Education and trajectories of cognitive decline over 9 years in very old people: methods and risk analysis

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Abstract

Background: the investigation of cognitive decline in the older population has been hampered by analytical considerations. Most studies of older people over prolonged periods suffer from loss to follow-up, yet this has seldom been investigated fully to date. Such considerations limit our understanding of how basic variables such as education can affect cognitive trajectories.

Methods: we examined cognitive trajectories in a population-based cohort study in Cambridge, UK, of people aged 75 and over in whom multiple interviews were conducted over time. Cognitive function was assessed using the Mini-Mental State Examination (MMSE). Socio-demographic variables were measured, including educational level and social class. An age-based quadratic latent growth model was fitted to cognitive scores. The effect of socio-demographic variables was examined on all latent variables and the probability of death and dropout.

Results: at baseline, age, education, social class and mobility were associated with cognitive performance. Education and social class were not related to decline or its rate of change. In contrast, poor mobility was associated with lower cognitive performance, increased cognitive decline and increased rate of change of cognitive decline. Gender, age, mobility and cognitive ability predicted death and dropout.

Conclusions: contrary to much of the current literature, education was not related to rate of cognitive decline or change in this rate as measured by MMSE. Higher levels of education do not appear to protect against cognitive decline, though if the MMSE is used in the diagnostic process, individuals with less education may be diagnosed as having dementia somewhat earlier.

Keywords: MMSE, education, cognitive decline, longitudinal studies, old age

Introduction

Cognitive decline is a central feature of the ageing process which affects growing numbers of the population as mortality rates decline globally [1]. The extreme end of decline in cognition is dementia but decline in the non-demented population has also been shown repeatedly with some cognitive functions more affected than others. Although cognitive decline is known to increase with age, measurement of trajectories and production of these trajectories are much less certain. The Mini-Mental State Examination (MMSE) [2] is one of the most widely used tools to assess global cognitive functioning as it correlates with biological and neurological markers associated with dementia [3–6].

There is consensus that more educated individuals achieve higher levels of cognitive performance, but results from a considerable body of evidence of research about the effect of education have been inconsistent. Anstey and Christensen [7], in a review of the literature, identified few studies that examined the effect of education as a risk factor for cognitive...
decline. They found reports that suggested that rates of decline were less rapid for highly educated individuals, studies that failed to find an effect of more rapid decline for the better educated and studies in which the effect of education was restricted to subgroups or certain cognitive tests. Theoretical hypotheses that would explain all these differences have been extensively discussed [8, 9]. However, before conclusions can be made about the effect of education on true cognitive decline, basic issues such as the populations and age cohorts examined and methods of measurement and analysis need to be considered.

Methodological differences in the examination of change, the analysis of missing data and restrictions imposed by features of study design may also explain at least some of the differences reported. For instance, not all studies examining the relationship between cognition and education have considered global measures of cognition. Many have only examined specific cognitive abilities such as fluid intelligence or cognitive speed [10, 11]. Where global measures of cognition have been used, results are still likely to be affected by characteristics inherent to items within the measuring tests used, such as ceiling or floor effects. That is, if large portions of the sample have scores at the upper or lower ends of the scale, results are less likely to reflect changes. The selection of variables used to control parameters of interest may also explain some of these differences in results. For example, in many studies, model parameters such as cognitive performance and rate of decline have not been controlled for gender or other potential confounders, despite longer life expectancy of women, and the fact that educational attainment, lifestyle factors and genetics differ by gender [12–15].

Other study characteristics such as the use of data from non-population-based samples and the number of data waves available for analysis may provide further reasons for conflicting results. Examples include those studies where respondents were volunteers, patients or other selected groups as in the Religious Order Study [16, 17], where results obtained are likely to be different to those expected in the general population.

Most studies have investigated cognitive decline fitting linear models that allowed for the examination of the effect of education on linear model parameters, i.e. cognitive performance and rate of decline. However, processes such as terminal decline that have been identified in the literature [18, 19] suggest that decline is not linear. Determining the shape of the curve that best describes cognitive decline is often hampered by insufficient waves of data collection to assure identifiability of parametric models with quadratic or higher terms. Consequently, the effect of education on parameters such as the change in rate of decline has not often been examined.

