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Cognitive Impairment and Survival at Older Ages

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Abstract

Several studies suggest that cognitive impairment is a risk factor for mortality among older adults. However, the mechanisms that generate the association between cognitive function and survival are not well understood. Proposals attempting to explain why the association is observed focus on the role of health and diseases and on terminal decline. Poor health may affect both cognitive function and survival, and the association between cognitive impairment and mortality could be spurious. The terminal decline hypothesis suggests that factors related to the death of the individual cause a decline in intellectual performance, and that the onset of this decline may be detected in some instances several years prior to the death of the persons.

We investigated these issues in a sample of 2,401 Danish twins aged 75 years and older. At baseline in 1995 the Mini-Mental State Exam was administered to assess participants' cognitive functioning, and subjective and objective health measures were also collected. We related cognitive function to 6-year survival. As expected, cognitive impairment was associated with an increased risk of death. Interestingly, this effect was attenuated but not eliminated after statistical controls for a number of health measures, suggesting that the association between cognitive function and survival is robust and can only in part be attributed to health factors.

A second set of analyses addressed the terminal decline hypothesis. Surviving participants were re-contacted and re-interviewed in 1997 and 1999. A total of 984 individuals participated in all three waves. Consistent with the terminal decline hypothesis, there was evidence that decline in cognitive function was more pronounced among the deceased when compared to the survivors. However, a history of cognitive decline did not predict mortality above and beyond the current level of cognitive functioning.

Introduction

With aging, both “normal” senescent age-related changes and late-onset diseases may affect the brain, producing declines in performance and resulting in mild or severe cognitive impairment. In contemporary industrialized societies, approximately 5 to 10 percent of the population aged more than 65 years suffer from dementia. Milder cognitive dysfunction is estimated to be at least two times as prevalent (Graham et al. 1997). Cognitive impairment represents a major public health burden with adverse psychosocial and economic consequences for the affected persons and their families. There are also a number of research reports suggesting that cognitive impairment predicts subsequent mortality (for reviews see Berg 1996; Siegler 1975; Small and Bäckman 1999).

Understanding the pattern in determinants of late-life survival becomes increasingly important as the population ages (Christensen and Vaupel 1996). However, the mechanisms that generate the association between cognitive impairment and mortality are not well understood. It has often been speculated that the association arises as a consequence of other factors. In the present study we examined two groups of potentially confounding covariates; namely indicators of socioeconomic status and indicators of health. It is known that persons with higher socioeconomic status tend to live longer (Kitagawa and Hauser 1973). It is also known that socioeconomic status and cognitive function are correlated (Lindenberger and Baltes 1997), and the observed association between cognitive function and survival could be due to the higher socioeconomic status of those with higher cognitive scores.

A similar argument has been made for health factors (Small and Bäckman 1999). Morbidity has an impact on cognitive performance (van Boxtel et al. 1998) as well as on mortality. Thus the association between cognitive impairment and mortality could be spurious, perhaps entirely due to health factors. In context of the present study we had access to several health measures and we explored whether inclusion of these measures

would attenuate or even eliminate the association between cognitive function and survival.

It has also been argued that it is not the level of cognitive function that is important when it comes to mortality and survival, but rather change and decline in function. Specifically, it could be that the cognitive status is much less important than a trajectory or history of decline. Kleemeier (1962) proposed the so-called terminal decline hypothesis, which is still widely entertained today. The hypothesis suggests “that factors related to the death of the individual cause a decline in intellectual performance, and that the onset of this decline may be detected in some instances several years prior to the death of the person” (Kleemeier 1962, p. 293). If this were the case, then we would expect that every sample of older persons includes a number of individuals in their terminal decline phase, and consequently, associations between baseline cognitive function and mortality risk would be observed. Convincing empirical demonstration of terminal decline has remained somewhat elusive, because it is very difficult to separate death-related changes from normative age-related decrements in cognitive function. It is also unclear whether most or all people are eventually affected by terminal decline. It could be that only subgroups are susceptible to death-related decline in function, such as people with Alzheimer’s disease. In the context of the present study we first explored whether terminal decline was present in a sample of persons aged 75 years and older. In a second step we investigated whether a history of decline was associated with mortality, above and beyond the current level of cognitive function.

