Original Article

Cognitive Dysfunction and Physical Disability Are Associated with Mortality in Extremely Elderly Patients

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A few reports have demonstrated that cognitive or physical dysfunction is associated with increased mortality in very elderly patients, those over 80 years of age. Using simple clinical tests, we evaluated the impact of cognitive or physical dysfunction on future total and cardiovascular deaths. We conducted a multicenter prospective study of 523 extremely elderly outpatients, aged ≥80 years (mean±SD age: 84±5.3 years). These patients had normal activities of daily living at baseline. They were followed for an average of 34 months (range: 3–70 months), after which the total and cardiovascular deaths were evaluated. Cognitive and physical functions were evaluated by a short-term memory test using visual working memory and the get-up-and-go test, respectively. Seventy-five deaths, including 36 cardiovascular deaths, occurred during the follow-up period. In a Cox regression analysis model controlling for age, sex, body mass index (BMI), diastolic blood pressure (BP), cholesterol level, and history of cardiovascular diseases, cognitive dysfunction was found to be an independent risk factor for total death (p<0.001), and cognitive dysfunction (p<0.001) and physical dysfunction (p=0.05) were independent risk factors for cardiovascular death. The determinants of cognitive dysfunction were associated with a lower diastolic BP (p=0.04) adjusted for age, BMI, and a history of cardiovascular disease. Cognitive function, which was associated with lower BP levels, and physical function were the independent predictors of total and cardiovascular mortality among all cardiovascular risk factors in the very elderly, those at least 80 years of age. (*Hypertens Res* 2008; 31: 1331–1338)

Key Words: **elderly people, short-term memory, get-up-and-go test, blood pressure**

Introduction

In older subjects, activities of daily living, such as those involving cognitive function or physical activity, have been reported to be important factors in mortality (*1–4*). Various segments of the population have been studied to show the relationship between cognitive impairment and survival, using a number of cognitive function tests. It is now generally accepted that overt cognitive dysfunction leads to significantly shortened survival (*1*, *5*, *6*). It is well known that physical dysfunction in elderly people also is associated with an elevated mortality (*3*, *4*). However, most of the previous reports consisted of subjects less than 80 years of age; few studies have examined the relationship between cognitive or physical function and mortality in a very elderly population. Cognitive dysfunction may be caused mainly by atherosclerotic disease, including hypertension (*7*). However, the exact causes of cognitive and physical dysfunction in the extremely elderly remain to be elucidated.

A number of screening tools have been developed to identify cognitive or physical dysfunction (*8*, *9*). Because it is

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very hard to perform various screening tests for elderly patients in routine clinical practice, simple and feasible tests of cognitive and physical dysfunction are necessary. We investigated whether or not simple measures of cognitive and physical function can predict mortality, and whether or not there is any interaction between BP level and cognitive or physical dysfunction in relation to mortality in a very elderly Japanese population.

Methods

Subjects

The present study was based on 523 elderly outpatients who were followed prospectively for an average of 34 months. This represents 97.9% of the 523 patients who were initially enrolled in the study from 25 participating institutions (20 clinics, 5 hospitals) between June 2001 and November 2005.

These patients were enrolled if they met all of the following criteria: 1) age ≥80 years; 2) attending a clinic or hospital without difficulty in walking; and 3) living without assistance. Thirty-four subjects were excluded because of incomplete datasets. Therefore, a total of 489 subjects were analyzed in the present study. Those patients who had a severe visual or hearing impairment, a previous diagnosis of renal failure (serum creatinine level >176.8 mmol/L), hepatic damage, or a known terminal illness were excluded in advance. All of the subjects gave informed consent to participate in the study. This study was approved by the Research Ethics Committee, Division of Cardiovascular Medicine, Jichi Medical University School of Medicine, Japan.

Clinic blood pressure (BP) was measured after resting for at least 5 min in the sitting position. Diabetes mellitus was defined as a fasting glucose level >7.8 mmol/L, a random nonfasting glucose level of 11.1 mmol/L, hemoglobin A1c >6.2%, or the use of oral hypoglycemic agents or insulin. Hyperlipidemia was defined as a total cholesterol level >6.2 mmol/L or the use of an oral lipid-lowering agent. Current smoking was defined as a current smoking habit. Habitual drinking was defined as alcohol consumption on more than 5 d per week. Body mass index (BMI) was calculated as weight (kg)/height (m)^2. A history of cardiovascular disease (CVD) was defined as a history of ischemic heart disease, congestive heart failure, or stroke.

