Determinants of cognitive function in old age

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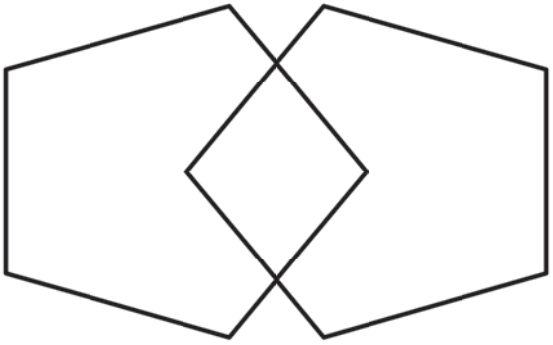
Chapter 4

Cognitive decline precedes late-life longitudinal changes in vascular risk factors



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Abstract

Introduction

Although obesity, hypercholesterolemia, and hypertension in midlife are risk factors for dementia in late-life, dementia is associated with lower body mass index, cholesterol levels, and blood pressures. It is unclear whether declines in these vascular risk factors are preceded by declines in cognitive function or vice versa.

Materials and methods

Within the Leiden 85-plus Study, a prospective population based study of 599 subjects aged 85 years, we annually measured body mass index, total cholesterol, HDL cholesterol, and glucose levels, blood pressure, and assessed global cognitive function using the Mini Mental State Examination (MMSE) during a five year follow-up.

Results

For the whole population who survived up till 90 years, strong annual declines in MMSE score, body mass index, total cholesterol levels, glucose levels, and blood pressure, and an annual increase in HDL cholesterol levels were observed during the follow-up period (all $p \leq 0.010$). Annual changes in MMSE score from age 85 to 87 years associated positively with annual changes from age 87 to 90 years in total and HDL cholesterol levels ($p=0.002$ and $p=0.013$), systolic and diastolic blood pressure ($p=0.008$ and $p=0.048$), but not BMI. Parameter value changes from age 85 to 87 years did not associate with changes in MMSE score from age 87 to 90 years.

Discussion

In old age, cognitive decline precedes declines in total cholesterol levels, HDL cholesterol levels, and blood pressure, and not vice versa. Possibly, brain lesions in metabolic and blood pressure regulation centers cause dysregulation of lipid metabolism and blood pressure.

Introduction

In late-life, dementia is associated with a lower body mass index, lower cholesterol levels, and lower blood pressures, although obesity, hypercholesterolemia, and hypertension in midlife are risk factors for dementia in late-life [1-4]. With increasing age, declines in these vascular risk factors have been observed in the general population from midlife to late-life [5-7]. The magnitude of the declines has been linked to the presence and severity of chronic diseases, including dementia [8-12].

Controversy exists whether the declines of these parameters precede clinical dementia, or that the declines are the result of clinical dementia. Longitudinal studies have shown large declines in body mass index, cholesterol levels, and blood pressures up to 15 years prior to the clinical diagnosis of dementia [10-12]. However, other studies have shown larger declines in both body mass index and blood pressure in Alzheimer's disease patients compared to age-matched controls in the years following diagnosis [8,9]. A substantial part of metabolic and blood pressure control is determined by brain regulatory centers, such as the hypothalamus and amygdales. Therefore, neurodegenerative lesions in these centers may be the cause of dysregulation in metabolism and blood pressures. Because clinical dementia is the result of ongoing neurodegeneration, studies reporting on declines in parameter values prior to dementia may be obscured by already present neurodegenerative disease and may result in faulty conclusions on the causal pathway behind the associations. We assessed whether late-life declines in values of midlife risk factors for dementia are preceded by declines in global cognitive function or vice versa in an elderly population.

Within the Leiden 85-plus Study, a population based prospective follow-up study, body weight, standard laboratory tests, blood pressure, and global cognitive function were annually assessed during a five year follow-up period. We analyzed the association between annual changes in midlife vascular risk factors that associate with late-life dementia and the annual change in global cognitive function in preceding and following years.

Materials and methods

Participants

Between September 1, 1997, and September 1, 1999, a total of 705 inhabitants of the community of Leiden, the Netherlands, reached the age of 85 years. Among these 85-year-old persons, we initiated a follow up study to investigate determinants of successful aging. There were no selection criteria on health or demographic characteristics. Fourteen inhabitants died before they could be enrolled. The response rate was 87%; a total of 599 subjects (397 women and 202 men) participated [13]. There were no significant differences in various demographic characteristics between the 599 respondents and the source population. Subjects were visited within one month after the subjects' 85th birthday at their home for face-to-face interviews and neuropsychological testing. Subjects were revisited annually until age 90 years. The Medical Ethical Committee of the Leiden University Medical Centre approved the study, and informed consent was obtained from all subjects.