Data and Method

Study Population and Sample

Our data came from the Longitudinal Study of Aging Danish Twins (Christensen et al. 1999), a population-based Danish twin study. In March 1995 a survey was conducted among all Danish twins who were 75 years or older. Among the 3,099 individuals in the study population, extensive interview information was obtained on

2,401 individuals, corresponding to a participation rate of 77%. Interviews were conducted at the twin's residence. When a twin was unable to participate due to physical or mental handicaps, a proxy-responder was sought (closest relative). A total of 2,188 interviews were conducted with twins, and 213 interviews were conducted with proxies.

In 1997 and again in 1999, the surviving participants were re-contacted and the survey was repeated. 1,595 twins (81% of the surviving 1995 participants) were re-interviewed in the 1997 wave. 984 twins (74% of the surviving two-wave participants) were re-interviewed in the 1999 wave.

Measure of Cognitive Impairment

The Mini-Mental State Examination (MMSE; Folstein et al. 1975) was used to assess cognitive impairment. The MMSE is a short interviewer-administered test including brief measures of calculation, language, orientation, recall and registration, with scores ranging from 0 to 30. For the purpose of the present analyses, scores on the MMSE were graded into four levels (high normal, low normal, mild impairment, severe impairment). Cutoffs for these levels are reported in the first column of Table 1. The chosen cutoffs are consistent with recommendations in the literature (e.g., McDowell and Newell 1996).

--- insert Table 1

Measures of Socioeconomic Status

Two measures of socioeconomic status were employed. Elementary education was chosen as a measure reflecting socioeconomic status early in life. For the purpose of the present analyses, elementary education was graded into three levels: less than 7th grade, 7th-8th grade, and 9th grade and above. Social class was chosen as a measure of socioeconomic status in late life. Twins and their spouses were assigned to one of five social classes (Christensen et al. 1998; Hansen 1984). Twins were assigned to the social status of their spouse (alive or deceased) if it was higher than their own. For the purpose of the present analyses, social class was graded into two levels. The two highest social

classes were collapsed into level “high social class,” the three lowest social classes were collapsed into level “low social class.”

Health Measures

Three measures of health were employed. The number of hospitalizations from 1977 to 1994 was used as an externally assessed measure of general health. The National Danish Discharge Registry comprises information on practically all discharges from somatic hospitals in Denmark. Hospital information was obtained for all but 123 of twins through register linkage (Christensen et al. 1999). The present study was based on hospitalization of the twins in the period from January 1, 1977, through December 31, 1994. The number of hospitalizations was graded into four levels (“0”, “1 to 2”, “3 to 5”, and “6 or more” hospitalizations).

A composite measure of functional abilities was selected to measure persons’ functional health status. The composite measure reflects physical strength, it is based on self-reports and comprises 11 items focusing on mobility and the ability to walk, run, climb stairs and carry weights (Christensen et al. 2000). For the purpose of the present analyses, scores of the composite measure were divided into four levels according to quarters of the performance distribution (< 25th percentile; ≥ 25th and < 50th percentile; ≥ 50th and < 75th percentile; ≥ 75th percentile).

A single-item subjective health measure was used to assess self-rated health. Participants were asked, “Do you think that your health is generally excellent, good, acceptable, poor, or very poor?” For the purpose of the present analyses, participants’ responses were divided into four levels (“excellent”, “good”, “acceptable”, and “poor or very poor” health).

Missing Values

Researchers studying cognitive function in older adults typically encounter a sizeable portion of missing data. It is unlikely that this type of missing data occurs at random. In dealing with missing values researchers have applied strategies such as listwise deletion

or imputation of estimated values based on regression models. We chose a different approach with the goal to obtain an estimate of the mortality risk associated with incomplete data on the MMSE. Specifically, for the MMSE and for other risk factor we included an additional level comprising the persons with missing data on that factor. Inspection of the relative risk associated with missing MMSE provides an estimate of the degree to which incomplete data on the MMSE are related to mortality. Anstey et al. (2001) reported that having incomplete cognitive and sensory data was associated with an elevated mortality risk in persons aged 70 and older, suggesting that missing data are predictive of subsequent mortality. Consequently, we expected that persons with missing MMSE data would have an increased mortality risk when compared to persons with complete data.