Short-Term Memory Test Using Visual Working Memory

We used the short-term memory test to evaluate cognitive function. The subjects were shown three figures (a spoon, a pen, and a watch; Fig. 1) and were asked to name each figure out loud and to memorize those names. All of the subjects correctly named the figures, when they see the figures. Then the subjects were asked to recall them 5 min later. The number of figures recalled was counted as the test score.

Fig. 1. *Figures used in the short-term memory test.*

The Get-Up-and-Go Test

The get-up-and-go test was used to evaluate physical function (*10*). This test measures the time (in s) required for the subject to stand up from an arm chair, walk a distance of 3 m, walk back to the chair, and sit down. This simple test is a comprehensive evaluation of the subject's balance, gait, speed, and functional ability. We divided the times on this test into quartiles and considered the top quartile group (those taking the longest time) as the physical dysfunction group.

Follow-Up and Events

The patients' medical records were reviewed intermittently after enrollment. Follow-up assessments were performed from January 2001 to March 2007; the mean follow-up period was 34 months, with a range of 3 to 70 months. When a patient failed to come to the clinic/hospital, we interviewed the patient or a family member by telephone. We defined the total deaths as an endpoint in this study. Total death was defined as all causes of death, including cardiovascular. Cardiovascular death was defined as death due to coronary heart disease, heart failure, sudden cardiac death, or stroke.

Statistical Analysis

The data are expressed as means±SD and percentages. A two-sided unpaired *t*-test and the χ^2 test were used to test differences between the two groups in the mean values of continuous measures and prevalence rates, respectively. Spearman's correlation was used for bivariate analysis between the memory test score and the get-up-and-go test time. The cumulative incidences of mortality were plotted as Kaplan-Meier curves, and the differences were assessed by the log-rank test. The hazard ratios (HR) with 95% confidence intervals (CI) of mortality were calculated with a Cox regression analysis even after adjustments for the significant covariates. The odds ratios (OR) with a 95% CI for a memory

Table 1. Characteirsitics of the Very Elderly Patients with Score 0 of Short-Term Memory Test

	0	1, 2 and 3	*p*
n	38	451	
Age, years	86.4±5.2	83.9±3.4	<0.001
Male, %	32	37	0.53
BMI, kg/m²	21.4±2.9	22.8±3.4	0.02
Smoking, %	9.1	8.5	0.91
Alcohol, %	10.8	24.9	0.06
Diabetes, %	18.4	17.2	0.85
Hyperlipidemia, %	26.3	33.3	0.36
Antihypertensive drug, %	79.0	75.4	0.62
History of CVD, %	57.9	37.9	0.02
Systolic blood pressure, mmHg	134.3±20.0	141.8±19.0	0.03
Diastolic blood pressure, mmHg	70.8±14.8	75.7±11.1	0.01
Pulse rate, bpm	74.2±13.8	73.6±12.6	0.81
Cholesterol, mg/dL	202.7±42.9	195.6±32.9	0.33
Get-up-and-go test, s	15.5±7.7	13.7±7.9	0.17

Data shows mean±SD and percentage. BMI, body mass index; CVD, cardiovascular disease.

Table 2. Characteristics of the Very Elderly Patients with Longest Time of the Get-Up-and-Go Test

	Q1–Q3	Q4	*p*
n	358	125	
Age, years	83.6±3.4	85.5±4.2	<0.001
Male, %	38	30	0.08
BMI, kg/m²	22.8±3.4	22.6±3.2	0.59
Smoking, %	8.5	7.5	0.74
Alcohol, %	27.8	14.7	0.003
Diabetes, %	18.4	3.9	0.22
Hyperlipidemia, %	36.2	25.8	0.03
Antihypertensive drug, %	76.1	75.0	0.79
History of CVD, %	34.6	49.2	0.003
Systolic blood pressure, mmHg	141.6±18.8	141.1±20.3	0.84
Diastolic blood pressure, mmHg	75.3±11.1	74.8±12.4	0.67
Pulse rate, bpm	73.6±12.2	73.9±13.8	0.86
Cholesterol, mg/dL	197.6±35.0	194.9±32.4	0.46
Short-term memory score	2.3±8.9	2.0±1.0	0.04

Data shows mean±SD and percentage. BMI, body mass index; CVD, cardiovascular disease.

score of 0 and for the top quartile on the get-up-and-go test were calculated using multiple logistic analysis, even after adjustments for significant covariates. The statistical calculations were performed using SPSS version 11.0 software program (SPSS Inc., Chicago, USA). A p value of less than 0.05 was considered to indicate statistical significance.