Attrition plays a key role in longitudinal studies of aging. Considering cognitive change as an incremental process [20], several studies [21, 22] have calculated change scores using complete subsamples of the data, a practice likely to produce biased results, unless those who drop out are no different from those staying in the study, or in other words, missing data are missing completely at random [23]. Random effects models [24] produce estimates that are robust against a missing at random missing data assumption [23], that is, when the missing data process is only dependent on observed data. As random effects models allow for individually varying times of observation, age-based models can be fitted to describe cognitive change, as opposed to models based on ‘time since baseline’, a more artificial construct within epidemiological studies [25]. Latent growth models can also be fitted on this age-based temporal matrix. Furthermore, latent growth models produce estimates of mean latent variables that can be used to describe an unobserved mean trajectory curve that groups together individuals in addition to growth factors or person-specific parameters, which allow for the examination of person-specific trajectories of cognitive decline. Such methods have rarely been used in cognitive trajectories of MMSE in the very old people. The analysis presented here investigates the effect of education on cognitive performance, rate of decline and on change of rate of decline fitting a quadratic age-based latent growth model to data from a population-based longitudinal study of older people, the Cambridge City over 75s Cohort Study [26].

Methods

Description of study

The Cambridge City over 75s Cohort Study [26] is a population-based study which began in 1985. People aged at least 75 years in 1985 who were registered at five primary care practices and one in three from a sixth practice in the Cambridge City area were recruited. Those who agreed (95% response rate) were screened by trained interviewers in their home, and socio-demographic information was collected. Cognitive status was assessed using the MMSE [2]. When a question was not asked or was not applicable in the MMSE test due to sensory or physical impairment, the item was scored as zero and included in the calculation of the final MMSE score. Individuals were asked at what age they left school. The average age at which participants left school (14 years old) was used as a cutoff point to define two educational categories. Social class was assessed by asking participants what was their main occupation before retirement. Married women were asked about their husband’s main occupation. Social class was grouped as manual/semiskilled and non-manual or higher. Information about activities of daily living was also collected. Mobility was defined as present if a participant responded they could walk unaided around town or the block.

The screening interview was followed by a more detailed clinical interview of all participants scoring 23 or less on the MMSE and a third of those with scores of 24 and 25 points. Further, waves of interviews were carried out to establish incidence of dementia. After baseline, interviews were conducted on all the survivors an average of 2, 7 and 9 years later. Data from the four interviews were examined here. The characteristics of individuals at baseline are shown in Table 1.
the examination of relevant plots.

ment of model assumptions was examined visually through estimates. Mplus version 4 was used to fit the model. Fulfil-
nitive Monte Carlo integration were used to calculate model estimating techniques with numerical integration performed nitive decline across study participants. Maximum likelihood the quadratic term represents the mean rate of change in cog-
of decline between the ages of 80.8 years and 2 years later, and study. The slope of the fitted curve represents the mean rate status at the age of 80.8 years, the average age at entry to the parameterisation of the latent growth model was such that time

= 6.4) and 23.5 (SD = 5.6) with median values of 26 at baseline and 25 for all other three follow-up interviews. Table 2 shows the characteristics of dropouts by interview wave. Cognitive scores before dropout of individuals who dropped out and those who remained in the study were compared at each interview using an unpaired \( t \)-test. At all interviews, the hypothesis of equality of means was rejected at 5%. The results obtained from modelling the probability of death and dropout consistently identified individuals with lower cognitive scores and poor mobility as more likely to dropout. At the third interview, conducted 7 years after baseline, women were also found to be less likely to die and dropout than men. At the last interview wave, in addition to lower cognitive score, mobility and gender, individuals in the youngest age cohort were also found to be less likely to die and dropout of the study. Table 2 shows odds ratio results for death and dropout at each interview wave by predictor of death and dropout.

A small number of participants did not take part in some of the study interview waves but rejoined the study later. Data from them were only considered up to their first dropout to produce a non-intermittent dataset. All participants were observed at baseline, but 43.4, 24.5 and 16.6% of the sample dropped out for the first time at the second, third and fourth interviews, respectively. These include dropout due to death.