Mortality Follow-up

Mortality follow-up for all participants was conducted through register linkage with the Civil Registration System. 1154 individuals (48.1% of those with interview information in 1995) had died as of January 1, 2001, and their date of death was recorded.

Procedure and Statistical Model

Cox proportional hazards regression models (Cox 1972) were evaluated for the effects of risk factors. We used the PHREG procedure (Allison 1995) from the SAS software package to estimate Cox regression models.

Results

Level of Cognitive Impairment and Survival

A first analysis focused on the bivariate association between level of cognitive impairment and mortality. From Model 1 in Table 1 it can be seen that the risk of death increased monotonically with decreasing level of cognitive function. Interestingly, those without an exam had the highest risk. These are the persons who participated by proxy or

refused to take the MMSE. Their mortality risk was more than five times higher when compared to person who scored in the “high normal” range.

We then inspected the relative risks obtained from a series of hierarchical models to gain insights into the pattern of association between cognitive impairment and mortality. Model 2 in Table 1 included statistical controls for age and sex. This adjustment reduced the relative risks associated with levels of cognitive impairment by about 20 to 25 percent. Model 3 in Table 1 additionally controlled for two measures reflecting socioeconomic status early and late in life (elementary education and social class, respectively). Relative risks associated with levels of cognitive impairment remained virtually unaltered, indicating the association between cognitive function and survival cannot be attributed to level of elementary education or social class.

In a next step we asked whether the association remains after controls for three health measures (hospitalizations between 1977 and 1994, functional abilities, and self-rated health). Adjustment for health measures reduced the relative risk by more than one half. It seems, then, that health factors are quite important when it comes to explaining the relation between cognitive function and mortality. However, it is noteworthy that even after adjustment for these health factors, cognitive impairment was still related to mortality, although the association was less pronounced.

In a final step we explored whether there were age and sex differences in the predictive pattern. We addressed this question by including interaction terms (age group x MMSE; sex x MMSE) in the regression model. Neither the interaction involving age group (ages 75-84 versus ages 85+) nor the interaction involving sex reached statistical significance. Thus it appears that the association between cognitive impairment and survival is similar for ages 75-84 and ages 85+, as well as for women and men.

It is known that genetic influences on cognitive function are substantial (McGue and Christensen 2001). There is also evidence that genetic factors affect length of life (Herskind et al. 1996; McGue et al. 1993). The analyses presented above included a sub-

sample of $n = 480$ intact twin pairs and this sub-sample may have affected our estimates of the association between cognitive function and survival. We examined this issue in a set of separate analyses relying exclusively on unrelated twins. Specifically, for this set of analyses we randomly selected and omitted one twin from each intact twin pair. The relative risks obtained among 1,920 unrelated twins were very similar to relative risks observed in the full sample, suggesting that the inclusion of persons who share all or half of their genes did not artificially inflate the reported relative risks.

Terminal Decline

We investigated patterns of terminal decline among 984 twins who participated in the first three waves of the Longitudinal Study of Aging Danish twins in 1995, 1997, and 1999. Complete data on the MMSE were available for 858 twins. 126 persons (12.8 percent of the three-wave participants) had missing MMSE data at one or more measurement occasions – these persons were not considered in the longitudinal analyses.

In a first step, we examined average MMSE performance separately for those who survived ($n = 755$) and those who died ($n = 103$) prior to January 2001. Figure 1 displays their average MMSE scores in 1995, 1997, and 1999. On average, there was some decline for both survivors and the deceased. However, the average decline in cognitive function was much more pronounced in those who died before the year 2001. This pattern fits well with the terminal decline hypothesis: there was modest decline in the survivors, but much steeper decline in those who were near to death.

--- insert Figure 1

In a next step we moved from average performance to individual trajectories. We inspected plots of individual trajectories with the goal to find out whether there were clear-cut differences between the trajectories of the survivors as compared to those of the deceased. Figure 2 shows a plot of 50 randomly selected trajectories from the survivors and 50 randomly selected trajectories from the deceased. It can be seen that the trajectories of the survivors and the deceased did not differ in an obvious way. Rather it

appears that trajectories reflecting decline, maintenance, and even increase in cognitive function were present in both groups. This suggests that there were large inter-individual differences in intra-individual change among both survivors and the deceased.