Results

Patient Characteristics

The study included 176 men and 313 women with a mean age of 84±5.3 years. The mean BMI was 22.8±3.4 kg/m². The prevalences of habitual smoking and alcohol use were 8.5% and 24%, respectively. Hyperlipidemia was observed in 33% of the patients, diabetes mellitus was observed in 17%, and a history of CVD was observed in 39%. At baseline, the mean systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate were 141±19 mmHg, 75±11 mmHg, and 74±13 bpm, respectively. Seventy-six percent of the patients were taking one or more antihypertensive medications.

Determinants of Cognitive and Physical Function

Table 1 shows the differences in characteristics between

Table 3. Baseline Characteristics of Survived and Death Group

	Survived (*n*=414)	All cause of death (*n*=75)	Cardiovascular death (*n*=36)
Age, years	84±3.6	86±4.5***	86±4.5**
Male, %	34	46*	44
BMI, kg/m^2	23±3.4	22±3.4**	23±3.1
Smoking, %	8	6	6
Alcohol, %	24	22	26
Hyperlipidemia, %	34	28	29
Diabetes mellitus, %	17	19	21
Hsitody of CVD, %	37	41*	51*
Systolic blood pressure, mmHg	141±19	141±19	143±19
Diastolic blood pressure, mmHg	75±11	76±11	77±12
Pulse rate, bpm	73±13	75±12	77±13
Cholesterol, mg/dL	198.4±32.6	189.6±40.5*	187.3±33.0*
Antihypertensive drugs (yes), %	76	69	74
Aspirin (yes), %	20	23	23
Short-term memory score=0, %	6.8	13.6*	16.7*
Top quartile of get-up-and-go test, %	24	40***	41**

BMI, body mass index; CVD, cardiovascular disease. *$p<0.1$, **$p<0.05$, ***$p<0.01$ *vs*. survived group.

patients with a score of 0 in the short-term memory test and those with a score of 1 or 2. The patients scoring 0 were older than those with a higher score. The BMI, SBP, and DBP were lower in the 0-scoring patients than in the subjects with a higher score. The prevalence of a history of CVD was higher in the 0-scoring patients. Logistic regression analysis revealed that cognitive dysfunction (short-term memory score=0) was associated with DBP (OR=0.96, 95% CI=0.93–0.99, $p=0.04$) and tended to be associated with SBP (OR=0.98; 95% CI=0.96–1.00, $p=0.10$) after adjustment for age, BMI, and history of CVD.

Table 2 shows the differences in characteristics between the top quartile group and the other groups in the get-up-and-go test. Those in the top quartile group were older than those in any other group. The top quartile group had the lowest prevalences of habitual alcohol use and history of hyperlipidemia, and the highest prevalence of a history of CVD. According to logistic regression analysis, physical dysfunction (represented by the top quartile group in the get-up-and-go test) was associated with hyperlipidemia (OR=0.55; 95% CI=0.32–0.97, $p=0.04$) and habitual alcohol use (OR=1.60; 95% CI=1.04–2.45, $p=0.03$) after adjustment for age and a history of CVD.

There was a significant negative correlation between the memory test score and the get-up-and-go test time ($r=-0.16$, $p<0.001$); that is, those with better memory were also more able-bodied.

Cognitive and Physical Functions and Mortality

During the follow-up period (average duration, 34 months), there were a total of 75 fatal events, including 36 fatal cardiovascular events (2 from coronary artery disease, 20 from heart failure, 3 sudden cardiac deaths, 1 from aortic disease, and 10 from stroke). Table 3 shows the characteristics of the patients organized according to cause of death. Subjects in the all-cause and cardiovascular death groups were older than those in the survived group. BMI was lower in the all-cause death group than in the survived group. The prevalence of a history of CVD was higher in both mortality groups than in the survived group. Cholesterol levels tended to be lower in both mortality groups than in the survived group. Concerning memory test scores, the prevalence of a score of 0 tended to be higher in both death groups than in the survived group, and the top quartile in the get-up-and-go test had a higher prevalence in both death groups than in the survived group.