### Statistical methods

Working under a selection modelling framework [27], we fitted a joint model in which one of the factors was a condi-
tional quadratic growth model that described marginal change and the other factor, an explicit formulation of a missing data model. All three latent variables of the quadratic latent growth model were adjusted for the socio-demographic vari-
ables described in Table 1. A logistic regression was used to model the probability of death and dropout [28], that is, the probability of individual \( i \) dropping out at time \( t \) was modelled as dependent on the individual’s MMSE score at time \( t - 1 \) and other potential risk factors for dropout. The parameterisation of the latent growth model was such that the intercept of the mean curve represents mean cognitive status at the age of 80.8 years, the average age at entry to the study. The slope of the fitted curve represents the mean rate of decline between the ages of 80.8 years and 2 years later, and the quadratic term represents the mean rate of change in cognitive decline across study participants. Maximum likelihood estimating techniques with numerical integration performed via Monte Carlo integration were used to calculate model estimates. Mplus version 4 was used to fit the model. Fulfil-
ment of model assumptions was examined visually through the examination of relevant plots.

### Results

At baseline and follow-up interviews, mean MMSE scores were calculated at 24.2 (SD = 5.9), 23.2 (SD = 6.4), 23.0 (SD = 6.4) and 23.5 (SD = 5.6) with median values of 26 at baseline and 25 for all other three follow-up interviews. Table 2 shows the characteristics of dropouts by interview wave. Cognitive scores before dropout of individuals who dropped out and those who remained in the study were compared at each interview using an unpaired \( t \)-test. At all interviews, the hypothesis of equality of means was rejected at 5%. The results obtained from modelling the probability of death and dropout consistently identified individuals with lower cognitive scores and poor mobility as more likely to dropout. At the third interview, conducted 7 years after baseline, women were also found to be less likely to die and dropout than men. At the last interview wave, in addition to lower cognitive score, mobility and gender, individuals in the youngest age cohort were also found to be less likely to die and dropout of the study. Table 2 shows odds ratio results for death and dropout at each interview wave by risk factor and their confidence intervals.

Mean cognitive performance at the average age of entry to the study, 80.8 years, was estimated at a value of 26.5 (SE = 0.8), the mean rate of decline between the ages of 80.8 and 82.8 years was estimated at \(-0.5\) (SE = 0.1) and its rate of
probably due to the small number of the very old people. Large value, it was not found to be statistically significant, the effect of age on rate of decline being estimated at a relatively small rate of decline. As expected, higher educational level and social class, better mobility and younger age at baseline were identified as statistically significant positive factors for cognitive performance. Women and participants with better mobility were found to experience a slower decline with age than men and participants with poorer mobility. Despite the effect of age on rate of decline being estimated at a relatively large value, it was not found to be statistically significant, probably due to the small number of the very old people.

Individuals with better mobility were found to experience less change in their rate of decline than individuals with poorer levels of mobility. Education was not found to influence the rate of change, only cognitive performance at the average age of entry to the study.

**Discussion**

The key findings from this analysis are that age-related cognitive decline as measured by the MMSE does not occur at constant rate, although the speed of its change is slow. Considerable variability was found between individuals about mean curve parameters, confirming heterogeneity between individuals in cognitive performance, rate of decline and its change. The relatively small decline observed here is similar to other cohort results [16, 21, 22] over a shorter time frame, in the same cohort [29]. These studies report that individuals seen experienced a little change over time. This plateau has also been described previously by Wernicke and Reischies [30] who hypothesised the existence of a lower asymptote for cognitive decline beyond which cognition does not decline. Our experience is that people become untestable in the lower end of MMSE with few individuals scoring under 10. Few studies [18, 19, 31–33] have more than three data waves available, particularly in such old groups. Consequently, the examination of the effect of risk factors on the change in rate of decline has not often been conducted and, therefore, there is not much evidence about the evolution of rate of decline in cognitive performance in the literature.

Our results regarding the role of education on the cognitive performance and rate of decline have identified higher levels of education as a positive factor for cognitive performance but not for rate of decline or its change. These results add support to previously reported null effects [33–37]. Another potential marker of protection, social class, highly correlated to education was also not related to change, as reported by some studies [38].