Serum parameters

Non-fasted blood samples were collected at each annual visit early in the morning. Glucose, total cholesterol, and HDL cholesterol were determined by use of a fully automated Hitachi 747 and Hitachi 911 system (Hitachi Ltd, Tokyo, Japan). Glucose levels were used as a surrogate for glycemic control, because of its continuous character, necessary for the annual follow-up analyses, and because of a lack of other annually assessments of glycemic control.

Blood pressure

Annually, blood pressure was measured, using a mercury sphygmomanometer, in seated position. During one visit two blood pressure measurements were done, the first after at least five minutes of rest and no vigorous exercise in the preceding thirty minutes, the second after approximately 90 minutes at the end of the visit. The systolic value was measured at Korotkoff sound 1, and the diastolic value was measured at Korotkoff sound 5. For each year, the mean value of the two measurements was calculated and used in further analyses.

Body mass index

Weight was measured annually and length was measured at baseline. Body mass index was calculated by dividing the annual weight in kilograms by the square length in meters (kg/m^2).

Global cognitive function
Global cognitive functioning was assessed with the Mini-Mental State Examination (MMSE), with lower scores indicating worse global cognitive functioning [14].

Level of education
Level of education of each subject was determined by the number of years a subject went to school. Information was obtained at the first visit using a questionnaire. Low education was defined by 6 or less years of schooling, whereas high education was defined by 7 or more years of schooling.

Dementia
Prevalence and incidence of dementia was determined by using information obtained from questionnaires. Annually, questionnaires, including a question about the presence of a diagnosis of dementia, were filled out by general practitioners and treating physicians of study subjects.

Statistical analyses
All analyses were confined to participants who survived up till the end of follow-up at age 90 years. Differences in parameter values between participants surviving up till 90 years and participants who died before 90 years were tested using independent samples t-tests. Differences in sex distribution among the two groups were analyzed using Chi^2-tests.
Annual changes in all parameter values, including MMSE score, were calculated using linear regression analysis with year of follow-up as independent variable and parameter values as dependent variables in the model. Analyses were also stratified for sex.
To test whether annual changes in MMSE score associated with annual changes in parameter values in the years following the change in MMSE, regression coefficients for the change in MMSE from age 85 to 87 years and regression coefficients for the change in parameter values from age 87 to 90 years were calculated using linear regression models. The calculated regression coefficients of MMSE score from age 85 to 87 years were used as independent variables (both as sex-specific quartiles and absolute values) in linear regression models to study their association with the regression coefficients of the parameter values from age 87 to 90 years. Finally, in a reversal of analysis, regression coefficients of parameter values from age 85 to 87 years were associated with regression coefficients of MMSE score from age 87 to 90 years. All calculations were performed using SPSS software (version 16.0.1, SPSS Inc, Chicago, Ill).

Results

Table 1. **Baseline characteristics of survivors and non-survivors until age 90 years.**

Parameter	Survivors (n=319)	Non-survivors (n=280)	p-value
Men (%)	88 (28%)	114 (41%)	0.001 [1]
>6 years education (%)	117 (37%)	92 (33%)	0.329 [1]
Prevalent dementia (%)	15 (5%)	34 (12%)	<0.001 [1]
MMSE, points	25.6 (4.2)	21.7 (7.9)	<0.001 [2]
BMI, kg/m^2	27.5 (4.4)	26.9 (4.5)	0.135 [2]
Cholesterol, mmol/l	5.84 (1.04)	5.56 (1.21)	0.004 [2]
HDL cholesterol, mmol/l	1.36 (0.36)	1.26 (0.44)	0.002 [2]
Glucose, mmol/l	7.01 (2.75)	6.97 (2.54)	0.871 [2]
Systolic BP, mmHg	157.8 (17.7)	152.0 (19.3)	<0.001 [2]
Diastolic BP, mmHg	78.4 (8.5)	74.7 (10.3)	<0.001 [2]

Legend. Continuous values are presented as means and their standard deviations. P-values represent the statistical difference in [1]frequencies, calculated using Chi^2-testing, or the statistical difference in [2]values, calculated using independent samples t-test, between subjects who survived up till age 90 years and subjects who died before age 90 years.