--- insert Figure 2

When it comes to the prediction of mortality, is it sufficient to know a person's cognitive status, or does information about the person's change in cognitive function improve the prediction? In order to address this question, we tried to summarize the slope of each twin's trajectory by a simple measure. Using data stemming from three measurement occasions it is possible in principle to investigate curvilinear patterns of change. However, we restricted our attention to a linear model of change, which is less dependent on chance fluctuations in the data. For each twin we calculated an average MMSE gain measure, obtained as the slope parameter of a linear regression of MMSE score on time-in-study (in years). Thus the MMSE gain measure reflects the individual's average rate-of-change in MMSE per year for the period from 1995 to 1999. We then used the MMSE gain measure to predict short-term mortality up to January 2001.

The MMSE gain measure was related to mortality risk (see Table 2). For every MMSE point gained per year, the mortality risk was lowered by 26 percent. Or, conversely, for every MMSE point lost per year, the risk of death was increased by 26 percent. This result remained unaltered when we statistically controlled for initial MMSE level in 1995, suggesting that decline in cognitive function was associated with mortality above and beyond initial level of function.

--- insert Table 2

We then applied a harder test to assess the role of change in the prediction of mortality, involving adjustment for final MMSE level in 1999. This analysis was designed to investigate whether a history of decline in cognitive function is predictive of mortality above and beyond the *current* level of functioning. From Table 2 it can be seen final MMSE level in 1999 was associated with short-term mortality. Addition of the

MMSE gain measure did not significantly improve the prediction ($\chi^2 = 1.1$, $df = 1$, $p > .05$). However, it should be noted that final MMSE level in 1999 and MMSE gain were highly correlated ($r = .77$, $p < .01$). That is, individuals who experienced large declines in MMSE were also highly likely to score low at the final MMSE assessment. Thus it was very hard for MMSE gain to predict mortality beyond final assessment, despite the evidence for terminal decline (cf. Figure 1). Nevertheless, the analysis presented in Table 2 suggests that a history of decline in cognitive function was not associated with mortality above and beyond the current level of functioning. In sum, there was evidence that terminal decline in cognitive function occurred in some of the twins. Current level of cognitive function was associated with subsequent mortality, but a history of decline did not add to the prediction.

Discussion

A number of recent research reports implicated higher levels of cognitive function as a predictor of survival (Anstey et al. 2001; Bassuk et al. 2000; Bosworth et al. 1999; Maier and Smith 1999; Neale et al. 2001; Smits et al. 1999; Whalley and Deary 2001). The present study replicated this finding in a sample of old and very old Danish twins. The Mini-Mental State exam was included as a screen for cognitive impairment with clinically relevant cutoffs. With decreasing level of cognitive function, mortality risk increased considerably. For example, individuals who were classified as severely impaired had a more than three times higher risk of dying compared to those who scored in the high normal range. A sizeable portion of this effect can be attributed to other known risk factors such as age and health status. After statistical controls for these other factors, the effects of cognitive impairment were reduced in their magnitude. However, it is noteworthy that cognitive function remained a significant and sizeable predictor of survival even after adjustments for these other factors.

Incomplete data on the MMSE was associated with a substantially increased risk of death. It seems likely that incomplete data is indicative of very poor cognitive

function. In the present study, 89% of missing data on the MMSE occurred because some twins were unable to participate due to physical or mental handicaps and proxy responders were sought. Thus it is probably the case that the true association between cognitive function and survival is even more pronounced than was reported here.

There are several proposals in the literature attempting to explain why an association between cognitive function and survival is observed. Results from the present study suggest that the role of socioeconomic factors is negligible. We do not wish to dispute the importance of socioeconomic factors – they are clearly important with respect to inequalities in health and survival (Marmot et al. 1995). However, the association between cognitive impairment and mortality can probably not be attributed to individual differences in socioeconomic factors.