The simple measure of mobility emerged as a powerful factor related to decline and change in decline; mobility has increasingly been recognised as a key feature for the development of frailty and dependence. Other potential causes of cognitive decline could be modelled. With additional data and further waves of investigation aspects such as ApoE genotype, head trauma and other medical conditions could be used to investigate the differences in rate of decline.

Attrition has severe effects on studies of older people. We have examined attrition explicitly and were able to identify predictors of death and dropout whilst adjusting the joint likelihood for the missing data mechanism hypothesised. The factors we found to be associated with death and dropout were lower MMSE performance, lower mobility, gender and age but not social class nor education as has been reported in other studies [32, 39]. Our findings regarding the effect of older age at baseline and gender on the probability of death and dropout agree with results previously reported in this context [40], although they are likely to be explained by the larger life expectancy of women and a survivor effect.

### Table 3. Estimates (SE) of effect of risk factors on cognitive performance, rate of decline and change in rate of decline obtained from regression models where the outcome variables were cognitive performance, rate of decline and change in rate of decline

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Cognitive performance</th>
<th>Rate of decline</th>
<th>Change in rate of decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women versus men</td>
<td>−0.2 (0.3)</td>
<td>−0.07 (0.05)*</td>
<td>0.07 (0.02)</td>
</tr>
<tr>
<td>Age at baseline ≤ 85 years old versus 85+ cohort</td>
<td>3.9 (0.3)*</td>
<td>0.25 (0.16)</td>
<td>0.07 (0.03)</td>
</tr>
<tr>
<td>Left school younger than 14 years old versus left school aged at least 15 years old</td>
<td>−1.0 (0.3)*</td>
<td>0.01 (0.05)</td>
<td>−0.02 (0.02)</td>
</tr>
<tr>
<td>Non-manual profession versus manual profession</td>
<td>1.0 (0.3)*</td>
<td>0.05 (0.06)</td>
<td>0.01 (0.02)</td>
</tr>
<tr>
<td>Married versus not ever married</td>
<td>0.1 (0.3)</td>
<td>0.01 (0.05)</td>
<td>−0.02 (0.02)</td>
</tr>
<tr>
<td>Good versus poor mobility</td>
<td>2.3 (0.2)*</td>
<td>−0.13 (0.06)*</td>
<td>0.02 (0.03)*</td>
</tr>
</tbody>
</table>

*Statistically significant at the 5% level.

change at −0.04 (SE = 0.01). See Figure 1 for a graphical representation of the estimated mean quadratic curve that describes the mean cognitive decline over 9 years. The large residual variances estimated about these parameters indicated the existence of heterogeneity across individuals.

Table 3 shows estimates of the effects of risk factors on mean cognitive performance, rate of decline and change in rate of decline. As expected, higher educational level and social class, better mobility and younger age at baseline were identified as statistically significant positive factors for cognitive performance. Women and participants with better mobility were found to experience a slower decline with age than men and participants with poorer mobility. Despite the effect of age on rate of decline being estimated at a relatively large value, it was not found to be statistically significant, probably due to the small number of the very old people.
A limitation of this paper is that MMSE may be relatively insensitive to differential patterns of decline and therefore significant effects may not emerge. However, this is offset by the strengths of the study, which is a large population-based cohort followed over an extended period. It is also evident that MMSE is adequate to show variations between individuals and to show decline over the period studied. The MMSE is a widely used instrument so, whatever its limitations, these data are meaningful to a clinical and academic readership.

**Conclusion**

Contrary to much of the current literature, education was not related to rate of cognitive decline or change in this rate as measured by MMSE. Higher levels of education do not appear to protect against cognitive decline, though if the MMSE is used in the diagnostic process, individuals with less education may be diagnosed as having dementia somewhat earlier.

**Key points**

- Age-related cognitive decline was modelled jointly with the probability of death or dropout to identify risk factors associated with both processes.
- Higher educational level and social class, better mobility and younger age at baseline were identified as positive factors for cognitive performance.
- Women and participants with better mobility experienced a slower decline than men and participants with poorer mobility.
- Lower MMSE performance, lower mobility, gender and age were found to be associated with death and dropout.

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**Conflicts of interest**

The authors declare no conflict of interest.

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