From the 599 participants in the current study, 280 participants died before the end of the five year follow-up (Table 1). Compared to participants who survived beyond the age of 90 years, participants who died before the age of 90 years were more likely to be men (41% vs. 28%), had a 3.9 points lower MMSE score at baseline, a 0.28 mmol/l lower total cholesterol level, a 0.10 mmol/l lower HDL cholesterol level, and a 5.6 mmHg lower systolic and 3.7 mmHg lower diastolic blood pressure (all $p<0.005$). Baseline body mass index and glucose levels were not different between survivors and non-survivors. Twenty one participants from the remaining 319 participants were not included in the current study, due to missing of at least two measurements during follow-up.

Table 2 shows the mean annual change in parameter values from age 85 to 90 years in all 298 remaining participants. Strong annual declines were observed for MMSE score, body mass index, total cholesterol levels, systolic blood pressures, diastolic blood pressures (all $p<0.001$), and glucose levels ($p=0.010$), and an annual increase was observed for HDL cholesterol levels ($p<0.001$). In gender-stratified analyses strong annual changes were found in both men and women for all parameters, although larger declines in total cholesterol levels, systolic blood pressures, and diastolic blood pressures were observed in men.

Table 2. **Change in parameter values from age 85 to 90 years in all subjects who survived until age 90 years (n=298).**

Parameter	Change per year (95% CI)	P for trend
MMSE score (points)	-0.68 (-0.84 to -0.53)	<0.001
Body mass index (kg/m^2)	-0.30 (-0.42 to -0.17)	<0.001
Total cholesterol level (mmol/l)	-0.12 (-0.15 to -0.09)	<0.001
HDL cholesterol level (mmol/l)	+0.04 (0.02 to 0.05)	<0.001
Glucose level (mmol/l)	-0.08 (-0.14 to -0.02)	0.010
Systolic blood pressure (mmHg)	-1.59 (-2.06 to -1.12)	<0.001
Diastolic blood pressure (mmHg)	-1.36 (-1.60 to -1.12)	<0.001

Legend. Change in parameter values per year and p for trend were calculated using linear regression analysis, with year of follow-up as independent variable in the model.

To test whether annual changes in MMSE scores were predictive for annual changes in the other parameters we analyzed the association between quartiles of annual changes in MMSE score from age 85 to 87 years and annual changes in parameter values from age 87 to 90 years. Table 3 shows that participants with the largest annual decline in MMSE score from age 85 to 87 years had the largest decline in total cholesterol levels, HDL cholesterol levels, and systolic blood pressures from age 87 to 90 years. A similar trend was observed for diastolic blood pressure, although not significant. When using annual change in MMSE as a continuous variable in a linear regression model, adjusted for sex and parameter values at age 87 years, similar positive associations were found for total cholesterol levels (p=0.002), HDL cholesterol levels (p=0.013), systolic blood pressure (p=0.008), and diastolic blood pressure (p=0.048). In reversed analysis, annual changes in all parameter values from age 85 to 87 years did not associate with the annual change in MMSE score from age 87 to 90 years (all p>0.07) (table 4). Adjustment for level of education did not materially change the results. Moreover, restricting the analyses to subjects without dementia at baseline and to subjects with an MMSE score of 24 points or higher at baseline showed similar associations.

Table 3. **Annual change in parameter values from age 87 to 90 years dependent on quartiles of annual change in MMSE score from age 85 to 87 years (n=298).**

Quartiles of annual change in MMSE score from age 85 to 87 years	Annual change from age 87 to 90 years					
	BMI (kg/m^2/yr) (SE)	Total cholesterol (mmol/l/yr) (SE)	HDL cholesterol (mmol/l/yr) (SE)	Glucose (mmol/l/yr) (SE)	Systolic BP (mmHg/yr) (SE)	Diastolic BP (mmHg/yr) (SE)
-9 to -1.5	-0.37 (0.13)	-0.18 (0.03)	-0.04 (0.01)	-0.04 (0.07)	-3.44 (0.65)	-1.74 (0.36)
-1.5 to -0.5	-0.54 (0.11)	-0.11 (0.03)	-0.01 (0.01)	-0.05 (0.06)	-1.20 (0.58)	-0.83 (0.33)
-0.5 to 0.0	-0.44 (0.12)	-0.08 (0.03)	0.00 (0.01)	-0.18 (0.07)	-1.16 (0.64)	-0.84 (0.36)
0.5 to 3.0	-0.34 (0.11	-0.05 (0.03)	+0.02 (0.01)	-0.16 (0.06)	-0.85 (0.57)	-0.72 (0.32)
P for trend	0.599	0.001	0.001	0.095	0.007	0.061