An alternative explanation for the link between cognitive function and survival focuses on the role of health. Physical health may affect both cognitive function and mortality (Berg, 1996), and the association between cognitive function and survival could be spurious. The present study lends some support to this proposal. Adjustment for three measures of health reduced the relative mortality risks associated with levels of cognitive function by more than one half. This suggests that the association can in part be attributed to health factors, although the etiologic mechanism remains to be specified.

Extensive and fine-grained models for measuring health status have been proposed (e.g., Idler 1992). It could be argued that controls for participants' health were not extensive enough in the present study, because only three measures of health were included. But then, the measures of health that were included were strongly related to survival, and nevertheless they did not eliminate the association between cognitive impairment and mortality. Moreover, in older adults chronological age is itself a substantial carrier of additional health information, and the link between cognitive function and survival was evident even after controls for both age and health measures. Thus, results from the present study suggest that cognitive function does make a

difference in terms of survival, regardless of health. This conclusion is consistent with evidence from other studies that controlled for a large array of health measures (Smits et al. 1999) and physician-observed ICD diagnoses of illnesses (Maier and Smith, 1999).

If socioeconomic and health factors cannot fully account for the link between cognitive impairment and mortality, why do we observe this association? It is possible that cognitive impairment results in maladaptive everyday behavior, which in turn may increase individuals' risk of death. Everyday adaptive capacity comprises a large set of everyday behavior, practices, and routines, which are directly or indirectly related to health and, ultimately, to survival. For example, it is adaptive to keep health care appointments, to remember to take necessary medication, to maintain sound preventive care and nutrition, to recognize signs and symptoms of disease, to seek timely medical assistance, to operate electronic devices according to instructions, to obey traffic rules, and so forth. Cognitive impairment may compromise an individual's everyday adaptive capacity in many ways, thereby increasing the susceptibility to death from a variety of causes.

Many researchers recognized that behavioral adaptations may mediate the relation between cognitive function and survival (Bosworth et al. 1999; Swan et al. 1995). It would be interesting to know how much of the effect of cognitive function on survival is mediated through everyday behavioral adaptations. Unfortunately, it is very difficult to address this question empirically, because a comprehensive measure of everyday adaptive capacity has yet to be established. Some studies of cognition and mortality included a small set of health practices, such as smoking status or alcohol consumption (e.g., Bassuk et al. 2000; Swan et al. 1995). Health practices did not emerge as prominent mediators of the effect of cognition on survival. However, the true effect of behavioral adaptations was probably severely underestimated in these studies, because only few and select aspects of everyday adaptive capacity were measured.

Cognitive function appears to be a marker of the human organism's capacity to survive. It has often been suggested that terminal decline can account for some or all of this. In the present study we undertook several longitudinal analyses with the goal to clarify the relationship of terminal decline to mortality. Analyses comparing survivors and the deceased indicated a pattern consistent with the notion of terminal decline. On average, there was minor decline in the survivors and accelerated decline in the deceased. Inspection of individual trajectories, however, suggested that there is considerable inter-individual variability in patterns of cognitive decline. Among all persons who were near to death, it appeared that some experienced terminal decline while others did not. Future research should seek to determine the factors that characterize those who experience terminal decline. In this context it might be interesting to examine whether terminal decline is more prevalent among certain causes of death such as Alzheimer's disease, cardiac disease, or stroke.

Cognitive decline was associated with higher mortality in this sample of Danish twins aged 75 years and older. Does cognitive decline confer an increased mortality risk above and beyond the level of functioning? This question is probably best addressed by choosing the resulting level of functioning as a comparison standard. We found that a history of cognitive decline did not confer an added mortality risk beyond the resulting level of function. That is, although there was evidence for terminal decline in this study, the decline per se did not signal an unfavorable prognosis not accounted for by the current level of functioning.

Conclusion

In a sample of Danish twins aged 75 and older, cognitive impairment was an independent predictor of 6-year mortality after statistical controls for age, sex, measures of socioeconomic status, and measures of health. Effects appeared to be similar in women and men, as well as for ages 75-84 and ages 85+. Incomplete data on the cognitive measure was associated with a substantially increased risk of death. There was evidence

that terminal decline in cognitive function was present among those who died. However, a history of decline did not predict mortality above and beyond current level of functioning.