Figure 2 shows the Kaplan-Meier cumulative incidences for total mortality and cardiovascular mortality among the three memory-score groups. Figure 3 shows the Kaplan-Meier cumulative incidences for total mortality and cardiovascular mortality among the quartiles in the get-up-and-go test. In a Cox regression analysis controlling for age, male gender, BMI, a history of CVD, DBP, and cholesterol level, the short-term memory score was an independent predictor of total mortality, while the get-up-and-go time tended to be an independent predictor of total mortality. In addition, performance on each test was thus found to be an independent predictor of cardiovascular mortality (Table 4).

Discussion

This study demonstrated that, in Japanese outpatients aged 80 years or older, cognitive and physical dysfunction as evaluated by simple tests were the most important predictors of

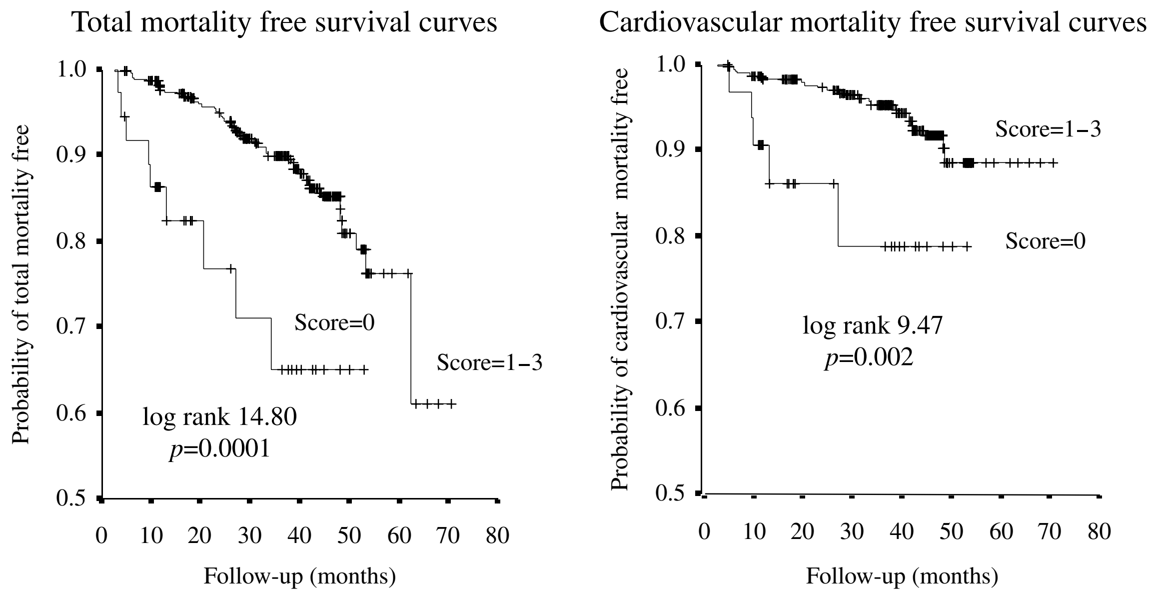

Fig. 2. *Relationship between cognitive function and total or cardiovascular mortality. Kaplan-Meier cumulative incidence of total or cardiovascular mortality in patients divided according to memory test scores.*

