains. Our results may therefore indicate that low blood pressure is associated with intact subcortical cognitive functions in old age, speculatively due to a lower risk of subclinical small vessel lesions.

Cognitive decline is perhaps not an inevitable consequence of ageing. Several recent studies show a link between cognitive impairment and vascular risk factors: hypertension [2, 14, 15]; myocardial infarction and peripheral vascular disease [18]; diabetes mellitus [2, 19]; and atrial fibrillation [20, 21]. If we prevent vascular disease, we may also prevent some cases of cognitive decline. A substudy of the Medical Research Council Thrombosis Prevention Trial provided tentative evidence that aspirin may protect cognitive function in men at risk of cardiovascular disease [22].

A few randomized clinical trials have addressed the question of whether antihypertensive treatment prevents cognitive impairment. The results have so far been negative [23–25]. Participants in clinical trials are highly selected with regard to compliance, and thus also with regard to high baseline cognitive function. Also, among the participants, the drop-out rate is likely to be higher among subjects developing cognitive deterioration during follow-up than in those with stable functions. These mechanisms are likely to contribute to the negative results so far. Recent findings from the Syst–Eur trial indicate that antihypertensive treatment may prevent dementia in patients with systolic hypertension [26]. Interestingly, most cases of dementia were diagnosed as Alzheimer's disease.

We conclude that the hypothesis that treatment that lowers blood pressure protects from age-associated cognitive decline needs to be further explored.

Key points

- Recent studies have shown that hypertension is a risk factor for cognitive decline and dementia.
- In our study cohort, low diastolic blood pressure at age 50 was associated with higher performance 20 years later in cognitive tests assessing attention, verbal fluency and psychomotor speed.
- Low blood pressure, or other factors associated with low blood pressure, may be beneficial in keeping subcortical functions intact.
- The hypothesis that optimal antihypertensive treatment may protect from cognitive impairment needs to be further investigated.

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