References

- Allison PD (1995) Survival analysis using the SAS system: a practical guide. SAS Institute Inc, Cary
- Anstey KJ, Luszcz MA, Giles LC, Andrews GR (2001) Demographic, health, cognitive, and sensory variables as predictors of mortality in very old adults. *Psychol Aging* 16: 3-11
- Bassuk SS, Wypij D, Bergman LF (2000) Cognitive impairment and mortality in community-dwelling elderly. *Am J Epidemiol* 151: 676-688
- Berg S (1996) Aging, behavior, and terminal decline. In: Birren JE, Schaie KW (eds) *Handbook of the psychology of aging*, 4th edn. Academic Press, New York, pp 323-337
- Bosworth HB, Schaie KW, Willis SL (1999) Cognitive and sociodemographic risk factors for mortality in the Seattle Longitudinal Study. *J Gerontol B-Psychol* 54: P272-P282
- Christensen K, Gaist D, Jeune B, Vaupel JW (1998) A tooth per child? *Lancet* 352: 204
- Christensen K, Holm NV, McGue M, Corder L, Vaupel JW (1999) A Danish population-based twin study on general health in the elderly. *J Aging Health* 11: 49-69
- Christensen K, McGue M, Yashin A, Iachine I, Holm NV, Vaupel JW (2000) Genetic and environmental influences on functional abilities among Danish twins aged 75 years and older. *J Gerontol A-Biol* 55: M446-M452
- Christensen K, Vaupel, JW (1996) Determinants of longevity: genetic, environmental, and medical factors. *J Intern Med* 240: 333-341
- Cox DR (1972) Regression models and life tables (with discussion). *J Roy Stat Soc B* 34: 187-220

Folstein MF, Folstein SE, McHugh PR (1975) "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiat Res* 12: 189-198

Graham JE, Rockwood K, Beattie BL, Eastwood R, Gauthier S, Tuokko H, McDowell I (1997) Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet* 349: 1793-1796

Hansen EJ (1984) *Socialgrupper i Danmark*. Socialforskningsinstituttet, Copenhagen

Herskind AM, McGue M, Holm NV, Sorensen TIA, Harvald B, Vaupel JW (1996) The heritability of human longevity: a population-based study of 2872 Danish twin pairs born 1870-1900. *Hum Genet* 97: 319-323

Idler EL (1992) Self-assessed health and mortality: A review of studies. In: Maes S, Leventhal H, Johnston M (eds) *International Review of Health Psychology*, Wiley, New York, pp. 33-54

Kleemeier R (1962) Intellectual changes in the senium. *Proceedings of the Social Statistics Section of the American Statistical Association* 1: 290-295

Kitagawa EM, Hauser PM (1973) *Differential mortality in the United States: a study in socioeconomic epidemiology*. Harvard University Press, Cambridge

Lindenberger U, Baltes PB (1997) Intellectual functioning in old and very old age: cross-sectional results from the Berlin Aging Study. *Psychol Aging* 12: 410-432

Maier H, Smith J (1999) Psychological predictors of mortality in old age. *J Gerontol B-Psychol* 54: P44-P54

Marmot M, Bobak M, Davey Smith G (1995) Explanations for social inequalities in health. In: Amick BC, Levine S, Tarlov AR, Walsh D (eds) *Society and health*, Oxford University Press, New York, pp. 172-210

McDowell I, Newell C (1996) *Measuring health: a guide to rating scales and questionnaires*. Oxford University Press, New York

McGue M, Christensen K (2001) The heritability of cognitive functioning in very old adults: evidence from Danish twins aged 75 years and older. *Psychol Aging* 16: 272-280.

McGue M, Vaupel JW, Holm N, Harvald B (1993) Longevity is moderately heritable in a sample of Danish twins born 1870-1880. *J Gerontol* 48: B237-B244

Neale R, Brayne C, Johnson AL (2001) Cognition and survival: an exploration in a large multicentre study of the population aged 65 years and over. *Int J Epidemiol* 30: 1383-1388

Siegler IC (1975) The terminal drop hypothesis: Fact or artifact? *Exp Aging Res* 1: 169-185

Small BJ, Bäckman L (1999) Time to death and cognitive performance. *Curr Dir Psychol Sci* 8: 168-172