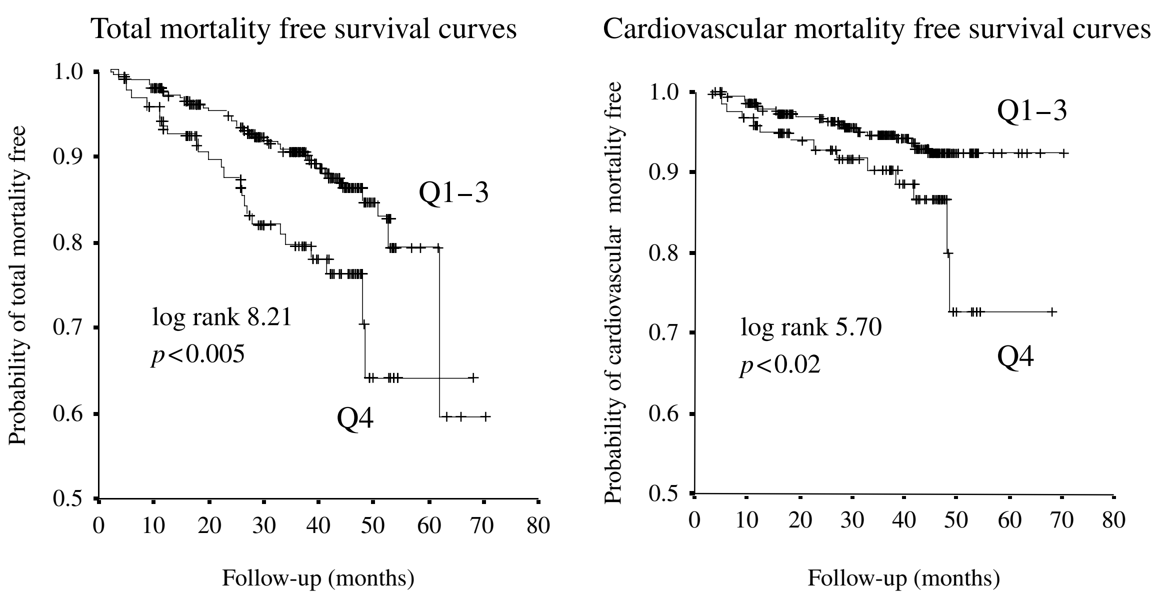

Fig. 3. *Relationship between get-up-and-go test performance and total or cardiovascular mortality. Kaplan-Meier cumulative incidence of total or cardiovascular mortality in patients divided into quartiles in get-up-and-go test performance.*

total and cardiovascular mortality, independent of age and conventional risk factors.

Cognitive Function and Total and Cardiovascular Mortality

In this study, the lowest scores on the simple short-term memory test were associated with total and cardiovascular mortality. The subjects in this study had preserved their general intellect and activities of daily living, and thus they had no severe dementia. Dementia has been shown to be a risk factor for a high mortality rate in the elderly (*1*, *2*), but even non-demented healthy elderly people complain of memory loss, with some showing actual memory impairment. The progno-

Table 4. Cox Regression Analysis for Mortality

	Total mortality		Cardiovascular mortality	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age	1.00 (0.92–1.10)	0.95	0.97 (0.85–1.11)	0.64
Male (1=male, 0=female)	1.91 (0.99–3.71)	0.05	1.94 (0.80–4.70)	0.14
Body mass index	0.85 (0.76–0.95)	0.003	0.96 (0.84–1.10)	0.56
History of CVD, % (1=yes, 0=no)	1.86 (0.98–3.54)	0.06	1.91 (0.81–4.51)	0.14
Diastolic blood pressure	1.02 (0.99–1.04)	0.28	1.02 (0.99–1.06)	0.31
Cholesterol	1.00 (0.99–1.01)	0.53	0.99 (0.98–1.01)	0.31
Prevalence of short-term memory (1=score 0, 0=score 1–3)	7.46 (2.80–19.89)	<0.001	10.88 (2.98–39.7)	<0.001
Top quartile of get-up-and-go test	1.91 (0.98–3.75)	0.06	2.41 (1.00–5.84)	0.05

HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease.

sis is uncertain for individuals who have mild memory impairment but have otherwise preserved their general status, such as their intellectual ability and their physical activity in daily living. Several studies have indicated that patients with mild cognitive impairment have an increased risk for developing Alzheimer's disease, with the rate ranging from 5% to 22% per year (*11–13*). Mild cognitive impairment, a heterogeneous classification, includes people who present with focal abnormalities, lifelong developmental disabilities, or psychiatric illness (*13*, *14*). There are no definitive studies on the diagnosis of mild cognitive impairment. A number of screening tools have been developed to identify it. Several previous studies have reported the outcomes of patients with mild cognitive impairment using various criteria (*11–13*). It is very difficult to use all of the screening tools in the usual clinical settings. Therefore, a simple test for short-term memory, such as that used in this study, might be an effective method for evaluating cognitive function in the very elderly.

Physical Function and Total and Cardiovascular Mortality

This study showed that the physical function of very elderly patients was associated with total and cardiovascular mortality, according to the results of the get-up-and-go test, which incorporated a series of tasks: standing up from a seated position, walking, turning, stopping, and sitting down. The get-up-and-go test can be used to assess balance deficiency and the risk of falling in the very elderly (*10*). Some studies have reported that a fall was not only associated with decreased activities of daily life, but also was an independent predictor of mortality in elderly patients (*15*, *16*). Our study suggested that a balance deficiency as the cause of a fall might increase the risk of mortality in the very elderly. The get-up-and-go test can be also used to assess the muscle power capacity of elderly subjects. Generally, physical activity has well-known benefits for several chronic disorders. In extremely elderly patients, the physical activities of daily life, such as standing and walking, which are included in the get-up-and-go test, might be an important predictor of mortality.