Legend. Annual changes in parameter values from age 87 to 90 years and annual change in MMSE score from age 85 to 87 years were calculated using linear regression. Annual change in MMSE score from age 85 to 87 years was divided in quartiles on the sex-specific median in subjects who survived until 90 years only. P for trend was calculated using linear regression analysis with quartiles of annual change in MMSE score as independent variable and annual change in parameter values as dependent variable, with adjustment for parameter values at age 87 years and MMSE score at age 85 years. Quartiles per sex; men: 1^{st}, -9.0 to -1.5; 2^{nd}, -1.0 to -0.5; 3^{rd}, 0.0 to 0.0; 4^{th}, 0.5 to 2.5; women: 1^{st}, -6.5 to -2.0; 2^{nd}, -1.5 to -1.0; 3^{rd}, -0.5 to 0.0; 4^{th}, 0.5 to 3.0.

Table 4. **Annual change in MMSE score from age 87 to 90 years dependent on quartiles of annual changes in parameter values from age 85 to 87 years (n=298).**

Quartiles of annual change in parameter values from age 85 to 87 years	Annual change in MMSE score from age 87 to 90 years (points/yr) (SE)				P for trend
	1st quartile	2nd quartile	3rd quartile	4th quartile	
Body mass index	-0.80 (0.17)	-0.70 (0.16)	-0.57 (0.16)	-0.63 (0.17)	0.386
Total cholesterol	-0.70 (0.17)	-0.71 (0.17)	-0.50 (0.16)	-0.78 (0.17)	0.946
HDL cholesterol	-0.78 (0.17)	-0.86 (0.17)	-0.51 (0.17)	-0.54 (0.17)	0.151
Glucose	-0.52 (0.18)	-0.59 (0.16)	-0.87 (0.17)	-0.70 (0.17)	0.348
Systolic blood pressure	-0.56 (0.18)	-0.82 (0.17)	-0.79 (0.16)	-0.52 (0.18)	0.796
Diastolic blood pressure	-0.52 (0.17)	-0.73 (0.17)	-0.66 (0.16)	-0.78 (0.17)	0.376

Legend. Annual changes in MMSE score from age 87 to 90 years and annual changes in parameter values from age 85 to 87 years were calculated using linear regression. Annual changes in parameter values from age 85 to 87 years were divided in quartiles on the sex-specific median in subjects who survived until 90 years only. P for trend was calculated using linear regression analysis with quartiles of annual changes in parameter values as independent variable and annual change in MMSE score as dependent variable, with adjustment for MMSE score at age 87 years and parameter values at age 85 years.

Discussion

The main finding of our study is that late-life changes in global cognitive function preceded changes in values of midlife vascular risk factors in following years, whereas changes in values of midlife vascular risk factors did not precede changes in global cognitive function. The largest declines in global cognitive function associated with the largest declines in total cholesterol levels, HDL cholesterol levels, systolic blood pressures, and diastolic blood pressures in the following years, but not with body mass index.

The observed mean annual changes in all parameter values are in line with previous findings, although our population is generally older than the populations reported on earlier. Results from cross-sectional data showed that body mass indices decreased per older age-group, starting at age 55-64 years for men and 65-74 years for women [5]. Another study showed that total cholesterol levels decreased and HDL cholesterol levels increased during 20 years follow-up in men aged 45-68 years at baseline [15]. Concurring results on decreasing glucose levels with increasing age have been published [16], and also blood pressures have been shown to decrease with increasing age in a population followed from age 70-90 years [7].

In our temporal analyses we showed that declines in global cognitive function preceded declines in total cholesterol levels, HDL cholesterol levels and blood pressure, and not *vice versa*. Previous studies partly support our findings. One study showed that longitudinal changes in HDL cholesterol levels did not associate with cognitive function during follow-up [17], and two other studies showed marked decreases in blood pressure with increasing severity of dementia [9,18]. However, other studies do not confirm our results. Previous studies have shown that total cholesterol levels declined up till 15-21 years prior to clinical dementia or impaired cognitive function [6,12]. Moreover, blood pressure has been shown to decrease in the years before the onset of dementia [19], although only in the last three years before diagnosis [11]. Because patients who are diagnosed with clinical dementia already suffer from considerable cognitive impairment, it is possible that in the years preceding the diagnosis similar temporal associations between cognitive decline and declines in cholesterol levels and blood pressures would have been present as in our study.