Smits CHM, Deeg DJH, Kriegsman DMW, Schmand B (1999) Cognitive functioning and health as determinants of mortality in an older population. *Am J Epidemiol* 150: 978-986

Swan GE, Carmelli D, LaRue A (1995) Performance on the digit symbol substitution test and 5-year mortality in the Western Collaborative Group Study. *Am J Epidemiol* 141: 32-40

Van Boxtel MP, Buntinx F, Houx PJ, Metsemakers JF, Knotterus A, Jolles J (1998) The relation between morbidity and cognitive performance in a normal aging population. *J Gerontol A-Biol* 53: M147-M154

Whalley LJ, Deary IJ (2001) Longitudinal cohort study of childhood IQ and survival up to age 76. *Brit Med J* 322: 819-822.

Author Note

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Table 1
Percentages and number of people who died until 2001, by level of cognitive impairment, and association of cognitive impairment with mortality among a sample of 2,401 persons who participated in the Longitudinal Study of Aging Danish Twins in 1995.

Mini-Mental State Exam	Total no.	Persons who died		Relative risk adjusted for							
		%	No.	Unadjusted (Model 1) ^a		Age and sex (Model 2) ^b		Age, sex, and SES (Model 3) ^c		Age, sex, SES, and health (Model 4) ^d	
				RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
High normal (28-30)	637	31.1	198	1		1		1		1	
Low normal (24-27)	844	40.2	339	1.38	1.16, 1.64*	1.27	1.07, 1.52*	1.29	1.08, 1.53*	1.11	0.93, 1.33
Mild impairment (18-23)	494	55.9	276	2.23	1.86, 2.68*	1.84	1.53, 2.22*	1.86	1.54, 2.26*	1.35	1.11, 1.65*
Severe impairment (<18)	186	75.3	140	3.77	3.03, 4.68*	2.92	2.34, 3.65*	2.96	2.35, 3.73*	1.71	1.35, 2.18*
Missing	240	83.8	201	5.65	4.63, 6.88*	4.70	3.84, 5.77*	4.70	3.79, 5.83*	1.67	0.96, 2.89

Note. RR = relative risk; CI = confidence interval.

^a Relative risks were obtained from a Cox regression model including the Mini-Mental State Exam.

^b Relative risks were obtained from a Cox regression model including the Mini-Mental State exam, age at interview, and sex.

^c Relative risks were obtained from a Cox regression model including the Mini-Mental State exam, age at interview, sex, elementary education, and social class.

^d Relative risks were obtained from a Cox regression model including the Mini-Mental State exam, age at interview, sex, elementary education, social class, hospitalizations 1977-1994, functional abilities, and self-rated health.

* $p < .01$.

Table 2

Mortality risk until 2001 associated with initial MMSE in 1995, final MMSE in 1999, and change in MMSE among a sample of 858 persons who participated in the first three waves of the Longitudinal Study of Aging Danish Twins from 1995 to 1999.

Risk factor	Unadjusted ^a		Change and initial level ^b		Change and final level ^c	
	RR	95% CI	RR	95% CI	RR	95% CI
MMSE gain per year 1995-1999	0.74	0.65, 0.85*	0.74	0.65, 0.85*	0.87	0.68, 1.13
Initial MMSE in 1995	0.97	0.92, 1.03	0.96	0.91, 1.02		
Final MMSE in 1999	0.93	0.91, 0.96*			0.96	0.91, 1.01

Note. RR = relative risk; CI = confidence interval.

^a Unadjusted relative risks were obtained from a separate Cox regression model for each risk factor, that is, excluding other factors.

^b Relative risks were obtained from a Cox regression model including MMSE gain per year 1995-1999 and initial MMSE in 1995.

^c Relative risks were obtained from a Cox regression model including MMSE gain per year 1995-1999 and final MMSE in 1999.

* $p < .01$.

Figure Captions

Figure 1. Average MMSE-score and 95 percent confidence interval by year and vital status in 2001 among 858 persons who participated in the first three waves of the Longitudinal Study of Aging Danish Twins from 1995 to 1999.

Figure 2. 100 randomly selected intra-individual trajectories of cognitive function. Each line denotes the trajectory of a person. Survivors are shown in blue, the deceased in red.