Other Factors and Total and Cardiovascular Mortality

In this study, cholesterol levels tended to be lower in the mortality groups than in the survived group, but they were not associated with mortality according to a Cox regression analysis. Otherwise, lower BMI was associated with total mortality. Some studies have demonstrated that mortality in older people is related to BMI, and have suggested that being overweight results in lower mortality than being underweight (*17*, *18*). A high cholesterol level has also been reported to be associated with a lower dementia risk in very elderly subjects (*19*). Dietary factors therefore potentially play a role in the etiology of cognitive decline and dementia. Weight loss in individuals with moderate to severe dementia is associated with greater morbidity and mortality (*20*). The cognitive decline itself may also influence nutritional status. Achieving adequate nutrition in very elderly subjects is therefore an important factor in the survival of such individuals.

Determinants of Cognitive and Physical Function

In this study, cognitive dysfunction was associated with lower SBP and DBP levels. Hypertension has been reported to be a risk factor for cognitive dysfunction (*7*), and hypertensive treatment for BP reduction has been shown to prevent the progression of cognitive dysfunction in middle-aged and younger elderly patients (*21*, *22*). However, in very elderly people, the relationship between BP and cognitive function has been a subject of debate. In particular, few reports have shown the relationship between BP and cognitive function in patients aged 80 years or older. One study reported that BP was inversely associated with the risk of dementia in 85-year-old patients, which is in agreement with our results (*23*). Another study reported an inverse relationship between BP level and all-cause mortality in patients over 85, but the reason for this association remains unclear (*24*). Aging may possibly induce sluggishness in baroreceptor and sympathetic nervous system responsiveness; such a change would contribute to an alteration in the regional blood flow and to the progression of atherogenesis, thus leading to microvascular abnormalities (*25*). A sufficiently high BP may therefore be necessary to guarantee adequate cardiac and cerebral perfusion. In our study, although BP levels were not directly associated with mortality, they might contribute to the process of cognitive dysfunction, which leads to mortality. Therefore, in extremely elderly patients, we may need to treat BP without excessively lowering it.

In our study, the top quartile group in the get-up-and-go test, which was an independent predictor of mortality, was associated with a low prevalence of hyperlipidemia and a high prevalence of habitual alcohol drinking. It is debatable whether hyperlipidemia or alcohol consumption is associated with mortality in extremely elderly people. Some reports have examined the significance of treatment for hyperlipidemia (*26*, *27*), and another study found that such treatment appears to be no longer beneficial to very old people (*28*). Alcohol consumption has also been suggested to have a J-shaped association with cerebrovascular disease (*29*).

Cognitive and Physical Function

In this study, a negative correlation was observed between the short-term memory test score and the get-up-and-go test time. Several studies have also reported on the relationship between cognitive and physical function (*30*, *31*). Regular physical exercise is an important element in overall health promotion (*32*) and might also be an effective strategy for delaying the onset of dementia (*33*). The biological mechanisms by which physical exercise might preserve brain function include improved cerebral blood flow (*34*) and oxygen delivery, and the induction of fibroblast growth factor in the hippocampus (*35*). In extremely elderly subjects, there was an interaction between cognitive dysfunction and physical dysfunction, and each form of dysfunction was consequently associated with a poor prognosis.

Study Limitations

Since no reports have utilized the simple tests used in this study, we could not validate the use of our simple test of cognitive function. In addition, in our study, the subset of subjects who were followed for more than 3 years was too small to determine whether or not there was truly a plateau in the number of subjects who developed dementia. Moreover, there might be an overlap in this study between the group with the lowest score on the memory test and dementia.

Conclusion

In very elderly subjects, cognitive and physical dysfunctions were found to be independent predictors of mortality after adjustment for conventional cardiovascular risk factors. If the simple tests of cognitive and physical functions used in this study are valid and effective predictors of mortality, they might be widely used and have utility in the care of very elderly people. Regular physical exercise is an important element in overall health promotion and might also be an effective strategy for delaying the onset of dementia and thus for reducing mortality in extremely elderly people. It is also suggested that a lower BP might lead to the progression of cognitive dysfunction.

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