Biologically, our finding that the change in cognitive function preceded, and not followed, the change in cholesterol levels, HDL levels, and blood pressures, hints to intracerebral damage causing metabolic derangement. The pathophysiological processes that lead to cognitive decline and metabolic derangement may thus occur in parallel. Our data suggest that cognitive decline may be present in the presence of mild cerebral disease, whereas metabolic derangement may only occur in the presence of more advanced cerebral disease.
Neurodegenerative or cerebral vascular lesions in blood pressure regulation centers, such as amygdales and hypothalamus [20,21], are likely to cause blood pressure dysregulation. More specifically, a deficit in cholinergic neurons, among others localized in the hypothalamus [22], can result in decreased sympathetic activity with subsequent lower blood pressures.
The changes in total and HDL cholesterol levels may also be explained by lesions in brain regulatory centers. The brain plays an important role in the regulation of energy metabolism, amongst which the regulation of lipid metabolism. Key regulator in the brain is the hypothalamus, which responds to signals from the cortex and amygdales, but also to adipose tissue-secreted adipokines, such as leptin and adiponectin, which signal gain and loss of adipose tissue [23]. Moreover, animal studies have shown that white adipose tissue is innervated by sympathetic nervous system neurons, and that hypothalamic histamine neurons accelerate lipolysis in adipose tissue, which suggests a central regulation of peripheral lipid metabolism [24,25].
Surprisingly therefore is our finding that declines in cognitive function are not followed by declines in body mass index. A large part of hypothalamic control of

energy balance, besides its influence on lipid metabolism, is determined by the influence on feeding behavior. Lesions in hypothalamic regions would therefore likely result in changes in eating behavior and subsequently in changes in body mass index. Previous studies have indeed shown that patients with Alzheimer's disease have an increased weight loss [8,26]. Possibly, declines in body mass index are a late sign of neurodegenerative disease when cognitive deterioration, such as decreased executive function and apathy, further impair food seeking behavior, whereas changes in lipid metabolism could already occur as the result of more subtle hypothalamic dysfunction or damage, earlier in the course of the disease. As opposed to the previous reports from case control studies we performed a population based study in which the contrast between cognitively impaired and cognitively intact subjects was not so strong, which could explain the absence of changes in body mass index related to cognitive decline. This absence could further account for the absence of an association between changes in cognitive function and changes in glucose levels, which were used as a representation of glycemic control.

A limitation of the current study is that brain imaging in our population is not available. To further explore our hypothesis about structural brain damage and the resultant hypothalamic dysfunction as the cause of annual changes in parameter values, longitudinal functional and structural brain imaging could clarify the relations in more depth. Another possible limitation of the current study is that our population consisted of 85 year old subjects, who survived until the age of 90 years. Therefore, our findings cannot be extrapolated beyond this age group. However, a substantial proportion of the total population reaches this old age, since from the original birth cohort 1914-1916, 15% of the men and 36% of the women reached the age of 85 years. Moreover, the incidence of cognitive impairment and dementia increases steeply with increasing age, making our population very suitable to test our hypothesis. Therefore the availability of repeated annual measurements of both cognitive function and values of midlife risk factors of dementia during 5 years of follow-up is a strong point of our study. This enabled us to test the temporal associations between the annual changes in both directions. Another strong point of our study is the population based character of our study without inclusion criteria on health and demographics. This makes it possible to extrapolate our results to other populations in the same age range.

Inherent to the concept of our study design, the results of our study are based on subjects only who survived until age 90 years, whereas subjects who died between age 85 and 90 years were not included. We have shown earlier that compared to

surviving subjects, these subjects had stronger annual declines in cognitive function and also in parameter values such as cholesterol and blood pressure, in the years preceding death (van Vliet *et al*, manuscript submitted). One might expect that this selective attrition could have influenced our results as a large proportion of the subjects who were present at baseline have died during follow-up. However, although selective attrition may have attributed to the formation of a selective group of survivors, this does not necessarily diminish the importance of our findings that in this group of individuals a decline in cognitive function preceded the metabolic and hemodynamic changes that we observed later in life and not the other way round.

Our finding that a decline in cognitive function precedes declines in total cholesterol levels, HDL cholesterol levels, and blood pressures could imply that possible interventions to maintain metabolic control would not influence the control of cognitive function. On the other hand, cholesterol is a key element in the maintenance of cellular membranes, and the formation of steroid hormones and bile. Moreover, increasing blood pressures may be needed to maintain adequate tissue perfusion, and in particular brain perfusion. Therefore, the possible metabolic dysregulation by hypothalamic dysfunction as the result of neurodegenerative or cerebral vascular disease could push the system in a vicious circle, which might be broken by interventions in lipid metabolism and blood pressure regulation. However, future research should first be focused on the influence of changes in brain structure and function, specifically in regulatory centers, such as the amygdales and hypothalamus, and their relation with metabolic regulation.

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